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UNIT I Principles of Drug Therapy 1 Pharmacokinetics I. OVERVIEW Pharmacokinetics refers to what the body does to a drug, whereas pharmacodynamics (see Chapter 2) describes what the drug does to the body. Once administered through one of several available routes, four pharmacokinetic properties determine the speed of onset of drug action, the intensity of the drug's effect, and the duration of drug action (Figure 1.1): • Absorption: First, drug absorption from the site of administration permits entry of the therapeutic agent (either directly or indirectly) into plasma. • Distribution: Second, the drug may then reversibly leave the bloodstream and distribute into the interstitial and intracellular fluids. • Metabolism: Third, the drug may be biotransformed by metabolism by the liver, or other tissues. • Elimination: Finally, the drug and its metabolites are eliminated from the body in urine, bile, or feces. Pharmacokinetic parameters allow the clinician to design and optimize treatment regimens, including decisions as to the route of administration for a specific drug, the amount and frequency of each dose, and the duration of treatment. II. ROUTES OF DRUG ADMINISTRATION The route of administration is determined primarily by the properties of the drug (for example, water or lipid solubility, ionization) and by the therapeutic objectives (for example, the desirability of a rapid onset of action, the need for long-term treatment, or restriction of delivery to a local site). Major routes of drug administration include enteral, parenteral, and topical among others. Figure 1.2 illustrates the subcategories of these routes as well as other methods of drug administration. Drug at site of administration 1 Absorption (input) Drug in plasma 2 Distribution Drug in tissues 3 Metabolism Metabolite(s) in tissues 4 Elimination (output) Drug and/or metabolite(s) in urine, bile, or feces Figure 1.1 Schematic representation of drug absorption, distribution, metabolism, and elimination. A. Enteral Enteral administration, or administering a drug by mouth, is the safest and most common, convenient, and economical method of drug administration. When the drug is given in the mouth, it may be swallowed, allowing oral delivery, or it may be placed under the tongue (sublingual), facilitating direct absorption into the bloodstream. Pharm 5th 3-21-11.indb 1 3/21/11 2:19:36 PM 2 1. Pharmacokinetics Parenteral: IV, IM, SC Sublingual Inhalation Oral Transdermal patch Topical Rectal Figure 1.2 Commonly used routes of drug administration. IV = intravenous; IM = intramuscular; SC = subcutaneous. 1. Oral: Giving a drug by mouth provides many advantages to the patient. Oral drugs are easily self-administered and, compared to drugs given parenterally, have a low risk of systemic infections that could complicate treatment. Moreover, toxicities and overdose by the oral route may be overcome with antidotes, such as activated charcoal. On the other hand, the pathways involved in oral drug absorption are the most complicated, and the low pH of the stomach may inactivate some drugs. A wide range of oral preparations is available including enteric-coated and extended-release preparations. a. Enteric-coated preparations: An enteric coating is a chemical envelope that resists the action of the fluids and enzymes in the stomach but dissolves readily in the upper intestine. Such coating is useful for certain groups of drugs (for example, omeprazole) that are acid unstable. Enteric coatings protect the drug from stomach acid, delivering them instead to the less acidic intestine, where the coating dissolves and allows the drug to be released. Similarly, drugs that have an irritant effect on the stomach, such as aspirin, can be coated with a substance that will dissolve only in the small intestine, thereby protecting the stomach. b. Extended-release preparations: Extended-release medications have special coatings or ingredients that control how fast the drug is released from the pill into the body. Having a longer duration of action may improve patient compliance, because the medication does not have to be taken as often. Additionally, extended-release dosage forms may maintain concentrations within an acceptable therapeutic range over a long period of time, as opposed to immediate-release dosage forms, which may result in larger peaks and troughs in plasma concentrations. These extended-release formulations are advantageous for drugs with short half-lives. For example, the half-life of morphine is 2 to 4 hours in adults. Oral morphine must be administered six times in 24 hours to obtain a continuous analgesic effect. However, only two doses are needed when controlled-release tablets are used. Unfortunately, many of the extended release formulations may have been developed to create a marketing advantage over conventional-release products, rather than because of documented clinical advantage. 2. Sublingual: Placement under the tongue allows a drug to diffuse into the capillary network and, therefore, to enter the systemic circulation directly. Sublingual administration of an agent has several advantages, including rapid absorption, convenience of administration, low incidence of infection, bypass of the harsh gastrointestinal (GI) environment, and avoidance of first-pass metabolism (the drug is absorbed into the superior vena cava). The buccal route (between cheek and gum) is similar to the sublingual route. B. Parenteral The parenteral route introduces drugs directly across the body's barrier defenses into the systemic circulation. Parenteral administration is used for drugs that are poorly absorbed from the GI tract (for example, heparin) and for agents that are unstable in the GI tract (for example, insulin). Parenteral administration is also used for treatment Pharm 5th 3-21-11.indb 2 3/21/11 2:19:37 PM II. Routes Of Drug Administration 1. Intravenous (IV): IV injection is the most common parenteral route. For drugs that are not absorbed orally, such as the neuromuscular blocker atracurium, there is often no other choice. IV delivery permits a rapid effect and a maximum degree of control over the circulating levels of the drug. When injected as a bolus, the full amount of a drug is delivered to the systemic circulation almost immediately. The same dose also may be administered as an IV infusion during a longer time, resulting in a decrease in the peak plasma concentration and an increase in the time the drug is present in the circulation. IV injection is advantageous for administering chemicals that may cause irritation when administered via other routes, because the substance is rapidly diluted by the blood. However, unlike drugs in the GI tract, those that are injected cannot be recalled by strategies, such as by binding to activated charcoal. IV injection may inadvertently introduce bacteria and other infective particles through contamination at the site of injection. It may also precipitate blood constituents, induce hemolysis, or cause other adverse reactions by the too-rapid delivery of high concentrations of a drug to the plasma and tissues. Therefore, patients must be carefully monitored for unfavorable drug reactions, and the rate of infusion must be carefully controlled. 2. Intramuscular (IM): Drugs administered IM can be in aqueous solutions, which are absorbed rapidly (Figure 1.3), or in specialized depot preparations, which are absorbed slowly. Depot preparations often consist of a suspension of the drug in a nonaqueous vehicle such as polyethylene glycol. As the vehicle diffuses out of the muscle, the drug precipitates at the site of injection. The drug then dissolves slowly, providing a sustained dose over an extended period of time. Examples of sustained-release drugs are haloperidol (see p. 165) and depot medroxyprogesterone (see p. 323). These drugs produce extended neuroleptic and contraceptive effects, respectively. 3. Subcutaneous (SC): This route of administration, like IM injection, requires absorption via simple diffusion and is somewhat slower than the IV route. SC injection minimizes the risks of hemolysis or thrombosis associated with IV injection and may provide constant, slow, and sustained effects. This route should not be used with drugs that cause tissue irritation, because severe pain and necrosis may occur. [Note: Minute amounts of epinephrine are sometimes combined with a drug administered subcutaneously to restrict its area of action. Epinephrine acts as a local vasoconstrictor and decreases removal of a drug, such as lidocaine, from the site of administration.] Other examples of drugs given via SC administration include solids, such as a single rod containing the contraceptive etonogestrel that is implanted for long-term activity (see p. 325), and programmable mechanical pumps that can be implanted to deliver insulin in diabetic patients. Pharm 5th 3-21-11.indb 3 A Subcutaneous injection Intramuscular injection Epidermis Dermis Muscle Subcutaneous tissue B 200 Plasma concentration (ng/mL) of unconscious patients and under circumstances that require a rapid onset of action. In addition, these routes have the highest bioavailability and are not subject to first-pass metabolism or harsh GI environments. Parenteral administration provides the most control over the actual dose of drug delivered to the body. However, these administrations are irreversible and may cause pain, fear, local tissue damage, and infections. The three major parenteral routes are intravascular (intravenous or intra-arterial), intramuscular, and subcutaneous (see Figure 1.2). Each route has advantages and drawbacks. 3 5 mg intravenous midazolam 100 0 5 mg intramuscular midazolam 0 30 60 Time (minutes) 90 Figure 1.3 A. Schematic representation of subcutaneous and intramuscular injection. B. Plasma concentrations of midazolam after intravenous and intramuscular injection. 3/21/11 2:19:38 PM 4 1. Pharmacokinetics C. Other 1. Oral inhalation: Inhalation routes, both oral and nasal (see below), provide rapid delivery of a drug across the large surface area of the mucous membranes of the respiratory tract and pulmonary epithelium, producing an effect almost as rapidly as does IV injection. This route of administration is used for drugs that are gases (for example, some anesthetics) and those that can be dispersed in an aerosol. This route is particularly effective and convenient for patients with respiratory complaints (such as asthma or chronic obstructive pulmonary disease), because the drug is delivered directly to the site of action, thereby minimizing systemic side effects. Examples of drugs administered via this route include bronchodilators, such as albuterol, and corticosteroids, such as fluticasone. A Skin Clear backing Drug reservoir Drug-release membrane Contact adhesive Drug diffusing from reservoir into subcutaneous tissue B 2. Nasal inhalation: This route involves administration of drugs directly into the nose. Agents include nasal decongestants, such as oxymetazoline, and anti-inflammatory corticosteroids such as mometasone furoate. Desmopressin is administered intranasally in the treatment of diabetes insipidus. Salmon calcitonin, a peptide hormone used in the treatment of osteoporosis, is also available as a nasal spray. 3. Intrathecal/intraventricular: The blood-brain barrier (see p. 10) typically delays or prevents the absorption of drugs into the central nervous system (CNS). When local, rapid effects are needed, it is necessary to introduce drugs directly into the cerebrospinal fluid. For example, intrathecal amphotericin B is used in treating cryptococcal meningitis (see p. 430). 4. Topical: Topical application is used when a local effect of the drug is desired. For example, clotrimazole is applied as a cream directly to the skin in the treatment of dermatophytosis. 5. Transdermal: This route of administration achieves systemic effects by application of drugs to the skin, usually via a transdermal patch (Figure 1.4). The rate of absorption can vary markedly, depending on the physical characteristics of the skin at the site of application as well as the lipid solubility of the drug. This route is most often used for the sustained delivery of drugs, such as the antianginal drug nitroglycerin, the antiemetic scopolamine, and nicotine transdermal patches, which are used to facilitate smoking cessation. Figure 1.4 A. Schematic representation of a transdermal patch. B. Transdermal nicotine patch applied to arm. Pharm 5th 3-21-11.indb 4 6. Rectal: Because 50 percent of the drainage of the rectal region bypasses the portal circulation, the biotransformation of drugs by the liver is minimized with rectal administration. Like the sublingual route of administration, the rectal route has the additional advantage of preventing the destruction of the drug by intestinal enzymes or by low pH in the stomach. The rectal route is also useful if the drug induces vomiting when given orally, if the patient is already vomiting, or if the patient is unconscious. [Note: The rectal route is commonly used to administer antiemetic agents.] On the other hand, rectal absorption is often erratic and incomplete, and many drugs irritate the rectal mucosa. Figure 1.5 summarizes the characteristics of the common routes of administration. 3/21/11 2:19:38 PM II. Routes Of Drug Administration ROUTE OF ADMINISTRATION Oral 5 ABSORPTION PATTERN ADVANTAGES DISADVANTAGES • Variable; affected by many factors • Safest and most common, convenient, and economical route of administration • • • • Intravenous • Absorption not required • Can have immediate effects • Ideal if dosed in large volumes • Suitable for irritating substances and complex mixtures • Valuable in emergency situations • Dosage titration permissible • Ideal for high-molecular-weight proteins and peptide drugs • Unsuitable for oily or poorly absorbed substances • Bolus injection may result in adverse effects • Most substances must be slowly injected • Strict aseptic techniques needed Subcutaneous • Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained • Suitable for slow-release drugs • Ideal for some poorly soluble suspensions • Pain or necrosis if drug is irritating • Unsuitable for drugs administered in large volumes Intramuscular • Depends on drug diluents: Aqueous solution: prompt Depot preparations: slow and sustained • Suitable if drug volume is moderate • Suitable for oily vehicles and certain irritating substances • Preferable to intravenous if patient must self administer • Affects certain lab tests (creatine kinase) • Can be painful • Can cause intramuscular hemorrhage (precluded during anticoagulation therapy) Transdermal (patch) • Slow and sustained • Bypasses the first-pass effect • Convenient and painless • Ideal for drugs that are lipophilic, thus requiring prolonged administration • Ideal for drugs that are quickly eliminated from the body • Some patients are allergic to patches, which can cause irritation • Drug must be highly lipophilic • May cause delayed delivery of drug to pharmacological site of action • Limited to drugs that can be taken in small daily doses Rectal • Erratic and variable • • • • • Drugs may irritate the rectal mucosa • Not a well-accepted route. Inhalation • Systemic absorption may occur. This is not always desirable • Absorption is rapid; can have immediate effects • Ideal for gases • Effective for patients with respiratory problems • Dose can be titrated • Localized effect to target lungs: lower doses used compared to that with oral or parental administration • Fewer systemic side effects • Most addictive route (drug can enter the brain quickly) • Patient may have difficulty regulating dose • Some patients may have difficulty using inhalers Sublingual • Depends on the drug: Few drugs (for example, nitroglycerin) have rapid, direct systemic absorption Most drugs erratically or incompletely absorbed • Bypasses first-pass effect • Bypasses destruction by stomach acid • Drug stability maintained because the pH of saliva relatively neutral • May cause immediate pharmacological effects • Limited to certain types of drugs • Limited to drugs that can be taken in small doses • May lose part of the drug dose if swallowed Partially bypasses first-pass effect Bypasses destruction by stomach acid Ideal if drug causes vomiting Ideal in patients who are vomiting, or comatose Limited absorption of some drugs Food may affect absorption Patient compliance is necessary Drugs may be metabolized before systemic absorption Figure 1.5 The absorption pattern, advantages, and disadvantages of the most common routes of administration. Pharm 5th 3-21-11.indb 5 3/21/11 2:19:39 PM 6 1. Pharmacokinetics III. ABSORPTION OF DRUGS A Passive diffusion Passive diffusion of a water-soluble drug through an aqueous channel or pore Drug D D D D A. Mechanisms of absorption of drugs from the GI tract Drug D D Absorption is the transfer of a drug from its site of administration to the bloodstream via one of several mechanisms. The rate and efficiency of absorption depend on both factors in the environment where the drug is absorbed and the drug's chemical characteristics and route of administration (which influence its bioavailability). For IV delivery, absorption is complete. That is, the total dose of drug administered reaches the systemic circulation (100% bioavailability). Drug delivery by other routes may result in only partial absorption and, thus, lower bioavailability. Passive diffusion of a lipid-soluble drug dissolved in a membrane Extracellular D space Depending on their chemical properties, drugs may be absorbed from the GI tract by passive diffusion, facilitated diffusion, active transport, or endocytosis. Cell membrane Cytosol D D B Facilitated diffusion Drug D D D Drug transporter D D D D C Active transport D ATP ADP D D Drug transporter D D Endocytosis D D D D Large drug Figure 1.6 Schematic representation of drugs crossing a cell membrane. ATP = adenosine triphosphate; ADP = adenosine diphosphate. Pharm 5th 3-21-11.indb 6 1. Passive diffusion: The driving force for passive absorption of a drug is the concentration gradient across a membrane separating two body compartments. In other words, the drug moves from a region of high concentration to one of lower concentration. Passive diffusion does not involve a carrier, is not saturable, and shows a low structural specificity. The vast majority of drugs gain access to the body by this mechanism. Water-soluble drugs penetrate the cell membrane through aqueous channels or pores, whereas lipid-soluble drugs readily move across most biologic membranes due to their solubility in the membrane lipid bilayers (Figure 1.6A). 2. Facilitated diffusion: Other agents can enter the cell through specialized transmembrane carrier proteins that facilitate the passage of large molecules. These carrier proteins undergo conformational changes, allowing the passage of drugs or endogenous molecules into the interior of cells and moving them from an area of high concentration to an area of low concentration. This process is known as facilitated diffusion. It does not require energy, can be saturated, and may be inhibited by compounds that compete for the carrier (Figure 1.6B). 3. Active transport: This mode of drug entry also involves specific carrier proteins that span the membrane. A few drugs that closely resemble the structure of naturally occurring metabolites are actively transported across cell membranes using these specific carrier proteins. Energy-dependent active transport is driven by the hydrolysis of adenosine triphosphate (Figure 1.6C). It is capable of moving drugs against a concentration gradient, from a region of low drug concentration to one of higher drug concentration. The process shows saturation kinetics for the carrier, much in the same way that an enzyme-catalyzed reaction shows a maximal velocity at high substrate levels where all the active sites are filled with substrate.1 Active transport systems are selective and may be competitively inhibited by other cotransported substances. 4. Endocytosis and exocytosis: These types of drug delivery systems transport drugs of exceptionally large size across the cell memINFO LINK 1See Chapter 5 in Lippincott's Illustrated Reviews: Biochemistry for a discussion of enzyme kinetics. 3/21/11 2:19:40 PM III. Absorption Of Drugs 7 brane. Endocytosis involves engulfment of a drug molecule by the cell membrane and transport into the cell by pinching off the drugfilled vesicle (Figure 1.6D). Exocytosis is the reverse of endocytosis and is used by cells to secrete many substances by a similar vesicle formation process. Vitamin B_{12} is transported across the gut wall by endocytosis, whereas certain neurotransmitters (for example, norepinephrine) are stored in intracellular membrane-bound vesicles in the nerve terminal and are released by exocytosis. A Weak acid Lipid membrane + H A- HA B. Factors influencing absorption 1. Effect of pH on drug absorption: Most drugs are either weak acids or weak bases. Acidic drugs (HA) release a proton (H^+), causing a charged anion ($A^–$) to form:2 HA → H + + A– HA ← Body compartment Weak bases (BH^+) can also release an H^+. However, the protonated form of basic drugs is usually charged, and loss of a proton produces the uncharged base (B): Lipid membrane A drug passes through membranes more readily if it is uncharged (Figure 1.7). Thus, for a weak acid, the uncharged, protonated HA can permeate through membranes, and $A^–$ cannot. For a weak base, the uncharged form, B, penetrates through the cell membrane, but BH^+, the protonated form, does not. Therefore, the effective concentration of the permeable form of each drug at its absorption site is determined by the relative concentrations of the charged and uncharged forms. The ratio between the two forms is, in turn, determined by the pH at the site of absorption and by the strength of the weak acid or base, which is represented by the ionization constant, pKa (Figure 1.8). [Note: The pKa is a measure of the strength of the interaction of a compound with a proton. The lower the pKa of a drug, the more acidic it is. Conversely, the higher the pKa, the more basic is the drug.] Distribution equilibrium is achieved when the permeable form of a pH 3 4 + B + H BH + B Body compartment Body compartment Figure 1.7 A. Diffusion of the non-ionized form of a weak acid through a lipid membrane. B. Diffusion of the nonionized form of a weak base through a lipid membrane. When pH = pKa, [HA] = [$A^–$] and [BH^+] = [B] When pH is greater than pKa, the deprotonated forms $A^–$ and B predominate. pH < pKa 2 BH + H 2See Chapter 1 in Lippincott's Illustrated Reviews: Biochemistry for a discussion of acid-base chemistry. When pH is less than pKa, the protonated forms HA and BH^+ predominate. Body compartment B Weak base → B + H^+ BH^+ ← INFO LINK A- + H pH > pKa 5 6 7 8 9 10 11 pKa Figure 1.8 The distribution of a drug between its ionized and non-ionized forms depends on the ambient pH and pKa of the drug. For illustrative purposes, the drug has been assigned a pKa of 6.5. Pharm 5th 3-21-11.indb 7 3/21/11 2:19:43 PM 8 1. Pharmacokinetics drug achieves an equal concentration in all body water spaces. [Note: Highly lipid-soluble drugs rapidly cross membranes and often enter tissues at a rate determined by blood flow.] 2. Blood flow to the absorption site: Because blood flow to the intestine is much greater than the flow to the stomach, absorption from the intestine is favored over that from the stomach. [Note: Shock severely reduces blood flow to cutaneous tissues, thereby minimizing the absorption from SC administration.] 3. Total surface area available for absorption: With a surface rich in brush borders containing microvilli, the intestine has a surface area about 1000-fold that of the stomach, making absorption of the drug across the intestine more efficient. 4. Contact time at the absorption surface: If a drug moves through the GI tract very quickly, as can happen with severe diarrhea, it is not well absorbed. Conversely, anything that delays the transport of the drug from the stomach to the intestine delays the rate of absorption of the drug. [Note: Parasympathetic input increases the rate of gastric emptying, whereas sympathetic input (prompted, for example, by exercise or stressful emotions) as well as anticholinergics (for example, dicyclomine), delays gastric emptying. Also, the presence of food in the stomach both dilutes the drug and slows gastric emptying. Therefore, a drug taken with a meal is generally absorbed more slowly.] Drug (extracelluar) 5. Expression of P-glycoprotein: P-glycoprotein is a multidrug transmembrane transporter protein responsible for transporting various molecules, including drugs, across cell membranes (Figure 1.9). It is expressed throughout the body, and its functions include: • In the liver: transporting drugs into bile for elimination • In kidneys: pumping drugs into urine for excretion • In the placenta: transporting drugs back into maternal blood, thereby reducing fetal exposure to drugs • In the intestines: transporting drugs into the intestinal lumen and reducing drug absorption into the blood • In the brain capillaries: pumping drugs back into blood, limiting drug access to the brain ADP + Pi Drug (intracellular) ATP Thus, in areas of high expression, P-glycoprotein reduces drug absorption. In addition to transporting many drugs out of cells, it is also associated with multidrug resistance (see p. 485). C. Bioavailability Figure 1.9 The six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell. Bioavailability is the fraction of administered drug that reaches the systemic circulation. For example, if 100 mg of a drug are administered orally, and 70 mg of this drug are absorbed unchanged, the bioavailability is 0.7, or 70 percent. Determining bioavailability is important for calculating drug dosages for non-intravenous routes of administration. The route by which a drug is administered, as well as the chemical and physical properties of the agent, affects its bioavailability. 1. Determination of bioavailability: Bioavailability is determined by comparing plasma levels of a drug after a particular route of administration (for example, oral administration) with plasma drug levels Pharm 5th 3-21-11.indb 8 3/21/11 2:19:44 PM III. Absorption Of Drugs 2. Factors that influence bioavailability: In contrast to IV administration, which confers 100% bioavailability, oral administration of a drug often involves first-pass metabolism. This biotransformation, in addition to the drug's chemical and physical characteristics, determines the amount of the agent that reaches the circulation and at what rate. a. First-pass hepatic metabolism: When a drug is absorbed across the GI tract, it first enters the portal circulation before entering the systemic circulation (Figure 1.11). If the drug is rapidly metabolized in the liver or gut wall during this initial passage, the amount of unchanged drug that gains access to the systemic circulation is decreased. [Note: First-pass metabolism by the intestine or liver limits the efficacy of many drugs when taken orally. For example, more than 90 percent of nitroglycerin is cleared during a single passage through the liver, which is the primary reason why this agent is administered via the sublingual route]. Drugs that exhibit high first-pass metabolism should be given in sufficient quantities to ensure that enough of the active drug reaches the target concentration. b. Solubility of the drug: Very hydrophilic drugs are poorly absorbed because of their inability to cross the lipid-rich cell membranes. Paradoxically, drugs that are extremely hydrophobic are also poorly absorbed, because they are totally insoluble in aqueous body fluids and, therefore, cannot gain access to the surface of cells. For a drug to be readily absorbed, it must be largely hydrophobic, yet have some solubility in aqueous solutions. This is one reason why many drugs are either weak acids or weak bases. c. Chemical instability: Some drugs, such as penicillin G, are unstable in the pH of the gastric contents. Others, such as insulin, are destroyed in the GI tract by degradative enzymes. d. Nature of the drug formulation: Drug absorption may be altered by factors unrelated to the chemistry of the drug. For example, particle size, salt form, crystal polymorphism, enteric coatings, and the presence of excipients (such as binders and dispersing agents) can influence the ease of dissolution and, therefore, alter the rate of absorption. D. Bioequivalence: Bioavailability = Plasma concentration of drug achieved by IV injection, in which the total agent rapidly enters the circulation. When the drug is given orally, only part of the administered dose appears in the plasma. By plotting plasma concentrations of the drug versus time, the area under the curve (AUC) can be measured. This curve reflects the extent of absorption of the drug. [Note: By definition, this is 100 percent for drugs delivered intravenously.] Bioavailability of a drug administered orally is the ratio of the area calculated for oral administration compared with the area calculated for IV injection if doses are equivalent (Figure 1.10). 9 AUC oral x 100 AUC injected Drug injected AUC (injected) Drug given orally AUC (oral) Time Drug administered Figure 1.10 Determination of the bioavailability of a drug. AUC = area under curve. Drugs administered IV enter directly into the systemic circulation and have direct access to the rest of the body. Portal circulation IV Liver Oral Rest of body Drugs administered orally are first exposed to the liver and may be extensively metabolized before reaching the rest of body. Figure 1.11 First-pass metabolism can occur with orally administered drugs. IV = intravenous. Two related drug preparations are bioequivalent if they show comparable bioavailability and similar times to achieve peak blood concentrations. Pharm 5th 3-21-11.indb 9 3/21/11 2:19:45 PM 10 1. Pharmacokinetics E. Therapeutic equivalence Two similar drug products are therapeutically equal if they are pharmaceutically equivalent with similar clinical and safety profiles. [Note: Clinical effectiveness often depends on both the maximum serum drug concentrations and on the time required (after administration) to reach peak concentration. Therefore, two drugs that are bioequivalent may not be therapeutically equivalent.] IV. DRUG DISTRIBUTION 1.5 Serum concentration 1.25 1 Elimination phase 0.75 0.5 0.25 Distribution phase 0 1 2 Time 3 4 Rapid injection of drug Figure 1.12 Drug concentrations in serum after a single injection of drug. Assume that the drug distributes and is subsequently eliminated. Drug distribution is the process by which a drug reversibly leaves the bloodstream and enters the interstitium (extracellular fluid) and then the cells of the tissues. For a drug administered IV, when absorption is not a factor, the initial phase (that is, from immediately after administration through the rapid fall in concentration) represents the distribution phase, during which a drug rapidly disappears from the circulation and enters the tissues (Figure 1.12). This is followed by the elimination phase (see p. 13), when drug in the plasma is in equilibrium with drug in the tissues. The delivery of a drug from the plasma to the interstitium primarily depends on cardiac output and regional blood flow, capillary permeability, the tissue volume , the degree of binding of the drug to plasma and tissue proteins, and the relative hydro phobicity of the drug. A. Blood flow The rate of blood flow to the tissue capillaries varies widely as a result of the unequal distribution of cardiac output to the various organs. Blood flow to the brain, liver, and kidney is greater than that to the skeletal muscles. Adipose tissue, skin, and viscera have still lower rates of blood flow. Variance in blood flow partly explains the short duration of hypnosis produced by a bolus IV injection of propofol (see p. 144). High blood flow, together with the high lipid solubility of thiopental, permits it to rapidly move into the CNS and produce anesthesia. A subsequent slower distribution to skeletal muscle and adipose tissue lowers the plasma concentration sufficiently so that the higher concentrations within the CNS decrease, and, thus, consciousness is regained. B. Capillary permeability Capillary permeability is determined by capillary structure and by the chemical nature of the drug. Capillary structure varies widely in terms of the fraction of the basement membrane that is exposed by slit junctions between endothelial cells. In the liver and spleen, a large part of the basement membrane is exposed due to large, discontinuous capillaries through which large plasma proteins can pass (Figure 1.13A). This is in contrast to the brain, where the capillary structure is continuous, and there are no slit junctions (Figure 1.13B). To enter the brain, drugs must pass through the endothelial cells of the capillaries of the CNS or be actively transported. For example, a specific transporter for the large neutral amino acid transporter carries levodopa into the brain. By contrast, lipid-soluble drugs readily penetrate into the CNS because they can dissolve in the membrane of the endothelial cells. Ionized, or polar drugs generally fail to enter the CNS because they are unable to pass through the endothelial cells of the CNS, which have no slit junctions. These tightly juxtaposed cells form tight junctions that constitute the so-called blood-brain barrier. Pharm 5th 3-21-11.indb 10 3/21/11 2:19:46 PM IV. Drug Distribution C. Binding of drugs to plasma proteins and tissues 1. Binding to plasma proteins: Reversible binding to plasma proteins sequesters drugs in a nondiffusible form and slows their transfer out of the vascular compartment. Binding is relatively nonselective regarding chemical structure and takes place at sites on the protein to which endogenous compounds, such as bilirubin, normally attach. Plasma albumin is the major drug-binding protein and may act as a drug reservoir (that is, as the concentration of the free drug decreases due to elimination by metabolism or excretion, the bound drug dissociates from the protein). This maintains the free-drug concentration as a constant fraction of the total drug in the plasma. 2. Binding to tissue proteins: Numerous drugs accumulate in tissues, leading to higher concentrations of the drug in tissues than in the extracellular fluids and blood. Drugs may accumulate as a result of binding to lipids, proteins or nucleic acids. Drugs may also be actively transported into tissues. These tissue reservoirs may serve as a major source of the drug and prolong its actions or, on the other hand, can cause local drug toxicity. [For example, acrolein, the metabolite of cyclophosphamide is toxic to the kidney because of its accumulation in renal cells.] 3. Hydrophobicity: The chemical nature of a drug strongly influences its ability to cross cell membranes. Hydrophobic drugs readily move across most biologic membranes. These drugs can dissolve in the lipid membranes and, therefore, permeate the entire cell's surface. The major factor influencing the hydrophobic drug's distribution is the blood flow to the area. By contrast, hydrophilic drugs do not readily penetrate cell membranes and must pass through the slit junctions. D. Volume of distribution The apparent volume of distribution, Vd, can be thought of as the fluid volume that is required to contain the entire drug in the body at the same concentration measured in the plasma. It is calculated by dividing the dose that ultimately gets into the systemic circulation by the plasma concentration at time zero (C_0). Vd = Amount of drug in the body C_0 Although Vd has no physiologic or physical basis, it can be useful to compare the distribution of a drug with the volumes of the water compartments in the body (Figure 1.14). 1. Distribution into the water compartments in the body: Once a drug enters the body, from whatever route of administration, it has the potential to distribute into any one of three functionally distinct compartments of body water or to become sequestered in a cellular site. a. Plasma compartment: If a drug has a very large molecular weight or binds extensively to plasma proteins, it is too large to move out through the endothelial slit junctions of the capillaries and, thus, is effectively trapped within the plasma (vascular) compartment. As a consequence, the drug distributes in a volume (the plasma) that is about 6 percent of the body weight or, in a Pharm 5th 3-21-11.indb 11 11 A Structure of endothelial cells in the liver Large fenestrations allow drugs to move between blood and interstitium in the liver. Drug Slit junctions Basement membrane of a brain B Structure capillary Astrocyte foot processes Basement membrane Brain endothelial cell At tight junctions, two adjoining cells merge so that the cells are physically joined and form a continuous wall that prevents many substances from entering the brain. Tight junction of a C Permeability brain capillary Charged drug Lipid-soluble drugs Carrier-mediated transport Figure 1.13 Cross section of liver and brain capillaries. 3/21/11 2:20:16 PM 12 1. Pharmacokinetics 70-kg individual, about 4 L of body fluid. Heparin (see p. 251) shows this type of distribution. Total body water b. Extracellular fluid: If a drug has a low molecular weight but is Plasma Interstitial volume hydrophilic, it can move through the endothelial slit junctions of the capillaries into the interstitial fluid. However, hydrophilic drugs cannot move across the lipid membranes of cells to enter the water phase inside the cell. Therefore, these drugs distribute into a volume that is the sum of the plasma water and the interstitial fluid, which together constitute the extracellular fluid. This is about 20 percent of the body weight, or about 14 L in a 70kg individual. Aminoglycoside antibiotics (see p. 399) show this type of distribution. Intracellular volume 42 liters c. Total body water: If a drug has a low molecular weight and is hydrophobic, not only can it move into the interstitium through the slit junctions, but it can also move through the cell membranes into the intracellular fluid. The drug, therefore, distributes into a volume of about 60 percent of body weight, or about 42 L in a 70-kg individual. Ethanol exhibits this apparent volume of distribution. Intracellular volume Extracellular volume 28 liters Interstitial volume 10 liters 14 liters Plasma volume 4 liters Figure 1.14 Relative size of various distribution volumes within a 70-kg individual. 2. Apparent volume of distribution: A drug rarely associates exclusively with only one of the water compartments of the body. Instead, the vast majority of drugs distribute into several compartments, often avidly binding cellular components, such as, lipids (abundant in adipocytes and cell membranes), proteins (abundant in plasma and within cells), and nucleic acids (abundant in the nuclei of cells). Therefore, the volume into which drugs distribute is called the apparent volume of distribution, or Vd. Vd is a useful pharmacokinetic parameter for calculating a drug's loading dose (see p. 12) 3. Determination of Vd: The fact that drug clearance is usually a firstorder process allows calculation of Vd. First order means that a constant fraction of the drug is eliminated per unit of time. This process can be most easily analyzed by plotting the log of the plasma drug concentration (Cp) versus time (Figure 1.15). The concentration of drug in the plasma can be extrapolated back to time zero (the time of injection) on the Y axis to determine C_0, which is the concentration of drug that would have been achieved if the distribution phase had occurred instantly. This allows calculation of Vd as Vd = Dose C_0 For example, if 10 mg of drug are injected into a patient and the plasma concentration is extrapolated back to time zero, the concentration is C_0 = 1 mg/L (from the graph shown in Figure 1.15), and then Vd = 10 mg/1 mg/L = 10 L. 4. Effect of Vd on drug half-life: Pharm 5th 3-21-11.indb 12 A large Vd has an important influence on the half-life of a drug, because drug elimination depends on the amount of drug delivered to the liver or kidney (or other organs where metabolism occurs) per unit of time. Delivery of drug to the organs of elimination depends not only on blood flow, but also on the fraction of the drug in the 3/21/11 2:20:17 PM V. Drug Clearance Through Metabolism 13 Once a drug enters the body, the process of elimination begins. The three major routes involved are: 1) hepatic metabolism, 2) elimination in bile, and 3) elimination in urine. Together, these elimination processes cause the plasma concentration of a drug to decrease exponentially. That is, at any given time, a constant fraction of the drug present is eliminated in a unit of time (Figure 1.15A). Most drugs are eliminated according to first-order kinetics, although some, such as aspirin in high doses, are eliminated according to zero-order or non-linear kinetics. Metabolism leads to products with increased polarity, which will allow the drug to be eliminated. Clearance (CL) estimates the amount of drug cleared from the body per unit of time. Total CL is a composite estimate reflecting all mechanisms of drug elimination and is calculated as: $CL = 0.693 \times Vd/t_{1/2}$ where $t_{1/2}$ is the drug's elimination half-life, Vd is the apparent volume of distribution, and 0.693 is the natural log constant. Drug half-life is often used as a measure of drug CL, because, for many drugs, Vd is a constant. A. Kinetics of metabolism 1. First-order kinetics: The metabolic transformation of drugs is catalyzed by enzymes, and most of the reactions obey Michaelis-Menten kinetics.3 V [C] v = rate of drug metabolism = max Km + [C] Distribution phase 1 Most drugs show an exponential decrease in concentration with time during the elimination phase. 2 1 0 0 2 3 Time Rapid injection of drug v = rate of drug metabolism = Vmax [C] Km That is, the rate of drug metabolism and elimination is directly proportional to the concentration of free drug, and first-order kinetics are observed (Figure 1.16). This means that a constant fraction of INFO LINK Pharm 5th 3-21-11.indb 13 3See Chapter 5 in Lippincott's Illustrated Reviews: Biochemistry for a discussion of Michaelis-Menten kinetics. 1 4 Extrapolation to time zero gives C_0, the hypothetical drug concentration predicted if the distribution had been achieved instantly. B 4 3 2 C_0 = 1 0.5 0.4 0.3 0.2 $t_{1/2}$ 0.1 0 In most clinical situations, the concentration of the drug, [C], is much less than the Michaelis constant, Km, and the Michaelis-Menten equation reduces to: Elimination phase 4 Plasma concentration (Cp) V. DRUG CLEARANCE THROUGH METABOLISM A Plasma concentration plasma. If the Vd for a drug is large, most of the drug is in the extraplasmic space and is unavailable to the excretory organs. Therefore, any factor that increases Vd can lead to an increase in the half-life and extend the duration of action of the drug. [Note: An exceptionally large Vd indicates considerable sequestration of the drug in some tissues or compartments.] 1 2 Time 3 4 Rapid injection of drug The half-life (the time it takes to reduce the plasma drug concentration by half) is equal to 0.69 Vd/CL. Figure 1.15 Drug concentrations in plasma after a single injection of drug at time = 0. A. Concentration data are plotted on a linear scale. B. Concentration data are plotted on a log scale. 3/21/11 2:20:18 PM 14 1. Pharmacokinetics With a few drugs, such as aspirin, ethanol, and phenytoin, the doses are very large. Therefore, the plasma drug concentration is much greater than Km, and drug metabolism is zero order, that is, constant and independent of the drug dose. drug is metabolized per unit of time (that is, with every half-life the concentration reduces by 50%). First-order kinetics is sometimes referred to clinically as linear kinetics. 2. Zero-order kinetics: With a few drugs, such as aspirin, ethanol , and phenytoin, the doses are very large. Therefore [C] is much greater than Km, and the velocity equation becomes Rate of drug metabolism 100 v = rate of drug metabolism = The enzyme is saturated by a high free-drug concentration, and the rate of metabolism remains constant over time. This is called zeroorder kinetics (sometimes referred to as clinically as nonlinear kinetics). A constant amount of drug is metabolized per unit of time, and the rate of elimination is constant and does not depend on the drug concentration. 50 0 0 Vmax [C] = Vmax [C] Dose of drug With most drugs the plasma drug concentration is less than Km, and drug elimination is first order, that is, proportional to the drug dose. Figure 1.16 Effect of drug dose on the rate of metabolism. B. Reactions of drug metabolism The kidney cannot efficiently eliminate lipophilic drugs that readily cross cell membranes and are reabsorbed in the distal convoluted tubules. Therefore, lipid-soluble agents must first be metabolized into more polar (hydrophilic) substances in the liver using two general sets of reactions, called Phase I and Phase II (Figure 1.17). 1. Phase I: Phase I reactions convert lipophilic molecules into more polar molecules by introducing or unmasking a polar functional group, such as –OH or $–NH_2$. Phase I metabolism may increase, decrease, or leave unaltered the drug's pharmacologic activity. a. Phase I reactions utilizing the P450 system: The Phase I reactions most frequently involved in drug metabolism are catalyzed by the cytochrome P450 system (also called microsomal mixed-function oxidases): Drug + O_2 + NADPH + H^+ → Drugmodified + H_2O + $NADP^+$ The oxidation proceeds by the drug binding to the oxidized form of cytochrome P450, and then oxygen is introduced through a reductive step, coupled to NADPH:cytochrome P450 oxidoreductase. The P450 system is important for the metabolism of many endogenous compounds (such as steroids, lipids, etc.) and Some drugs directly enter Phase II metabolism. Drug Phase I Following Phase I, the drug may be activated, unchanged, or, most often, inactivated. Oxidation, reduction, and/or hydrolysis Phase II Conjugation products Conjugated drug is usually inactive. Figure 1.17 The biotransformation of drugs. Pharm 5th 3-21-11.indb 14 3/21/11 2:20:19 PM V. Drug Clearance Through Metabolism for the biotransformation of exogenous substances (xenobiotics). Cytochrome P450, designated as CYP, is a superfamily of hemecontaining isozymes that are located in most cells but are primarily found in the liver and GI tract. 1) Nomenclature: The family name is indicated by CYP added to an arabic number, followed by a capital letter for the subfamily, for example, CYP3A (Figure 1.18). Another number is added to indicate the specific isozyme, as in CYP3A4. 2) Specificity: Because there are many different genes that encode multiple enzymes, there are likewise many different P450 isoforms. These enzymes have the capacity to modify a large number of structurally diverse substrates. In addition, an individual drug may be a substrate for more than one isozyme. Four isozymes are responsible for the vast majority of P450catalyzed reactions. They are CYP3A4/5, CYP2D6, CYP2C8/9, and CYP1A2 (see Figure 1.18). Considerable amounts of CYP3A4 are found in intestinal mucosa, accounting for the first-pass metabolism of drugs such as chlorpromazine and clonazepam. 3) Genetic variability: P450 enzymes exhibit considerable genetic variability among individuals and racial groups. Variations in P450 activity may alter a drug's efficacy and the risk of adverse events. CYP2D6, in particular, has been shown to exhibit genetic polymorphism.4 CYP2D6 mutations result in very low capacities to metabolize substrates. Some individuals, for example, obtain no benefit from the opioid analgesic codeine, because they lack the CYP2D6 enzyme that O-demethylates and activates the drug. The frequency of this polymorphism is in part racially determined, with a prevalence of 5 to 10 percent in European Caucasians as compared to less than 2 percent of Southeast Asians. Similar polymorphisms have been characterized for the CYP2C subfamily of isozymes. The addition of a U.S. Food and Drug Administration black box warning to clopidogrel highlights the significance of this polymorphism. Patients who are poor CYP2C19 metabolizers have a higher incidence of cardiovascular events (for example, stroke or myocardial infarction) when taking clopidogrel. This agent is a prodrug, and CYP2C19 activation is required to convert it to its (active) metabolite. Although CYP3A4 exhibits a greater than 10-fold variability between individuals, no polymorphisms have been identified so far for this P450 isozyme. 15 CYP2E1 4% CYP2C19 8% CYP2D6 CYP2C8/9 19% 16% CYP3A4/5 36% CYP1A2 11% CYP2A6 3% CYP2B6 3% Figure 1.18 Relative contribution of cytochrome P450 (CYP) isoforms to drug biotransformatin. 4) Inducers: The CYP450–dependent enzymes are an important target for pharmacokinetic drug interactions. One such interaction is the induction of selected CYP isozymes. Xenobiotics (chemicals not normally produced or expected to be present in the body) may induce the activity of these enzymes by inducing the expression of the genes encoding INFO LINK Pharm 5th 3-21-11.indb 15 4See Chapter 33 in Lippincott's Illustrated Reviews: Biochemistry for a discussion of genetic polymorphism. 3/21/11 2:20:19 PM 16 1. Pharmacokinetics the enzyme or by stabilizing the enzymes. Certain drugs (for example, phenobarbital, rifampin, and carbamazepine) are capable of increasing the synthesis of one or more CYP isozymes. This results in increased biotransformation of drugs and can lead to significant decreases in plasma concentrations of drugs metabolized by these CYP isozymes, as measured by AUC (a measure of drug exposure), with concurrent loss of pharmacologic effect. For example, rifampin, an antituberculosis drug (see p. 424), significantly decreases the plasma concentrations of human immunodeficiency virus (HIV) protease inhibitors,5 thereby diminishing their ability to suppress HIV virion maturation. Figure 1.19 lists some of the more important inducers for representative CYP isozymes. Consequences of increased drug metabolism include: 1) decreased plasma drug concentrations, 2) decreased drug activity if the metabolite is inactive, 3) increased drug activity if the metabolite is active, and 4) decreased therapeutic drug effect. Isozyme: CYP2C9/10 COMMON SUBSTRATES Warfarin Phenytoin Ibuprofen Tolbutamide INDUCERS Phenobarbital Rifampin Isozyme: CYP2D6 COMMON SUBSTRATES Desipramine Imipramine Haloperidol Propranolol INDUCERS None* Isozyme: CYP3A4/5 COMMON SUBSTRATES Carbamazepine Cyclosporine Erythromycin Nifedipine Verapamil 5) Inhibitors: Inhibition of CYP isozyme activity is an important source of drug interactions that lead to serious adverse events. The most common form of inhibition is through competition for the same isozyme. Some drugs, however, are capable of inhibiting reactions for which they are not substrates (for example, ketoconazole), leading to drug interactions. Numerous drugs have been shown to inhibit one or more of the CYP-dependent biotransformation pathways of warfarin. For example, omeprazole is a potent inhibitor of three of the CYP isozymes responsible for warfarin metabolism. If the two drugs are taken together, plasma concentrations of warfarin increase, which leads to greater inhibition of coagulation and risk of hemorrhage and other serious bleeding reactions. [Note: The more important CYP inhibitors are erythromycin, ketoconazole, and ritonavir, because they each inhibit several CYP isozymes.] Cimetidine blocks the metabolism of theophylline, clozapine, and warfarin. Natural substances may also inhibit drug metabolism. For instance, because grapefruit and its juice inhibits CYP3A4, drugs such as nifedipine, clarithromycin, and simvastatin, which are metabolized by this system, persist in greater amounts in the systemic circulation, leading to higher blood levels and the potential to increase the drugs' therapeutic and/or toxic effects. INDUCERS Carbamazepine Dexamethasone Phenobarbital Phenytoin Rifampin Figure 1.19 Some representative cytochrome P450 isozymes. CYP = cytochrome P. *Unlike most other CYP450 enzymes, CYP2D6 is not very susceptible to enzyme induction. b. Phase I reactions not involving the P450 system: These include amine oxidation (for example, oxidation of catecholamines or histamine), alcohol dehydrogenation (for example, ethanol oxidation), esterases (for example, metabolism of pravastatin in liver), and hydrolysis (for example, of procaine). 2. Phase II: This phase consists of conjugation reactions. If the metabolite from Phase I metabolism is sufficiently polar, it can be excreted by the kidneys. However, many Phase I metabolites are too lipophilic INFO LINK Pharm 5th 3-21-11.indb 16 5See Chapter 28 in Lippincott's Illustrated Reviews: Microbiology for a discussion of HIV protease inhibitors. 3/21/11 2:20:20 PM VI. Drug Clearance By The Kidney to be retained in the kidney tubules. A subsequent conjugation reaction with an endogenous substrate, such as glucuronic acid, sulfuric acid, acetic acid, or an amino acid, results in polar, usually more water-soluble compounds that are most often therapeutically inactive. A notable exception is morphine-6-glucuronide , which is more potent than morphine. Glucuronidation is the most common and the most important conjugation reaction. Neonates are deficient in this conjugating system, making them particularly vulnerable to drugs such as chloramphenicol, which is inactivated by the addition of glucuronic acid, resulting in gray baby syndrome (see p. 405). [Note: Drugs already possessing an –OH, $–NH_2$, or –COOH group may enter Phase II directly and become conjugated without prior Phase I metabolism.] The highly polar drug conjugates may then be excreted by the kidney or in bile. 3. Reversal of order of the phases: Not all drugs undergo Phase I and II reactions in that order. For example, isoniazid is first acetylated (a Phase II reaction) and then hydrolyzed to isonicotinic acid (a Phase I reaction). VI. DRUG CLEARANCE BY THE KIDNEY Elimination of drugs from the body requires the agents to be sufficiently polar for efficient excretion. Removal of a drug from the body occurs via a number of routes, the most important being through the kidney into the urine. A patient in renal failure may undergo extracorporeal dialysis, which removes small molecules such as drugs. A. Renal elimination of a drug Elimination of drugs via the kidneys into urine involves the three processes of glomerular filtration, active tubular secretion, and passive tubular reabsorption. 1. Glomerular filtration: Drugs enter the kidney through renal arteries, which divide to form a glomerular capillary plexus. Free drug (not bound to albumin) flows through the capillary slits into Bowman's space as part of the glomerular filtrate (Figure 1.20). The glomerular filtration rate (125 mL/min) is normally about 20 percent of the renal plasma flow (600 mL/min). Lipid solubility and pH do not influence the passage of drugs into the glomerular filtrate. However, varying the glomerular filtration rate and plasma binding of the drugs may affect this process. 17 1 Free drug enters glomerular filtrate Bowman's capsule 2 Active secretion Proximal tubule Loop of Henle 3 Passive reabsorption of lipid-soluble, un-ionized drug, which has been concentrated so that the intraluminal concentration is greater than that in the perivascular space Distal tubule Collecting duct Ionized, lipidinsoluble drug into urine Figure 1.20 Drug elimination by the kidney. 2. Proximal tubular secretion: Drugs that were not transferred into the glomerular filtrate leave the glomeruli through efferent arterioles, which divide to form a capillary plexus surrounding the nephric lumen in the proximal tubule. Secretion primarily occurs in the proximal tubules by two energy-requiring active transport (carrierrequiring) systems: one for anions (for example, deprotonated forms of weak acids) and one for cations (for example, protonated forms of weak bases). Each of these transport systems shows low specificity and can transport many compounds. Thus, competition between drugs for these carriers can occur within each transport system (for example, see probenecid, p. 513). [Note: Premature infants and neonates have an incompletely developed tubular secretory mechanism and, thus, may retain certain drugs in the glomerular filtrate.] Pharm 5th 3-21-11.indb 17 3/21/11 2:20:20 PM 18 1. Pharmacokinetics Drug Drug Proximal tubule Loop of Henle Distal tubule Passive reabsorption of lipid-soluble, unionized drug Drug Phase I and II metabolism Ionized or polar metabolite 3. Distal tubular reabsorption: As a drug moves toward the distal convoluted tubule, its concentration increases and exceeds that of the perivascular space. The drug, if uncharged, may diffuse out of the nephric lumen, back into the systemic circulation. Manipulating the pH of the urine to increase the ionized form of the drug in the lumen may be done to minimize the amount of back-diffusion and, hence, increase the clearance of an undesirable drug. As a general rule, weak acids can be eliminated by alkalinization of the urine, whereas elimination of weak bases may be increased by acidification of the urine. This process is called "ion trapping." For example, a patient presenting with phenobarbital (weak acid) overdose can be given bicarbonate , which alkalinizes the urine and keeps the drug ionized, thereby decreasing its reabsorption. If overdose is with a weak base, such as amphetamine, acidification of the urine with NH_4Cl leads to protonation of the drug (that is, it becomes charged) and an enhancement of its renal excretion. 4. Role of drug metabolism: Most drugs are lipid soluble and, without chemical modification, would diffuse out of the kidney's tubular lumen when the drug concentration in the filtrate becomes greater than that in the perivascular space. To minimize this reabsorption, drugs are modified primarily in the liver into more polar substances using two types of reactions: Phase I reactions (see p. 14), which involve either the addition of hydroxyl groups or the removal of blocking groups from hydroxyl, carboxyl, or amino groups, and Phase II reactions (see p. 16) that use conjugation with sulfate, glycine, or glucuronic acid to increase drug polarity. The conjugates are ionized, and the charged molecules cannot back-diffuse out of the kidney lumen (Figure 1.21). VII. CLEARANCE BY OTHER ROUTES Figure 1.21 Effect of drug metabolism on reabsorption in the distal tubule. Other routes of drug clearance include via intestines, the bile, the lungs, and milk in nursing mothers, among others . The feces are primarily involved in elimination of unabsorbed orally ingested drugs or drugs that are secreted directly into the intestines or in bile. While in the intestinal tract, most compounds are not reabsorbed and eliminated in the feces. The lungs are primarily involved in the elimination of anesthetic gases (for example, halothane and isoflurane). Elimination of drugs in breast milk is clinically relevant as a potential source of undesirable side effects to the infant. A suckling baby will be exposed, to some extent, to medications and/or its metabolites being taken by the mother. Excretion of most drugs into sweat, saliva, tears, hair, and skin occurs only to a small extent. However, deposition of drugs in hair and skin has been used as a forensic tool in many criminal cases. Total body clearance, the culmination of all clearance methods, and drug half-life are important measures of drug clearance calculated to prevent drug toxicity. A. Total body clearance The total body (systemic) clearance, CL_{total} or CL_t, is the sum of the clearances from the various drug-metabolizing and drug-eliminating organs. The kidney is often the major organ of excretion; however, the liver also contributes to drug loss through metabolism and/or excretion into the bile. A patient in renal failure may sometimes benefit from a drug that is excreted by this pathway, into the intestine and feces, rather than Pharm 5th 3-21-11.indb 18 3/21/11 2:20:21 PM VIII. Design And Optimization Of Dosage Regimen 19 through the kidney. Some drugs may also be reabsorbed through the enterohepatic circulation, thus prolonging their half-lives. Total clearance can be calculated by using the following equation: $CL_{total} = CL_{hepatic} + CL_{renal} + CL_{pulmonary} + CL_{other}$ where $CL_{hepatic}$ + CL_{renal} are typically the most important. B. Clinical situations resulting in changes in drug half-life When a patient has an abnormality that alters the half-life of a drug, adjustment in dosage is required. It is important to be able to predict in which patients a drug is likely to have a change in half-life. The halflife of a drug is increased by 1) diminished renal plasma flow or hepatic blood flow, for example, in cardiogenic shock, heart failure, or hemorrhage; 2) decreased ability to extract drug from plasma, for example, as seen in renal disease; and 3) decreased metabolism, for example, when another drug inhibits its biotransformation or in hepatic insufficiency, as with cirrhosis. On the other hand, the half-life of a drug may decrease by 1) increased hepatic blood flow, 2) decreased protein binding, and 3) increased metabolism. VIII. DESIGN AND OPTIMIZATION OF DOSAGE REGIMEN To initiate drug therapy, the clinician designs a dosage regimen administered either by continuous infusion or in intervals of time and dose, depending on various patient and drug factors, including how rapidly a steady state (rate of administration equals that of elimination) must be achieved. The regimen can be further refined, or optimized, to achieve maximum benefit with minimum adverse effects. A. Continuous-infusion regimens Therapy may consist of a single administration of a drug, for example, a single dose of a sleep-inducing agent, such as zolpidem. More commonly, however, therapy consists of continued administration of a drug, either as an IV infusion or in oral fixed-dose/fixed-time interval regimens (for

example, “one tablet every 4 hours”), each of which results in accumulation of the drug until a steady state occurs. Steady state is the point at which the amount of drug being administered equals the amount being eliminated, such that the plasma and tissue levels remain constant in the case of IV administration and fluctuate around a mean in the case of oral fixed dosage. 1. Plasma concentration of a drug following IV infusion: With continuous IV infusion, the rate of drug entry into the body is constant. In the majority of cases, the elimination of a drug is first order, that is, a constant fraction of the agent is cleared per unit of time. Therefore, the rate of drug exit from the body increases proportionately as the plasma concentration increases. Following the initiation of an IV infusion, the plasma concentration of drug rises until the rate of drug eliminated from the body precisely balances the input rate (Figure 1.22.) Thus, a steady state is achieved in which the plasma concentration of drug remains constant. Drug input Drug output Figure 1.22 At steady state, input (rate of infusion) equals output (rate of elimination). a. Influence of the rate of drug infusion on the steady state: It can be shown that the steady-state plasma concentration is directly proportional to the infusion rate. For example, if the infusion rate Pharm 5th 3-21-11.indb 19 3/21/11 2:20:21 PM 20 1. Pharmacokinetics is doubled, the plasma concentration ultimately achieved at the steady state is doubled (Figure 1.23). Furthermore, the steadystate concentration is inversely proportional to the clearance of the drug. Thus, any factor that decreases clearance, such as liver or kidney disease, increases the steady-state concentration of an infused drug (assuming Vd remains constant). Factors that increase clearance of a drug, such as increased metabolism, decrease the steady-state concentrations of an infused drug. Note: A faster rate of infusion does not change the time needed to achieve steady state. Only the steady-state concentration changes. Steady-state region b. Time required to reach the steady-state drug concentration: The concentration of drug rises from zero at the start of the infusion to its ultimate steady-state level, Css (see Figure 1.23). The fractional rate of approach to a steady state is achieved by a first-order process. Plasma concentration of drug CSS High rate of infusion (2 times Ro mg/min) Low rate of infusion (Ro mg/min) 0 Start of infusion 1) Exponential approach to steady state: The rate constant for attainment of steady state is the rate constant for total body elimination of the drug. Thus, 50 percent of the final steady-state concentration of drug is observed after the time elapsed since the infusion, t, is equal to t1/2, where t1/2 (or half-life) is the time required for the drug concentration to change by 50 percent. Waiting another half-life allows the drug concentration to approach 75 percent of Css (Figure 1.24). The drug concentration is 90 percent of the final steady-state concentration in 3.3 times t1/2. Thus, a drug will reach steady state in about four half-lives. Time Figure 1.23 Effect of infusion rate on the steady-state concentration of drug in the plasma. Ro = rate of drug infusion; Css = steady-state concentration. 2) Effect of the rate of drug infusion: The sole determinant of the rate that a drug approaches steady state is the t1/2, and this rate is influenced only by the factors that affect the halflife. The rate of approach to steady state is not affected by the Drug infusion stopped; wash-out begins Start of drug infusion Steady-state drug concentration = CSS = 100 The wash-out of the drug is exponential with the same time constant as that during drug infusion. For example, drug concentration declines to 50 percent of the steady-state level in t1/2. Plasma concentration of drug 90 75 2t1/2 3.3t1/2 0 Fifty percent of the steady-state drug concentration is achieved in t1/2. t1/2 50 t1/2 2t1/2 3.3t1/2 0 Time 0 Ninety percent of the steady-state drug concentration is achieved in 3.3t1/2. Figure 1.24 Rate of attainment of steady-state concentration of a drug in the plasma. Pharm 5th 3-21-11.indb 20 3/21/11 2:20:22 PM rate of drug infusion. Although increasing the rate of drug infusion concomitantly increases the rate at which any given concentration of drug in the plasma is achieved, it does not influence the time required to reach the ultimate steady-state concentration. This is because the steady-state concentration of drug rises directly with the infusion rate (see Figure 1.23). 3) Rate of drug decline when the infusion is stopped: When the infusion is stopped, the plasma concentration of a drug declines (washes out) to zero with the same time course observed in approaching the steady state (see Figure 1.24). B. Fixed-dose/fixed-time regimens Administration of a drug by fixed doses rather than by continuous infusion is often more convenient. However, fixed doses, given at fixed-time intervals, such as with multiple IV injections or multiple oral administration, result in time-dependent fluctuations in the circulating level of drug, which contrasts with the smooth ascent of drug concentration observed with continuous infusion. 1. Multiple IV injections: When a drug is given repeatedly at regular intervals, the plasma concentration increases until a steady state is reached (Figure 1.25). Because most drugs are given at intervals shorter than five half-lives and are eliminated exponentially with time, some drug from the first dose remains in the body at the time that the second dose is administered, some from the second dose remains at the time that the third dose is given, and so forth. Therefore, the drug accumulates until, within the dosing interval, the rate of drug loss (driven by an elevated plasma concentration) exactly balances the rate of drug administration, that is, until a steady state is achieved. 21 Amount of drug in body (arbitrary units) VIII. Design And Optimization Of Dosage Regimen Injection of two units of drug 3 once daily Injection of one unit of drug twice daily 2 A B C 1 Continous infusion of two units of drug per day 0 0 1 Days 2 3 Rapid injection of drug Figure 1.25 Predicted plasma concentrations of a drug given by infusion (A), twice-daily injection (B), or once-daily injection (C). Model assumes rapid mixing in a single body compartment and a half-life of 12 hours. a. Effect of dosing frequency: The plasma concentration of a drug oscillates about a mean. Using smaller doses at shorter intervals reduces the amplitude of the swings in drug concentration. However, the steady-state concentration of the drug, and the rate at which the steady state is approached, are not affected by the frequency of dosing. b. Example of achievement of steady state using different dosage regimens: Curve B of Figure 1.25 shows the amount of drug in the body when 1 g of drug is administered IV to a patient, and the dose is repeated at a time interval that corresponds to the half-life of the drug. At the end of the first dosing interval, 0.50 units of drug remain from the first dose when the second dose is administered. At the end of the second dosing interval, 0.75 units are present when the third dose is taken. The minimal amount of drug during the dosing interval progressively increases and approaches a value of 1.00 unit, whereas the maximal value immediately following drug administration progressively approaches 2.00 units. Therefore, at the steady state, 1.00 unit of drug is lost during the dosing interval, which is exactly matched by the rate at which the drug is administered. That is, the “rate in” equals the “rate out.” As in the case for IV infusion, 90 percent of the steady-state value is achieved in 3.3 times t1/2. Pharm 5th 3-21-11.indb 21 3/21/11 2:20:23 PM 22 1. Pharmacokinetics 2. Multiple oral administrations: Most drugs that are administered on an outpatient basis are taken orally on a fixed-dose/fixed-time-interval regimen such as a specific dose taken one, two, or three times daily. In contrast to IV injection, orally administered drugs may be absorbed slowly, and the plasma concentration of the drug is influenced by both the rate of absorption and the rate of drug elimination (Figure 1.26). REPEATED FIXED DOSE Repeated oral administration of a drug results in oscillations in plasma concentrations that are influenced by both the rate of drug absorption and the rate of drug elimination. Plasma concentration of drug (arbitrary units) C. Optimization of dose 2.0 1.5 1.0 0.5 00 10 20 30 40 50 Time (hrs) 60 70 SINGLE FIXED DOSE A single dose of drug given orally results in a single peak in plasma concentration followed by a continuous decline in drug level. Figure 1.26 Predicted plasma concentrations of a drug given by repeated oral administrations. The goal of therapy with a given drug is to achieve and maintain concentrations within a therapeutic response window while minimizing toxicity and/or side effects. With careful titration, most drugs can achieve this goal. If the therapeutic window (see. p. 35) of the drug is small (for example, digoxin, warfarin, and cyclosporine), a plasma concentration range within which therapy is effective will be defined. The dosage required to maintain therapy will be computed and administered as a maintenance dose or a loading dose (when rapid effects are warranted), and drug concentrations are subsequently measured. The dosage and dosage frequency can then be adjusted if not within the therapeutic range. 1. Maintenance of dose: Drugs are generally administered to maintain a steady-state concentration within the therapeutic window. To achieve a given concentration, the rate of administration and the rate of elimination of the drug are important. It takes four to five half-lives of a drug to achieve steady-state systemic concentrations. The dosing rate can be determined by knowing the target concentration in plasma (Cp), clearance (CL) of the drug from the systemic circulation, and the fraction (F) absorbed (bioavailability): Dosing Rate = (target Cplasma)(CL) F 2. Loading dose: A delay in achieving the desired plasma levels of drug may be clinically unacceptable. Therefore, a “loading dose” of drug can be injected as a single dose to achieve the desired plasma level rapidly, followed by an infusion to maintain the steady state (maintenance dose, Figure 1.27). In general, the loading dose can be calculated as: Drug concentration in plasma With loading dose Loading dose = (Vd)(desired steady-state plasma concentration)/F Without loading dose Elimination t1/2 Time Dosing started Figure 1.27 Accumulation of drug administered orally without a loading dose, and with a single oral loading dose administered at t=0. Pharm 5th 3-21-11.indb 22 For IV infusion, the bioavailability is 100%, and the equation becomes: Loading dose = (Vd) (desired steady-state plasma concentration) Loading doses can be given as a single dose or a series of doses. Loading doses are given if the time required to achieve half-life is relatively long and the therapeutic benefit of the drug is required immediately (for example, lidocaine for arrhythmias). Disadvantages to the use of loading doses include increased risk of drug toxicity and a longer time for the concentration of the drug to fall if excess drug level occurs. A loading dose is most useful for drugs that are eliminated from the body relatively slowly. Such drugs require only a low maintenance dose in order to keep the amount of the drug in the body at a therapeutic concentration. However, without an initial 3/21/11 2:20:23 PM VIII. Design And Optimization Of Dosage Regimen 23 higher dose, it would take a long time for the amount of the drug in the body to reach a therapeutic value that corresponds to the steadystate level. 3. Dose adjustment: The amount of a drug administered for a given condition is optimized for an “average patient.” This approach overlooks interpatient variability, and, in some instances, pharmacokinetic principles may be used to optimize therapy for a given individual or patient population while minimizing side effects or toxicities. Monitoring the drug and correlating it with therapeutic benefits provides another tool to individualize therapy. [Note: For drugs with low therapeutic indices, plasma concentrations are measured and dose adjustments made where appropriate.] Vd is useful because it can be used to calculate the amount of drug needed to achieve a desired plasma concentration. For example, assume the cardiac output of a heart failure patient is not well controlled due to inadequate plasma levels of digoxin. Suppose the concentration of the drug in the plasma is C1, and the desired level (target concentration) of digoxin (known from clinical studies) is C2, a higher concentration. The clinician needs to know how much additional drug should be administered to bring the circulating level of the drug from C1 to C2. (Vd)(C1) = amount of drug initially in the body (Vd)(C2) = amount of drug in the body needed to achieve the desired plasma concentration The difference between the two values is the additional dosage needed, which equals Vd (C2 – C1). Figures 1.28 shows the time course of drug concentration when treatment is started or dose changed. Dosages doubled Drug concentration in plasma Intravenous infusion Oral dose Elimination t1/2 The plasma concentrations during oral therapy fluctuate around the steady-state levels obtained with intravenous therapy. Dosing changed When dosages are doubled, halved, or stopped during steady-state administration, the time required to achieve a new steady-state level is independent of the route of administration. Dosages halved Time Figure 1.28 Accumulation of drug following sustained administration and following changes in dosing. Oral dosing was at intervals of 50 percent of t1/2. Pharm 5th 3-21-11.indb 23 3/21/11 2:20:24 PM 24 1. Pharmacokinetics Study Questions Choose the ONE best answer. 1.1 A drug, given as a 100-mg single dose, results in a peak plasma concentration of 20 µg/mL. The apparent volume of distribution is (assume a rapid distribution and negligible elimination prior to measuring the peak plasma level): Correct answer = D. Vd = D/C, where D = the total amount of drug in the body, and C = the plasma concentration of drug. Thus, Vd = 100 mg/20 mg/mL = 100 mg/20 mg/L = 5 L. A. 0.5 L. B. 1 L. C. 2 L. D. 5 L. E. 10 L. 1.2 A drug with a half-life of 12 hours is administered by continuous intravenous infusion. How long will it take for the drug to reach 90 percent of its final steadystate level? Correct answer = D. A drug approaches 90 percent of the final steady state in (3.3)(t1/2) = (3.3)(12) = ~40 hours. A. 18 hours. B. 24 hours. C. 30 hours. D. 40 hours. E. 90 hours. 1.3 Which of the following results in a doubling of the steady-state concentration of a drug? A. Doubling the rate of infusion. B. Maintaining the rate of infusion but doubling the loading dose. C. Doubling the rate of infusion and doubling the concentration of the infused drug. D. Tripling the rate of infusion. E. Quadrupling the rate of infusion. 1.4 A heart failure patient shows digoxin toxicity. She received 125 mcg as standard dose. Serum levels were reported to be 2 ng /mL (2 mcg/L). Target therapeutic level is 0.8 ng/mL. What dose should she receive? A. 25 mcg. B. 50 mcg. C. 75 mcg. D 100 mcg. E. 125 mcg. 1.5 The addition of glucuronic acid to a drug: A. Decreases its water solubility. B. Usually leads to inactivation of the drug. C. Is an example of a Phase I reaction. D. Occurs at the same rate in adults and newborns. E. Involves cytochrome P450. Pharm 5th 3-21-11.indb 24 Correct answer = A. The steady-state concentration of a drug is directly proportional to the infusion rate. Increasing the loading dose provides a transient increase in drug level, but the steady-state level remains unchanged. Doubling both the rate of infusion and the concentration of infused drug leads to a fourfold increase in the steady-state drug concentration. Tripling or quadrupling the rate of infusion leads to either a three- or fourfold increase in the steady-state drug concentration. Correct answer = B. Vd = dose/C = 125 mcg / 2 mcg/L = 62.5 L. Vd (C2 – C1) = dose to be received = 62.5 (0.8 mcg/L – 2 mcg/L) = –75 mcg. Subtract this dose from standard dose. New dose to be administered = 125 mcg – 75 mcg = 50 mcg. Correct answer = B. The addition of glucuronic acid prevents recognition of the drug by its receptor. Glucuronic acid is charged, and the drug conjugate has increased water solubility. Conjugation is a Phase II reaction. Neonates are deficient in the conjugating enzymes. Cytochrome P450 is involved in Phase I reactions. 3/21/11 2:20:24 PM Drug–Receptor Interactions and Pharmacodynamics 2 I. OVERVIEW Pharmacodynamics describes the actions of a drug on the body and the influence of drug concentrations on the magnitude of the response. Most drugs exert their effects, both beneficial and harmful, by interacting with receptors (that is, specialized target macromolecules) present on the cell surface or within the cell. The drug–receptor complex initiates alterations in biochemical and/or molecular activity of a cell by a process called signal transduction (Figure 2.1). 1 II. SIGNAL TRANSDUCTION 2 Drugs act as signals, and their receptors act as signal detectors. Many receptors signal their recognition of a bound ligand by initiating a series of reactions that ultimately result in a specific intracellular response. [Note: The term “ligand” refers to a small molecule that binds to a site on a receptor protein. The ligand may be a naturally occurring molecule or a drug.] “Second messenger” molecules (also called effector molecules) are part of the cascade of events that translates ligand binding into a cellular response. Unoccupied receptor does not influence intracellular processes. Receptor Receptor with bound ligand is activated. It has altered physical and chemical properties, which leads to interaction with cellular molecules to cause a biologic response. Drug Receptor A. The drug–receptor complex Cells have different types of receptors, each of which is specific for a particular ligand and produces a unique response. The heart, for example, contains membrane receptors that bind and respond to epinephrine or norepinephrine as well as muscarinic receptors specific for acetylcholine. These receptors dynamically interact to control the heart’s vital functions. The magnitude of the response is proportional to the number of drug–receptor complexes: → Drug–receptor complex → Biologic effect Drug + Receptor ← This concept is closely related to the formation of complexes between enzyme and substrate or antigen and antibody. These interactions have many common features, perhaps the most noteworthy being specificity of the receptor for a given ligand. However, the receptor not only has the ability to recognize a ligand, but can also couple or transduce this binding into a response by causing a conformational change or a biochemical effect. Most receptors are named to indicate the type of drug/chemical that interacts best with it. For example, the receptor for histamine is called a histamine receptor. Although much of this chapter will be centered on the interaction of drugs with specific receptors, it is important to be aware that not all drugs exert Pharm 5th 3-21-11.indb 25 Biologic response Activated receptor Signal transduction Figure 2.1 The recognition of a drug by a receptor triggers a biologic response. 3/21/11 2:20:25 PM 26 2. Drug–Receptor Interactions and Pharmacodynamics their effects by interacting with a receptor. Antacids, for instance, chemically neutralize excess gastric acid, thereby reducing the symptoms of “heartburn.” B. Receptor states Classically, the binding of a ligand was thought to cause receptors to change from an inactive state (R) to an activated state (R*). The activated receptor then interacts with intermediary effector molecules to produce a biologic effect. This induced-fit model is a simple and intuitive scheme and is used in the illustrations in this chapter. More recent information suggests that receptors exist in at least two states, inactive (R) and active R* states that are in reversible equilibrium with one another. In the absence of an agonist, R* typically represents a small fraction of the total receptor population (that is, the equilibrium favors the inactive state). Drugs occupying the receptor can stabilize the receptor in a given conformational state. Some drugs may cause similar shifts in equilibrium between R to R* as an endogenous ligand. For example, drugs acting as agonists bind to the active state of the receptors and, thus, rapidly shift the equilibrium from R to R*. Other drugs may induce a change that may be different from the endogenous ligand. These changes render the receptor less functional or nonfunctional. C. Major receptor families Pharmacology defines a receptor as any biologic molecule to which a drug binds and produces a measurable response. Thus, enzymes, nucleic acids, and structural proteins can be considered to be pharmacologic receptors. However, the richest sources of therapeutically exploitable pharmacologic receptors are proteins that are responsible for transducing extracellular signals into intracellular responses. These receptors may be divided into four families: 1) ligand-gated ion channels, 2) G protein–coupled receptors, 3) enzyme–linked receptors, and 4) intracellular receptors (Figure 2.2). The type of receptor a A Ligand-gated ion channels Example: Cholinergic nicotinic receptors B G protein–coupled receptors Example: α and β adrenoceptors C Enzyme-linked receptors Example: Insulin receptors D Intracellular receptors Example: Steroid receptors γ β α Ions Changes in membrane potential or ionic concentration within cell R Protein phosphorylation R-PO4 Protein and receptor phosphorylation Protein phosphorylation and altered gene expression INTRACELLULAR EFFECTS Figure 2.2 Transmembrane signaling mechanisms. A. Ligand binds to the extracellular domain of a ligand-gated channel. B. Ligand binds to a domain of a transmembrane receptor, which is coupled to a G protein. C. Ligand binds to the extracellular domain of a receptor that activates a kinase enzyme. D. Lipid-soluble ligand diffuses across the membrane to interact with its intracellular receptor. R = inactive protein. Pharm 5th 3-21-11.indb 26 3/21/11 2:20:25 PM II. Signal Transduction ligand will interact with depends on the chemical nature of the ligand. Hydrophilic ligands interact with receptors that are found on the cell surface (Figures 2.2A, B, C). In contrast, hydrophobic ligands can enter cells through the lipid bilayers of the cell membrane to interact with receptors found inside cells (Figure 2.2D). 1. Transmembrane ligand-gated ion channels: The first receptor family comprises ligand-gated ion channels that are responsible for regulation of the flow of ions across cell membranes (see Figure 2.2A). The activity of these channels is regulated by the binding of a ligand to the channel. Response to these receptors is very rapid, enduring for only a few milliseconds. These receptors mediate diverse functions, including neurotransmission, cardiac conduction, and muscle contraction. For example, stimulation of the nicotinic receptor by acetylcholine results in sodium influx, generation of an action potential, and activation of contraction in skeletal muscle. Benzodiazepines, on the other hand, enhance the stimulation of the γ-aminobutyric acid (GABA) receptor by GABA, resulting in increased chloride influx and hyperpolarization of the respective cell. Although not ligand-gated, ion channels, such as the voltagegated sodium channel, are important drug receptors for several drug classes, including local anesthetics. 2. Transmembrane G protein–coupled receptors: A second family of receptors consists of G protein–coupled receptors. These receptors comprise a single α helical peptide that has seven membranespanning regions. The extracellular domain of this receptor usually contains the ligand-binding area (a few ligands interact within the receptor transmembrane domain). Intracellularly, these receptors are linked to a G protein (Gs, Gi, and others) having three subunits, an α subunit that binds guanosine triphosphate (GTP) and a βγ subunit (Figure 2.3). Binding of the appropriate ligand to the extracellular region of the receptor activates the G protein so that GTP replaces guanosine diphosphate (GDP) on the α subunit. Dissociation of the G protein occurs, and both the α-GTP subunit and the βγ subunit subsequently interact with other cellular effectors, usually an enzyme, a protein, or an ion channel. These effectors then activate second messengers that are responsible for further actions within the cell. Stimulation of these receptors results in responses that last several seconds to minutes. G protein–coupled receptors are the most abundant type of receptors, and their activation accounts for the actions of most therapeutic agents. Important processes mediated by G protein–coupled receptors include neurotransmission, olfaction, and vision. a. Second messengers: These are essential in conducting and amplifying signals coming from G protein–coupled receptors. A common pathway turned on by Gs, and other types of G proteins, is the activation of adenylyl cyclase by α-GTP subunits, which results in the production of cyclic adenosine monophosphate (cAMP)—a second messenger that regulates protein phosphorylation. G proteins also activate phospholipase C, which is responsible for the generation of two other second messengers, namely inositol-1,4,5-trisphosphate (IP3) and diacyl glycerol (DAG). IP3 is responsible for the regulation of intracellular free calcium concentrations, and of other proteins as well. DAG activates several enzymes such as protein kinase C (PKC) within the cell leading to a myriad of physiological effects. Pharm 5th 3-21-11.indb 27 27 Unoccupied receptor does not interact with Gs protein. 1 Extracellular space Hormone or neurotransmitter Cell membrane Receptor γ β α GDP Gs protein with bound GDP Cytosol 2 Inactive adenylyl cyclase Occupied receptor changes shape and interacts with Gs protein. Gs protein releases GDP and binds GTP. γ β α GTP 3 Inactive adenylyl cyclase GDP GTP α Subunit of Gs protein dissociates and activates adenylyl cyclase. β γ ATP α GTP 4 Active adenylyl cyclase cAMP + PPi When hormone is no longer present, the receptor reverts to its resting state. GTP on the α subunit is hydrolyzed to GDP, and adenylyl cyclase is deactivated. β γ α GDP Pi Inactive adenylyl cyclase Figure 2.3 The recognition of chemical signals by G protein–coupled membrane receptors triggers an increase (or, less often, a decrease) in the activity of adenylyl cyclase. PPi = inorganic pyrophosphate. 3/21/11 2:20:28 PM 28 2. Drug–Receptor Interactions and Pharmacodynamics S S α Insulin receptor (inactive) SS α S S β β Tyrosine Tyrosine Insulin 1 Insulin binding activates receptor tyrosine kinase activity in the intracellular domain of the β subunit of the insulin receptor. S S α SS α S S Insulin receptor (active) β β P —Tyrosine P —Tyrosine IRS-tyr IRS-tyr— 2 Tyrosine residues of the β subunit are autophosphorylated. 3 Receptor tyrosine kinase phosphorylates other proteins, for example, insulin receptor substrates (IRS). Activation of multiple signaling pathways 4 Phosphorylated IRSs promote activation of other protein kinases and phosphatases, leading to biologic actions of insulin. Biologic effects of insulin Figure 2.4 Insulin receptor. Pharm 5th 3-21-11.indb 28 P 3. Enzyme-linked receptors: A third major family of receptors consists of a protein that spans the membrane once and may form dimers or multisubunit complexes. These receptors also have cytosolic enzyme activity as an integral component of their structure and function (Figure 2.4). Binding of a ligand to an extracellular domain activates or inhibits this cytosolic enzyme activity. Duration of responses to stimulation of these receptors is on the order of minutes to hours. Metabolism, growth, and differentiation are important biological functions controlled by these types of receptors. The most common enzyme-linked receptors (epidermal growth factor, platelet-derived growth factor, atrial natriuretic peptide, insulin, and others) are those that have a tyrosine kinase activity as part of their structure. Typically, upon binding of the ligand to receptor subunits, the receptor undergoes conformational changes, converting kinases from their inactive forms to active forms. The activated receptor autophosphorylates and then phosphorylates tyrosine residues on specific proteins (see Figure 2.4). The addition of a phosphate group can substantially modify the three-dimensional structure of the target protein, thereby acting as a molecular switch. For example, when the peptide hormone insulin binds to two of its receptor subunits, their intrinsic tyrosine kinase activity causes autophosphorylation of the receptor itself. In turn, the phosphorylated receptor phosphorylates target molecules (insulin-receptor substrate peptides) that subsequently activate other important cellular signals, such as inositol triphosphate and the mitogen-activated protein (MAP) kinase system. This cascade of activations results in a multiplication of the initial signal, much like that which occurs with G protein–coupled receptors. 4. Intracellular receptors: The fourth family of receptors differs considerably from the other three in that the receptor is entirely intracellular, and, therefore, the ligand must diffuse into the cell to interact with the receptor (Figure 2.5). This places constraints on the physical and chemical properties of the ligand, because it must have sufficient lipid solubility to be able to move across the target cell membrane. Because these receptor ligands are lipid soluble, they are transported in the body attached to plasma proteins such as albumin. The primary targets of these ligand-receptor complexes are transcription factors. The activation or inactivation of these factors causes the transcription of DNA into RNA and translation of RNA into an array of proteins. For example, steroid hormones exert their action on target cells via this receptor mechanism. Binding of the ligand with its receptor follows a general pattern in which the receptor becomes activated because of the dissociation from a variety of proteins. The activated ligand–receptor complex migrates or translocates to the nucleus, where it binds to specific DNA sequences, resulting in the regulation of gene expression. The time course of activation and response of these receptors is much longer than that of the other mechanisms described above. Because gene expression and, therefore, protein synthesis is modified, cellular responses are not observed until considerable time has elapsed (30 minutes or more), and the duration of the response (hours to days) is much greater than that of other receptor families. Other targets of intracellular ligands are structural proteins, enzymes, RNA, and ribosomes. For example, tubulin is the target of antineoplastic agents such as paclitaxel (see p. 500), the enzyme dihydrofolate reductase is the target of antimicrobials such as trimethoprim (see p. 416), and the 50s 3/21/11 2:20:30 PM II. Signal Transduction subunit of the bacterial ribosome is the target of macrolide antibiotics such as erythromycin (see p. 401). D. Some characteristics of signal transduction 29 A lipid-soluble drug diffuses across the cell membrane and moves to the nucleus of the cell. Signal transduction has two important features: 1) the ability to amplify small signals and 2) mechanisms to protect the cell from excessive stimulation. 1. Signal amplification: A characteristic of many receptors, particularly those that respond to hormones, neurotransmitters, and peptides, is their ability to amplify signal duration and intensity. The family of G protein–linked receptors exemplifies many of the possible responses initiated by ligand binding to a receptor. Specifically, two phenomena account for the amplification of the ligand–receptor signal. First, a single ligand–receptor complex can interact with many G proteins, thereby multiplying the original signal manyfold. Second, the activated G proteins persist for a longer duration than the original ligand–receptor complex. The binding of albuterol, for example, may only exist for a few milliseconds, but the subsequent activated G proteins may last for hundreds of milliseconds. Further prolongation and amplification of the initial signal is mediated by the interaction between G proteins and their respective intracellular targets. Because of this amplification, only a fraction of the total receptors for a specific ligand may need to be occupied to elicit a maximal response from a cell. Systems that exhibit this behavior are said to have spare receptors. Spare receptors are exhibited by insulin receptors, where it has been estimated that 99 percent of the receptors are “spare.” This constitutes an immense functional reserve that ensures that adequate amounts of glucose enter the cell. On the other end of the scale is the human heart, in which about 5 to 10 percent of the total β-adrenoceptors are spare. An important implication of this observation is that little functional reserve exists in the failing heart, because most receptors must be occupied to obtain maximum contractility. 2. Desensitization and down-regulation of receptors: Repeated or continuous administration of an agonist (or an antagonist) may lead to changes in the responsiveness of the receptor. To prevent potential damage to the cell (for example, high concentrations of calcium, initiating cell death), several mechanisms have evolved to protect a cell from excessive stimulation. When repeated administration of a drug results in a diminished effect, the phenomenon is called tachyphylaxis. The receptor becomes desensitized to the action of the drug (Figure 2.6). In this phenomenon, the receptors are still present on the cell surface but are unresponsive to the ligand. Receptors can also be down-regulated in the presence of continual stimulation. Binding of the agonist results in molecular changes in the membrane-bound receptors, such that the receptor undergoes endocytosis and is sequestered within the cell, unavailable for further agonist interaction. These receptors may be recycled to the cell surface, restoring sensitivity, or, alternatively, may be further processed and degraded, decreasing the total number of receptors available. Some receptors, particularly voltage-gated channels, require a finite time (rest period) following stimulation before they can be activated again. During this recovery phase they are said to be “refractory” or “unresponsive.” Pharm 5th 3-21-11.indb 29 Drug TARGET CELL Drug Drug Inactive receptor Activated receptor complex The drug binds to a receptor. CYTOSOL NUCLEUS Gene The drug–receptor complex binds to chromatin, activating the transcription of specific genes. mRNA mRNA Specific proteins Biologic effects Figure 2.5 Mechanism of intracellular receptors. mRNA = messenger RNA. 3/21/11 2:20:32 PM 30 2. Drug–Receptor Interactions and Pharmacodynamics III. DOSE–RESPONSE RELATIONSHIPS Repeated administration of an agonist (such as epinephrine) over a short time period results in diminished response of the cell. Response An agonist is defined as an agent that can bind to a receptor and elicit a biologic response. An agonist usually mimics the action of the original endogenous ligand on the receptor such as norepinephrine on β1 receptors of the heart. The magnitude of the drug effect depends on the drug concentration at the receptor site, which, in turn, is determined by both the dose of drug administered and by the drug’s pharmacokinetic profile, such as rate of absorption, distribution, metabolism, and elimination. A. Graded dose–response relations As the concentration of a drug increases, the magnitude of its pharmacologic effect also increases. The response is a graded effect, meaning that the response is continuous and gradual. Plotting the magnitude of the response against increasing doses of a drug produces a graph, the graded dose–response curve, that has the general shape depicted in Figure 2.7A. The curve can be described as a rectangular hyperbola, which is a familiar curve in biology because it can be applied to diverse biological events, such as ligand binding, enzymatic activity, and responses to pharmacologic agents. Two important properties of drugs, potency and efficacy, can be determined by graded dose– response curves. Time 0 0 10 50 10 50 10 40 20 40 20 40 20 30 30 30 Repeated injection of drug Following a period of rest, administration of the drug results in a response of the original magnitude. 1. Potency: The first property is potency, a measure of the amount of drug necessary to produce an effect of a given magnitude. The concentration of drug producing an effect that is 50 percent of the maximum is used to determine potency and is commonly designated as the EC50. In Figure 2.7, the EC50 for Drugs A and B are indicated. Drug A is more potent than Drug B, because a lesser amount of Drug A is needed when compared to Drug B to obtain 50-percent effect. Thus, therapeutic preparations of drugs will reflect the potency. For example, candesartan and irbesartan are angiotensin-receptor blockers that are used alone or in combination with other drugs to treat hypertension. Candesartan is more potent than irbesartan, because the dose range for candesartan is 4 to 32 mg, as compared to a dose A Percentage of maximal effect Figure 2.6 Desensitization of receptors. 100 B Drug A Drug B 50 EC50 0 [Drug] The EC50 is the concentration of the drug that produces a response equal to 50 percentof the maximal response. Percentage of maximal effect 0 50 100 Drug A Drug B 50 EC50 0 log[Drug]] The potency of drugs can be compared using the EC50: the smaller the EC50, the more potent the drug. Figure 2.7 The effect of dose on the magnitude of pharmacologic response. Panel A is a linear graph. Panel B is a semilogarithmic plot of the same data. EC50 = drug dose that shows 50 percent of maximal response. Pharm 5th 3-21-11.indb 30 3/21/11 2:20:34 PM III. Dose–Response Relationships 31 B. Effect of drug concentration on receptor binding The quantitative relationship between drug concentration and receptor occupancy applies the law of mass action to the kinetics of the binding of drug and receptor molecules: → Drug–receptor complex → Biologic effect Drug + Receptor ← By making the assumption that the binding of one drug molecule does not alter the binding of subsequent molecules and applying the law of mass action, we can mathematically express the relationship between the percentage (or fraction) of bound receptors and the drug concentration: [DR] [Rt] = [D] Kd + [D] (1) where [D] = the concentration of free drug, [DR] = the concentration of bound drug, [Rt] = the total concentration of receptors and is equal to the sum of the concentrations of unbound (free) receptors and bound receptors, and Kd = the equilibrium dissociation constant for the drug from the receptor. The value of Kd can be used to determine the affinity of a drug for its receptor. Affinity describes the strength of the interaction (binding) between a ligand and its receptor. The higher the Kd value, the weaker the interaction and the lower the affinity. The opposite phenomenon occurs when a drug has a low Kd. The binding of the ligand to the receptor is strong, and the affinity is high. Equation (1) defines a curve that has the shape of a rectangular hyperbola (Figure 2.9A). As the concentration of free drug increases, the ratio of the concentrations of bound receptors to total receptors approaches unity. The binding of the drug to its receptor initiates events that ultimately lead to a measurable biologic response, Thus it not surprising that the curves shown in Figure 2.9 and those representing the relationship between dose and effect (see Figure 2.7) are similar. Pharm 5th 3-21-11.indb 31 Drug C shows lower potency and lower efficacy than Drugs A and B. Biologic effect 100 50 Drug A Drug B Drug C Log drug concentration 0 EC50 for Drug A EC50 for Drug B EC50 for Drug C Figure 2.8 Typical dose–response curve for drugs showing differences in potency and efficacy. (EC50 = drug dose that shows fifty percent of maximal response.) A 1 [Bound receptors] [Total receptors] 2. Efficacy: The second drug property that can be determined from graded dose–response plots is the efficacy of the drug. This is the ability of a drug to elicit a response when it interacts with a receptor. Efficacy is dependent on the number of drug–receptor complexes formed and the efficiency of the coupling of receptor activation to cellular responses. Analogous to the maximal velocity for enzymecatalyzed reactions, the maximal response (Emax), or efficacy, is more important than drug potency. A drug with greater efficacy is more therapeutically beneficial than one that is more potent. Maximal efficacy of a drug assumes that all receptors are occupied by the drug, and no increase in response will be observed if more drugs are added. This concept holds true only if there are no "spare receptors" present (see p. 29). Figure 2.8 shows the response to drugs of differing potency and efficacy. Drug A is more potent than Drug B, but both show the same efficacy. 0.5 0 Dose B 1 [Bound receptors] [Total receptors] range of 75 to 300 mg for irbesartan. Candesartan would be Drug A and irbesartan would be Drug B in Figure 2.7. Semilogarithmic plots are often used, because the range of doses (or concentrations) may span several orders of magnitude. By plotting the log of the concentration, the complete range of doses can be graphed. As shown in Figure 2.7B, the curves become sigmoidal in shape, which simplifies the interpretation of the dose response. 0.5 0 Log dose Figure 2.9 The effect of dose on the magnitude of drug binding. 3/21/11 2:20:35 PM 32 2. Drug–Receptor Interactions and Pharmacodynamics C. Relationship of drug binding to pharmacologic effect A full agonist produces complete activation of a receptor at high drug concentrations. Partial agonist binding results in less than 100% activation, even at very high concentrations. Receptor activity 100 Full agonist The mathematical model that describes drug concentration and receptor binding can be applied to dose (drug concentration) and response (or effect), providing the following assumptions are met: 1) The magnitude of the response is proportional to the amount of receptors bound or occupied, 2) the Emax occurs when all receptors are bound, and 3) binding of the drug to the receptor exhibits no cooperativity. In this case, [E] [Emax] 75 = [D] Kd + [D] (2) Partial agonist where [E] = the effect of the drug at concentration [D] and [Emax] = the maximal effect of the drug. 50 IV. AGONISTS 25 0 Inverse agonist Log drug concentration Inverse agonists produces a response below the baseline response measured in the absence of drug. In this example, approximately 12 percent of the receptors show constitutive activity in the absence of agonist. Figure 2.10 Effects of full agonists, partial agonists, and inverse agonist on receptor activity. An agonist binds to a receptor and produces a biologic response. An agonist may mimic the response of the endogenous ligand on the receptor, or it may elicit a different response from the receptor and its transduction mechanism. A. Full agonists If a drug binds to a receptor and produces a maximal biologic response that mimics the response to the endogenous ligand, it is known as a full agonist (Figure 2.10). Receptors exist in active or inactive conformational states that are in reversible equilibrium with one another. Drugs occupying the receptor can stabilize the receptor in a given conformational state. Thus, another definition of an agonist is a drug that binds to a receptor, stabilizing the receptor in its active conformational state. For example, phenylephrine is an agonist at α1-adrenoceptors, because it produces effects that resemble the action of the endogenous ligand, norepinephrine. Upon binding to α1-adrenoceptors on the membranes of vascular smooth muscle, phenylephrine stabilizes the receptor in its active state. This leads to the mobilization of intracellular Ca2+, causing interaction of the smooth muscle actin and myosin filaments. The shortening of the muscle cells decreases the diameter of the arteriole, causing an increase in resistance to the flow of blood through the vessel. Blood pressure, therefore, rises to maintain the blood flow. As this brief description illustrates, an agonist may have many effects that can be measured, including actions on intracellular molecules, cells, tissues, and intact organisms. All of these actions are attributable to interaction of the drug molecule with the receptor molecule. In general, a full agonist has a strong affinity for its receptor and good efficacy. B. Partial agonists Partial agonists have efficacies (intrinsic activities) greater than zero but less than that of a full agonist (Figure 2.10). Even if all the receptors are occupied, partial agonists cannot produce an Emax of as great a magnitude as that of a full agonist. However, a partial agonist may have an affinity that is greater than, less than, or equivalent to that of a full agonist. A unique feature of these drugs is that, under appropriate conditions, a partial agonist may act as an antagonist of a full agonist. Consider what would happen to the Emax of a receptor saturated with Pharm 5th 3-21-11.indb 32 3/21/11 2:20:36 PM V. Antagonists an agonist in the presence of increasing concentrations of a partial agonist (

directly to skeletal muscle without the mediation of ganglia. As noted earlier, the somatic nervous system is under voluntary control, whereas the autonomic system is involuntary. Responses in the somatic division are generally faster than those in the ANS. H. Summary of differences between sympathetic, parasympathetic, and motor nerves Major differences in the anatomical arrangement of neurons lead to variations of the functions in each division (Figure 3.6). The sympathetic nervous system is widely distributed, innervating practically all effector systems in the body. In contrast, the parasympathetic division's distribution is more limited. The sympathetic preganglionic fibers have a much broader influence than the parasympathetic fibers and synapse with a larger number of postganglionic fibers. This type of organization SYMPATHETIC 2 REFLEX RESPONSE Efferent reflex impulses via the autonomic nervous system cause: • Inhibition of parasympathetic and activation of sympathetic divisions • Increased peripheral resistance and cardiac output • Increased blood pressure Figure 3.5 Baroreceptor reflex arc responds to a decrease in blood pressure. PARASYMPATHETIC Sites of origin Thoracic and lumbar region of the spinal cord (thoracolumbar) Brain and sacral area of spinal cord (craniosacral) Length of fibers Short preganglionic Long postganglionic Location of ganglia Close to spinal cord Within or near effector organs Preganglionic fiber branching Extensive Minimal Distribution Wide Limited Type of response Diffuse Discrete Long preganglionic Short postganglionic Figure 3.6 Characteristics of the sympathetic and parasympathetic nervous systems. Pharm 5th 3-21-11.indb 41 3/21/11 2:20:41 PM 42 3. The Autonomic Nervous System ermits a diffuse discharge of the sympathetic nervous system. The p parasympathetic division is more circumscribed, with mostly one-toone interactions, and the ganglia are also close to, or within, organs they innervate. This limits the amount of branching that can be done by this division. [A notable exception to this arrangement is found in the myenteric plexus, where one preganglionic neuron has been shown to interact with 8000 or more postganglionic fibers.] The anatomical arrangement of the parasympathetic system results in the distinct functions of this division. The somatic nervous system innervates skeletal muscles. One somatic motor neuron axon is highly branched, and each branch innervates a single muscle fiber. Thus, one somatic motor neuron may innervate 100 muscle fibers. This arrangement leads to the formation of a motor unit. The lack of ganglia and the myelination of the motor nerves enable a fast response by this (somatic nervous) system. Endocrine signaling III. CHEMICAL SIGNALING BETWEEN CELLS Hormone Target cell Blood vessel Direct contact Gap junction Signaling cell Target cells A. Hormones Specialized endocrine cells secrete hormones into the bloodstream where they travel throughout the body, exerting effects on broadly distributed target cells in the body. (Hormones are described in Chapters 23 through 26.) B. Local mediators Synaptic signaling Target cell Nerve cell Neurotransmission in the ANS is an example of the more general process of chemical signaling between cells. In addition to neurotransmission, other types of chemical signaling include the secretion of hormones and the release of local mediators (Figure 3.7). Neurotransmitter Figure 3.7 Some commonly used mechanisms for transmission of regulatory signals between cells. Most cells in the body secrete chemicals that act locally, that is, on cells in their immediate environment. Because these chemical signals are rapidly destroyed or removed, they do not enter the blood and are not distributed throughout the body. Histamine (see p. 550) and the prostaglandins (see p. 549) are examples of local mediators. C. Neurotransmitters All neurons are distinct anatomic units, and no structural continuity exists between them. Communication between nerve cells, and between nerve cells and effector organs, occurs through the release of specific chemical signals, called neurotransmitters, from the nerve terminals. This release is triggered by the arrival of the action potential at the nerve ending, leading to depolarization. An increase in intracellular Ca^{2+} initiates fusion of the synaptic vesicles with the presynaptic membrane and release of their contents. The neurotransmitters rapidly diffuse across the synaptic cleft, or space (synapse), between neurons and combine with specific receptors on the postsynaptic (target) cell (Figure 3.8 and see Chapter 2). 1. Membrane receptors: All neurotransmitters, and most hormones and local mediators, are too hydrophilic to penetrate the lipid bilayers of target-cell plasma membranes. Instead, their signal is mediated by binding to specific receptors on the cell surface of target organs. [Note: A receptor is defined as a recognition site for a substance. It has a binding specificity and is coupled to processes that eventually evoke a response. Most receptors are proteins. Pharm 5th 3-21-11.indb 42 3/21/11 2:20:42 PM III. Chemical Signaling Between Cells 43 AUTONOMIC SOMATIC Sympathetic innervation of adrenal medulla Sympathetic Parasympathetic Acetylcholine Acetylcholine Acetylcholine Preganglionic neuron Ganglionic transmitter Nicotinic receptor Nicotinic receptor Nicotinic receptor Adrenal medulla Neuroeffector transmitter No ganglia Nicotinic receptor Postganglionic neurons Epinephrine and norepinephrine releasedinto the blood* Norepinephrine Acetylcholine Acetylcholine Adrenergic receptor Adrenergic receptor Muscarinic receptor Nicotinic receptor Effector organs Skeletal muscle Figure 3.8 Summary of the neurotransmitters released and the types of receptors found within the autonomic and somatic nervous systems. [Note: This schematic diagram does not show that the parasympathetic ganglia are close to or on the surface of the effector organs and that the postganglionic fibers are usually shorter than the preganglionic fibers. By contrast, the ganglia of the sympathetic nervous system are close to the spinal cord. The postganglionic fibers are long, allowing extensive branching to innervate more than one organ system. This allows the sympathetic nervous system to discharge as a unit.] *Epinephrine 80% and norepinephrine 20% released from adrenal medulla. 2. Types of neurotransmitters: Although over fifty signal molecules in the nervous system have tentatively been identified, six signal compounds, including norepinephrine (and the closely related epinephrine), acetylcholine, dopamine, serotonin, histamine, and γ-aminobutyric acid (GABA), are most commonly involved in the actions of therapeutically useful drugs. Each of these chemical signals binds to a specific family of receptors. Acetylcholine and nor epinephrine are the primary chemical signals in the ANS, whereas a wide variety of neurotransmitters function in the CNS. Not only are these neurotransmitters released on nerve stimulation, but also cotransmitters, such as adenosine, often accompany them and modulate the transmission process. Pharm 5th 3-21-11.indb 43 3/21/11 2:20:42 PM 44 3. The Autonomic Nervous System a. Acetylcholine: The autonomic nerve fibers can be divided into two groups based on the chemical nature of the neurotransmitter released. If transmission is mediated by acetylcholine, the neuron is termed cholinergic (Figure 3.9 and Chapters 4 and 5). Acetylcholine mediates the transmission of nerve impulses across autonomic ganglia in both the sympathetic and parasympathetic nervous systems. It is the neurotransmitter at the adrenal medulla. Transmission from the autonomic postganglionic nerves to the effector organs in the parasympathetic system, and a few sympathetic system organs, also involves the release of acetylcholine. In the somatic nervous system, transmission at the neuromuscular junction (that is, between nerve fibers and voluntary muscles) is also cholinergic (see Figure 3.9). b. Norepinephrine and epinephrine: When norepinephrine or epinephrine is the transmitter, the fiber is termed adrenergic (adrenaline being another name for epinephrine). In the sympathetic system, norepinephrine mediates the transmission of AUTONOMIC Sympathetic innervation of adrenal medulla Sympathetic SOMATIC Parasympathetic Preganglionic neuron Ganglionic transmitter Acetylcholine Nicotinic receptor Acetylcholine Nicotinic receptor Epinephrine released into the blood Adrenergic receptor No ganglia Nicotinic receptor Postganglionic neurons Adrenal medulla Neuroeffector transmitter Acetylcholine Norepinephrine Adrenergic receptor Effector organs Acetylcholine Muscarinic receptor Acetylcholine Nicotinic receptor Skeletal muscle Figure 3.9 Cholinergic (red) and adrenergic (blue) neurons found within the autonomic and somatic nervous systems. Pharm 5th 3-21-11.indb 44 3/21/11 2:20:43 PM IV. Second–messenger Systems In Intracellular Response nerve impulses from autonomic postganglionic nerves to effector organs. Norepinephrine and adrenergic receptors are discussed in Chapters 6 and 7. A summary of the neuromediators released, and the type of receptors within the peripheral nervous system, is shown in Figure 3.9. [Note: A few sympathetic fibers, such as those involved in sweating, are cholinergic, and, for simplicity, they are not shown in the figure. Also postganglionic renal smooth muscle is innervated by dopamine] 45 A Receptors coupled to ion channels Neurotransmitter Extracellular space Cl– Cell membrane Cell membrane IV. SECOND–MESSENGER SYSTEMS IN INTRACELLULAR RESPONSE The binding of chemical signals to receptors activates enzymatic processes within the cell membrane that ultimately results in a cellular response, such as the phosphorylation of intracellular proteins or changes in the conductivity of ion channels. A neurotransmitter can be thought of as a signal, and a receptor as a signal detector and transducer. Second-messenger molecules produced in response to a neurotransmitter binding to a receptor translate the extracellular signal into a response that may be further propagated or amplified within the cell. Each component serves as a link in the communication between extracellular events and chemical changes within the cell (see Chapter 2). Cl– Cytosol Changes in membrane potential or ionic concentration within cell B Receptors coupled to adenylyl cyclase Hormone or neurotransmitter β γ α A. Membrane receptors affecting ion permeability Neurotransmitter receptors are membrane proteins that provide a binding site that recognizes and responds to neurotransmitter molecules. Some receptors, such as the postsynaptic receptors of nerve or muscle, are directly linked to membrane ion channels. Therefore, binding of the neurotransmitter occurs rapidly (within fractions of a millisecond) and directly affects ion permeability (Figure 3.10A). [Note: The effect of acetyl choline on these chemically gated ion channels is discussed on p. 27.] ATP GTP Active adenylyl cyclase cAMP + PPi Protein phosphorylation C Receptors coupled to diacylglycerol and inositol trisphosphate B. Regulation involving second-messenger molecules Many receptors are not directly coupled to ion channels. Rather, the receptor signals its recognition of a bound neurotransmitter by initiating a series of reactions that ultimately result in a specific intracellular response. Second-messenger molecules, so named because they intervene between the original message (the neurotransmitter or hormone) and the ultimate effect on the cell, are part of the cascade of events that translates neurotransmitter binding into a cellular response, usually through the intervention of a G protein. The two most widely recognized second messengers are the adenylyl cyclase system and the calcium/phosphatidylinositol system (Figure 3.10B and C). [Note: Gs is one protein involved in the activation of adenylyl cyclase, and Gq is one subunit that activates phospholipase C to release diacylglycerol and inositol trisphosphate (see p. 27).] Hormone or neurotransmitter Receptor γ β α Gq protein Diacylglycerol Phospholipase C Inositol trisphosphate Protein phosphorylation and increased intracellular Ca^{2+} Figure 3.10 Three mechanisms whereby binding of a neurotransmitter leads to a cellular effect. Pharm 5th 3-21-11.indb 45 3/21/11 2:20:44 PM 46 3. The Autonomic Nervous System Study Questions Choose the ONE best answer. 3.1 Which one of the following statements concerning the parasympathetic nervous system is correct? A. The parasympathetic system uses norepinephrine as a neurotransmitter. B. The parasympathetic system often discharges as a single, functional system. C. The parasympathetic division is involved in accommodation of near vision, movement of food, and urination. D. The postganglionic fibers of the parasympathetic division are long compared to those of the sympathetic nervous system. E. The parasympathetic system controls the secretion of the adrenal medulla. 3.2 Which one of the following is characteristic of parasympathetic stimulation? A. Decrease in intestinal motility. B. Inhibition of bronchial secretion. C. Contraction of sphincter muscle in the iris of the eye (miosis). D. Contraction of sphincter of urinary bladder. E. Increase in heart rate. 3.3 Which of the following is characteristic of the sympathetic nervous system? A Discrete response to activation. B. Actions mediated by muscarinic and nicotinic receptors. C. Effects only mediated by norepinephrine. D. Responses predominate during physical activity or when experiencing fright. E. Subjected to voluntary control. 3.4 Patient presents with salivation, lacrimation, urination and defecation as side effects of a medication. Which one of the following receptors mediates the actions of this drug? A. Nicotinic receptors. B. a Receptors. C. Muscarinic receptors. D. b Receptors. Pharm 5th 3-21-11.indb 46 Correct answer = C. The parasympathetic system maintains essential bodily functions, such as vision, movement of food, and urination. It uses acetylcholine, not norepinephrine, as a neurotransmitter, and it discharges as discrete fibers that are activated separately. The postganglionic fibers of the parasympathetic system are short compared to those of the sympathetic division. The adrenal medulla is under control of the sympathetic system. Correct answer = C. The parasympathetic nervous system is essential in maintenance activities, such as digestion and waste removal. Therefore, increased intestinal motility to facilitate peristalsis, relaxation of urinary bladder sphincters to cause urination, and increased bronchial secretions result. Increase in heart rate is a function of the sympathetic nervous system. Correct answer = D. The sympathetic nervous system is activated by "fight or flight" stimuli. To achieve rapid activation of this system, the sympathetic nervous system often discharges as a unit. The receptors that mediate sympathetic nervous system effects on neuroeffector organs are α and β receptors. Because the sympathetic nervous system is a division of the autonomic nervous system, it is not subject to voluntary control and functions below conscious thought. Correct answer = C. The muscarinic receptors of the parasympathetic nervous system maintain essential body functions such as digestion and waste elimination. The nicotinic receptors are a receptor for acetylcholine. It plays a major role in skeletal muscles, ganglia and synthesis of catecholamines in the adrenal medulla. a and b receptors are receptors for norepinephrine and epinephrine and activation of these receptors does not produce these effects. 3/21/11 2:20:45 PM 4 Cholinergic Agonists I. OVERVIEW Drugs affecting the autonomic nervous system (ANS) are divided into two groups according to the type of neuron involved in their mechanism of action. The cholinergic drugs, which are described in this and the following chapter, act on receptors that are activated by acetylcholine (ACh), whereas the adrenergic drugs (discussed in Chapters 6 and 7) act on receptors stimulated by norepinephrine or epinephrine. Cholinergic and adrenergic drugs both act by either stimulating or blocking receptors of the ANS. Figure 4.1 summarizes the cholinergic agonists discussed in this chapter. II. THE CHOLINERGIC NEURON The preganglionic fibers terminating in the adrenal medulla, the autonomic ganglia (both parasympathetic and sympathetic), and the postganglionic fibers of the parasympathetic division use ACh as a neurotransmitter (Figure 4.2). Also the postganglionic sympathetic division of sweat glands use acetylcholine. In addition, cholinergic neurons innervate the muscles of the somatic system and also play an important role in the central nervous system (CNS). [Note: Patients with Alzheimer disease have a significant loss of cholinergic neurons in the temporal lobe and entorhinal cortex. Most of the drugs available to treat the disease are acetylcholinesterase (AChE) inhibitors (see p. 108).] A. Neurotransmission at cholinergic neurons DIRECT ACTING Acetylcholine MIOCHOL-E Bethanechol URECHOLINE Carbachol MIOSTAT, ISOPTO CARBACHOL Cevimeline EVOXAC Pilocarpine SALAGEN, ISOPTO CARPINE INDIRECT ACTING (reversible) Ambenonium MYTELASE Donepezil ARICEPT Galantamine RAZADYNE Neostigmine PROSTIGMIN Physostigmine ANTILIRIUM Pyridostigmine MESTINON Rivastigmine EXELON Tacrine COGNEX INDIRECT ACTING (irreversible) Echothiophate PHOSPHOLINE IODIDE REACTIVATION OF ACETYLCHOLINESTERASE Pralidoxime PROTOPAM Figure 4.1 Summary of cholinergic agonists. Neurotransmission in cholinergic neurons involves six sequential steps: 1) synthesis, 2) storage, 3) release, 4) binding of ACh to a receptor, 5) degradation of the neurotransmitter in the synaptic cleft (that is, the space between the nerve endings and adjacent receptors located on nerves or effector organs), and 6) recycling of choline and acetate (Figure 4.3). 1. Synthesis of acetylcholine: Choline is transported from the extracellular fluid into the cytoplasm of the cholinergic neuron by an energy-dependent carrier system that cotransports sodium and can be inhibited by the drug hemicholinium. [Note: Choline has a quaternary nitrogen and carries a permanent positive charge, and, thus, cannot diffuse through the membrane.] The uptake of choline is the rate-limiting step in ACh synthesis. Choline acetyltransferase catalyzes the reaction of choline with acetyl coenzyme A (CoA) to form ACh (an ester) in the cytosol. Acetyl CoA is derived from the mitochondria and is produced by the pyruvate oxidation and fatty acid oxidation. Pharm 5th 3-21-11.indb 47 3/21/11 2:20:45 PM 48 4. Cholinergic Agonists 2. Storage of acetylcholine in vesicles: ACh is packaged and stored into presynaptic vesicles by an active transport process coupled to the efflux of protons. The mature vesicle contains not only ACh but also adenosine triphosphate (ATP) and proteoglycan. [Note: ATP has been suggested to be a cotransmitter acting at prejunctional purinergic receptors to inhibit the release of ACh or norepinephrine.] Cotransmission from autonomic neurons is the rule rather than the exception. This means that most synaptic vesicles will contain the primary neurotransmitter (here, ACh) as well as a cotransmitter that will increase or decrease the effect of the primary neurotransmitter. The neurotransmitters in vesicles appear as beadlike structures, known as varicosities, along the nerve terminal of the presynaptic neuron. 3. Release of acetylcholine: When an action potential propagated by voltage-sensitive sodium channels arrives at a nerve ending, voltage-sensitive calcium channels on the presynaptic membrane open, causing an increase in the concentration of intracellular calcium. Elevated calcium levels promote the fusion of synaptic vesicles with the cell membrane and the release of their contents into the synaptic space. This release can be blocked by botulinum toxin. In contrast, the toxin in black widow spider venom causes all the ACh stored in synaptic vesicles to empty into the synaptic gap. AUTONOMIC SOMATIC Sympathetic innervation of adrenal medulla Sympathetic Parasympathetic Acetylcholine Acetylcholine Acetylcholine Preganglionic neuron Ganglionic transmitter Nicotinic receptor Nicotinic receptor Nicotinic receptor Postganglionic neurons Adrenal medulla Neuroeffector transmitter No ganglia Epinephrine and norepinephrine released into the blood Norepinephrine Acetylcholine Acetylcholine Adrenergic receptor Adrenergic receptor Muscarinic receptor Nicotinic receptor Effector organs Skeletal muscle Figure 4.2 Sites of actions of cholinergic agonists in the autonomic and somatic nervous systems. Pharm 5th 3-21-11.indb 48 3/21/11 2:20:45 PM II. The Cholinergic Neuron 49 4. Binding to the receptor: ACh released from the synaptic vesicles diffuses across the synaptic space and binds to either of two postsynaptic receptors on the target cell, to presynaptic receptors in the membrane of the neuron that released the ACh, or to other targeted presynaptic receptors. The postsynaptic cholinergic receptors on the surface of the effector organs are divided into two classes: muscarinic and nicotinic (see Figure 4.2 and p. 46). Binding to a receptor leads to a biologic response within the cell, such as the initiation of a nerve impulse in a postganglionic fiber or activation of specific enzymes in effector cells, as mediated by second-messenger molecules (see p. 29 and below). 5. Degradation of acetylcholine: The signal at the postjunctional effector site is rapidly terminated, because AChE cleaves ACh to choline and acetate in the synaptic cleft (see Figure 4.3). [Note: Butyrylcholinesterase, sometimes called pseudocholinesterase, is found in the plasma but does not play a significant role in the termination of ACh's effect in the synapse.] Choline AcCoA Na^+ Choline Na^+ 1 SYNTHESIS OF ACETYLCHOLINE Transport of choline is inhibited by hemicholinium. Acetylcholine 6 2 RECYCLING OF CHOLINE UPTAKE INTO STORAGE VESICLES Acetylcholine is protected from degradation in the vesicle. Choline is taken up by the neuron. + Ca^{2+} Synaptic vesicle Ca^{2+} Presynaptic receptor 5 DEGRADATION OF ACETYLCHOLINE Acetylcholine is rapidly hydrolyzed by acetylcholinesterase in the synaptic cleft. Acetylcholine 3 RELEASE OF NEUROTRANSMITTER Release is blocked by botulinum toxin. Spider venom causes release of acetylcholine. Choline Acetate 4 BINDING TO THE RECEPTOR Postsynaptic receptor is activated by binding of the neurotransmitter. INTRACELLULAR RESPONSE Figure 4.3 Synthesis and release of acetylcholine from the cholinergic neuron. AcCoA = acetyl coenzyme A. Pharm 5th 3-21-11.indb 49 3/21/11 2:20:48 PM 50 4. Cholinergic Agonists 6. Recycling of choline: Choline may be recaptured by a sodium-coupled, high-affinity uptake system that transports the molecule back into the neuron. There, it is acetylated into ACh that is stored until released by a subsequent action potential. A Muscarinic receptors Muscarine Acetylcholine Nicotine III. CHOLINERGIC RECEPTORS (CHOLINOCEPTORS) High affinity Low affinity Two families of cholinoceptors, designated muscarinic and nicotinic receptors, can be distinguished from each other on the basis of their different affinities for agents that mimic the action of ACh (cholinomimetic agents or parasympathomimetics). A. Muscarinic receptors B Nicotinic receptors Muscarine Acetylcholine Nicotine Low affinity Figure 4.4 Types of cholinergic receptors. High affinity Muscarinic receptors belong to the class of G protein–coupled receptors. These receptors, in addition to binding ACh, also recognize muscarine, an alkaloid that is present in certain poisonous mushrooms. By contrast, the muscarinic receptors show only a weak affinity for nicotine (Figure 4.4A). Binding studies and specific inhibitors, as well as cDNA characterization, have distinguished five subclasses of muscarinic receptors: M1, M2, M3, M4, and M5. Although five muscarinic receptors have been identified by gene cloning, only M1, M2, and M3 receptors have been functionally characterized. 1. Locations of muscarinic receptors: These receptors have been found on ganglia of the peripheral nervous system and on the autonomic effector organs, such as the heart, smooth muscle, brain, and exocrine glands (see Figure 3.3). Specifically, although all five subtypes have been found on neurons, M1 receptors are also found on gastric parietal cells, M2 receptors on cardiac cells and smooth muscle, and M3 receptors on the bladder, exocrine glands, and smooth muscle. [Note: Drugs with muscarinic actions preferentially stimulate muscarinic receptors on these tissues, but at high concentration they may show some activity at nicotinic receptors.] 2. Mechanisms of acetylcholine signal transduction: A number of different molecular mechanisms transmit the signal generated by ACh occupation of the receptor. For example, when the M1 or M3 receptors are activated, the receptor undergoes a conformational change and interacts with a G protein, designated Gq, that in turn activates phospholipase C.1 This leads to the hydrolysis of phosphatidylinositol-(4,5)-bisphosphate to yield diacylglycerol and inositol (1,4,5)-trisphosphate. Both inositol (1,4,5)-trisphosphate and diacylglycerol are second messengers. Inositol (1,4,5)-trisphosphate causes an increase in intracellular Ca^{2+} (see Figure 3.10C, p. 41). This cation can then interact to stimulate or inhibit enzymes or to cause hyperpolarization, secretion, or contraction. Diacylglycerol activates protein kinase C. This enzyme phosphorylates numerous proteins within the cell. In contrast, activation of the M2 subtype on the cardiac muscle stimulates a G protein, designated Gi, which inhibits adenylyl cyclase2 and increases K^+ conductance (see Figure 3.10B, p. 45). The heart responds with a decrease in rate and force of contraction. 1See Chapter 17 in Lippincott's Illustrated Reviews: Biochemistry for a INFO LINK discussion of inositol trisphosphate and intracellular signaling. 2See Chapter 8 in Lippincott's Illustrated Reviews: Biochemistry for a discussion of adenylyl cyclase and intracellular signaling. Pharm 5th 3-21-11.indb 50 3/21/11 2:20:48 PM IV. Direct-Acting Cholinergic Agonists 51 3. Muscarinic agonists and antagonists: Attempts are currently underway to develop muscarinic agonists and antagonists that are directed against specific receptor subtypes. For example, pirenzepine, a tricyclic anticholinergic drug, has a greater selectivity for inhibiting M1 muscarinic receptors, such as in the gastric mucosa. At therapeutic doses, pirenzepine does not cause many of the side effects seen with the non-subtype-specific drugs; however, it does produce a reflex tachycardia on rapid infusion due to blockade of M2 receptors in the heart. Therefore, the usefulness of pirenzepine as an alternative to proton pump inhibitors in the treatment of gastric and duodenal ulcers is questionable. Darifenacin is a competitive muscarinic receptor antagonist with a greater affinity for the M3 receptor than for the other muscarinic receptors. The drug is used in the treatment of overactive bladder. [Note: At present, no clinically important agents interact solely with the M4 and M5 receptors.] B. Nicotinic receptors These receptors, in addition to binding ACh, also recognize nicotine but show only a weak affinity for muscarine (see Figure 4.4B). The nicotinic receptor is composed of five subunits and it functions as a ligand-gated ion channel (see Figure 3.10A). Binding of two ACh molecules elicits a conformational change that allows the entry of sodium ions, resulting in the depolarization of the effector cell. Nicotine at low concentration stimulates the receptor, and at high concentration blocks the receptor. Nicotinic receptors are located in the CNS, adrenal medulla, autonomic ganglia, and the neuromuscular junction (NMJ). Those at the NMJ are sometimes designated NM, and the others, NN. The nicotinic receptors of autonomic ganglia differ from those of the NMJ. For example, ganglionic receptors are selectively blocked by hexamethonium, whereas NMJ receptors are specifically blocked by tubocurarine. Bond cleaved by acetylcholinesterase O H3C C O A. Acetylcholine Acetylcholine [ah-see-teel-KOE-leen] is a quaternary ammonium compound that cannot penetrate membranes. Although it is the neurotransmitter of parasympathetic and somatic nerves as well as autonomic ganglia, it lacks therapeutic importance because of its multiplicity of actions (leading to diffuse effects) and its rapid inactivation by the cholinesterases. ACh has both muscarinic and nicotinic activity. Its actions include: Pharm 5th 3-21-11.indb 51 CH 2 N + O H2 N CH 3 CH 3 CH 3 Acetylcholine CH 3 CH 3 + O CH CH 2 N CH 3 Bethanechol CH 3 (derivative of acetylcholine) C IV. DIRECT-ACTING CHOLINERGIC AGONISTS Cholinergic agonists (also known as parasympathomimetics) mimic the effects of ACh by binding directly to cholinoceptors. These agents may be broadly classified into two groups: choline esters, which include ACh, and synthetic esters of choline, such as carbachol and bethanechol. Naturally occurring alkaloids, such as pilocarpine, constitute the second group (Figure 4.5). All of the direct-acting cholinergic drugs have longer durations of action than ACh. Some of the more therapeutically useful drugs (pilocarpine and bethanechol) preferentially bind to muscarinic receptors and are sometimes referred to as muscarinic agents. [Note: Muscarinic receptors are located primarily, but not exclusively, at the neuroeffector junction of the parasympathetic nervous system.] However, as a group, the direct-acting agonists show little specificity in their actions, which limits their clinical usefulness. CH 2 Ester of carbamic acid; resists hydrolysis by acetylcholinesterase O H2N CH 3 C O CH 2 CH 2 N + CH 3 CH 3 Carbachol (derivative of acetylcholine) H5 C 2 O CH 2 O N CH 3 N Pilocarpine (natural product) Figure 4.5 Comparison of the structures of some cholinergic agonists. 3/21/11 2:20:49 PM 52 4. Cholinergic Agonists Diarrhea Diaphoresis Miosis Nausea Urinary urgency 1. Decrease in heart rate and cardiac output: The actions of ACh on the heart mimic the effects of vagal stimulation. For example, if injected intravenously, ACh produces a brief decrease in cardiac rate (negative chronotropy) and stroke volume as a result of a reduction in the rate of firing at the sinoatrial (SA) node. [Note: It should be remembered that normal vagal activity regulates the heart by the release of ACh at the SA node.] 2. Decrease in blood pressure: Injection of ACh causes vasodilation and lowering of blood pressure by an indirect mechanism of action. ACh activates M3 receptors found on endothelial cells lining the smooth muscles of blood vessels. This results in the production of nitric oxide from arginine.3 [Note: nitric oxide (NO) is also known as endothelium-derived relaxing factor.] (See p. 363 for more detail on NO.) NO then diffuses to vascular smooth muscle cells to stimulate protein kinase G production, leading to hyperpolarization and smooth muscle relaxation via phosphodiesterase-3 inhibition. In the absence of administered cholinergic agents, the vascular receptors have no known function, because ACh is never released into the blood in any significant quantities. Atropine blocks these muscarinic receptors and prevents ACh from producing vasodilation. 3. Other actions: In the gastrointestinal (GI) tract, acetylcholine increases salivary secretion and stimulates intestinal secretions and motility. It also enhances bronchiolar secretions. In the genitourinary tract, ACh increases the tone of the detrusor urinae muscle, causing expulsion of urine. In the eye, ACh is involved in stimulating ciliary muscle contraction for near vision and in the constriction of the pupillae sphincter muscle, causing miosis (marked constriction of the pupil). ACh (1% solution) is instilled into the anterior chamber of the eye to produce miosis during ophthalmic surgery. B. Bethanechol Figure 4.6 Some adverse effects observed with cholinergic agonists. Bethanechol [be-THAN-e-kole] is an unsubstituted carbamoyl ester, structurally related to ACh, in which the acetate is replaced by carbamate, and the choline is methylated (see Figure 4.5). Hence, it is not hydrolyzed by AChE (due to the esterification of carbamic acid), although it is inactivated through hydrolysis by other esterases. It lacks nicotinic actions (due to the addition of the methyl group) but does have strong muscarinic activity. Its major actions are on the smooth musculature of the bladder and GI tract. It has about a 1-hour duration of action. 1. Actions: Bethanechol directly stimulates muscarinic receptors, causing increased intestinal motility and tone. It also stimulates the detrusor muscle of the bladder, whereas the trigone and sphincter are relaxed. These effects increase voiding pressure and decrease bladder capacity to cause expulsion of urine. 2. Therapeutic applications: In urologic treatment, bethanechol is used to stimulate the atonic bladder, particularly in postpartum or postoperative, nonobstructive urinary retention. Bethanechol may also be used to treat neurogenic atony as well as megacolon. INFO LINK Pharm 5th 3-21-11.indb 52 3 See Chapter 13 in Lippincott's Illustrated Reviews: Biochemistry for a discussion of the roles of nitric oxide. 3/21/11 2:20:50 PM IV. Direct-Acting Cholinergic Agonists 53 3. Adverse effects: Bethanechol causes the effects of generalized cholinergic stimulation (Figure 4.6). These include sweating, salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm. Atropine sulfate may be administered to overcome severe cardiovascular or bronchoconstrictor responses to this agent. C. Carbachol (carbamylcholine) Carbachol [KAR-ba-kole] has both muscarinic as well as nicotinic actions. It lacks the methyl group present in bethanechol (see Figure 4.5). Like bethanechol, carbachol is an ester of carbamic acid and a poor substrate for AChE (see Figure 4.5). It is biotransformed by other esterases but at a much slower rate. 1. Actions: Carbachol has profound effects on both the cardiovascular and GI systems because of its ganglion-stimulating activity, and it may first stimulate and then depress these systems. It can cause release of epinephrine from the adrenal medulla by its nicotinic action. Locally instilled into the eye, it mimics the effects of ACh, causing miosis and a spasm of accommodation in which the ciliary muscle of the eye remains in a constant state of contraction. 2. Therapeutic uses: Because of its high potency, receptor nonselectivity, and relatively long duration of action, carbachol is rarely used therapeutically except in the eye as a miotic agent to treat glaucoma by causing pupillary contraction and a decrease in intraocular pressure. Onset of action for miosis is 10 to 20 minutes. Intraocular pressure is reduced for 4 to 8 hours. 3. Adverse effects: At doses used ophthalmologically, little or no side effects occur due to lack of systemic penetration (quaternary amine). Eye treated with pilocarpine Miosis (contraction of the pupil) D. Pilocarpine The alkaloid pilocarpine [pye-loe-KAR-peen] is a tertiary amine and is stable to hydrolysis by AChE (see Figure 4.5). Compared with ACh and its derivatives, it is far less potent but is uncharged and will penetrate the CNS at therapeutic doses. Pilocarpine exhibits muscarinic activity and is used primarily in ophthalmology. 1. Actions: Applied topically to the cornea, pilocarpine produces rapid miosis and contraction of the ciliary muscle. When the eye undergoes this miosis, it experiences a spasm of accommodation. The vision becomes fixed at some particular distance, making it impossible to focus (Figure 4.7). [Note the opposing effects of atropine, a muscarinic blocker, on the eye (see p. 59).] Pilocarpine is one of the most potent stimulators of secretions (secretagogue) such as sweat, tears, and saliva, but its use for producing these effects has been limited due to its lack of selectivity. The drug is beneficial in promoting salivation in patients with xerostomia resulting from irradiation of the head and neck. Sjögren's syndrome, which is characterized by dry mouth and lack of tears, is treated with oral pilocarpine tablets and cevimeline, a cholinergic drug that also has the drawback of being nonspecific. Pharm 5th 3-21-11.indb 53 Untreated eye Mydriasis (dilation of the pupil) Eye treated with atropine Figure 4.7 Actions of pilocarpine and atropine on the iris and ciliary muscle of the eye. 3/21/11 2:20:50 PM 54 4. Cholinergic Agonists 2. Therapeutic use in glaucoma: Pilocarpine is used to treat glaucoma and is the drug of choice in the emergency lowering of intraocular pressure of both narrow-angle (or closed-angle) and wide-angle (also called open-angle) glaucoma. Pilocarpine is extremely effective in opening the trabecular meshwork around Schlemm's canal, causing an immediate drop in intraocular pressure as a result of the increased drainage of aqueous humor. This action occurs within a few minutes, lasts 4 to 8 hours, and can be repeated. The organophosphate echothiophate inhibits AChE and exerts the same effect for a longer duration. [Note: Carbonic anhydrase inhibitors, such as acetazolamide, as well as the β-adrenergic blocker timolol, are effective in treating chronic glaucoma but are not used for emergency lowering of intraocular pressure.] The miotic action of pilocarpine is also useful in reversing mydriasis due to atropine. 3. Adverse effects: Pilocarpine can enter the brain and cause CNS disturbances. Poisoning with this agent is characterized by exaggeration of various parasympathetic effects, including profuse sweating (diaphoresis) and salivation. The effects are similar to those produced by consumption of mushrooms of the genus Inocybe. Parenteral atropine, at doses that can cross the blood-brain barrier, is administered to counteract the toxicity of pilocarpine. V. INDIRECT-ACTING CHOLINERGIC AGONISTS: ACETYLCHOLINESTERASE INHIBITORS (REVERSIBLE) NEURON Acetate Acetylcholine Choline Echothiophate Edrophonium Neostigmine Physostigmine INCREASED INTRACELLULAR RESPONSE Figure 4.8 Mechanisms of action of indirect (reversible) cholinergic agonists. Pharm 5th 3-21-11.indb 54 AChE is an enzyme that specifically cleaves ACh to acetate and choline and, thus, terminates its actions. It is located both pre- and postsynaptically in the nerve terminal where it is membrane bound. Inhibitors of AChE indirectly provide a cholinergic action by prolonging the lifetime of ACh produced endogenously at the cholinergic nerve endings. This results in the accumulation of ACh in the synaptic space (Figure 4.8). Therefore, these drugs can provoke a response at all cholinoceptors in the body, including both muscarinic and nicotinic receptors of the ANS as well as at NMJs and in the brain. The reversible AChE inhibitors can be broadly classified as short-acting or intermediate-acting agents. A. Edrophonium Edrophonium [ed-row-FOE-nee-um] is the prototype short-acting AChE inhibitor. Edrophonium binds reversibly to the active center of AChE, preventing hydrolysis of ACh. It is rapidly absorbed and has a short duration of action of 10 to 20 minutes due to rapid renal elimination. Edrophonium is a quaternary amine, and its actions are limited to the periphery. It is used in the diagnosis of myasthenia gravis, which is an autoimmune disease caused by antibodies to the nicotinic receptor at NMJs. This causes their degradation, making fewer receptors available for interaction with the neurotransmitter. Intravenous injection of edrophonium leads to a rapid increase in muscle strength. Care must be taken, because excess drug may provoke a cholinergic crisis (atropine is the antidote). Edrophonium may also be used to assess cholinesterase inhibitor therapy, for differentiating cholinergic and myasthenic crises, and for reversing the effects of nondepolarizing neuromuscular blockers after surgery. Due to the availability of other agents, edrophonium use has become limited. 3/21/11 2:20:51 PM V. Indirect-Acting Cholinergic Agonists 55 B. Physostigmine Physostigmine [fi-zoe-STIG-meen] is a nitrogenous carbamic acid ester found naturally in plants and is a tertiary amine. It is a substrate for AChE, and it forms a relatively stable carbamoylated intermediate with the enzyme, which then becomes reversibly inactivated. The result is potentiation of cholinergic activity throughout the body. Contraction of visceral smooth muscle 1. Actions: Physostigmine has a wide range of effects as a result of its action, and stimulates not only the muscarinic and nicotinic sites of the ANS but also the nicotinic receptors of the NMJ. Its duration of action is about 2 to 4 hours, and it is considered to be an intermediate-acting agent. Physostigmine can enter and stimulate the cholinergic sites in the CNS. 2. Therapeutic uses: The drug increases intestinal and bladder motility, which serve as its therapeutic action in atony of either organ (Figure 4.9). Placed topically in the eye, it produces miosis and spasm of accommodation, as well as a lowering of intraocular pressure. It is used to treat glaucoma, but pilocarpine is more effective. Physostigmine is also used in the treatment of overdoses of drugs with anticholinergic actions, such as atropine, phenothiazines, and tricyclic antidepressants. 3. Adverse effects: The effects of physostigmine on the CNS may lead to convulsions when high doses are used. Bradycardia and a fall in cardiac output may also occur. Inhibition of AChE at the skeletal NMJ causes the accumulation of ACh and, ultimately, results in paralysis of skeletal muscle. However, these effects are rarely seen with therapeutic doses. C. Neostigmine Miosis BP Hypotension Bradycardia Figure 4.9 Some actions of physostigmine. Neostigmine [nee-oh-STIG-meen] is a synthetic compound that is also a carbamic acid ester, and it reversibly inhibits AChE in a manner similar to that of physostigmine. 1. Actions: Unlike physostigmine, neostigmine has a quaternary nitrogen. Therefore, it is more polar, is absorbed poorly from the GI tract, and does not enter the CNS. Its effect on skeletal muscle is greater than that of physostigmine, and it can stimulate contractility before it paralyzes. Neostigmine has an intermediate duration of action, usually 30 minutes to 2 hours. 2. Therapeutic uses: It is used to stimulate the bladder and GI tract, as an antidote for tubocurarine and other competitive neuromuscularblocking agents (see p. 65). Neostigmine is also used symptomatically to treat myasthenia gravis. Neostigmine and other AChE inhibitors preserve endogenous ACh, which can stimulate a greater number of ACh receptors at the muscle endplate. 3. Adverse effects: Adverse effects of neostigmine include those of generalized cholinergic stimulation, such as salivation, flushing, decreased blood pressure, nausea, abdominal pain, diarrhea, and bronchospasm. Neostigmine does not cause CNS side effects and is not used to overcome toxicity of central-acting antimuscarinic agents such as atropine. Neostigmine is contraindicated when intestinal or urinary bladder obstruction is present. It should not be used for patients who have peritonitis or inflammatory bowel disease. Pharm 5th 3-21-11.indb 55 3/21/11 2:20:51 PM 56 4. Cholinergic Agonists D. Pyridostigmine and ambenonium PHOSPHORYLATION OF ENZYME Enzyme inactivated Pralidoxime (PAM) can remove the inhibitor E. Tacrine, donepezil, rivastigmine, and galantamine O C2H5–O–P–O–C2H5 S–R Echothiophate O-H Active site of acetylcholinesterase RSH O C2H5–O–P–O–C2H5 O Acetylcholinesterase (inactive) H 2O C2H5–OH O Aging (loss of alkyl group) C2H5–O–P–OH PAM O Acetylcholinesterase (irreversibly inactive) O C2H5–O–P–O–C2H5 PAM O-H Acetylcholinesterase (active) Figure 4.10 Covalent modification of acetylcholinesterase by echothiophate. Also shown is the reactivation of the enzyme with pralidoxime. R = (CH3)3N+–CH2–CH2–RSH = (CH3)3N+–CH2–CH2–S-H Pharm 5th 3-21-11.indb 56 Pyridostigmine [peer-id-oh-STIG-meen] and ambenonium [am-be-NOEnee-um] are other cholinesterase inhibitors that are used in the chronic management of myasthenia gravis. Their durations of action are intermediate (3 to 6 hours and 4 to 8 hours, respectively), but longer than that of neostigmine. Adverse effects of these agents are similar to those of neostigmine. As mentioned above, patients with Alzheimer disease have a deficiency of cholinergic neurons in the CNS. This observation led to the development of anticholinesterases as possible remedies for the loss of cognitive function. Tacrine [TAK-reen] was the first to become available, but it has been replaced by others because of its hepatotoxicity. Despite the ability of donepezil [doe-NEP-e-zil], rivastigmine [ri-va-STIG-meen], and galantamine [ga-LAN-ta-meen] to delay the progression of Alzheimer disease, none can stop its progression. GI distress is their primary adverse effect (see p. 108). VI. INDIRECT-ACTING CHOLINERGIC AGONISTS: ANTICHOLINESTERASES (IRREVERSIBLE) A number of synthetic organophosphate compounds have the capacity to bind covalently to AChE. The result is a long-lasting increase in ACh at all sites where it is released. Many of these drugs are extremely toxic and were developed by the military as nerve agents. Related compounds, such as parathion, are used as insecticides. A. Echothiophate 1. Mechanism of action: Echothiophate [ek-oe-THI-oh-fate] is an organophosphate that covalently binds via its phosphate group to the serine-OH group at the active site of AChE (Figure 4.10). Once this occurs, the enzyme is permanently inactivated, and restoration of AChE activity requires the synthesis of new enzyme molecules. Following covalent modification of AChE, the phosphorylated enzyme slowly releases one of its ethyl groups. The loss of an alkyl group, which is called aging, makes it impossible for chemical reactivators, such as pralidoxime, to break the bond between the remaining drug and the enzyme. 2. Actions: Actions include generalized cholinergic stimulation, paralysis of motor function (causing breathing difficulties), and convulsions. Echothiophate produces intense miosis and, thus, has found therapeutic use. Intraocular pressure falls from the facilitation of outflow of aqueous humor. Atropine in high dosages can reverse many of the muscarinic and some of the central effects of echothiophate. 3. Therapeutic uses: An ophthalmic solution of the drug is applied topically to the eye for the chronic treatment of open-angle glaucoma. Echothiophate is not a first-line agent in the treatment of glaucoma. In addition to its other side effects, the potential risk for causing cataracts limits its use. A summary of the actions of some of the cholinergic agonists is presented in Figure 4.11. 3/21/11 2:20:52 PM VII. Toxicology Of Acetylcholinesterase Inhibitors Bethanechol • Used in treatment of urinary retention • Binds preferentially at muscarinic receptors Carbachol • Produces miosis during ocular surgery • Used topically to reduce intraocular pressure in open-angle or narrow-angle glaucoma, particularly in patients who have become tolerant to pilocarpine Pilocarpine • Reduces intraocular pressure in openangle and narrow-angle glaucoma • Binds preferentially at muscarinic receptors • Uncharged, tertiary amine that can penetrate the CNS Physostigmine • Increases intestinal and bladder motility • Reduces intraocular pressure in glaucoma • Reverses CNS and cardiac effects of tricyclic antidepressants • Reverses CNS effects of atropine • Uncharged, tertiary amine that can penetrate the CNS Neostigmine • Prevents postoperative abdominal distention and urinary retention • Used in treatment of myasthenia gravis • Used as an antidote for tubocurarine • Has long duration of action (2 to 4 hrs) Edrophonium • For diagnosis of myasthenia gravis • As antidote for tubocurarine • Has short duration of action (10 to 20 min) 57 Rivastigmine, galantamine, donepezil • Used as first-line treatments for Azheimer disease, though confers modest benefit • Have not been shown to reduce healthcare costs or delay institutionalization • Can be used with memantine (N-methyl-D-aspartate antagonist) with moderate to severe disease Echothiophate • Used in treatment of open-angle glaucoma • Has long duration of action (1 week) Acetylcholine • Has no therapeutic uses Figure 4.11 Summary of actions of some cholinergic agonists. CNS = central nervous system. VII. TOXICOLOGY OF ACETYLCHOLINESTERASE INHIBITORS AChE inhibitors are commonly used as agricultural insecticides in the United States, which has led to numerous cases of accidental intoxication with these agents. In addition, they are frequently used for suicidal and homicidal purposes. Toxicity with these agents is manifested as nicotinic and muscarinic signs and symptoms. Depending on the agent, the effects can be peripheral or affect the whole body. A. Reactivation of acetylcholinesterase: Pralidoxime can reactivate inhibited AChE. However, it is unable to penetrate into the CNS. The presence of a charged group allows it to approach an anionic site on the enzyme, where it essentially displaces the phosphate group of the organophosphate and regenerates the enzyme. If given before aging of the alkylated enzyme occurs, it can reverse the effects of echothiophate, except for those in the CNS. With the newer nerve agents, which produce aging of the enzyme complex within seconds, pralidoxime is less effective. Pralidoxime is a weak AChE inhibitor and, at higher doses, may cause side effects similar to other AChE inhibitors (see Figures 4.6 and 4.9). In addition, it cannot overcome toxicity of reversible AChE inhibitors (for example, physostigmine). B. Other treatments: Atropine is administered to prevent muscarinic side effects of these agents. Such effects include increased bronchial secretion and saliva, bronchoconstriction, and bradycardia. Diazepam is also administered to reduce the persistent convulsion caused by these agents. General supportive measures, such as maintenance of patent airway, oxygen supply, and artificial respiration, may be necessary as well. Pharm 5th 3-21-11.indb 57 3/21/11 2:20:53 PM 58 1. Cholinergic Agonists Study Questions Choose the ONE best answer. 4.1 A patient with an acute attack of glaucoma is treated with pilocarpine. The primary reason for its effectiveness in this condition is its: A. Action to terminate acetylcholinesterase. B. Selectivity for nicotinic receptors. C. Ability to inhibit secretions, such as tears, saliva, and sweat. D. Ability to lower intraocular pressure. E. Inability to enter the brain. 4.2 A soldier's unit has come under attack with a nerve agent. The symptoms exhibited are skeletal muscle paralysis, profuse bronchial secretions, miosis, bradycardia, and convulsions. The alarm indicates exposure to an organophosphate. What is the correct treatment? A. Do nothing until you can confirm the nature of the nerve agent. B. Administer atropine, and attempt to confirm the nature of the nerve agent. C. Administer atropine and 2-PAM (pralidoxime). D. Administer pralidoxime. 4.3 A patient on a diagnostic test for myasthenia gravis would be expected to have improved neuromuscular function after being treated with: A. Donepezil. B. Edrophonium. C. Atropine. D. Echothiophate. E. Neostigmine. 4.4 The drug of choice for treating decreased salivation accompanying head and neck irradiation is: A. Physostigmine. B. Scopolamine. C. Carbachol. D. Acetylcholine. E. Pilocarpine. Pharm 5th 3-21-11.indb 58 Correct answer = D. Pilocarpine can abort an acute attack of glaucoma, because it causes pupillary constriction to lower intraocular pressure. It binds mainly to muscarinic receptors and can enter the brain. It is not effective in inhibiting secretions. Correct answer = C. Organophosphates exert their effect by irreversibly binding to acetylcholinesterase (AChE) and, thus, can cause a cholinergic crisis. Administration of atropine will block the muscarinic sites, but it will not reactivate the enzyme, which will remain blocked for a long period of time. Therefore, it is essential to also administer pralidoxime as soon as possible to reactivate the enzyme before aging occurs. Administering pralidoxime alone will not protect the patient against the effects of acetylcholine resulting from AChE inhibition. Correct answer = B. Edrophonium is a short-acting inhibitor of acetylcholinesterase (AChE) that is used to diagnose myasthenia gravis. It is a quaternary compound and does not enter the central nervous system. Donepezil, isoflurophate, and neostigmine are also AChEs but with longer actions. Donepezil is used in the treatment of Alzheimer disease. Echothiophate has some activity in treating open-angle glaucoma. Neostigmine is used in the treatment of myasthenia gravis but is not used in its diagnosis. Atropine is a cholinergic antagonist and, thus, would have the opposite effects. Correct answer = E. Pilocarpine, taken orally, has proven to be beneficial in this situation. All the others choices except scopolamine are cholinergic agonists. However, their ability to stimulate salivation is less than that of pilocarpine, and their other effects are more troublesome. 3/21/11 2:20:53 PM Cholinergic Antagonists I. OVERVIEW The cholinergic antagonists (also called cholinergic blockers, para sympatholytics, or anticholinergic drugs) bind to cholinoceptors, but they do not trigger the usual receptor-mediated intracellular effects. The most useful of these agents selectively block muscarinic receptors of the para sympathetic nerves. The effects of parasympathetic innervation are, thus, interrupted, and the actions of sympathetic stimulation are left unopposed. A second group of drugs, the ganglionic blockers, show a preference for the nicotinic receptors of the sympathetic and parasympathetic ganglia. Clinically, they are the least important of the anticholinergic drugs. A third family of compounds, the neuromuscular-blocking agents, interfere with transmission of efferent impulses to skeletal muscles. These agents are used as skeletal muscle relaxant adjuvants in anesthesia during surgery, intubation, and various orthopedic procedures. Figure 5.1 summarizes the cholinergic antagonists discussed in this chapter. II. ANTIMUSCARINIC AGENTS Commonly known as antimuscarinics, these agents (for example, atropine and scopolamine) block muscarinic receptors (Figure 5.2), causing inhibition of all muscarinic functions. In addition, these drugs block the few exceptional sympathetic neurons that are cholinergic, such as those innervating salivary and sweat glands. In contrast to the cholinergic agonists, which have limited usefulness therapeutically, the cholinergic blockers are beneficial in a variety of clinical situations. Because they do not block nicotinic receptors, the antimuscarinic drugs have little or no action at skeletal neuromuscular junctions (NMJs) or autonomic ganglia. [Note: A number of antihistaminic and antidepressant drugs also have antimuscarinic activity.] A. Atropine 5 ANTIMUSCARINIC AGENTS Atropine ISOPTO ATROPINE, Benztropine COGENTIN Cyclopentolate AK-PENTOLATE, CYCLOGYL Darifenacin ENABLEX Fesoterodine TOVIAZ Ipratropium ATROVENT Oxybutynin DITROPAN, GELNIQUE, OXYTROL Scopolamine ISOPTO HYOSCINE, SCOPACE, TRANSDERM SCŌP Solifenacin VESICARE Tiotropium SPIRIVA HANDIHALER Tolterodine DETROL Trihexyphenidyl ARTANE Tropicamide MYDRIACYL, TROPICACYL Trospium chloride SANCTURA GANGLIONIC BLOCKERS Mecamylamine not available Nicotine COMMIT, NICODERM, NICORETTE, NICOTROL INHALER NEUROMUSCULAR BLOCKERS Atracurium only generic Cisatracurium NIMBEX Pancuronium PAVULON Rocuronium ZEMURON Succinylcholine ANECTINE, QUELICIN Vecuronium only generic Figure 5.1 Summary of cholinergic antagonists. Atropine [A-troe-peen] is a tertiary amine belladonna alkaloid with a high affinity for muscarinic receptors. It binds competitively and prevents acetylcholine (ACh) from binding to those sites (Figure 5.3). Atropine acts both centrally and peripherally. Its general actions last about 4 hours, except when placed topically in the eye, where the action may last for days. Neuroeffector organs have varying sensitivity to atropine. The greatest inhibitory effects are on bronchial tissue and the secretion of sweat and saliva (Figure 5.4). Pharm 5th 3-21-11.indb 59 3/21/11 2:20:53 PM 60 5. Cholinergic Antagonists AUTONOMIC Sympathetic innervation of adrenal medulla Sympathetic SOMATIC Parasympathetic Preganglionic neuron Ganglionic transmitter Acetylcholine Acetylcholine Nicotinic receptor Nicotinic receptor Epinephrine and norepinephrine released into the blood Norepinephrine Adrenergic receptor Adrenergic receptor Site of action of antimuscarinic drugs Effector organs Effector organs Figure 5.2 Sites of actions of cholinergic antagonists. Scopolamine Atropine Acetylcholine Muscarinic receptor Figure 5.3 Competition of atropine and scopolamine with acetylcholine for the muscarinic receptor. Pharm 5th 3-21-11.indb 60 Sites of action of ganglionic blockers Nicotinic receptor Postganglionic neurons Adrenal medulla Neuroeffector transmitter No ganglia Acetylcholine Acetylcholine Muscarinic receptor Site of action of neuromuscular blockers Acetylcholine Nicotinic receptor Skeletal muscle 1. Actions: a. Eye: Atropine blocks all cholinergic activity on the eye, resulting in persistent mydriasis (dilation of the pupil, see Figure 4.6, p. 52), unresponsiveness to light, and cycloplegia (inability to focus for near vision). In patients with narrow-angle glaucoma, intraocular pressure may rise dangerously. Shorter-acting agents, such as the antimuscarinic tropicamide, or an α -adrenergic drug, such as phenylephrine, are generally favored for producing mydriasis in ophthalmic examinations. b. Gastrointestinal (GI): Atropine (as the active isomer, l-hyoscyamine) can be used as an antispasmodic to reduce activity of the GI tract. Atropine and scopolamine (which is discussed below) are probably the most potent drugs available that produce this effect. Although gastric motility is reduced, hydrochloric acid production is not significantly affected. Thus, the drug is not effective in promoting healing of peptic ulcer. [Note: Pirenzepine (see p. 51), an M1-muscarinic antagonist, does reduce gastric acid secretion at doses that do not antagonize other systems.] In addition, doses of atropine that reduce spasms also reduce saliva secretion, ocular accommodation, and micturition (urination). These effects decrease patient compliance with the use of these medications. 3/21/11 2:20:54 PM II. Antimuscarinic Agents 61 c. Urinary system: Atropine-like drugs are also used to reduce hypermotility states of the urinary bladder. It is still occasionally used in enuresis (involuntary voiding of urine) among children, but α-adrenergic agonists with fewer side effects may be more effective. e. Secretions: Atropine blocks the salivary glands, producing a drying effect on the oral mucous membranes (xerostomia). The salivary glands are exquisitely sensitive to atropine. Sweat and lacrimal glands are similarly affected. [Note: Inhibition of secretions by sweat glands can cause elevated body temperature, which can be dangerous in children and the elderly.] >10.0 mg Dose of atropine d. Cardiovascular: Atropine produces divergent effects on the cardiovascular system, depending on the dose (Figure 5.4). At low doses, the predominant effect is a decreased cardiac rate (bradycardia). Originally thought to be due to central activation of vagal efferent outflow, the effect is now known to result from blockade of the M1 receptors on the inhibitory prejunctional (or presynaptic) neurons, thus permitting increased ACh release. With higher doses of atropine, the M2 receptors on the sinoatrial node are blocked, and the cardiac rate increases modestly. This generally requires at least 1 mg of atropine, which is a higher dose than ordinarily given. Arterial blood pressure is unaffected, but, at toxic levels, atropine will dilate the cutaneous vasculature. 5.0 mg Hallucinations and delirium; coma Rapid heart rate; palpitation; marked dryness of the mouth; dilation of pupil; some blurring of near vision 2.0 mg 0.5 mg Slight cardiac slowing; some dryness of the mouth; inhibition of sweating Figure 5.4 Dose-dependent effects of atropine. 2. Therapeutic uses: a. Ophthalmic: In the eye, topical atropine exerts both mydriatic and cycloplegic effects, and it permits the measurement of refractive errors without interference by the accommodative capacity of the eye. [Note: Phenylephrine or similar α-adrenergic drugs are preferred for pupillary dilation if cycloplegia is not required]. Shorter-acting antimuscarinics (cyclopentolate and tropicamide) have largely replaced atropine due to the prolonged mydriasis observed with atropine (7–14 days versus 6–24 hours with other agents). Atropine may induce an acute attack of eye pain due to sudden increases in eye pressure in individuals with narrow-angle glaucoma. b. Antispasmodic: Atropine (as the active isomer, l-hyoscyamine) is used as an antispasmodic agent to relax the GI tract and bladder. c. Antidote for cholinergic agonists: Atropine is used for the treatment of overdoses of cholinesterase inhibitor insecticides and some types of mushroom poisoning (certain mushrooms contain cholinergic substances that block cholinesterases). Massive doses of the antagonist may be required over a long period of time to counteract the poisons. The ability of atropine to enter the central nervous system (CNS) is of particular importance. The drug also blocks the effects of excess ACh resulting from acetylcholinesterase (AChE) inhibitors such as physostigmine. d. Antisecretory: The drug is sometimes used as an antisecretory agent to block secretions in the upper and lower respiratory tracts prior to surgery. Pharm 5th 3-21-11.indb 61 3/21/11 2:20:54 PM 62 5. Cholinergic Antagonists 3. Pharmacokinetics: Atropine is readily absorbed, partially metabolized by the liver, and eliminated primarily in urine. It has a half-life of about 4 hours. Scopolamine For nausea due to . . . Motion sickness Figure 5.5 Scopolamine is an effective anti–motion sickness agent. Blurred vision 4. Adverse effects: Depending on the dose, atropine may cause dry mouth, blurred vision, "sandy eyes," tachycardia, urinary retention, and constipation. Effects on the CNS include restlessness, confusion, hallucinations, and delirium, which may progress to depression, collapse of the circulatory and respiratory systems, and death. Low doses of cholinesterase inhibitors, such as physostigmine, may be used to overcome atropine toxicity. In older individuals, the use of atropine to induce mydriasis and cycloplegia is considered to be too risky, because it may exacerbate an attack of glaucoma due to an increase in intraocular pressure in someone with a latent condition. It may also induce troublesome urinary retention in this population. Atropine may be dangerous in children, because they are sensitive to its effects, particularly to the rapid increases in body temperature that it may elicit. B. Scopolamine Confusion Mydriasis Constipation Scopolamine [skoe-POL-a-meen], another tertiary amine plant alkaloid, produces peripheral effects similar to those of atropine. However, scopolamine has greater action on the CNS (unlike with atropine, CNS effects are observed at therapeutic doses) and a longer duration of action in comparison to those of atropine. It has some special actions as indicated below. 1. Actions: Scopolamine is one of the most effective anti–motion sickness drugs available (Figure 5.5). Scopolamine also has the unusual effect of blocking short-term memory. In contrast to atropine, scopolamine produces sedation, but at higher doses it can produce excitement instead. Scopolamine may produce euphoria and is susceptible to abuse. 2. Therapeutic uses: Although similar to atropine, therapeutic use of scopolamine is limited to prevention of motion sickness (for which it is particularly effective) and to blocking short-term memory. [Note: As with all such drugs used for motion sickness, it is much more effective prophylactically than for treating motion sickness once it occurs. The amnesic action of scopolamine makes it an important adjunct drug in anesthetic procedures.] 3. Pharmacokinetics and adverse effects: These aspects are similar to those of atropine. Urinary Retention Figure 5.6 Adverse effects commonly observed with cholinergic antagonists. Pharm 5th 3-21-11.indb 62 C. Ipratropium and tiotropium Inhaled ipratropium [i-pra-TROE-pee-um] and inhaled tiotropium [ty-ohTROPE-ee-um] are quaternary derivatives of atropine. These agents are approved as bronchodilators for maintenance treatment of bronchospasm associated with chronic obstructive pulmonary disease (COPD), both chronic bronchitis and emphysema. These agents are also pending approval for treating asthma in patients who are unable to take adrenergic agonists. Because of their positive charges, these drugs do not enter the systemic circulation or the CNS, isolating their effects to 3/21/11 2:20:58 PM III. Ganglionic Blockers the pulmonary system. Tiotropium is administered once daily, a major advantage over ipratropium, which requires dosing up to four times daily. Both are delivered via inhalation. Important characteristics of the muscarinic antagonists are summarized in Figures 5.6 and 5.7. D. Tropicamide and cyclopentolate These agents are used similarly to atropine as ophthalmic solutions for mydriasis and cycloplegia. Their duration of action is shorter than that of atropine. Tropicamide produces mydriasis for 6 hours, and cyclopentolate for 24 hours. E. Benztropine and trihexyphenidyl These agents are centrally acting antimuscarinic agents that have been used for many years in the treatment of Parkinson disease. With the advent of other drugs (for example, levodopa/carbidopa), they have been largely replaced. However, benztropine and trihexyphenidyl are useful as adjuncts with other antiparkinsonian agents to treat all types of parkinsonian syndromes, including antipsychotic-induced extrapyramidal symptoms. These drugs may be helpful in geriatric patients who cannot tolerate stimulants. F. Darifenacin, fesoterodine, oxybutynin, solifenacin, tolterodine, and trospium chloride These synthetic atropine-like drugs are used to treat overactive urinary bladder disease. By blocking muscarinic receptors in the bladder, intravesicular pressure is lowered, bladder capacity is increased, and the frequency of bladder contractions is reduced. Side effects of these agents include dry mouth, constipation, and blurred vision, which limit tolerability of these agents if used continually. Oxybutynin is available as a transdermal system (topical patch), which is better tolerated because it causes less dry mouth than do oral formulations, and is more widely accepted with greater patient acceptance. The overall efficacies of these antimuscarinic drugs are similar. III. GANGLIONIC BLOCKERS 63 Drug Therapeutic uses Muscarinic blockers Trihexyphenidyl • Treatment of Parkinson Benztropine Darifenacin Fesoterodine Oxybutynin Solifenacin Tolterodine Trospium disease • Treatment of overactive urinary bladder Cyclopentolate Tropicamide Atropine* • In ophthalmology, to Atropine* • To treat spastic disorders produce mydriasis and cycloplegia prior to refraction of the GI and lower urinary tract • To treat organophosphate poisoning • To suppress respiratory secretions prior to surgery Scopolamine • In obstetrics, with morphine to produce amnesia and sedation • To prevent motion sickness Ipratropium • Treatment of COPD Ganglionic blockers Nicotine • None Figure 5.7 Summary of cholinergic antagonists. *Contraindicated in narrow-angle glaucoma. GI = gastrointestinal; COPD = chronic obstructive pulmonary disease. Ganglionic blockers specifically act on the nicotinic receptors of both parasympathetic and sympathetic autonomic ganglia. Some also block the ion channels of the autonomic ganglia. These drugs show no selectivity toward the parasympathetic or sympathetic ganglia and are not effective as neuromuscular antagonists. Thus, these drugs block the entire output of the autonomic nervous system at the nicotinic receptor. Except for nicotine, the other drugs mentioned in this category are nondepolarizing, competitive antagonists. The responses of the nondepolarizing blockers are complex, and nearly all the physiological responses to these agents can be predicted by knowledge of the predominant tone of a given organ system. For example, the predominant tone in the arterioles is sympathetic. In the presence of a nondepolarizing blocker, this system is affected the most, leading to vasodilation. The parasympathetic nervous system is the predominant tone in many organ systems (see p. 39). Thus, the presence of a ganglionic blocker will also produce atony of the bladder and GI tract, cycloplegia, xerostomia, and tachycardia. Therefore, ganglionic blockade is rarely used therapeutically, but often serves as a tool in experimental pharmacology. Pharm 5th 3-21-11.indb 63 3/21/11 2:20:59 PM 64 5. Cholinergic Antagonists Nicotine Dopamine Pleasure, appetite suppression Norepinephrine Arousal, appetite suppression Acetylcholine Arousal, cognitive enhancement Glutamate Learning, memory enhancement Serotonin Mood modulation, appetite suppression β-Endorphin Reduction of anxiety and tension GABA Reduction of anxiety and tension Figure 5.8 Neurochemical effects of nicotine. GABA = γ-Aminobutyric acid. A. Nicotine A component of cigarette smoke, nicotine [NIK-oh-teen] is a poison with many undesirable actions. It is without therapeutic benefit and is deleterious to health. Depending on the dose, nicotine depolarizes autonomic ganglia, resulting first in stimulation and then in paralysis of all ganglia. The stimulatory effects are complex and result from increased release of neurotransmitter (Figure 5.8), due to effects on both sympathetic and parasympathetic ganglia. For example, enhanced release of dopamine and norepinephrine may be associated with pleasure as well as appetite suppression, the latter of which may contribute to lower body weight. The overall response of a physiological system is a summation of the stimulatory and inhibitory effects of nicotine. These include increased blood pressure and cardiac rate (due to release of transmitter from adrenergic terminals and from the adrenal medulla) and increased peristalsis and secretions. At higher doses, the blood pressure falls because of ganglionic blockade, and activity in both the GI tract and bladder musculature ceases. (See p. 124 for a full discussion of nicotine.) B. Mecamylamine Mecamylamine [mek-a-MILL-a-meen] produces a competitive nicotinic blockade of the ganglia. Mecamylamine has been supplanted by superior agents with fewer side effects. IV. NEUROMUSCULAR-BLOCKING DRUGS These drugs block cholinergic transmission between motor nerve endings and the nicotinic receptors on the neuromuscular endplate of skeletal muscle (see Figure 5.2). These neuromuscular blockers are structural analogs of ACh, and they act either as antagonists (nondepolarizing type) or agonists (depolarizing type) at the receptors on the endplate of the NMJ. Neuromuscular blockers are clinically useful during surgery for producing complete muscle relaxation, without having to use higher anesthetic doses to achieve comparable muscular relaxation. Such agents are also useful in orthopedic surgery and in facilitating tracheal intubation as well. A second group of muscle relaxants, the central muscle relaxants, are used to control spastic muscle tone. These drugs include diazepam, which binds at γ-aminobutyric acid (GABA) receptors; dantrolene, which acts directly on muscles by interfering with the release of calcium from the sarcoplasmic reticulum; and baclofen, which probably acts at GABA receptors in the CNS. A. Nondepolarizing (competitive) blockers The first drug that was found to be capable of blocking the skeletal NMJ was curare [koo-RAH-ree], which native South American hunters of the Amazon region used to paralyze prey. The drug tubocurarine [tooboe-kyoo-AR-een] was ultimately purified and introduced into clinical practice in the early 1940s. Although tubocurarine is considered to be the prototype agent in this class, it has been largely replaced by other agents because of its adverse side effects (see Figure 5.11). This agent is no longer available in the United States. The neuromuscular-blocking agents have significantly increased the safety of anesthesia, because less anesthetic is required to produce muscle relaxation, allowing patients to recover quickly and completely after surgery. [Note: Higher doses of anesthesia may produce respiratory paralysis and cardiac depression, increasing recovery time after surgery.] Neuromuscular blockers should not be used to substitute for inadequate depth of anesthesia. Pharm 5th 3-21-11.indb 64 3/21/11 2:20:59 PM IV. Neuromuscular-Blocking Drugs 65 1. Mechanism of action: a. At low doses: Nondepolarizing neuromuscular-blocking drugs interact with the nicotinic receptors to prevent the binding of ACh (Figure 5.9). Thus, these drugs prevent depolarization of the muscle cell membrane and inhibit muscular contraction. Because these agents compete with ACh at the receptor without stimulating it, they are called competitive blockers. Their action can be overcome by increasing the concentration of ACh in the synaptic gap, for example, by administration of such cholinesterase inhibitors as neostigmine, pyridostigmine, and edrophonium. Anesthesiologists often employ this strategy to shorten the duration of the neuromuscular blockade. In addition, at low doses the muscle will respond to direct electrical stimulation from a peripheral nerve stimulator to varying degrees, depending on the extent of

neuromuscular blockade. Tubocurarine Acetylcholine Na + Nicotinic receptor at neuromuscular junction Figure 5.9 Mechanism of action of competitive neuromuscularblocking drugs. b. At high doses: Nondepolarizing blockers can block the ion channels of the endplate. This leads to further weakening of neuromuscular transmission, thereby reducing the ability of AChE inhibitors to reverse the actions of the nondepolarizing muscle relaxants. With complete blockade, no direct electrical stimulation is seen. 2. Actions: Not all muscles are equally sensitive to blockade by competitive blockers. Small, rapidly contracting muscles of the face and eye are most susceptible and are paralyzed first, followed by the fingers. Thereafter, the limbs, neck, and trunk muscles are paralyzed. Next, the intercostal muscles are affected, and, lastly, the diaphragm muscles are paralyzed. The muscles recover in the reverse manner, with the diaphragm muscles recovering first and contracting muscles of the face and the eye recovering last. Those agents that release histamine (for example, atracurium) can produce a fall in blood pressure, flushing, and bronchoconstriction. 3. Therapeutic uses: These blockers are used therapeutically as adjuvant drugs in anesthesia during surgery to relax skeletal muscle. They are also used to facilitate intubation as well as during orthopedic surgery (for example, fracture alignment and dislocation corrections). 4. Pharmacokinetics: All neuromuscular-blocking agents are injected intravenously because their uptake via oral absorption is minimal. These agents possess two or more quaternary amines in their bulky ring structure, making them orally ineffective. They penetrate membranes very poorly and do not enter cells or cross the blood-brain barrier. Many of the drugs are not metabolized, and their actions are terminated by redistribution (Figure 5.10). For example, pancuronium is excreted unchanged in urine. Atracurium is degraded spontaneously in plasma and by ester hydrolysis. [Note: Atracurium has been replaced by its isomer, cisatracurium. Atracurium releases histamine and is metabolized to laudanosine, which can provoke seizures. Cisatracurium, which has the same pharmacokinetic properties as atracurium, is less likely to have these effects.] The amino steroid drugs (vecuronium and rocuronium) are deacetylated in the liver, and their clearance may be prolonged in patients with hepatic disease. These drugs are also excreted unchanged in bile. The choice Pharm 5th 3-21-11.indb 65 Agents do not readily enter cells IV Vecuronium and rocuronium and metabolites appear mainly in bile Most drugs excreted primarily unchanged in urine Neuromuscular-blocking drugs Figure 5.10 Pharmacokinetics of the neuromuscular-blocking drugs. IV = intravenous. 3/21/11 2:21:01 PM 66 5. Cholinergic Antagonists Time to maximal blockade (min) Time to recover 25% of maximal response (min) Atracurium 2 40 Cisatracurium spontaneously degrades in plasma and is the only nondepolarizing neuromuscular blocker whose dose need not be reduced in patients with renal failure. It is often used in patients with multisystem organ failure because its metabolism is independent of hepatic or renal function. Cisatracurium is useful in mechanical ventilation of critically ill patients. Cisatracurium 3 90 Vagolytic (increased heart rate) of an agent will depend on how quickly muscle relaxation is needed and on the duration of the muscle relaxation. The onset and duration of action, as well as other characteristics of the neuromuscularblocking drugs, are shown in Figure 5.11. 5. Adverse effects: In general, agents are safe with minimal side effects. The adverse effects of the specific neuromuscular blockers are shown in Figure 5.11. 6. Drug interactions: a. Cholinesterase inhibitors: Drugs such as neostigmine, physo stigmine, pyridostigmine, and edrophonium can overcome the action of nondepolarizing neuromuscular blockers, but, with increased dosage, cholinesterase inhibitors can cause a depolarizing block as a result of elevated ACh concentrations at the endplate membrane. If the neuromuscular blocker has entered the ion channel, cholinesterase inhibitors are not as effective in overcoming blockade. b. Halogenated hydrocarbon anesthetics: Drugs such as halothane act to enhance neuromuscular blockade by exerting a stabilizing action at the NMJ. These agents sensitize the NMJ to the effects of neuromuscular blockers. Pancuronium 3 86 c. Aminoglycoside antibiotics: Drugs such as gentamicin and tobramycin inhibit ACh release from cholinergic nerves by competing with calcium ions. They synergize with pancuronium and other competitive blockers, enhancing the blockade. Rocuronium 1 43 d. Calcium-channel blockers: These agents may increase the neuro muscular block of competitive blockers as well as depolarizing blockers. B. Depolarizing agents Postoperative muscle pain is common; hyperkalemia and increased intraocular and intragastric pressure may occur. Drug may trigger malignant hyperthermia. Rapid onset makes succinylcholine useful for tracheal intubation in patients with gastric contents. Succinyl- 1.1 choline 8 Tubocurarine 2 38 Vecuronium 2 44 Figure 5.11 Onset and duration of action of neuromuscular-blocking drugs. Pharm 5th 3-21-11.indb 66 Depolarizing blocking agents work by depolarizing the plasma membrane of the muscle fiber, similar to the action of ACh. However, these agents are more resistant to degradation by AChE, and can thus more persistently depolarize the muscle fibers. Succinylcholine [suk-sin-il-KOEleen] is the only depolarizing muscle relaxant in use today. 1. Mechanism of action: The depolarizing neuromuscular-blocking drug succinylcholine attaches to the nicotinic receptor and acts like ACh to depolarize the junction (Figure 5.12). Unlike ACh, which is instantly destroyed by AChE, the depolarizing agent persists at high concentrations in the synaptic cleft, remaining attached to the receptor for a relatively longer time and providing constant stimulation of the receptor. [Note: The duration of action of succinylcholine is dependent on diffusion from the motor endplate and hydrolysis by plasma pseudocholinesterase.] The depolarizing agent first causes the opening of the sodium channel associated with the nicotinic receptors, which results in depolarization of the receptor (Phase I). This leads to a transient twitching of the muscle (fasciculations). Continued binding of the depolarizing agent renders the receptor incapable of transmitting further impulses. With time, continuous depolarization gives way to gradual repolarization as the sodium channel closes or is blocked. This causes a resistance to depolarization (Phase II) and flaccid paralysis. 3/21/11 2:21:01 PM IV. Neuromuscular-Blocking Drugs 2. Actions: The sequence of paralysis may be slightly different, but, as with the competitive blockers, the respiratory muscles are paralyzed last. Succinylcholine initially produces brief muscle fasciculations and a ganglionic block except at high doses, but it does have weak histamine-releasing action. [Note: Administering a small dose of nondepolarizing neuromuscular blocker prior to succinylcholine helps decrease or prevent the fasciculations which cause muscle soreness.] Normally, the duration of action of succinylcholine is extremely short, because this drug is rapidly broken down by plasma pseudocholinesterase. However, succinylcholine that gets to the NMJ is not metabolized by AChE, allowing the agent to bind to nicotinic receptors, and redistribution to plasma is necessary for metabolism (therapeutic benefits last only for a few minutes). [Note: Genetic variants in which plasma pseudocholinesterase levels are low or absent leads to prolonged neuromuscular paralysis.] 3. Therapeutic uses: Because of its rapid onset and short duration of action, succinylcholine is useful when rapid endotracheal intubation is required during the induction of anesthesia (a rapid action is essential if aspiration of gastric contents is to be avoided during intubation). It is also used during electroconvulsive shock treatment. 4. Pharmacokinetics: Succinylcholine is injected intravenously. Its brief duration of action (several minutes) results from redistribution and rapid hydrolysis by plasma pseudocholinesterase. Therefore, it is sometimes given by continuous infusion to maintain a longer duration of effect. Drug effects rapidly disappear upon discontinuation. 67 PHASE I Membrane depolarizes, resulting in an initial discharge that produces transient fasciculations followed by flaccid paralysis. Succinylcholine + - - - Depolarized ++ + Nicotinic receptor at a neuromuscular junction + ++ Na + PHASE II Membrane repolarizes, but receptor is desensitized to the effect of acetylcholine. 5. Adverse effects: a. Hyperthermia: When halothane (see p. 139) is used as an anesthetic, administration of succinylcholine has occasionally caused malignant hyperthermia (with muscular rigidity, metabolic acidosis, tachycardia, and hyperpyrexia) in genetically susceptible people (see Figure 5.11). This is treated by rapidly cooling the patient and by administration of dantrolene, which blocks release of Ca^{2+} from the sarcoplasmic reticulum of muscle cells, thereby reducing heat production and relaxing muscle tone. Na - - - - Succinylcholine ++ ++ ++ ++ Repolarized - - - - - - - - Figure 5.12 Mechanism of action of depolarizing neuromuscularblocking drugs. b. Apnea: Administration of succinylcholine to a patient who is genetically deficient in plasma cholinesterase or who has an atypical form of the enzyme can lead to prolonged apnea due to paralysis of the diaphragm. The rapid release of potassium may also contribute to prolonging apnea in patients with electrolyte imbalances who receive this drug. Patients with electrolyte imbalances who are also receiving digoxin or diuretics (such as congestive heart failure patients) should use succinylcholine cautiously or not at all. c. Hyperkalemia: Succinylcholine increases potassium release from intracellular stores. This may be particularly dangerous in burn patients and patients with massive tissue damage in which potassium has been rapidly lost from within cells. Pharm 5th 3-21-11.indb 67 3/21/11 2:21:02 PM 68 5. Cholinergic Antagonists Study Questions Choose the ONE best answer. 5.1 A 75-year-old man who was a smoker is diagnosed with chronic obstructive pulmonary disease and suffers from occasional bronchospasm. Which of the following would be effective in treating him? A. Ipratropium aerosol. B. Scopolamine patches. C. Mecamylamine. D. Oxygen. E. Nicotine. 5.2 Which of the following may precipitate an attack of open-angle glaucoma if instilled into the eye? A. Physostigmine. B. Atropine. C. Pilocarpine. D. Echothiophate. E. Tropicamide. 5.3 The prolonged apnea sometimes seen in patients who have undergone an operation in which succinylcholine was used as a muscle relaxant has been shown to be due to: A. Urinary atony. B. Depressed levels of plasma cholinesterase. C. A mutation in acetylcholinesterase. D. A mutation in the nicotinic receptor at the neuromuscular junction. E. Weak histamine-releasing action. 5.4 A 50-year-old male farm worker is brought to the emergency room. He was found confused in the orchard and since then has lost consciousness. His heart rate is 45, and his blood pressure is 80/40 mm Hg. He is sweating and salivating profusely. Which of the following treatments is indicated? A. Physostigmine. B. Norepinephrine. C. Trimethaphan. D. Atropine. E. Edrophonium. 5.5 Nondepolarizing neuromuscular blockers are associated with all of the following except: A. Initial activation of ACh receptor and depolarization of the motor end plate. B. Effects are reversed by acetylcholinesterase inhibitors. C. Intermediate to long duration of action. D. Bind but do not activate ACh receptor. E. Most of these agents have minimal cardiovascular effects. Pharm 5th 3-21-11.indb 68 Correct answer = A. This is a drug of choice, especially in a patient who cannot tolerate an adrenergic agonist, which would dilate the bronchioles. Scopolamine's main effect is atropinic, and it is the most effective anti–motion sickness drug. Mecamylamine is a ganglionic blocker and completely inappropriate in this situation. Oxygen would improve aeration but would not dilate the bronchial musculature. Nicotine would exacerbate his condition. Correct answer = B. The mydriatic effect of atropine can result in the narrowing of the canal of Schlemm leading to an increase in intraocular pressure. Physostigmine, pilocarpine, and echothiophate would cause miosis. Tropicamide produces mydriasis without increasing intraocular pressure because of its shorter duration of action. Correct answer = B. These patients have a genetic deficiency of the nonspecific plasma cholinesterase that is required for the termination of succinylcholine's action. The other choices would not produce apnea. Correct answer = D. The patient is exhibiting signs of cholinergic stimulation. Because he is a farmer, insecticide poisoning is a likely diagnosis. Thus, either intravenous or intramuscular doses of atropine are indicated to antagonize the muscarinic symptoms. Physostigmine and edrophonium are cholinesterase inhibitors and would exacerbate the problem. Norepinephrine would not be effective in combating the cholinergic stimulation. Trimethaphan, being a ganglionic blocker, would also worsen the condition. Correct answer = A. Activation of the ACh receptor is attributed to depolarizing agents (succinylcholine). B, C, and D are true for nondepolarizing agents. Pancuronium may cause tachycardia and hypertension; rocuronium and vecuronium have favorable cardiovascular safety profiles. 3/21/11 2:21:02 PM 6 Adrenergic Agonists I. OVERVIEW DIRECT-ACTING AGENTS The adrenergic drugs affect receptors that are stimulated by norepinephrine or epinephrine. Some adrenergic drugs act directly on the adrenergic receptor (adrenoceptor) by activating it and are said to be sympathomimetic. Others, which will be dealt with in Chapter 7, block the action of the neurotransmitters at the receptors (sympatholytics), whereas still other drugs affect adrenergic function by interrupting the release of norepinephrine from adrenergic neurons. This chapter describes agents that either directly or indirectly stimulate adrenoceptors (Figure 6.1). Albuterol ACCUNEB, PROAIR HFA, VENTOLIN II. THE ADRENERGIC NEURON PERFOROMIST Adrenergic neurons release norepinephrine as the primary neurotrans mitter. These neurons are found in the central nervous system (CNS) and also in the sympathetic nervous system, where they serve as links between ganglia and the effector organs. The adrenergic neurons and receptors, located either presynaptically on the neuron or postsynaptically on the effector organ, are the sites of action of the adrenergic drugs (Figure 6.2). A. Neurotransmission at adrenergic neurons Neurotransmission in adrenergic neurons closely resembles that already described for the cholinergic neurons (see p. 47), except that norepinephrine is the neurotransmitter instead of acetylcholine. Neurotransmission takes place at numerous bead-like enlargements called varicosities. The process involves five steps: synthesis, storage, release, and receptor binding of norepinephrine, followed by removal of the neurotransmitter from the synaptic gap (Figure 6.3). 1. Synthesis of norepinephrine: Tyrosine is transported by a Na+linked carrier into the axoplasm of the adrenergic neuron, where it is hydroxylated to dihydroxyphenylalanine (DOPA) by tyrosine hydroxylase.1 This is the rate-limiting step in the formation of norepinephrine. DOPA is then decarboxylated by the enzyme dopa decarboxylase (aromatic l-amino acid decarboxylase) to form dopamine in the cytoplasm of the presynaptic neuron. INFO LINK Pharm 5th 3-21-11.indb 69 HFA Clonidine CATAPRES, DURACLON Dobutamine* DOBUTREX Dopamine* INTROPIN Epinephrine* ADRENALIN, EPIPEN, PRIMATENE MIST Fenoldopam CORLOPAM Formoterol FORADIL AEROLIZER, Isoproterenol* ISUPREL Metaproterenol ALUPENT Norepinephrine* LEVOPHED Phenylephrine NEO-SYNEPHRINE, SUDAFED PE Salmeterol SEREVENT DISKUS Terbutaline BRETHINE INDIRECT-ACTING AGENTS Amphetamine ADDERALL Cocaine DIRECT AND INDIRECT ACTING (mixed action) AGENTS Ephedrine various Pseudoephedrine SUDAFED Figure 6.1 Summary of adrenergic agonists. Agents marked with an asterisk (*) are catecholamines. 1See Chapter 21 in Lippincott's Illustrated Reviews: Biochemistry for a discussion of the synthesis of DOPA. 3/21/11 2:21:03 PM 70 6. Adrenergic Agonists Nicotinic receptor Nicotinic receptor Adrenal medulla Epinephrine released into the blood Norepinephrine Adrenergic receptor Adrenergic receptor Effector organs Figure 6.2 Sites of actions of adrenergic agonists. 2. Storage of norepinephrine in vesicles: Dopamine is then transported into synaptic vesicles by an amine transporter system that is also involved in the reuptake of preformed norepinephrine. This carrier system is blocked by reserpine (see p. 96). Dopamine is hydroxylated to form norepinephrine by the enzyme, dopamine b-hydroxylase. [Note: Synaptic vesicles contain dopamine or norepinephrine plus adenosine triphosphate (ATP) and b-hydroxylase as well as other cotransmitters.] In the adrenal medulla, norepinephrine is methylated to yield epinephrine, which is stored in chromaffin cells along with norepinephrine. On stimulation, the adrenal medulla releases about 80 percent epinephrine and 20 percent norepinephrine directly into the circulation. 3. Release of norepinephrine: An action potential arriving at the nerve junction triggers an influx of calcium ions from the extracellular fluid into the cytoplasm of the neuron. The increase in calcium causes vesicles inside the neuron to fuse with the cell membrane and expel (exocytose) their contents into the synapse. Drugs such as guanethidine block this release (see p. 96). 4. Binding to receptors: Norepinephrine released from the synaptic vesicles diffuses across the synaptic space and binds to either postsynaptic receptors on the effector organ or to presynaptic receptors on the nerve ending. The recognition of norepinephrine by the membrane receptors triggers a cascade of events within the cell, resulting in the formation of intracellular second messengers that act as links (transducers) in the communication between the neurotransmitter and the action generated within the effector cell. Adrenergic receptors use both the cyclic adenosine monophosphate (cAMP) secondmessenger system2 and the phosphatidylinositol cycle3 to transduce the signal into an effect. Norepinephrine also binds to presynaptic receptors that modulate the release of the neurotransmitter. 5. Removal of norepinephrine: Norepinephrine may 1) diffuse out of the synaptic space and enter the general circulation, 2) be metabolized to O-methylated derivatives by postsynaptic cell membrane– associated catechol O-methyltransferase (COMT) in the synaptic space, or 3) be recaptured by an uptake system that pumps the norepinephrine back into the neuron. The uptake by the neuronal membrane involves a sodium- or potassium-activated ATPase that can be inhibited by tricyclic antidepressants, such as imipramine, or by cocaine (see Figure 6.3). Uptake of norepinephrine into the presynaptic neuron is the primary mechanism for termination of norepinephrine's effects. 6. Potential fates of recaptured norepinephrine: Once norepinephrine reenters the cytoplasm of the adrenergic neuron, it may be taken up into adrenergic vesicles via the amine transporter system and be sequestered for release by another action potential, or it may persist in a protected pool in the cytoplasm. Alternatively, norepinephrine can be oxidized by monoamine oxidase (MAO) present in neuronal mitochondria. The inactive products of norepinephrine metabolism are excreted in urine as vanillylmandelic acid, metanephrine, and normetanephrine. 2See Chapter 8 in Lippincott's Illustrated Reviews: Biochemistry for a INFO LINK discussion of the cyclic AMP second messenger system. 3See Chapter 17 in Lippincott's Illustrated Reviews: Biochemistry for a discussion of the phosphatidylinositol cycle. Pharm 5th 3-21-11.indb 70 3/21/11 2:21:03 PM II. The Adrenergic Neuron 71 1 SYNTHESIS OF NOREPINEPHRINE 2 Hydroxylation of tyrosine is the rate-limiting step. Inactive metabolites Urine MAO Tyrosine Na+ Dopamine enters a vesicle and is converted to norepinephrine. Norepinephrine Norepinephrine is protected from degradation in the vesicle. Tyrosine Na+ Transport into the vesicle is inhibited by reserpine. DOPA Inactive metabolites Urine MAO 3 Dopamine Dopamine + Released norepinephrine is rapidly taken into the neuron. Presynaptic receptor Reuptake is inhibited by cocaine and imipramine. Urine Influx of calcium causes fusion of the vesicle with the cell membrane in a process known as exocytosis. Synaptic vesicle Ca^{2+} REMOVAL OF NOREPINEPHRINE RELEASE OF NEUROTRANSMITTER Release is blocked by guanethidine and bretylium. Ca^{2+} 5 UPTAKE INTO STORAGE VESICLES 4 Norepinephrine Inactive metabolites BINDING TO RECEPTOR Postsynaptic receptor is activated by the binding of neurotransmitter. Catechol-Omethyltransferase (COMT) 6 METABOLISM SYNAPTIC SPACE Norepinephrine is methylated by COMT and oxidized by MAO. INTRACELLULAR RESPONSE Figure 6.3 Synthesis and release of norepinephrine from the adrenergic neuron. (MAO = monoamine oxidase.) B. Adrenergic receptors (adrenoceptors) In the sympathetic nervous system, several classes of adrenoceptors can be distinguished pharmacologically. Two families of receptors, designated α and β, were initially identified on the basis of their responses to the adrenergic agonists epinephrine, norepinephrine, and isoproterenol. The use of specific blocking drugs and the cloning of genes has revealed the molecular identities of a number of receptor subtypes. These proteins belong to a multigene family. Alterations in the primary structure of the receptors influence their affinity for various agents. Pharm 5th 3-21-11.indb 71 3/21/11 2:21:07 PM 72 6. Adrenergic Agonists A α Adrenoceptors Epinephrine Norepinephrine Isoproterenol α Receptor High affinity Low affinity B β Adrenoceptors Isoproterenol Epinephrine Norepinephrine β Receptor High affinity Figure 6.4 Types of adrenergic receptors. Low affinity 1. α1 and α2 Receptors: The α-adrenoceptors show a weak response to the synthetic agonist isoproterenol, but they are responsive to the naturally occurring catecholamines epinephrine and norepinephrine (Figure 6.4). For α receptors, the rank order of potency is epinephrine ≥ norepinephrine >> isoproterenol. The α-adrenoceptors are subdivided into two subgroups, α1 and α2, based on their affinities for α agonists and blocking drugs. For example, the α1 receptors have a higher affinity for phenylephrine than do the α2 receptors. Conversely, the drug clonidine selectively binds to α2 receptors and has less effect on α1 receptors. a. α1 Receptors: These receptors are present on the postsynaptic membrane of the effector organs and mediate many of the classic effects, originally designated as α-adrenergic, involving constriction of smooth muscle. Activation of α1 receptors initiates a series of reactions through the G protein activation of phospholipase C, resulting in the generation of inositol-1,4,5-trisphosphate (IP3) and diacylglycerol (DAG) from phosphatidylinositol. IP3 initiates the release of Ca^{2+} from the endoplasmic reticulum into the cytosol, and DAG turns on other proteins within the cell (Figure 6.5). b. α2 Receptors: These receptors, which are located primarily on presynaptic nerve endings and on other cells, such as the b cell of the pancreas and on certain vascular smooth muscle cells, control adrenergic neuromediator and insulin output, respectively. When a sympathetic adrenergic nerve is stimulated, the released norepinephrine traverses the synaptic cleft and interacts with the α1 receptors. A portion of the released norepinephrine "circles back" and reacts with α2 receptors on the neuronal membrane (see Figure 6.5). The stimulation of the α2 receptor causes feedback inhibition of the ongoing release of norepinephrine from the stimulated adrenergic neuron. This inhibitory action decreases further output from the adrenergic neuron and serves as a local modulating mechanism for reducing sympathetic neuromediator output when there is high sympathetic activity. [Note: In this instance, these receptors are acting as inhibitory autoreceptors.] α2 receptors are also found on presynaptic parasympathetic neurons. Norepinephrine released from a presynaptic sympathetic neuron can diffuse to and interact with these receptors, inhibiting acetylcholine release [Note: In these instances, these receptors are behaving as inhibitory heteroreceptors.] This is another local modulating mechanism to control autonomic activity in a given area. In contrast to α1 receptors, the effects of binding at α2 receptors are mediated by inhibition of adenylyl cyclase and a fall in the levels of intracellular cAMP. c. Further subdivisions: The α1 and α2 receptors are further divided into α1A, α1B, α1C, and α1D and into α2A, α2B, and α2C. This extended classification is necessary for understanding the selectivity of some drugs. For example, tamsulosin is a selective α1A antagonist that is used to treat benign prostate hyperplasia. The drug is clinically useful because it targets α1A receptors found primarily in the urinary tract and prostate gland. 2. β Receptors: b receptors exhibit a set of responses different from those of the α receptors. These are characterized by a strong response Pharm 5th 3-21-11.indb 72 3/21/11 2:21:07 PM II. The Adrenergic Neuron 73 to isoproterenol, with less sensitivity to epinephrine and norepinephrine (see Figure 6.4). For β receptors, the rank order of potency is isoproterenol > epinephrine > norepinephrine. The β-adrenoceptors can be subdivided into three major subgroups, β1, β2, and β3, based on their affinities for adrenergic agonists and antagonists, although several others have been identified by gene cloning. [Note: It is known that β3 receptors are involved in lipolysis, but their role in other specific reactions is not known]. β1 receptors have approximately equal affinities for epinephrine and norepinephrine, whereas β2 receptors have a higher affinity for epinephrine than for norepinephrine. Thus, tissues with a predominance of β2 receptors (such as the vasculature of skeletal muscle) are particularly responsive to the hormonal effects of circulating epinephrine released by the adrenal medulla. Binding of a neurotransmitter at any of the three β receptors results in activation of adenylyl cyclase and, therefore, increased concentrations of cAMP within the cell. Synaptic vesicle ATP cAMP Adenylyl cyclase α2 Receptor Norepinephrine 3. Distribution of receptors: Adrenergically innervated organs and tissues tend to have a predominance of one type of receptor. For example, tissues such as the vasculature to skeletal muscle have both α1 and β2 receptors, but the β2 receptors predominate. Other tissues may have one type of receptor exclusively, with practically no significant numbers of other types of adrenergic receptors. For example, the heart contains predominantly β1 receptors. α1 Receptor Membrane phosphoinositides + 4. Characteristic responses mediated by adrenoceptors: It is useful to organize the physiologic responses to adrenergic stimulation according to receptor type, because many drugs preferentially stimulate or block one type of receptor. Figure 6.6 summarizes the most prominent effects mediated by the adrenoceptors. As a generalization, stimulation of α1 receptors characteristically produces vasoconstriction (particularly in skin and abdominal viscera) and an increase in total peripheral resistance and blood pressure. Conversely, stimulation of β1 receptors characteristically causes cardiac stimulation, whereas stimulation of β2 receptors produces vasodilation (in skeletal vascular beds) and smooth muscle relaxation. α2 Receptors Activation of the receptor decreases production of cAMP, leading to an inhibition of further release of norepinephrine from the neuron. DAG IP3 Ca 2+ α1 Receptors Activation of the receptor increases production of DAG and IP3, leading to an increase in intracellular calcium ions. Figure 6.5 Second messengers mediate the effects of α receptors. DAG = diacylglycerol; IP3 = inositol trisphosphate; ATP = adenosine triphosphate; cAMP = cyclic adenosine monophosphate. ADRENOCEPTORS α1 Vasoconstriction Increased peripheral resistance Increased blood pressure Mydriasis α2 β1 β2 Inhibition of norepinephrine release Tachycardia Vasodilation Increased lipolysis Inhibition of acetylcholine release Decreased peripheral resistance Increased myocardial contractility Inhibition of insulin release Increased release of renin Increased closure of internal sphincter of the bladder Bronchodilation Increased muscle and liver glycogenolysis Increased release of glucagon Relaxed uterine smooth muscle Figure 6.6 Major effects mediated by α and β adrenoceptors. Pharm 5th 3-21-11.indb 73 3/21/11 2:21:09 PM 74 6. Adrenergic Agonists OH HO CH H CH2 N CH3 Phenylephrine OH CH H CH N CH3 CH3 III. CHARACTERISTICS OF ADRENERGIC AGONISTS Ephedrine OH HO Most of the adrenergic drugs are derivatives of β-phenylethylamine (Figure 6.7). Substitutions on the benzene ring or on the ethylamine side chains produce a great variety of compounds with varying abilities to differentiate between α and β receptors and to penetrate the CNS. Two important structural features of these drugs are 1) the number and location of OH substitutions on the benzene ring and 2) the nature of the substituent on the amino nitrogen. H CH CH2 N H HO 5. Desensitization of receptors: Prolonged exposure to the catecholamines reduces the responsiveness of these receptors, a phenomenon known as desensitization. Three mechanisms have been suggested to explain this phenomenon: 1) sequestration of the receptors so that they are unavailable for interaction with the ligand; 2) down-regulation, that is, a disappearance of the receptors either by destruction or decreased synthesis, and 3) an inability to couple to G protein, because the receptor has been phosphorylated on the cytoplasmic side by either protein kinase α or β-adrenergic receptor kinase. Norepinephrine A. Catecholamines OH HO Sympathomimetic amines that contain the 3,4-dihydroxybenzene group (such as epinephrine, norepinephrine, isoproterenol, and dopamine) are called catecholamines. These compounds share the following properties: H CH CH2 N CH3 HO Epinephrine OH HO 1. High potency: Drugs that are catechol derivatives (with – OH groups in the 3 and 4 positions on the benzene ring) show the highest potency in directly activating α or β receptors. H CH CH2 N CH3 CH HO CH3 Isoproterenol Affinity for β receptors increases as group on the amine nitrogen gets larger. H HO CH2 CH2 N H HO Dopamine Figure 6.7 Structures of several important adrenergic agonists. Drugs containing the catechol ring are shown in yellow. Pharm 5th 3-21-11.indb 74 2. Rapid inactivation: Not only are the catecholamines metabolized by COMT postsynaptically and by MAO intraneuronally, but they are also metabolized in other tissues. For example, COMT is in the gut wall, and MAO is in the liver and gut wall. Thus, catecholamines have only a brief period of action when given parenterally, and they are ineffective when administered orally because of inactivation. 3. Poor penetration into the CNS: Catecholamines are polar and, therefore, do not readily penetrate into the CNS. Nevertheless, most of these drugs have some clinical effects (anxiety, tremor, and headaches) that are attributable to action on the CNS. B. Noncatecholamines Compounds lacking the catechol hydroxyl groups have longer half-lives, because they are not inactivated by COMT. These include phenylephrine, ephedrine, and amphetamine. Phenylephrine, which is an analog of epinephrine, has only a single – OH at position 3 on the benzene ring, whereas ephedrine lacks hydroxyls on the ring but has a methyl substitution at the α-carbon. These are poor substrates for MAO and, thus, show a prolonged duration of action, because MAO is an important route of detoxification. Increased lipid solubility of many of the noncatecholamines (due to lack of polar hydroxyl groups) permits greater access to the CNS. [Note: Ephedrine and amphetamine may act indirectly by causing the release of stored catecholamines.] 3/21/11 2:21:11 PM IV. Direct-Acting Adrenergic Agonists C. Substitutions on the amine nitrogen The nature and bulk of the substituent on the amine nitrogen is important in determining the β selectivity of the adrenergic agonist. For example, epinephrine, with a – CH3 substituent on the amine nitrogen, is more potent at β receptors than norepinephrine, which has an unsubstituted amine. Similarly, isoproterenol, which has an isopropyl substituent – CH (CH3)2 on the amine nitrogen (see Figure 6.7), is a strong β agonist with little α activity (see Figure 6.4). 75 INDIRECT ACTION Drug enhances release of norepinephrine from vesicles. NEURON D. Mechanism of action of the adrenergic agonists 1. Direct-acting agonists: These drugs act directly on α or β receptors, producing effects similar to those that occur following stimulation of sympathetic nerves or release of the hormone epinephrine from the adrenal medulla (Figure 6.8). Examples of direct-acting agonists include epinephrine, norepinephrine, isoproterenol, and phenylephrine. 2. Indirect-acting agonists: These agents, which include amphetamine, cocaine, and tyramine, may block the uptake of norepinephrine (uptake blockers) or are taken up into the presynaptic neuron and cause the release of norepinephrine from the cytoplasmic pools or vesicles of the adrenergic neuron (see Figure 6.8). As with neuronal stimulation, the norepinephrine then traverses the synapse and binds to the α or β receptors. Examples of uptake blockers and agents that cause norepinephrine release include cocaine and amphetamines, respectively. 3. Mixed-action agonists: Some agonists, such as ephedrine and its stereoisomer, pseudoephedrine, have the capacity both to stimulate adrenoceptors directly and to release norepinephrine from the adrenergic neuron (see Figure 6.8). MIXED ACTION Drug acts both directly and indirectly. SYNAPSE DIRECT ACTION POSTSYNAPTIC TARGET CELL MEMBRANE Drug directly activates receptor. Figure 6.8 Sites of action of direct-, indirect-, and mixed-acting adrenergic agonists. IV. DIRECT-ACTING ADRENERGIC AGONISTS Direct-acting agonists bind to adrenergic receptors without interacting with the presynaptic neuron. The activated receptor initiates synthesis of second messengers and subsequent intracellular signals. As a group, these agents are widely used clinically. A. Epinephrine Epinephrine [ep-i-NEF-rin] is one of four catecholamines (epinephrine, norepinephrine, dopamine, and dobutamine) commonly used in therapy. The first three occur naturally in the body as neurotransmitters, and the latter is a synthetic compound. Epinephrine is synthesized from tyrosine in the adrenal medulla and released, along with small quantities of norepinephrine, into the bloodstream. Epinephrine interacts with both α and β receptors. At low doses, β effects (vasodilation) on the vascular system predominate, whereas at high doses, α effects (vasoconstriction) are strongest. 1. Actions: a. Cardiovascular: The major actions of epinephrine are on the cardiovascular system. Epinephrine strengthens the contractility of the myocardium (positive inotropic: β1 action) and increases its rate of contraction (positive chronotropic: β1 action). Therefore, Pharm 5th 3-21-11.indb 75 3/21/11 2:21:13 PM 76 6. Adrenergic Agonists cardiac output increases. With these effects comes increased oxygen demands on the myocardium. Epinephrine activates β1 receptors on the kidney to cause renin release. Renin is an enzyme involved in the production of angiotensin II, a potent vasoconstrictor. Epinephrine constricts arterioles in the skin, mucous membranes, and viscera (α effects), and it dilates vessels going to the liver and skeletal muscle (β2 effects). Renal blood flow is decreased. Therefore, the cumulative effect is an increase in systolic blood pressure, coupled with a slight decrease in diastolic pressure (Figure 6.9). Epinephrine increases the rate and force of cardiac contraction. Pulse rate (per min) 100 Blood pressure (mm Hg) Infusion of epinephrine 180 50 b. Respiratory: Epinephrine causes powerful bronchodilation by acting directly on bronchial smooth muscle (β2 action). This action relieves all known allergic- or histamine-induced bronchoconstriction. In the case of anaphylactic shock, this can be lifesaving. In individuals suffering from an acute asthmatic attack, epinephrine rapidly relieves dyspnea (labored breathing) and increases tidal volume (volume of gases inspired and expired). Epinephrine also inhibits the release of allergy mediators such as histamines from mast cells. 120 60 Peripheral resistance High Low 0 15 Time (min) Epinephrine decreases the peripheral resistance. Systolic pressure is increased, and diastolic pressure is decreased. Figure 6.9 Cardiovascular effects of intravenous infusion of low doses of epinephrine. c. Hyperglycemia: Epinephrine has a significant hyperglycemic effect because of increased glycogenolysis in the liver (β2 effect), increased release of glucagon (β2 effect), and a decreased release of insulin (α2 effect). These effects are mediated via the cAMP mechanism. d. Lipolysis: Epinephrine initiates lipolysis through its agonist activity on the β receptors of adipose tissue, which, upon stimulation, activate adenylyl cyclase to increase cAMP levels. cAMP stimulates a hormone-sensitive lipase, which hydrolyzes triacylglycerols to free fatty acids and glycerol.4 2. Biotransformations: Epinephrine, like the other catecholamines, is metabolized by two enzymatic pathways: MAO and COMT, which has S-adenosylmethionine as a cofactor (see Figure 6.3). The final metabolites found in the urine are metanephrine and vanillylmandelic acid. [Note: Urine also contains normetanephrine, a product of norepinephrine metabolism.] 3. Therapeutic uses a. Bronchospasm: Epinephrine is the primary drug used in the emergency treatment of any condition of the respiratory tract when bronchoconstriction has resulted in diminished respiratory exchange. Thus, in treatment of acute asthma and anaphylactic shock, epinephrine is the drug of choice. Within a few minutes after subcutaneous administration, greatly improved respiratory exchange is observed, and administration may be repeated after a few hours. However, selective β2 agonists, such as albuterol, are presently favored in the chronic treatment of asthma because of a longer duration of action and minimal cardiac stimulatory effect. INFO LINK Pharm 5th 3-21-11.indb 76 4See Chapter 16 in Lippincott's Illustrated Reviews: Biochemistry for a discussion of hormone-sensitive lipase activity. 3/21/11 2:21:14 PM IV. Direct-Acting Adrenergic Agonists b. Anaphylactic shock: Epinephrine is the drug of choice for the treatment of Type I hypersensitivity reactions in response to allergens. c. Cardiac arrest: Epinephrine may be used to restore cardiac rhythm in patients with cardiac arrest regardless of the cause. d. Anesthetics: Local anesthetic solutions usually contain 1:100,000 parts epinephrine. The effect of the drug is to greatly increase the duration of the local anesthesia. It does this by producing vasoconstriction at the site of injection, thereby allowing the local anesthetic to persist at the injection site before being absorbed into the circulation and metabolized. Very weak solutions of epinephrine (1:100,000) can also be used topically to vasoconstrict mucous membranes to control oozing of capillary blood. 4. Pharmacokinetics: Epinephrine has a rapid onset but a brief duration of action (due to rapid degradation). The preferred route is intramuscular (anterior thigh) due to rapid absorption. In emergency situations, epinephrine is given intravenously (IV) for the most rapid onset of action. It may also be given subcutaneously, by endotracheal tube, and by inhalation (Figure 6.10). Oral administration is ineffective, because epinephrine and the other catecholamines are inactivated by intestinal enzymes. Only the metabolites are excreted in urine. 77 Aerosol Poor penetration into CNS Topical IV SC Metabolites appear in urine the urine Epinephrine Figure 6.10 Pharmacokinetics of epinephrine. CNS = central nervous system; IV = intravenously; SC = subcutaneously. 5. Adverse effects: a. CNS disturbances: Epinephrine can produce adverse CNS effects that include anxiety, fear, tension, headache, and tremor. b. Hemorrhage: The drug may induce cerebral hemorrhage as a result of a marked elevation of blood pressure. c. Cardiac arrhythmias: Epinephrine can trigger cardiac arrhythmias, particularly if the patient is receiving digoxin. d. Pulmonary edema: Epinephrine can induce pulmonary edema. 6. Interactions: a. Hyperthyroidism: Epinephrine may have enhanced cardiovascular actions in patients with hyperthyroidism. If epinephrine is required in such an individual, the dose must be reduced. The mechanism appears to involve increased production of adrenergic receptors on the vasculature of the hyperthyroid individual, leading to a hypersensitive response. b. Cocaine: In the presence of cocaine, epinephrine produces exaggerated cardiovascular actions, because cocaine prevents reuptake of catecholamines into the adrenergic neuron. Thus, like norepinephrine, epinephrine remains at the receptor site for longer periods of time (see Figure 6.3). c. Diabetes: Epinephrine increases the release of endogenous stores of glucose. In the diabetic, dosages of insulin may have to be increased. Pharm 5th 3-21-11.indb 77 3/21/11 2:21:15 PM 78 6. Adrenergic Agonists Norepinephrine induces reflex bradycardia. Pulse rate (per min) 100 Blood pressure (mm Hg) Infusion of norepinephrine 180 d. β-Blockers: These prevent epinephrine's effects on β receptors, leaving α receptor stimulation unopposed. This may lead to an increase in peripheral resistance and an increase in blood pressure. e. Inhalation anesthetics: These agents sensitize the heart to the effects of epinephrine, which may lead to tachycardia. B. Norepinephrine Because norepinephrine [nor-ep-ih-NEF-rin] is the neuromediator of adrenergic nerves, it should, theoretically, stimulate all types of adrenergic receptors. In practice, when the drug is given in therapeutic doses to humans, the α-adrenergic receptor is most affected. 50 1. Cardiovascular actions: a. Vasoconstriction: Norepinephrine causes a rise in peripheral resistance due to intense vasoconstriction of most vascular beds, including the kidney (α1 effect). Both systolic and diastolic blood pressures increase (Figure 6.11). [Note: Norepinephrine causes greater vasoconstriction than does epinephrine, because it does not induce compensatory vasodilation via β2 receptors on blood vessels supplying skeletal muscles, etc. The weak β2 activity of norepinephrine also explains why it is not useful in the treatment of asthma.] 120 60 Peripheral resistance High Low 0 15 Time (min) Norepinephrine causes increased systolic and diastolic pressure. Norepinephrine constricts all blood vessels, causing increased peripheral resistance. Figure 6.11 Cardiovascular effects of intravenous infusion of norepinephrine. b. Baroreceptor reflex: In isolated cardiac tissue, norepinephrine stimulates cardiac contractility. In vivo, however, little (if any) cardiac stimulation is noted. This is due to the increased blood pressure that induces a reflex rise in vagal activity by stimulating the baroreceptors. This reflex bradycardia is sufficient to counteract the local actions of norepinephrine on the heart, although the reflex compensation does not affect the positive inotropic effects of the drug (see Figure 6.11). c. Effect of atropine pretreatment: When atropine, which blocks the transmission of vagal effects, is given before norepinephrine, stimulation of the heart by norepinephrine is evident as tachycardia. 2. Therapeutic uses: Norepinephrine is used to treat shock, because it increases vascular resistance and, therefore, increases blood pressure. Other actions of norepinephrine are not considered to be clinically significant. It is never used for asthma or in combination with local anesthetics. Norepinephrine is a potent vasoconstrictor and will cause extravasation (discharge of blood from vessel into tissues) along the injection site. Impaired circulation from norepinephrine may be treated with the α -receptor antagonist phentolamine. [Note: When norepinephrine is used as a drug, it is sometimes called levarterenol [leev-are-TER-a-nole].] 3. Pharmacokinetics: Norepinephrine may be given IV for rapid onset of action. The duration of action is 1 to 2 minutes following the end of the infusion period. It is poorly absorbed after subcutaneous injection and is destroyed in the gut if administered orally. Metabolism is similar to that of epinephrine. Pharm 5th 3-21-11.indb 78 3/21/11 2:21:17 PM IV. Direct-Acting Adrenergic Agonists 79 4. Adverse effects: These are similar to those of epinephrine. In addition, norepinephrine may cause blanching and sloughing of skin along an injected vein (due to extreme vasoconstriction). Isoproterenol causes vasodilation but strongly increases cardiac force and rate. C. Isoproterenol b. Pulmonary: Inhalation products of isoproterenol are no longer available in the United States. c. Other effects: Other actions on β receptors, such as increased blood sugar and increased lipolysis, can be demonstrated, but are not clinically significant. 2. Therapeutic uses: Isoproterenol can be used to stimulate the heart in emergency situations. 3. Pharmacokinetics: Isoproterenol is a marginal substrate for COMT and is stable to MAO action. 4. Adverse effects: The adverse effects of isoproterenol are similar to those of epinephrine. D. Dopamine Dopamine [DOE-pa-meen], the immediate metabolic precursor of norepinephrine, occurs naturally in the CNS in the basal ganglia, where it functions as a neurotransmitter, as well as in the adrenal medulla. Dopamine can activate α- and β-adrenergic receptors. For example, at higher doses, it can cause vasoconstriction by activating α1 receptors, whereas at lower doses, it stimulates β1 cardiac receptors. In addition, D1 and D2 dopaminergic receptors, distinct from the α- and β-adrenergic receptors, occur in the peripheral mesenteric and renal vascular beds, where binding of dopamine produces vasodilation. D2 receptors are also found on presynaptic adrenergic neurons, where their activation interferes with norepinephrine release. Pulse rate (per min) a. Cardiovascular: Isoproterenol produces intense stimulation of the heart to increase its rate and force of contraction, causing increased cardiac output (Figure 6.12). It is as active as epinephrine in this action and, therefore, is useful in the treatment of atrioventricular (AV) block or cardiac arrest. Isoproterenol also dilates the arterioles of skeletal muscle (β2 effect), resulting in decreased peripheral resistance. Because of its cardiac stimulatory action, it may increase systolic blood pressure slightly, but it greatly reduces mean arterial and diastolic blood pressure (see Figure 6.12). 100 50 Blood pressure (mm Hg) 1. Actions: Infusion of isoproterenol 180 120 60 High Peripheral resistance Isoproterenol [eye-soe-proe-TER-e-nole] is a direct-acting synthetic catecholamine that predominantly stimulates both β1- and β2-adrenergic receptors. Its nonselectivity is one of its drawbacks and the reason why it is rarely used therapeutically. Its action on α receptors is insignificant. Low 0 10 Time (min) Isoproterenol causes a significant decrease in peripheral resistance. Isoproterenol causes markedly decreased diastolic pressure, with moderately increased systolic pressure. Figure 6.12 Cardiovascular effects of intravenous infusion of isoproterenol. 1. Actions: a. Cardiovascular: Dopamine exerts a stimulatory effect on the β1 receptors of the heart, having both inotropic and chronotropic effects (Figure 6.13). At very high doses, dopamine activates α1 receptors on the vasculature, resulting in vasoconstriction. Pharm 5th 3-21-11.indb 79 3/21/11 2:21:19 PM 80 6. Adrenergic Agonists b. Renal and visceral: Dopamine dilates renal and splanchnic arterioles by activating dopaminergic receptors, thereby increasing blood flow to the kidneys and other viscera (see Figure 6.13). These receptors are not affected by α- or β-blocking drugs. Therefore, dopamine is clinically useful in the treatment of shock, in which significant increases in sympathetic activity might compromise renal function. [Note: Similar dopamine receptors are found in the autonomic ganglia and in the CNS.] Isoproterenol β2 2. Therapeutic uses: Dopamine is the drug of choice for cardiogenic and septic shock and is given by continuous infusion. It raises the blood pressure by stimulating the β1 receptors on the heart to increase cardiac output and α1 receptors on blood vessels to increase total peripheral resistance. In addition, it enhances perfusion to the kidney and splanchnic areas, as described above. Increased blood flow to the kidney enhances the glomerular filtration rate and causes sodium diuresis. In this regard, dopamine is far superior to norepinephrine, which diminishes the blood supply to the kidney and may cause renal shutdown. It is also used to treat hypotension and severe congestive heart failure, primarily in patients with low or normal peripheral vascular resistance and in patients that have oliguria. Bronchodilation β2 Peripheral vasodilation 3. Adverse effects: An overdose of dopamine produces the same effects as sympathetic stimulation. Dopamine is rapidly metabolized to homovanillic acid by MAO or COMT, and its adverse effects (nausea, hypertension, and arrhythmias) are, therefore, short-lived. β1 Increased cardiac output E. Fenoldopam Fenoldopam [fen-OL-de-pam] is an agonist of peirpheral dopamine D1 receptors, and it also has moderate affinity for α2 receptors. It is used as a rapid-acting vasodilator to treat severe hypertension in hospitalized patients, acting on coronary arteries, kidney arterioles, and mesenteric arteries. Fenoldopam is a racemic mixture, and the R-isomer is the active component. It undergoes extensive first-pass metabolism and has a 10-minute elimination half-life after IV infusion. Headache, flushing, dizziness, nausea, vomiting, and tachycardia (due to vasodilation) may be observed with this agent. Increased blood flow F. Dopaminergic Dopamine Figure 6.13 Clinically important actions of isoproterenol and dopamine. Dobutamine 1. Actions: Dobutamine [doe-BYOO-ta-meen] is a synthetic, direct-acting catecholamine that is a β1 receptor agonist. It is available as a racemic mixture. One of the stereoisomers has a stimulatory activity. It increases cardiac rate and output with few vascular effects. 2. Therapeutic uses: Dobutamine is used to increase cardiac output in acute congestive heart failure (see p. 204) as well as for inotropic support after cardiac surgery. The drug increases cardiac output and does not significantly elevate oxygen demands of the myocardium, a major advantage over other sympathomimetic drugs. 3. Adverse effects: Dobutamine should be used with caution in atrial fibrillation, because the drug increases AV conduction. Other adverse effects are the same as those for epinephrine. Tolerance may develop on prolonged use. Pharm 5th 3-21-11.indb 80 3/21/11 2:21:21 PM IV. Direct-Acting Adrenergic Agonists 81 G. Oxymetazoline Oxymetazoline [OX-ee-mee-TAZ-ih-leen] is a direct-acting synthetic adrenergic agonist that stimulates both α1- and α2-adrenergic receptors. It is primarily used locally in the eye or the nose as a vasoconstrictor. Oxymetazoline is found in many over-the-counter short-term nasal spray decongestant products (applied every 12 hours) as well as in ophthalmic drops for the relief of redness of the eyes associated with swimming, colds, and contact lenses. The mechanism of action of oxymetazoline is direct stimulation of α receptors on blood vessels supplying the nasal mucosa and the conjunctiva to reduce blood flow and decrease congestion. Oxymetazoline is absorbed in the systemic circulation regardless of the route of administration and may produce nervousness, headaches, and trouble sleeping. When administered in the nose, burning of the nasal mucosa and sneezing may occur. Rebound congestion and dependence are observed with long-term use. H. Phenylephrine Phenylephrine [fen-ill-EF-reen] is a direct-acting, synthetic adrenergic drug that binds primarily to α1 receptors. It is not a catechol derivative and, therefore, not a substrate for COMT. Phenylephrine is a vasoconstrictor that raises both systolic and diastolic blood pressures. It has no effect on the heart itself but, rather, induces reflex bradycardia when given parenterally. It is often used topically on the nasal mucous membranes and in ophthalmic solutions for mydriasis. Phenylephrine acts as a nasal decongestant (applied every 4 hours) and produces vasoconstriction. The drug is used to raise blood pressure and to terminate episodes of supraventricular tachycardia (rapid heart action arising both from the AV junction and atria). Large doses can cause hypertensive headache and cardiac irregularities. I. Clonidine Clonidine [KLOE-ni-deen] is an α2 agonist that is used in essential hypertension to lower blood pressure because of its action in the CNS (see p. 238). It can be used to minimize the symptoms that accompany withdrawal from opiates, tobacco smoking, and benzodiazepines. Clonidine acts centrally to produce inhibition of sympathetic vasomotor centers, decreasing sympathetic outflow to the periphery. The most common side effects of clonidine are lethargy, sedation, constipation, and xerostomia. These effects generally decrease with therapy progression or dose reduction. Abrupt discontinuance must be avoided to prevent rebound hypertension. Onset of bronchodilation Duration of bronchodilation Epinephrine Isoproterenol Albuterol Salmeterol Terbutaline 0 5 Hours 10 Bronchodilation Figure 6.14 Onset and duration of bronchodilation effects of inhaled adrenergic agonists. J. Metaproterenol Metaproterenol [met-a-proe-TER-a-nole], although chemically similar to isoproterenol, is not a catecholamine, and it is resistant to methylation by COMT. The use of metaproterenol in recent years has decreased due to the availability of longer acting, more selective b2 agonists. K. Albuterol and terbutaline Albuterol [al-BYOO-ter-ole] and terbutaline [ter-BYOO-te-leen] are short-acting b2 agonists used primarily as bronchodilators and administered by a metered-dose inhaler (Figure 6.14). Terbutaline is used offlabel as a uterine relaxant to suppress premature labor. Side effects of b2 agonists are primarily due to excessive b2-receptor activation. One of the most common side effects of these agents is tremor, but patients Pharm 5th 3-21-11.indb 81 3/21/11 2:21:22 PM 82 6. Adrenergic Agonists tend to develop tolerance to this effect. Other side effects include restlessness, apprehension, and anxiety. The adverse effects may be reduced by starting with low doses and then titrating to higher doses as tolerance to the tremor develops. Systemically administered agents may cause tachycardia or arrhythmia (due to b1-receptor activation), especially in patients with underlying cardiac disease. Adverse cardio vascular effects also increase if patients are using monoamine oxidase inhibitors (MAOIs) concomitantly. It is recommended that there be about a 2-week gap between the use of a MAOI and a b2-receptor agonist. L. Salmeterol and formoterol Salmeterol [sal-ME-ter-ole] and formoterol [for-MOH-ter-ole] are b2-adrenergic selective agonists that are long-acting bronchodilators. A single dose by a metered-dose inhalation device, such as a dry powder inhaler, provides sustained bronchodilation over 12 hours, compared with less than 3 hours for albuterol. Unlike formoterol, however, salmeterol has a somewhat delayed onset of action (see Figure 6.14). These agents are not recommended as monotherapy but are highly efficacious when combined with a corticosteroid. Salmeterol and formoterol are the agents of choice for treating nocturnal asthma in symptomatic patients taking other asthma medications. Inhaled b2-receptor agonists should not be used in excess. Death has been reported in overuse of these medications. V. INDIRECT-ACTING ADRENERGIC AGONISTS Indirect-acting adrenergic agonists cause norepinephrine release from presynaptic terminals or inhibit the uptake of nor-epinephrine (see Figure 6.8). They potentiate the effects of norepinephrine produced endogenously, but these agents do not directly affect postsynaptic receptors. A. Amphetamine The marked central stimulatory action of amphetamine [am-FET-ameen] is often mistaken by drug abusers as its only action. However, the drug can also increase blood pressure significantly by α1-agonist action on the vasculature as well as b-stimulatory effects on the heart. Its peripheral actions are mediated primarily through the blockade of norepinephrine uptake and cellular release of stored catecholamines. Thus, amphetamine is an indirect-acting adrenergic drug. The actions and uses of amphetamine are discussed under stimulants of the CNS (see p. 127). The CNS stimulant effects of amphetamine and its derivatives have led to their use for treating hyperactivity in children, narcolepsy, and appetite control. Its use in pregnancy should be avoided because of adverse effects on the development of the fetus. Dextroamphetamine is the dextrorotatory isomer of amphetamine. Methamphetamine, methylphenidate, and dexmethylphenidate are other drugs closely related in structure or that have effects similar to amphetamine. They are used for similar indications as amphetamine. B. Tyramine Tyramine [TIE-ra-meen] is not a clinically useful drug, but it is important because it is found in fermented foods, such as aged cheese and Chianti wine (see p. 158). It is a normal byproduct of tyrosine metabolism. Normally, it is oxidized by MAO in the gastrointestinal tract, but, if the patient is taking MAOIs, it can precipitate serious vasopressor epi- Pharm 5th 3-21-11.indb 82 3/21/11 2:21:23 PM VI. Mixed-Action Adrenergic Agonists 83 sodes. Like amphetamines, tyramine can enter the nerve terminal and displace stored norepinephrine. The released catecholamine then acts on adrenoceptors. C. Cocaine Cocaine [koe-KANE] is unique among local anesthetics in having the ability to block the Na^{+}/K^{+}-activated ATPase (required for cellular uptake of norepinephrine) on the cell membrane of the adrenergic neuron. Consequently, norepinephrine accumulates in the synaptic space, resulting in enhancement of sympathetic activity and potentiation of the actions of epinephrine and norepinephrine. Therefore, small doses of the catecholamines produce greatly magnified effects in an individual taking cocaine as compared to those in one who is not. In addition, the duration of action of epinephrine and norepinephrine is increased. Like amphetamines, it can increase blood pressure by α1-agonist actions and β-stimulatory effects. [Note: Cocaine as a CNS stimulant and drug of abuse is discussed on pp. 120–121.] Arrhythmias VI. MIXED-ACTION ADRENERGIC AGONISTS Mixed-action drugs induce the release of norepinephrine from presynaptic terminals, and they activate adrenergic receptors on the postsynaptic membrane (see Figure 6.8). Headache A. Ephedrine and pseudoephedrine Ephedrine [eh-FED-rin] and pseudoephedrine [soo-doe-eh-FED-rin] are plant alkaloids that are now made synthetically. These drugs are mixedaction adrenergic agents. They not only release stored norepinephrine from nerve endings (see Figure 6.8) but also directly stimulate both α and β receptors. Thus, a wide variety of adrenergic actions ensue that are similar to those of epinephrine, although less potent. Ephedrine and pseudoephedrine are not catechols and are poor substrates for COMT and MAO. Therefore, these drugs have a long duration of action. Ephedrine and pseudoephedrine have excellent absorption orally and penetrate into the CNS, but pseudoephedrine has fewer CNS effects. Ephedrine is eliminated largely unchanged in urine, and pseudoephedrine undergoes incomplete hepatic metabolism before elimination in urine. Ephedrine raises systolic and diastolic blood pressures by vasoconstriction and cardiac stimulation. Ephedrine produces bronchodilation, but it is less potent than epinephrine or isoproterenol in this regard and produces its action more slowly. It has been used in the past for asthma to prevent attacks (rather than to treat the acute attack), although most experts recommend other medications (See Chapter 27). Ephedrine produces a mild stimulation of the CNS. This increases alertness, decreases fatigue, and prevents sleep. It also improves athletic performance. Pseudoephedrine is primarily used orally to treat nasal and sinus congestion and congestion of the eustachian tubes. [Note: The clinical use of ephedrine is declining because of the availability of better, more potent agents that cause fewer adverse effects. Ephedrine-containing herbal supplements (mainly ephedra-containing products) were banned by the U.S. Food and Drug Administration in April 2004 because of life-threatening cardiovascular reactions. Pseudoephedrine has been illegally converted to methamphetamine. Therefore, products containing pseudoephedrine have certain restrictions and must be kept behind the sales counter in the United States. Important characteristics of the adrenergic agonists are summarized in Figures 6.15, 6.16, and 6.17. Pharm 5th 3-21-11.indb 83 Hyperactivity Insomnia Nausea Tremors Figure 6.15 Some adverse effects observed with adrenergic agonists. 3/21/11 2:21:23 PM 84 6. Adrenergic Agonists TISSUE RECEPTOR TYPE ACTION OPPOSING ACTIONS Heart • Sinus and AV • Conduction pathway • Myofibrils β1 Automaticity Cholinergic receptors β1 Conduction velocity, automaticity Cholinergic receptors β1 Contractility, automaticity Vascular smooth muscle β2 Vasodilation α-Adrenergic receptors Bronchial smooth muscle β2 Bronchodilation Cholinergic receptors Kidneys β1 Renin release α1-Adrenergic receptors Liver β2, α1 Glycogenolysis and gluconeogenesis Adipose tissue β3 Lipolysis Skeletal muscle β2 Increased contractility Potassium uptake; glycogenolysis Dilates arteries to skeletal muscle Tremor Eye-ciliary muscle β2 Relaxation Cholinergic receptors GI tract β2 Motility Cholinergic receptors Gall bladder β2 Relaxation Cholinergic receptors Urinary bladder detrusor muscle β2 Relaxation Cholinergic receptors Uterus β2 Relaxation Oxytocin — α2-Adrenergic receptors — Figure 6.16 Summary of β-adrenergic receptors. AV = atrioventricular; GI = gastrointestinal. Pharm 5th 3-21-11.indb 84 3/21/11 2:21:24 PM VI Mixed-Action Adrenergic Agonists 85 DRUG RECEPTOR SPECIFICITY Epinephrine α1, α2 β1, β2 THERAPEUTIC USES Acute asthma Anaphylactic shock In local anesthetics to increase duration of action CATECHOLAMINES Rapid onset of action Norepinephrine α1, α2 β1 Treatment of shock Isoproterenol β1, β2 As a cardiac stimulant Dopamine Dopaminergic α1, β1 Brief duration of action Treatment of congestive heart failure Raise blood pressure Not administered orally Do not penetrate the bloodbrain barrier Treatment of shock Dobutamine β1 Treatment of acute heart failure Oxymetazoline α1 As a nasal decongestant Phenylephrine α1 As a nasal decongestant Raise blood pressure Treatment of paroxysmal supraventricular tachycardia Methoxamine α1 Treatment of supraventricular tachycardia Clonidine α2 Treatment of hypertension Albuterol Terbutaline β2 Treatment of bronchospasm (short acting) Longer duration of action Salmeterol Formoterol β2 Treatment of bronchospasm (long acting) All can be administered orally Amphetamine α, β, CNS As a CNS stimulant in treatment of children with attention deficit syndrome, narcolepsy, and for appetite control Ephedrine Pseudoephedrine α, β, CNS As a nasal decongestant NONCATECHOLAMINES Compared to catecholamines: Raise blood pressure Figure 6.17 Summary of the therapeutic uses of adrenergic agonists. CNS = central nervous system. Pharm 5th 3-21-11.indb 85 3/21/11 2:21:24 PM 86 6. Adrenergic Agonists Study Questions Choose the ONE best answer. 6.1 A 68-year-old man presents to the emergency department with acute heart failure. The patient requires immediate drug therapy to improve his cardiac function. Which one of the following drugs would be most beneficial? A. Albuterol. B. Dobutamine. C. Epinephrine. D. Norepinephrine. E. Phenylephrine. 6.2 Remedies for nasal stuffiness often contain which one of the following drugs? A. Albuterol. B. Atropine. C. Epinephrine. D. Norepinephrine. E. Phenylephrine. 6.3 Which one of the following drugs, when administered intravenously, can decrease blood flow to the skin, increase blood flow to skeletal muscle, and increase the force and rate of cardiac contraction? A. Epinephrine. B. Isoproterenol. C. Norepinephrine. D. Phenylephrine. E. Terbutaline. 6.4 The following circles represent pupillary diameter in one eye prior to and following the topical application of Drug X: Control Drug X Which of the following is most likely to be Drug X? A. Physostigmine. B. Acetylcholine. C. Terbutaline. D. Phenylephrine. E. Isoproterenol. Pharm 5th 3-21-11.indb 86 Correct answer = B. Dobutamine increases cardiac output without significantly increasing heart rate, a complicating condition in heart failure. Because epinephrine can significantly increase heart rate, it is not typically used for acute heart failure. Both norepinephrine and phenylephrine have significant α1-receptor–stimulating properties. The subsequent increase in blood pressure would worsen the heart failure. Albuterol, a β2-selective–receptor agonist, would not significantly improve contractility of the heart. Correct answer = E. Phenylephrine is an a1 agonist that constricts the nasal mucosa, thereby decreasing airway resistance. Norepinephrine and epinephrine also constrict the mucosa but have much too short a duration of action. Albuterol is a β2 agonist and has no effect on mucosal volume. Atropine, a muscarinic antagonist, only dries the mucosa but does not decrease its volume. Correct answer = A. Exogenous epinephrine stimulates α and β receptors equally well, leading to the constriction of blood vessels in tissues such as skin and dilation of other blood vessels in tissues such as skeletal muscle. Epinephrine also has positive chronotropic and inotropic effects in the heart. Exogenous norepinephrine constricts blood vessels only and causes a reflex bradycardia because of its strong α-adrenergic–stimulating properties. Phenylephrine has similar effects. Isoproterenol stimulates β receptors and would not cause vasoconstriction of cutaneous vessels. Correct answer = D. Phenylephrine is the only drug in the list that causes mydriasis, because it stimulates α receptors. Both physostigmine and acetylcholine cause pupillary constriction. The β-blockers terbutaline and isoproterenol do not influence pupillary diameter. 3/21/11 2:21:25 PM Adrenergic Antagonists I. OVERVIEW The adrenergic antagonists (also called blockers or sympatholytic agents) bind to adrenoceptors but do not trigger the usual receptor-mediated intracellular effects. These drugs act by either reversibly or irreversibly attaching to the receptor, thus preventing its activation by endogenous catecholamines. Like the agonists, the adrenergic antagonists are classified according to their relative affinities for α or b receptors in the peripheral nervous system. These drugs will interfere with the functions of the sympathetic nervous system. Numerous adrenergic antagonists have important roles in clinical medicine, primarily to treat diseases associated with the cardiovascular system. [Note: Antagonists that block dopamine receptors are most important in the central nervous system (CNS) and are, therefore, considered in that section (see p. 161).] The receptor-blocking drugs discussed in this chapter are summarized in Figure 7.1. II. α-ADRENERGIC BLOCKING AGENTS Drugs that block α adrenoceptors profoundly affect blood pressure. Because normal sympathetic control of the vasculature occurs in large part through agonist actions on α-adrenergic receptors, blockade of these receptors reduces the sympathetic tone of the blood vessels, resulting in decreased peripheral vascular resistance. This induces a reflex tachycardia resulting from the lowered blood pressure. The magnitude of the response depends on the sympathetic tone of the individual when the agent is given. Effects are more profound in an individual who is standing and less in a person who is supine. Hypovolemic patients will also have a more marked response as well. [Note: b receptors, including b1 adrenoceptors on the heart, are not affected by α blockade.] The α-adrenergic blocking agents, phenoxybenzamine and phentolamine, have limited clinical applications. 7 a BLOCKERS Alfuzosin UROXATRAL Doxazosin CARDURA Phenoxybenzamine DIBENZYLINE Phentolamine REGITINE Prazosin MINIPRESS Tamsulosin FLOMAX Terazosin HYTRIN Yohimbine YOCON b BLOCKERS Acebutolol SECTRAL Atenolol TENORMIN Betaxolol BETOPTIC-S, KERLONE Bisoprolol ZEBETA Carteolol CARTROL Carvedilol COREG, COREG CR Esmolol BREVIBLOC Labetalol TRANDATE Metoprolol LOPRESSOR, TOPROL-XL Nadolol CORGARD Nebivolol BYSTOLIC Penbutolol LEVATOL Pindolol VISKEN Propranolol INDERAL LA, INNOPRAN XL Timolol BETIMOL, ISTALOL, TIMOPTIC DRUGS AFFECTING NEUROTRANSMITTER UPTAKE OR RELEASE Guanethidine ISMELIN Reserpine SERPASIL A. Phenoxybenzamine Phenoxybenzamine [fen-ox-ee-BEN-za-meen] is nonselective, linking covalently to both α1- and α2-receptors (Figure 7.2). The block is irreversible and noncompetitive, and the only mechanism the body has for overcoming the block is to synthesize new adrenoceptors, which requires a day or longer. Therefore, the actions of phenoxybenzamine last about 24 hours after a single administration. After the drug is injected, a delay of a few hours occurs before α blockade develops. Pharm 5th 3-21-11.indb 87 Figure 7.1 Summary of blocking agents and drugs affecting neurotransmitter uptake or release. 3/21/11 2:21:25 PM 88 7. Adrenergic Antagonists 1. Actions: a. Cardiovascular effects: By blocking α receptors, phenoxybenzamine prevents vasoconstriction of peripheral blood vessels by endogenous catecholamines. The decreased peripheral resistance provokes a reflex tachycardia. Furthermore, the ability to block presynaptic inhibitory α2 receptors in the heart can contribute to an increased cardiac output. [Note: These receptors, when blocked, will result in more norepinephrine release, which stimulates β receptors on the heart, increasing cardiac output.] Thus, the drug has been unsuccessful in maintaining lowered blood pressure in hypertension, and its use has been discontinued for this purpose. Phenoxybenzamine Covalent bond Rapid Effector cell membrane Covalently inactivated α1 -adrenoceptor Figure 7.2 Covalent inactivation of α1 adrenoceptor by phenoxybenzamine. α-Adrenergic blockers have no effect on the actions of isoproterenol, which is a pure β agonist. Catecholamine Untreated control 200 Isoproterenol (mm Hg) 0 200 Epinephrine 0 200 Norepinephrine 0 Pretreatment with an αblocker Pretreatment with a βblocker α-Adrenergic blockers reverse the vasoconstrictive action of epinephrine. Figure 7.3 Summary of effects of adrenergic blockers on the changes in blood pressure induced by isoproterenol, epinephrine, and norepinephrine. Pharm 5th 3-21-11.indb 88 b. Epinephrine reversal: All α-adrenergic blockers reverse the α-agonist actions of epinephrine. For example, the vasoconstrictive action of epinephrine is interrupted, but vasodilation of other vascular beds caused by stimulation of β receptors is not blocked. Therefore, in the presence of phenoxybenzamine, the systemic blood pressure decreases in response to epinephrine (Figure 7.3). [Note: The actions of norepinephrine are not reversed, but are diminished because norepinephrine lacks significant β-agonist action on the vasculature.] Phenoxybenzamine has no effect on the actions of isoproterenol, which is a pure β agonist (see Figure 7.3). 2. Therapeutic uses: Phenoxybenzamine is used in the treatment of pheochromocytoma, a catecholamine-secreting tumor of cells derived from the adrenal medulla. Prior to surgical removal of the tumor, patients are treated with phenoxybenzamine to preclude the hypertensive crisis that can result from manipulation of the tissue. This drug is also useful in the chronic management of these tumors, particularly when the catecholamine-secreting cells are diffuse and, therefore, inoperable. Phenoxybenzamine is sometimes effective in treating Raynaud disease, frostbite, and acrocyanosis. Autonomic hyperreflexia, which predisposes paraplegic patients to strokes, can be managed with phenoxybenzamine. 3. Adverse effects: Phenoxybenzamine can cause postural hypotension, nasal stuffiness, nausea, and vomiting. It may inhibit ejaculation. It also may induce reflex tachycardia, which is mediated by the baroreceptor reflex. Phenoxybenzamine is contraindicated in patients with decreased coronary perfusion. B. Phentolamine In contrast to phenoxybenzamine, phentolamine [fen-TOLE-a-meen] produces a competitive block of α1 and α2 receptors. This drug's action lasts for approximately 4 hours after a single administration. Like phenoxybenzamine, it produces

postural hypotension and causes epinephrine reversal. Phentolamine-induced reflex cardiac stimulation and tachycardia are mediated by the baroreceptor reflex and by blocking the α2 receptors of the cardiac sympathetic nerves. The drug can also trigger arrhythmias and anginal pain, and phentolamine is contraindicated in patients with decreased coronary perfusion. Phentolamine is used for the short-term management of pheochromocytoma. It is also used locally to prevent dermal necrosis and extravasation due to norepinephrine administration as well as being used to treat hypertensive crisis due to abrupt withdrawal of clonidine and from ingesting tyramine-contain- 3/21/11 2:21:26 PM II. α-Adrenergic Blocking Agents 89 ing foods in patients taking nonselective monoamine oxidase inhibitors. Phentolamine is now rarely used for the treatment of impotence (it can be injected intracavernosally to produce vasodilation of penile arteries). C. Prazosin, terazosin, doxazosin, tamsulosin, and alfuzosin Prazosin [PRAY-zoe-sin], terazosin [ter-AY-zoe-sin], doxazosin [dox-AYzoe-sin], and tamsulosin [tam-SUE-loh-sin] are selective competitive blockers of the α1 receptor. In contrast to phenoxybenzamine and phentolamine, the first three drugs are useful in the treatment of hypertension. Tamsulosin and alfuzosin [al-FYOO-zoe-sin] are indicated for the treatment of benign prostatic hypertrophy (also known as benign prostatic hyperplasia, or BPH). Metabolism leads to inactive products that are excreted in urine except for those of doxazosin, which appear in feces. Doxazosin is the longest acting of these drugs. 1. Cardiovascular effects: All of these agents decrease peripheral vascular resistance and lower arterial blood pressure by causing the relaxation of both arterial and venous smooth muscle. Tamsulosin has the least effect on blood pressure. These drugs, unlike phenoxybenzamine and phentolamine, cause minimal changes in cardiac output, renal blood flow, and the glomerular filtration rate. 2. Therapeutic uses: Individuals with elevated blood pressure who have been treated with one of these drugs do not become tolerant to its action. However, the first dose of these drugs produces an exaggerated orthostatic hypotensive response (Figure 7.4) that can result in syncope (fainting). This action, termed a “first-dose” effect, may be minimized by adjusting the first dose to one-third or onefourth of the normal dose and by giving the drug at bedtime. These drugs improve lipid profiles and glucose metabolism in hypertensive patients. Prazosin and others are used to treat congestive heart failure. By dilating both arteries and veins, these agents decrease preload and afterload, leading to an increase in cardiac output and a reduction in pulmonary congestion. Unlike β blockers, these agents have not been found to prolong life in patients with heart failure. The α1-receptor antagonists have been used as an alternative to surgery in patients with symptomatic BPH (Figure 7.5). Blockade of the α receptors decreases tone in the smooth muscle of the bladder neck and prostate and improves urine flow. Tamsulosin is an inhibitor (with some selectivity) of the α1A receptors found on the smooth muscle of the prostate. This selectivity accounts for tamsulosin’s relatively minimal effect on blood pressure and its use in BPH, though dizziness (orthostasis) may rarely occur. [Note: Finasteride and dutasteride α1-ADRENERGIC ANTAGONISTS Figure 7.4 First dose of α1 receptor blocker may produce an orthostatic hypotensive response that can result in syncope (fainting). 5 α-REDUCTASE INHIBITORS Decrease in prostate size No Yes Peak onset 2–4 weeks 6–12 months Decrease in PSA No Yes Sexual dysfunction + ++ Hypotensive effects ++ – Commonly used drugs Tamsulosin and alfuzosin Finasteride and dutasteride Figure 7.5 Comparisons of treatments for benign prostatic hyperplasia. PSA = Prostate specific antigen. Pharm 5th 3-21-11.indb 89 3/21/11 2:21:27 PM 90 7. Adrenergic Antagonists BP Orthostatic hypotension Tachycardia Vertigo inhibit 5α-reductase, preventing the conversion of testosterone to dihydrotestosterone. These drugs are approved for the treatment of BPH by reducing prostate volume in selected patients (see p. 329).] 3. Adverse effects: α1 Blockers may cause dizziness, a lack of energy, nasal congestion, headache, drowsiness, and orthostatic hypotension (although to a lesser degree than that observed with phenoxybenzamine and phentolamine). These agents do not trigger reflex tachycardia to the same extent as the nonselective α-receptor blockers. An additive antihypertensive effect occurs when prazosin is given with either a diuretic or a b blocker, thereby necessitating a reduction in its dose. Due to a tendency to retain sodium (Na^+) and fluid, prazosin is frequently used along with a diuretic. These drugs do not affect male sexual function as severely as phenoxybenzamine and phentolamine. However, by blocking α receptors in the ejaculatory ducts and impairing smooth muscle contraction, inhibition of ejaculation and retrograde ejaculation have been reported. Tamsulosin has a caution about “floppy iris syndrome,” a condition in which the iris billows in response to intraoperative eye surgery. Figure 7.6 summarizes some adverse effects observed with α blockers. D. Yohimbine Sexual dysfunction Figure 7.6 Some adverse effects commonly observed with nonselective α-adrenergic blocking agents. Esmolol 10 min Acebutolol 3–4 hr Pindolol 3–4 hr Metoprolol 3–4 hr Propranolol 4–6 hr Timolol 4–6 hr Labetalol 4–6 hr Carvedilol 7–10 hr Nebivolol 10–30 hr Nadolol 14–24 hr Yohimbine [yo-HIM-bean] is a selective competitive α2 blocker. It is found as a component of the bark of the yohimbe tree and is sometimes used as a sexual stimulant. [Efficacy of yohimbine for the treatment of impotence has never been clearly demonstrated.] Yohimbine works at the level of the CNS to increase sympathetic outflow to the periphery. It directly blocks α2 receptors and has been used to relieve vasoconstriction associated with Raynaud disease. Yohimbine is contraindicated in CNS and cardiovascular conditions because it is a CNS and cardiovascular stimulant. III. b-ADRENERGIC BLOCKING AGENTS All the clinically available b blockers are competitive antagonists. Non selective b blockers act at both b1 and b2 receptors, whereas cardioselective b antagonists primarily block b1 receptors [Note: There are no clinically useful b2 antagonists.] These drugs also differ in intrinsic sympathomimetic activity, in CNS effects, blockade of sympathetic receptors, vasodilation, and in pharmacokinetics (Figure 7.7). Although all b blockers lower blood pressure in hypertension, they do not induce postural hypotension, because the α adrenoceptors remain functional. Therefore, normal sympathetic control of the vasculature is maintained. b blockers are also effective in treating angina, cardiac arrhythmias, myocardial infarction, congestive heart failure, hyperthyroidism, and glaucoma as well as serving in the prophylaxis of migraine headaches. [Note: The names of all b blockers end in “-olol” except for labetalol and carvedilol.] A. Propranolol: A nonselective β antagonist Propranolol [proe-PRAN-oh-lole] is the prototype b-adrenergic antagonist and blocks both b1 and b2 receptors with equal affinity. Sustainedrelease preparations for once-a-day dosing are available. 1. Actions: Figure 7.7 Elimination half-lives for some β blockers. Pharm 5th 3-21-11.indb 90 a. Cardiovascular: Propranolol diminishes cardiac output, having both negative inotropic and chronotropic effects (Figure 7.8). It directly depresses sinoatrial and atrioventricular activity. 3/21/11 2:21:28 PM III. β-Adrenergic Blocking Agents The resulting bradycardia usually limits the dose of the drug. During exercise or stress, when the sympathetic nervous system is activated, β blockers will attenuate the expected increase in heart rate. Cardiac output, work, and oxygen consumption are decreased by a blockade of β1 receptors, and these effects are useful in the treatment of angina (see p. 222). The β blockers are effective in attenuating supraventricular cardiac arrhythmias, but generally are not effective against ventricular arrhythmias (except those induced by exercise). At high doses, propranolol may cause a membrane-stabilizing effect on the heart, but this effect is insignificant if the drug is given at therapeutic doses. b. Peripheral vasoconstriction: Blockade of β receptors prevents β2-mediated vasodilation (see Figure 7.8). The reduction in cardiac output leads to decreased blood pressure. This hypotension triggers a reflex peripheral vasoconstriction that is reflected in reduced blood flow to the periphery. In patients with hypertension, total peripheral resistance returns to normal or decreases with long term use of propranolol. On balance, there is a gradual reduction of both systolic and diastolic blood pressures in hypertensive patients. No postural hypotension occurs, because the α1-adrenergic receptors that control vascular resistance are unaffected. 91 Propranolol β2 Bronchoconstriction Propranolol β2 Reflex peripheral vasoconstriction c. Bronchoconstriction: Blocking β2 receptors in the lungs of susceptible patients causes contraction of the bronchiolar smooth muscle (see Figure 7.8). This can precipitate a respiratory crisis in patients with chronic obstructive pulmonary disease (COPD) or asthma. Therefore, β blockers, particularly, nonselective ones, are contraindicated in patients with COPD or asthma. d. Increased Na^+ retention: Reduced blood pressure causes a decrease in renal perfusion, resulting in an increase in Na^+ retention and plasma volume (see Figure 7.8). In some cases, this compensatory response tends to elevate the blood pressure. For these patients, β blockers are often combined with a diuretic to prevent Na^+ retention. e. Disturbances in glucose metabolism: β Blockade leads to decreased glycogenolysis and decreased glucagon secretion. Therefore, if a patient with type 1 (formerly insulin-dependent) diabetes is to be given propranolol, very careful monitoring of blood glucose is essential, because pronounced hypoglycemia may occur after insulin injection. β Blockers also attenuate the normal physiologic response to hypoglycemia. f. Blocked action of isoproterenol: All β blockers, including propranolol, have the ability to block the actions of isoproterenol on the cardiovascular system. Thus, in the presence of a β blocker, isoproterenol does not produce either the typical cardiac stimulation or reductions in mean arterial pressure and diastolic pressure (see Figure 7.3). [Note: In the presence of a β blocker, epinephrine no longer lowers diastolic blood pressure or stimulates the heart, but its vasoconstrictive action (mediated by α receptors) remains unimpaired. The actions of norepinephrine on the cardiovascular system are mediated primarily by α receptors and are, therefore, unaffected.] Pharm 5th 3-21-11.indb 91 Na^+ Increased sodium retention Propranolol Rate Force β1 Decreased cardiac output Propranolol Acebutolol Atenolol Metoprolol Nebivolol Figure 7.8 Actions of propranolol and other β blockers. 3/21/11 2:21:30 PM 92 7. Adrenergic Antagonists 2. Pharmacokinetics: After oral administration, propranolol is almost completely absorbed because it is highly lipophilic. It is subject to first-pass effect, and only about 25 percent of an administered dose reaches the circulation. The volume of distribution of orally administered propranolol is quite large (4 liters/Kg), and the drug readily crosses the blood-brain barrier. Propranolol is extensively metabolized, and most metabolites are excreted in the urine. 3. Therapeutic effects: a. Hypertension: Propranolol does not reduce blood pressure in people with normal blood pressure. Propranolol lowers blood pressure in hypertension by several different mechanisms of action. Decreased cardiac output is the primary mechanism, but inhibition of renin release from the kidney, decrease in total peripheral resistance with long term use, and decreased sympathetic outflow from the CNS also contribute to propranolol’s antihypertensive effects (see p. 233). b. Migraine: Propranolol is also effective in reducing migraine episodes when used prophylactically (see p. 556). b Blockers are valuable in the treatment of chronic migraine, because these agents decrease the incidence and severity of the attacks. [Note: During an attack, sumatriptan is used, as well as other drugs.] c. Hyperthyroidism: Propranolol and other b blockers are effective in blunting the widespread sympathetic stimulation that occurs in hyperthyroidism. In acute hyperthyroidism (thyroid storm), b blockers may be lifesaving in protecting against serious cardiac arrhythmias. d. Angina pectoris: Propranolol decreases the oxygen requirement of heart muscle and, therefore, is effective in reducing the chest pain on exertion that is common in angina. Propranolol is, thus, useful in the chronic management of stable angina but not for acute treatment. Tolerance to moderate exercise is increased, and this is measurable by improvement in the electrocardiogram. However, treatment with propranolol does not allow strenuous physical exercise such as tennis. e. Myocardial infarction: Propranolol and other b blockers have a protective effect on the myocardium. Thus, patients who have had one myocardial infarction appear to be protected against a second heart attack by prophylactic use of b blockers. In addition, administration of a b blocker immediately following a myocardial infarction reduces infarct size and hastens recovery. The mechanism for these effects may be a blocking of the actions of circulating catecholamines, which would increase the oxygen demand in an already ischemic heart muscle. Propranolol also reduces the incidence of sudden arrhythmic death after myocardial infarction. 4. Adverse effects: a. Bronchoconstriction: Propranolol has a serious and potentially lethal side effect when administered to a patient with asthma (Figure 7.9). An immediate contraction of the bronchiolar smooth Pharm 5th 3-21-11.indb 92 3/21/11 2:21:30 PM III. β-Adrenergic Blocking Agents muscle prevents air from entering the lungs. Death by asphyxiation has been reported for patients with asthma whom were inadvertently administered the drug. Therefore, propranolol must never be used in treating any individual with COPD or asthma. b. Arrhythmias: Treatment with β blockers must never be stopped quickly because of the risk of precipitating cardiac arrhythmias, which may be severe. The β blockers must be tapered off gradually for at least a few weeks. Long-term treatment with a β antagonist leads to up-regulation of the β receptor. On suspension of therapy, the increased receptors can worsen angina or hypertension. c. Sexual impairment: Because sexual function in the male occurs through α-adrenergic activation, β blockers do not affect normal ejaculation or the internal bladder sphincter function. On the other hand, some men do complain of impaired sexual activity. The reasons for this are not clear and may be independent of β-receptor blockade. d. Metabolic disturbances: β Blockade leads to decreased glycogenolysis and decreased glucagon secretion. Fasting hypoglycemia may occur. In addition, β blockers can prevent the counterregulatory effects of catecholamines during hypoglycemia. The perception of symptoms such as tremor, tachycardia, and nervousness are blunted. [Note: Cardioselective β blockers are preferred in treating asthma patients who use insulin (see β1-selective antagonists).] A major role of β receptors is to mobilize energy molecules such as free fatty acids. [Note: Lipases in fat cells are activated, leading to the metabolism of triglycerides into free fatty acids.] Patients administered nonselective β blockers have increased low-density lipoprotein (“bad” cholesterol), increased triglycerides, and reduced high-density lipoprotein (“good” cholesterol). On the other hand, the serum lipid profile in dyslipidemia patients improves with the use of β1-selective antagonists such as metoprolol. 93 Fatigue Bronchoconstriction Sexual dysfunction Arrhythmias (upon abrupt withdrawal) Figure 7.9 Adverse effects commonly observed in individuals treated with propranolol. e. CNS effects: Propranolol has numerous CNS-mediated effects, including depression, dizziness, lethargy, fatigue, weakness, visual disturbances, hallucinations, short-term memory loss, emotional lability, vivid dreams (including nightmares), decreased performance, and depression manifested by insomnia. f. Drug interactions: Drugs that interfere with, or inhibit, the metabolism of propranolol, such as cimetidine, fluoxetine, paroxetine, and ritonavir, may potentiate its antihypertensive effects. Conversely, those that stimulate or induce its metabolism, such as barbiturates, phenytoin, and rifampin, can decrease its effects. B. Timolol and nadolol: Nonselective β antagonists Timolol [TIM-o-lole] and nadolol [NAH-doh-lole] also block β1- and β2adrenoceptors and are more potent than propranolol. Nadolol has a very long duration of action (see Figure 7.7). Timolol reduces the production of aqueous humor in the eye. It is used topically in the treatment of chronic open-angle glaucoma and, occasionally, for systemic treatment of hypertension. Pharm 5th 3-21-11.indb 93 3/21/11 2:21:31 PM 94 7. Adrenergic Antagonists CLASS OF DRUG DRUG NAMES MECHANISM OF ACTION β-Adrenergic antagonists Betaxolol, carteolol, levobunolol, (topical) metipranolol, timolol SIDE EFFECTS Decrease of aqueous humor production Ocular irritation; contraindicated in patients with asthma, obstructive airway disease, bradycardia, and congestive heart failure. α-Adrenergic agonists (topical) Apraclonidine, brimonidine Decrease of aqueous humor production and increase of aqueous outflow Red eye and ocular irritation, allergic reactions, malaise, and headache. Cholinergic agonists (topical) Pilocarpine, carbachol Increase of aqueous outflow Eye or brow pain, increased myopia, and decreased vision. Prostaglandin-like analogues (topical) Latanoprost, travoprost, bimatoprost Increase of aqueous humor outflow Red eye and ocular irritation, increased iris pigmentation, and excessive hair growth of eye lashes. Carbonic anhydrase inhibitors (topical and systemic) Dorzolamide and brinzolamide (topical), acetazolamide and methazolamide (oral) Decrease of aqueous humor production Transient myopia, nausea, diarrhea, loss of appetite and taste, and renal stones (oral drugs). Figure 7.10 Classes of drugs used to treat glaucoma. 1. Treatment of glaucoma: b Blockers, such as topically applied timolol, betaxolol, or carteolol are effective in diminishing intraocular pressure in glaucoma. This occurs by decreasing the secretion of aqueous humor by the ciliary body. Many patients with glaucoma have been maintained with these drugs for years. These drugs neither affect the ability of the eye to focus for near vision nor change pupil size, as do the cholinergic drugs. When administered to the eye, the onset is about 30 minutes, and the effects last for 12 to 24 hours. However, in an acute attack of glaucoma, pilocarpine is still the drug of choice. The b blockers are only used to treat this disease chronically. Other agents used in the treatment of glaucoma are summarized in Figure 7.10 C. Acebutolol, atenolol, metoprolol, bisoprolol, betaxolol, nebivolol, and esmolol: Selective β1 antagonists Drugs that preferentially block the b1 receptors have been developed to eliminate the unwanted bronchoconstrictor effect (b2 effect) of propran olol seen among asthma patients. Cardioselective b blockers, such as acebutolol [a-se-BYOO-toe-lole], atenolol [a-TEN-oh-lole], and metoprolol [me-TOE-proe-lole], antagonize b1 receptors at doses 50- to 100-fold less than those required to block b2 receptors. This cardioselectivity is, thus, most pronounced at low doses and is lost at high doses. [Note: Acebutolol has some intrinsic agonist activity.] 1. Actions: These drugs lower blood pressure in hypertension and increase exercise tolerance in angina (see Figure 7.8). Esmolol [EZ-moelole] has a very short lifetime (see Figure 7.7) due to metabolism of an ester linkage. It is only given intravenously if required during surgery or diagnostic procedures (for example, cystoscopy). In contrast to propranolol, the cardiospecific blockers have relatively little effect on pulmonary function, peripheral resistance, and carbohydrate metabolism. Nevertheless, asthma patients treated with these agents must Pharm 5th 3-21-11.indb 94 3/21/11 2:21:31 PM III. b-Adrenergic Blocking Agents be carefully monitored to make certain that respiratory activity is not compromised. Nebivolol also has vasodilator properties mediated by nitric oxide. 2. Therapeutic use in hypertension: The cardioselective b blockers are useful in hypertensive patients with impaired pulmonary function. Because these drugs have less effect on peripheral vascular b2 receptors, coldness of extremities, a common side effect of b-blocker therapy, is less frequent. Cardioselective b blockers are useful in diabetic hypertensive patients who are receiving insulin or oral hypoglycemic agents. D. Pindolol and acebutolol: Antagonists with partial agonist activity 1. Actions: a. Cardiovascular: Acebutolol (b1-selective antagonist) and pindolol (nonselective b blocker) [PIN-doe-lole] are not pure antagonists. Instead, they have the ability to weakly stimulate both b1 and b2 receptors (Figure 7.11) and are said to have intrinsic sympathomimetic activity (ISA). These partial agonists stimulate the b receptor to which they are bound, yet they inhibit stimulation by the more potent endogenous catecholamines, epinephrine and norepinephrine. The result of these opposing actions is a muchdiminished effect on cardiac rate and cardiac output compared to that of b blockers without ISA. b. Decreased metabolic effects: Blockers with ISA minimize the disturbances of lipid and carbohydrate metabolism that are seen with other b blockers. For example, these agents do not decrease plasma HDL levels. 2. Therapeutic use in hypertension: b blockers with ISA are effective in hypertensive patients with moderate bradycardia, because a further decrease in heart rate is less pronounced with these drugs. Carbohydrate metabolism is less affected with acebutolol and pindolol than it is with propranolol, making those agents valuable in the treatment of diabetic patients. [Note: The b blockers with ISA are not used as antiarrhythmic agents due to their partial agonist effect.] Figure 7.12 summarizes some of the indications for b blockers. 95 A Agonists (for example, epinephrine) β1 and β2 Receptor β1 and β2 Receptors activated CELLULAR EFFECTS B Antagonists (for example, propranolol) Epinephrine β1 and β2 Receptors blocked but not activated C Partial agonists (for example, pindolol and acebutolol) E. Labetalol and carvedilol: Antagonists of both α and β adrenoceptors 1. Actions: Labetalol [lah-BET-a-lole] and carvedilol [CAR-ve-dil-ol] are b blockers with concurrent α1-blocking actions that produce peripheral vasodilation, thereby reducing blood pressure. They contrast with the other b blockers that produce peripheral vasoconstriction, and these agents are, therefore, useful in treating hypertensive patients for whom increased peripheral vascular resistance is undesirable. They do not alter serum lipid or blood glucose levels. Carvedilol also decreases lipid peroxidation and vascular wall thickening, effects that have benefit in heart failure. 2. Therapeutic use in hypertension and heart failure: Labetalol is useful for treating the elderly or black hypertensive patient in whom increased peripheral vascular resistance is undesirable. [Note: In general, black hypertensive patients are not well controlled with b block- Pharm 5th 3-21-11.indb 95 β1 and β2 Receptors partially activated but unable to respond to more potent catecholamines DECREASED CELLULAR EFFECTS Figure 7.11 Comparison of agonists, antagonists, and partial agonists of β adrenoceptors. 3/21/11 2:21:32 PM 96 7. Adrenergic Antagonists Hypertension Propranolol, metoprolol, and other β blockers reduce cardiac output and renin secretion. Glaucoma Timolol and other β blockers reduce secretion of aqueous humor. Migraine Propranolol provides a prophylactic effect. ers.] Labetalol may be employed as an alternative to methyldopa in the treatment of pregnancy-induced hypertension. Intravenous labetalol is also used to treat hypertensive emergencies, because it can rapidly lower blood pressure (see p. 240). Acute administration of β blockers can trigger congestive heart failure or worsen the condition. However, large clinical trials have shown clinical benefits of carvedilol as well as metoprolol and bisoprolol in patients with stable chronic heart failure. These agents have also been shown to reduce mortality and hospitalization in this population. Carvedilol also used to prevent cardiovascular mortalities in patients with heart failure. 3. Adverse effects: Orthostatic hypotension and dizziness are associated with α1 blockade. Figure 7.13 summarizes the receptor specificities and uses of the β-adrenergic antagonists. IV. DRUGS AFFECTING NEUROTRANSMITTER RELEASE OR UPTAKE As noted on p. 127 some agonists, such as amphetamine and tyramine, do not act directly on the adrenoceptor. Instead, they exert their effects indirectly on the adrenergic neuron by causing the release of neurotransmitters from storage vesicles. Similarly, some agents act on the adrenergic neuron, either to interfere with neurotransmitter release or to alter the uptake of the neurotransmitter into the adrenergic nerve. However, due to the advent of newer and more effective agents with fewer side effects, these agents are seldom used therapeutically. These agents are included in this chapter due to their unique mechanisms of action and historical value. A. Reserpine Thyrotoxicosis Propranolol reduces cardiac rate and potential for arrhythmias. Arrhythmia prophylaxis after myocardial infarction Propranolol and metoprolol reduce cardiac output and renin secretion. Supraventricular tachycardias Propranolol and esmolol slow AV conduction velocity. Angina pectoris Propranolol, nadolol, and other β blockers reduce cardiac rate and force. Figure 7.12 Some clinical applications of β blockers. AV = atrioventricular. Pharm 5th 3-21-11.indb 96 Reserpine [re-SER-peen], a plant alkaloid, blocks the Mg^{2+}/adenosine triphosphate–dependent transport of biogenic amines, norepinephrine, dopamine, and serotonin from the cytoplasm into storage vesicles in the adrenergic nerves of all body tissues. This causes the ultimate depletion of biogenic amines. Sympathetic function, in general, is impaired because of decreased release of norepinephrine. The drug has a slow onset, a long duration of action, and effects that persist for many days after discontinuation. B. Guanethidine Guanethidine [gwahn-ETH-i-deen] blocks the release of stored norepinephrine as well as displaces norepinephrine from storage vesicles (thus producing a transient increase in blood pressure). This leads to gradual depletion of norepinephrine in nerve endings except for those in the CNS. Guanethidine commonly causes orthostatic hypotension and interferes with male sexual function. Supersensitivity to norepinephrine due to depletion of the amine can result in hypertensive crisis in patients with pheochromocytoma. C. Cocaine Cocaine [KOE-kane] is a widely available and highly addictive drug. The primary mechanism of action underlying the central and peripheral effects of cocaine is blockade of reuptake of the monoamines (norepinephrine, serotonin, and dopamine) into the presynaptic terminals from which these neurotransmitters are released (Figure 10.6). This blockade is caused by cocaine binding to the monoaminergic reuptake 3/21/11 2:21:37 PM IV. Drugs Affecting Neurotransmitter Release Or Uptake DRUG RECEPTOR SPECFICITY 97 THERAPEUTIC USES Propranolol β1, β2 Hypertension Migraine Hyperthyroidism Angina pectoris Myocardial infarction Nadolol β1, β2 Hypertension Timolol β1, β2 Glaucoma, hypertension Acebutolol 1 Atenolol Esmolol Metoprolol β1 Hypertension Nebivolol β1, NO Hypertension Pindolol 1 β1, β2 Hypertension Carvedilol Labetalol α1, β1, β2 Hypertension Congestive heart failure Figure 7.13 Summary of β-adrenergic antagonists. NO = nitric oxide. 1Acebutolol and pindolol are partial agonists. transporters and, thus, potentiates and prolongs the CNS and peripheral actions of these monoamines. In particular, the prolongation of dopaminergic effects in the brain’s pleasure system (limbic system) produces the intense euphoria that cocaine initially causes. Chronic intake of cocaine depletes dopamine. This depletion triggers the vicious cycle of craving for cocaine that temporarily relieves severe depression. See p. 126 for a more complete discussion of the actions of cocaine. Pharm 5th 3-21-11.indb 97 3/21/11 2:21:37 PM 98 7. Adrenergic Antagonists Study Questions Choose the ONE best answer. 7.1 The graphs below depict the changes in blood pressure caused by the intravenous administration of epinephrine before and after an unknown Drug X. Blood pressure (mm Hg) Untreated control After Drug X 160 120 80 40 Epinephrine Time Epinephrine Which of the following drugs is most likely Drug X? A. Atropine. B. Phenylephrine. C. Physostigmine. D. Prazosin. E. Propranolol. 7.2 A 38-year-old male has recently started monotherapy for mild hypertension. At his most recent office visit, he complains of tiredness and not being able to complete three sets of tennis. Which one of the following drugs is he most likely to be taking for hypertension? A. Albuterol. B. Atenolol. C. Ephedrine. D. Phentolamine. E. Prazosin. 7.3 A 60-year-old asthmatic man comes in for a checkup and complains that he is having some difficulty in “starting to urinate.” Physical examination indicates that the man has a blood pressure of 160/100 mm Hg and a slightly enlarged prostate. Which of the following medications would be useful in treating both of these conditions? A. Doxazosin. B. Labetalol. C. Phentolamine. D. Propranolol. E. Isoproterenol. Pharm 5th 3-21-11.indb 98 Correct answer = D. The dose of epinephrine increased both systolic and diastolic pressures, but because epinephrine dilates some and constricts other vessel beds, the rise in diastolic pressure is not as much. There is a marked increase in the pulse pressure. An α blocker, such as prazosin, prevents the peripheral vasoconstrictor effects of epinephrine, leaving the vasodilator (β2-stimulation) unopposed. This results in a marked decrease in the diastolic pressure coupled with a slight increase in systolic pressure due to increased cardiac output. This phenomenon is known as “epinephrine reversal” and it is characteristic of the effect of α blockers on the cardiovascular effects of epinephrine. None of the other drugs has α-blocking activity and, therefore, cannot produce this interaction. Correct answer = B. Atenolol is a β1 antagonist and is effective in lowering blood pressure in patients with hypertension. Side effects of β blockers include fatigue and exercise intolerance. Albuterol and ephedrine are not antihypertensive medications. Phentolamine and prazosin are antihypertensive drugs, but the side effects of α antagonists are not characterized by these symptoms. Correct answer = A. Doxazosin is a competitive blocker at the α1 receptor and lowers blood pressure. In addition, it blocks the α receptors in the smooth muscle of the bladder neck and prostate to improve urine flow. Labetalol and propranolol, although effective for treating the hypertension, are contraindicated in an asthma patient, and they would not improve urine flow. Phentolamine has too many adverse effects to be used as a antihypertensive agent. Isoproterenol is a β agonist and is not used as an antihypertensive. It would not affect urinary function. 3/21/11 2:21:38 PM UNIT III Drugs Affecting the Central Nervous System 8 Neurodegenerative Diseases I. OVERVIEW Most drugs that affect the central nervous system (CNS) act by altering some step in the neurotransmission process. Drugs affecting the CNS may act presynaptically by influencing the production, storage, release, or termination of action of neurotransmitters. Other agents may activate or block postsynaptic receptors. This chapter provides an overview of the CNS, with a focus on those neurotransmitters that are involved in the actions of the clinically useful CNS drugs. These concepts are useful in understanding the etiology and treatment strategies for the neurodegenerative disorders that respond to drug therapy: Parkinson disease, Alzheimer disease, multiple sclerosis (MS) and amyotrophic lateral sclerosis (ALS) (Figure 8.1). II. NEUROTRANSMISSION IN THE CNS In many ways, the basic functioning of neurons in the CNS is similar to that of the autonomic nervous system described in Chapter 3. For example, transmission of information in the CNS and in the periphery both involve the release of neurotransmitters that diffuse across the synaptic space to bind to specific receptors on the postsynaptic neuron. In both systems, the recognition of the neurotransmitter by the membrane receptor of the postsynaptic neuron triggers intracellular changes. However, several major differences exist between neurons in the peripheral autonomic nervous system and those in the CNS. The circuitry of the CNS is much more complex than that of the autonomic nervous system, and the number of synapses in the CNS is far greater. The CNS, unlike the peripheral autonomic nervous system, contains powerful networks of inhibitory neurons that are constantly active in modulating the rate of neuronal transmission. In addition, the CNS communicates through the use of more than 10 (and perhaps as many as 50) different neurotransmitters. In contrast, the autonomic nervous system uses only two primary neurotransmitters, acetylcholine and norepinephrine. Pharm 5th 3-21-11.indb 99 ANTI-PARKINSON DRUGS Amantadine SYMMETREL Apomorphine APOKYN Benztropine COGENTIN Biperiden AKINETON Bromocriptine PARLODEL, CYCLOSET Carbidopa LODOSYN Entacapone COMTAN Levodopa (w/Carbidopa) SINEMET, PARCOPA Pramipexole MIRAPEX Procyclidine KEMADRIN Rasagiline AZILECT Ropinirole REQUIP Rotigotine not available in U.S Selegiline (Deprenyl) ELDEPRYL, ZELAPAR Tolcapone TASMAR Trihexyphenidyl ARTANE ANTI-ALZHEIMER DRUGS Donepezil ARICEPT Galantamine RAZADYNE Memantine NAMENDA Rivastigmine EXELON Tacrine COGNEX Figure 8.1 Summary of agents used in the treatment of Parkinson disease, Alzheimer disease, multiple sclerosis, and amyotrophic lateral sclerosis. (Figure continues on next page.) 3/21/11 2:21:38 PM 100 8. Neurodegenerative Diseases ANTI-MULTIPLE SCLEROSIS DRUGS III. SYNAPTIC POTENTIALS Azathioprine AZASAN, IMURAN Cyclophosphamide CYTOXAN Dalfampridine AMPYRA Dexamethasone BAYCADRON, DECADRON Fingolimod GILENYA Glatiramer COPAXONE Interferon β1a AVONEX, REBIF Interferon β1b BETASERON, EXTAVIA Mitoxantrone NOVANTRONE Natalizumab TYSABRI Prednisone DELTASONE In the CNS, receptors at most synapses are coupled to ion channels. That is, binding of the neurotransmitter to the postsynaptic membrane receptors results in a rapid but transient opening of ion channels. Open channels allow specific ions inside and outside the cell membrane to flow down their concentration gradients. The resulting change in the ionic composition across the membrane of the neuron alters the postsynaptic potential, producing either depolarization or hyperpolarization of the postsynaptic membrane, depending on the specific ions that move and the direction of their movement. ANTI-ALS DRUGS Riluzole RILUTEK Figure 8.1(continued) Summary of agents used in the treatment of Parkinson disease, Alzheimer disease, multiple sclerosis, and amyotrophic lateral sclerosis (ALS). empty A Receptor (no agonists) Empty receptor is inactive, and the coupled sodium channel is closed. Na^+ POSTSYNAPTIC NEURON MEMBRANE A. Excitatory pathways Neurotransmitters can be classified as either excitatory or inhibitory, depending on the nature of the action they elicit. Stimulation of excitatory neurons causes a movement of ions that results in a depolarization of the postsynaptic membrane. These excitatory postsynaptic potentials (EPSP) are generated by the following: 1) Stimulation of an excitatory neuron causes the release of neurotransmitter molecules, such as glutamate or acetylcholine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of sodium (Na^+) ions. 2) The influx of Na^+ causes a weak depolarization, or EPSP, that moves the postsynaptic potential toward its firing threshold. 3) If the number of stimulated excitatory neurons increases, more excitatory neurotransmitter is released. This ultimately causes the EPSP depolarization of the postsynaptic cell to pass a threshold, thereby generating an all-or-none action potential. [Note: The generation of a nerve impulse typically reflects the activation of synaptic receptors by thousands of excitatory neurotransmitter molecules released from many nerve fibers.] Figure 8.2 shows an example of an excitatory pathway. B. Inhibitory pathways Acetylcholine receptor Sodium channel (closed) B Receptor binding of excitatory neurotransmitter Binding of acetylcholine causes the sodium ion channel to open. Acetylcholine Na^+ Stimulation of inhibitory neurons causes movement of ions that results in a hyperpolarization of the postsynaptic membrane. These inhibitory postsynaptic potentials (IPSP) are generated by the following: 1) Stimulation of inhibitory neurons releases neurotransmitter molecules, such as γ-aminobutyric acid (GABA) or glycine, which bind to receptors on the postsynaptic cell membrane. This causes a transient increase in the permeability of specific ions, such as potassium (K^+) and chloride (Cl^-) ions. 2) The influx of Cl^- and efflux of K^+ cause a weak hyperpolarization, or IPSP, that moves the postsynaptic potential away from its firing threshold. This diminishes the generation of action potentials. Figure 8.3 shows an example of an inhibitory pathway. C. Combined effects of the EPSP and IPSP Acetylcholine receptor Na^+ Na^+ Entry of Na^+ depolarizes the cell and increases neural excitability. Figure 8.2 Binding of the excitatory neurotransmitter, acetylcholine, causes depolarization of the neuron. Pharm 5th 3-21-11.indb 100 Most neurons in the CNS receive both EPSP and IPSP input. Thus, several different types of neurotransmitters may act on the same neuron, but each binds to its own specific receptor. The overall resultant action is due to the summation of the individual actions of the various neurotransmitters on the neuron. The neurotransmitters are not uniformly distributed in the CNS but are localized in specific clusters of neurons, the axons of which may synapse with specific regions of the brain. Many neuronal tracts, thus, seem to be chemically coded, and this may offer greater opportunity for selective modulation of certain neuronal pathways. 3/21/11 2:21:39 PM V. Overview Of Parkinson Disease IV. NEURODEGENERATIVE DISEASES Neurodegenerative diseases of the CNS include Parkinson disease, Alzheimer disease, MS and ALS. These devastating illnesses are characterized by the progressive loss of selected neurons in discrete brain areas, resulting in characteristic disorders of movement, cognition, or both. For example, Alzheimer disease is characterized by the loss of cholinergic neurons in the nucleus basalis of Maynert, whereas Parkinson disease is associated with a loss of dopaminergic neurons in the substantia nigra. The most prevalent of these disorders is Alzheimer disease, estimated to have affected some 4 million people in 2000. The number of cases is expected to increase as the proportion of elderly people in the population increases. V. OVERVIEW OF PARKINSON DISEASE 101 empty A Receptor (no agonists) Empty receptor is inactive, and the coupled chloride channel is closed. Cl^- POSTSYNAPTIC NEURON MEMBRANE GABA receptor Parkinsonism is a progressive neurological disorder of muscle movement, characterized by tremors, muscular rigidity, bradykinesia (slowness in initiating and carrying out voluntary movements), and postural and gait abnormalities. Most cases involve people over the age of 65, among whom the incidence is about 1 in 100 individuals. A. Etiology The cause of Parkinson disease is unknown for most patients. The disease is correlated with destruction of dopaminergic neurons in the substantia nigra with a consequent reduction of dopamine actions in the corpus striatum, parts of the brain’s basal ganglia system that are involved in motor control. The loss of dopamine neurons in the substantia nigra is evidenced by diminished overall uptake of dopamine precursors in this region, which can be visualized using positron-emission tomography and the dopamine analog fluorodopa (Figure 8.4). Genetic factors do not play a dominant role in the etiology of Parkinson disease, although they may exert some influence on an individual’s susceptibility to the disease. It appears increasingly likely that an as-yetunidentified environmental factor may play a role in the loss of dopaminergic neurons. 1. Substantia nigra: The substantia nigra, part of the extrapyramidal system, is the source of dopaminergic neurons (shown as red neurons in Figure 8.5) that terminate in the neostriatum. Each dopaminergic neuron makes thousands of synaptic contacts within the neostriatum and, therefore, modulates the activity of a large number of cells. These dopaminergic projections from the substantia nigra fire tonically rather than in response to specific muscular movements or sensory input. Thus, the dopaminergic system appears to serve as a tonic, sustaining influence on motor activity rather than participating in specific movements. 2. Neostriatum: Normally, the neostriatum is connected to the substantia nigra by neurons (shown as orange in Figure 8.5) that secrete the inhibitory transmitter GABA at their termini in the substantia nigra. In turn, cells of the substantia nigra send neurons (shown as red in Figure 8.5) back to the neostriatum, secreting the inhibitory transmitter dopamine at their termini. This mutual inhibitory pathway normally maintains a degree of inhibition of the two separate areas. In Parkinson disease, destruction of cells in the substantia nigra results in the degeneration of the nerve terminals responsible for Pharm 5th 3-21-11.indb 101 Chloride channel (closed) B Receptor binding of inhibitory neurotransmitter Binding of GABA causes the chloride ion channel to open. Cl^- GABA GABA receptor Cl^- Cl^- Cl^- Cl^- Entry of Cl^- hyperpolarizes the cell, making it more difficult to depolarize and, thereby, reducing neural excitability. Figure 8.3 Binding of the inhibitory neurotransmitter, γ-aminobutyric acid (GABA), causes hyperpolarization of the neuron. 3/21/11 2:21:40 PM 102 8. Neurodegenerative Diseases High FDOPA Low FDOPA Normal High FDOPA secreting dopamine in the neostriatum. Thus, the normal modulating inhibitory influence of dopamine on cholinergic neurons in the neostriatum is significantly diminished, resulting in overproduction or a relative overactivity of acetylcholine by the stimulatory neurons (shown as green in Figure 8.5). This triggers a chain of abnormal signaling, resulting in loss of the control of muscle movements. 3. Secondary parkinsonism: Parkinsonian symptoms infrequently follow viral encephalitis or multiple small vascular lesions. Drugs such as the phenothiazines and haloperidol, whose major pharmacologic action is blockade of dopamine receptors in the brain, may also produce parkinsonian symptoms. These drugs should not be used in Parkinson disease patients. B. Strategy of treatment Low FDOPA Parkinson's disease Figure 8.4 Positron-emission tomographic scan of the brain showing the difference in fluorodopa (FDOPA) levels between those with and without Parkinson’s disease. 2 Loss of the inhibitory effect of dopamine results in more production of acetylcholine, which triggers a chain of abnormal signaling leading to impaired mobility. Connections to muscle through motor cortex and spinal chord Neuron STIMULATORY ACh NEURON NEOSTRIATUM INHIBITORY GABA NEURON INHIBITORY DA NEURON Neuron SUBSTANTIA NIGRA 1 Cell death results in less dopamine release in the neostriatum. Figure 8.5 Role of substantia nigra in Parkinson disease. DA = dopamine; GABA = γ-aminobutyric acid; ACh = acetylcholine. Pharm 5th 3-21-11.indb 102 In addition to an abundance of inhibitory dopaminergic neurons, the neostriatum is also rich in excitatory cholinergic neurons that oppose the action of dopamine (see Figure 8.5). Many of the symptoms of parkinsonism reflect an imbalance between the excitatory cholinergic neurons and the greatly diminished number of inhibitory dopaminergic neurons. Therapy is aimed at restoring dopamine in the basal ganglia and antagonizing the excitatory effect of cholinergic neurons, thus reestablishing the correct dopamine/acetylcholine balance. Because long-term treatment with levodopa is limited by fluctuations in therapeutic responses, strategies to maintain CNS dopamine levels as constant as possible have been devised. VI. DRUGS USED IN PARKINSON DISEASE Currently available drugs offer temporary relief from the symptoms of the disorder, but they do not arrest or reverse the neuronal degeneration caused by the disease. A. Levodopa and carbidopa Levodopa [lee-voe-DOE-pa] is a metabolic precursor of dopamine (Figure 8.6). It restores dopaminergic neurotransmission in the corpus striatum by enhancing the synthesis of dopamine in the surviving neurons of the substantia nigra. In patients with early disease, the number of residual dopaminergic neurons in the substantia nigra (typically about 20 percent of normal) is adequate for conversion of levodopa to dopamine. Thus, in new patients, the therapeutic response to levodopa is consistent, and the patient rarely complains that the drug effects “wear off.” Unfortunately, with time, the number of neurons decreases, and fewer cells are capable of taking up exogenously administered levodopa and converting it to dopamine for subsequent storage and release. Consequently, motor control fluctuation develops. Relief provided by levodopa is only symptomatic, and it lasts only while the drug is present in the body. The effects of levodopa on the CNS can be greatly enhanced by coadministering carbidopa [kar-bi-DOE-pa], a dopa decarboxylase inhibitor that does not cross the blood-brain barrier. 1. Mechanism of action: a. Levodopa: Because parkinsonism results from insufficient dopamine in specific regions of the brain, attempts have been made to replenish the dopamine deficiency. Dopamine itself does not cross the blood-brain barrier, but its immediate precursor, 3/21/11 2:21:42 PM VI. Drugs Used In Parkinson Disease 103 levodopa, is actively transported into the CNS and is converted to dopamine in the brain (see Figure 8.6). Large doses of levodopa are required, because much of the drug is decarboxylated to dopamine in the periphery, resulting in side effects that include nausea, vomiting, cardiac arrhythmias, and hypotension. b. Carbidopa: Carbidopa, a dopa decarboxylase inhibitor, diminishes the metabolism of levodopa in the gastrointestinal tract and peripheral tissues, thereby increasing the availability of levodopa to the CNS. The addition of carbidopa lowers the dose of levodopa needed by four- to fivefold and, consequently, decreases the severity of the side effects arising from peripherally formed dopamine. 2. Actions: Levodopa decreases the rigidity, tremors, and other symptoms of parkinsonism. 3. Therapeutic uses: Levodopa in combination with carbidopa is a potent and efficacious drug regimen currently available to treat Parkinson disease. In approximately two-thirds of patients with Parkinson disease, levodopa–carbidopa treatment substantially reduces the severity of the disease for the first few years of treatment. Patients then typically experience a decline in response during the third to fifth year of therapy. 4. Absorption and metabolism: The drug is absorbed rapidly from the small intestine (when empty of food). Levodopa has an extremely short half-life (1 to 2 hours), which causes fluctuations in plasma concentration. This may produce fluctuations in motor response, which generally correlate with the plasma concentrations of levodopa, or perhaps give rise to the more troublesome “on-off” phenomenon, A. Fate of administered levodopa Tyrosine Tyrosine Dopa Dopa Administered levodopa Dopamine Synaptic vesicle Dopamine Metabolism in peripheral tissues Metabolism in GI tract Undesirable side effects B. Fate of administered levodopa plus carbidopa Neuron Dopamine receptor Administered levodopa Dopa Carbidopa Decreased metabolism in peripheral tissues Decreased metabolism in GI tract Fewer undesirable side effects Figure 8.6 Synthesis of dopamine from levodopa in the absence and presence of carbidopa, an inhibitor of dopamine decarboxylase in the peripheral tissues. GI = gastrointestinal. Pharm 5th 3-21-11.indb 103 3/21/11 2:21:42 PM 104 8. Neurodegenerative Diseases Anorexia FOOD Nausea 5. Adverse effects: a. Peripheral effects: Anorexia, nausea, and vomiting occur because of stimulation of the chemoreceptor trigger zone of the medulla (Figure 8.7). Tachycardia and ventricular extrasystoles result from dopaminergic action on the heart. Hypotension may also develop. Adrenergic action on the iris causes mydriasis, and, in some individuals, blood dyscrasias and a positive reaction to the Coombs test are seen. Saliva and urine are a brownish color because of the melanin pigment produced from catecholamine oxidation. Tachycardia BP Hypotension Psychiatric problems Figure 8.7 Adverse effects of levodopa. Diminished effect due to increased peripheral metabolism Pyridoxine Levodopa MAO inhibitors Hypertensive crisis due to increased catecholamines Figure 8.8 Some drug interactions observed with levodopa. MAO = monoamine oxidase. Pharm 5th 3-21-11.indb 104 in which the motor fluctuations are not related to plasma levels in a simple way. Motor fluctuations may cause the patient to suddenly lose normal mobility and experience tremors, cramps, and immobility. Ingestion of meals, particularly if high in protein, interferes with the transport of levodopa into the CNS. Large, neutral amino acids (for example, leucine and isoleucine) compete with levodopa for absorption from the gut and for transport across the blood-brain barrier. Thus, levodopa should be taken on an empty stomach, typically 45 minutes before a meal. Withdrawal from the drug must be gradual. b. CNS effects: Visual and auditory hallucinations and abnormal involuntary movements (dyskinesias) may occur. These CNS effects are the opposite of parkinsonian symptoms and reflect the overactivity of dopamine at receptors in the basal ganglia. Levodopa can also cause mood changes, depression, psychosis, and anxiety. 6. Interactions: The vitamin pyridoxine (B6) increases the peripheral breakdown of levodopa and diminishes its effectiveness (Figure 8.8). Concomitant administration of levodopa and monoamine oxidase inhibitors (MAOIs), such as phenelzine, can produce a hypertensive crisis caused by enhanced catecholamine production. Therefore, caution is required when they are used simultaneously. In many psychotic patients, levodopa exacerbates symptoms, possibly through the buildup of central catecholamines. In patients with glaucoma, the drug can cause an increase in intraocular pressure. Cardiac patients should be carefully monitored because of the possible development of cardiac arrhythmias. Antipsychotic drugs are generally contraindicated in parkinsonian patients, because these potently block dopamine receptors and produce a parkinsonian syndrome themselves. However low doses of certain “atypical” antipsychotic agents are sometimes used to treat levodopa-induced psychiatric symptoms. B. Selegiline and rasagiline Selegiline [seh-LEDGE-ah-leen], also called deprenyl [DE-pre-nill], selectively inhibits MAO Type B (which metabolizes dopamine) at low to moderate doses but does not inhibit MAO Type A (which metabolizes norepinephrine and serotonin) unless given at above recommended doses, where it loses its selectivity. By, thus, decreasing the metabolism of dopamine, selegiline has been found to increase dopamine levels in the brain (Figure 8.9). Therefore, it enhances the actions of levodopa when these drugs are administered together. Selegiline substantially reduces the required dose of levodopa. Unlike nonselective MAOIs, selegiline at recommended doses has little potential for causing hypertensive crises. However, if selegiline is administered at high doses, the selectivity of the 3/21/11 2:21:43 PM VI. Drugs Used In Parkinson Disease 105 drug is lost, and the patient is at risk for severe hypertension. Selegiline is metabolized to methamphetamine and amphetamine, whose stimulating properties may produce insomnia if the drug is administered later than midafternoon. (See p. 158 for the use of selegiline in treating depression). Rasagiline [ra-SA-gi-leen], an irreversible and selective inhibitor of brain monoamine oxidase Type B, has five times the potency of selegiline. Unlike selegiline, rasagiline is not metabolized to an amphetaminelike substance. Levels of dopamine increase Dopamine MAO B Selegiline Metabolites C. Catechol-O-methyltransferase inhibitors Normally, the methylation of levodopa by catechol-O-methyltransferase (COMT) to 3-O-methyldopa is a minor pathway for levodopa metabolism. However, when peripheral dopamine decarboxylase activity is inhibited by carbidopa, a significant concentration of 3-O-methyldopa is formed that competes with levodopa for active transport into the CNS (Figure 8.10). Inhibition of COMT by entacapone [en-TA-ka-pone] or tolcapone [TOLE-ka-pone] leads to decreased plasma concentrations of 3-O-methyldopa, increased central uptake of levodopa, and greater concentrations of brain dopamine. Both of these agents have been demonstrated to reduce the symptoms of “wearing-off ” phenomena seen in patients on levodopa–carbidopa. Entacapone and tolcapone are nitrocatechol derivatives that selectively and reversibly inhibit COMT. The two drugs differ primarily in their pharmacokinetics and in some adverse effects. Figure 8.9 Action of selegiline (deprenyl) in dopamine metabolism. MAO B = monoamine oxidase Type B. 1. Pharmacokinetics: Oral absorption of both drugs occurs readily and is not influenced by food. They are extensively bound to plasma albumin (>98 percent), with limited volumes of distribution. Tolcapone differs from entacapone in that the former penetrates the blood-brain barrier and inhibits COMT in the CNS. However, the inhibition of COMT in the periphery appears to be the primary therapeutic action. Tolcapone has a relatively long duration of action (probably due to its affinity for the enzyme) compared to entacapone, which requires more frequent dosing. Both drugs are extensively metabolized and eliminated in feces and urine. Dosage may need to be adjusted in patients with moderate or severe cirrhosis. 2. Adverse effects: Both drugs exhibit adverse effects that are observed in patients taking levodopa–carbidopa, including diarrhea, postural hypotension, nausea, anorexia, dyskinesias, hallucinations, A When peripheral dopamine decarboxylase activity is inhibited by carbidopa, a significant concentration of 3-O-methyldopa is formed, which competes with levodopa for active transport into the CNS. B Inhibition of COMT by entacapone leads to decreased plasma concentrations of 3-O-methyldopa, increased central uptake of levodopa, and greater concentrations of brain dopamine. 3-O-Methyldopa 3-O-Methyldopa COMT Administered levodopa Entacapone Levodopa Carbidopa Decreased metabolism in GI tract and peripheral tissues Dopa in CNS Administered levodopa COMT Levodopa Carbidopa Dopa in CNS Decreased metabolism in GI tract and peripheral tissues Figure 8.10 Effect of entacapone on dopa concentration in the central nervous system (CNS). COMT = catechol-O-methyltransferase. Pharm 5th 3-21-11.indb 105 3/21/11 2:21:44 PM 106 8. Neurodegenerative Diseases ZZ Z Sedation and sleep disorders. Most seriously, fulminating hepatic necrosis is associated with tolcapone use. Therefore, it should be used, along with appropriate hepatic function monitoring, only in patients in whom other modalities have failed. Entacapone does not exhibit this toxicity and has largely replaced tolcapone. D. Dopamine-receptor agonists Hallucinations Confusion Nausea BP Hypotension Figure 8.11 Some adverse effects of dopamine agonists. This group of anti-Parkinson compounds includes bromocriptine, an ergot derivative, and newer, nonergot drugs, ropinirole, pramipexole, and rotigotine. These agents have durations of action longer than that of levodopa and, thus, have been effective in patients exhibiting fluctuations in their response to levodopa. Initial therapy with the newer drugs is associated particularly with less risk of developing dyskinesias and motor fluctuations when compared to patients started with levodopa therapy. Bromocriptine, pramipexole, and ropinirole are all effective in patients with advanced Parkinson disease complicated by motor fluctuations and dyskinesias. However, these drugs are ineffective in patients who have shown no therapeutic response to levodopa. Apomorphine is also used in severe and advanced stages of the disease as an injectable dopamine agonist to supplement the oral medications commonly prescribed. 1. Bromocriptine: Bromocriptine [broe-moe-KRIP-teen], a derivative of the vasoconstrictive alkaloid, ergotamine, is a dopamine-receptor agonist. The dose is increased gradually during a period of 2 to 3 months. Side effects severely limit the utility of the dopamine agonists (Figure 8.11). The actions of bromocriptine are similar to those of levodopa, except that hallucinations, confusion, delirium, nausea, and orthostatic hypotension are more common, whereas dyskinesia is less prominent. In psychiatric illness, bromocriptine and levodopa may cause the mental condition to worsen. Serious cardiac problems may develop, particularly in patients with a history of myocardial infarction. In patients with peripheral vascular disease, a worsening of the vasospasm occurs, and in patients with peptic ulcer, there is a worsening of the ulcer. Because bromocriptine is an ergot derivative, it has the potential to cause pulmonary and retroperitoneal fibrosis. 2. Apomorphine, pramipexole, ropinirole, and rotigotine: These are nonergot dopamine agonists that have been approved for the treatment of Parkinson disease. Pramipexole [pra-mi-PEX-ole] and ropinirole [roe-PIN-i-role] are agonists at dopamine receptors. Apomorphine [A-po-mor-feen] and rotigotine [ro-TI-go-teen] are newer dopamine agonists available in injectable and transdermal delivery systems, respectively. Apomorphine is meant to be used for the acute management of the hypomobility “off” phenomenon. These agents alleviate the motor deficits in both levodopa-naïve patients (patients who have never been treated with levodopa) and patients with advanced Parkinson disease who are taking levodopa. Dopamine agonists may delay the need to use levodopa therapy in early Parkinson disease and may decrease the dose of levodopa in advanced Parkinson disease. Unlike the ergotamine derivatives, pramipexole and ropinirole do not exacerbate peripheral vasospasm, and they do not cause fibrosis. Nausea, hallucinations, insomnia, dizziness, constipation, and orthostatic hypotension are among the more distressing side effects of these drugs, but dyskinesias are less frequent than with levodopa (Figure 8.12). The dependence of pramipexole on renal function for Pharm 5th 3-21-11.indb 106 3/21/11 2:21:45 PM VI. Drugs Used In Parkinson Disease 107 E. Amantadine It was accidentally discovered that the antiviral drug amantadine [a-MAN-ta-deen], which is effective in the treatment of influenza (see p. 462), has an antiparkinsonism action. Amantadine has several effects on a number of neurotransmitters implicated in causing parkinsonism, including increasing the release of dopamine, blockading cholinergic receptors, and inhibiting the N-methyl-D-aspartate (NMDA) type of glutamate receptors. Current evidence supports an action at NMDA receptors as the primary action at therapeutic concentrations. [Note: If dopamine release is already at a maximum, amantadine has no effect.] The drug may cause restlessness, agitation, confusion, and hallucinations, and, at high doses, it may induce acute toxic psychosis. Orthostatic hypotension, urinary retention, peripheral edema, and dry mouth also may occur. Amantadine is less efficacious than levodopa, and tolerance develops more readily. However, amantadine has fewer side effects. The drug has little effect on tremor, but it is more effective than the anticholinergics against rigidity and bradykinesia. 75 Percentage of patients with motor complications its elimination cannot be overly stressed. For example, cimetidine, which inhibits renal tubular secretion of organic bases, increases the half-life of pramipexole by 40 percent. The fluoroquinolone antibiotics (see p. 409) and other inhibitors of the CYP1A2 hepatic enzyme have been shown to inhibit the metabolism of ropinirole and to enhance the AUC (area under the concentration vs. time) curve by some 80 percent. Rotigotine is a dopamine agonist used in the treatment of the signs and symptoms of early stage Parkinson disease. It is administered as a once-daily transdermal patch that provides even pharmacokinetics over 24 hours. Figure 8.13 summarizes some properties of these dopamine agonists. Dopamine agonists delay motor complications and are most commonly initiated before levodopa in patients who have mild disease and a younger age of onset because they may delay the need to start levodopa therapy. 54% 50 45% Levodopa 25 0 Ropinirole 20% At 5 years Levodopa Pramipexole 24.5% At 4 years Figure 8.12 Motor complications in patients treated with levodopa or dopamine agonists. F. Antimuscarinic agents The antimuscarinic agents are much less efficacious than levodopa and play only an adjuvant role in antiparkinsonism therapy. The actions of benztropine [BENZ-tro-peen], trihexyphenidyl [tri-hex-ee FEN-i-dill], procyclidine [pro-CY-cli-deen], and biperiden [bi-PER-i den] are similar, although individual patients may respond more favorably to one drug. Each of these drugs can induce mood changes and produce xerostomia (dryness of the mouth) and visual problems, as do all muscarinic blockers. They interfere with gastrointestinal peristalsis and are contraindicated in patients with glaucoma, prostatic hyperplasia, or pyloric stenosis. Blockage of cholinergic transmission produces effects similar to augmentation of dopaminergic transmission (again, because of the creation of an imbalance in the dopamine/acetylcholine ratio; see Figure 8.5). Adverse effects are similar to those caused by high doses of Characteristic Bioavailability >90% Ropinirole 55% Vd 7 L/kg 7.5 L/kg 84 L/kg Half-life 8 hours1 6 hours 7 hours3 Metabolism Negligible Extensive Extensive Renal Renal2 Renal2 Elimination Pramipexole Rotigotine 45% Figure 8.13 Pharmacokinetic properties of dopamine agonists of pramipexole, ropinirole, and rotigotine. Vd = volume of distribution. 1Increases to 12 hours in patients older than 65 years; 2Less than 10 percent excreted unchanged; 3Administered as a once-daily transdermal patch. Pharm 5th 3-21-11.indb 107 3/21/11 2:21:46 PM 108 8. Neurodegenerative Diseases atropine, for example, pupillary dilation, confusion, hallucination, sinus tachycardia, urinary retention, constipation, and dry mouth. Tremors Bradycardia Nausea Diarrhea FOOD Anorexia Myalgia Figure 8.14 Adverse effects of acetylcholinesterase inhibitors. VII. DRUGS USED IN ALZHEIMER DISEASE Pharmacologic intervention for Alzheimer disease is only palliative and provides modest short-term benefit. None of the currently available therapeutic agents have been shown to alter the underlying neurodegenerative process. Dementia of the Alzheimer type (versus the other forms of dementia that will not be addressed in this discussion, such as multi-infarct dementia or Lewy body dementia) has three distinguishing features: 1) accumulation of senile plaques (β-amyloid accumulations); 2) formation of numerous neurofibrillary tangles; and 3) loss of cortical neurons, particularly cholinergic neurons. Current therapies are aimed at either improving cholinergic transmission within the CNS or preventing excitotoxic actions resulting from overstimulation of NMDA-glutamate receptors in selected brain areas. A. Acetylcholinesterase inhibitors Numerous studies have linked the progressive loss of cholinergic neurons and, presumably, cholinergic transmission within the cortex to the memory loss that is a hallmark symptom of Alzheimer disease. It is postulated that inhibition of acetylcholinesterase (AChE) within the CNS will improve cholinergic transmission, at least at those neurons that are still functioning. Currently, four reversible AChE inhibitors are approved for the treatment of mild to moderate Alzheimer disease. They are donepezil [dah-NE-peh-zeel], galantamine [ga-LAN-ta-meen], rivastigmine [riva-STIG-meen], and tacrine [TAK-reen]. Except for galantamine, which is competitive, all are uncompetitive inhibitors of AChE and appear to have some selectivity for AChE in the CNS as compared to the periphery. Galantamine may also be acting as an allosteric modulator of the nicotinic receptor in the CNS and, therefore, secondarily may increase cholinergic neurotransmission through a separate mechanism. At best, these compounds provide a modest reduction in the rate of loss of cognitive functioning in Alzheimer patients. Rivastigmine is hydrolyzed by AChE to a carbamylate metabolite and has no interactions with drugs that alter the activity of cytochrome P450-dependent enzymes. The other agents are substrates for cytochrome P450 and have a potential for such interactions. Common adverse effects include nausea, diarrhea, vomiting, anorexia, tremors, bradycardia, and muscle cramps, all of which are predicted by the actions of the drugs to enhance cholinergic neurotransmission (Figure 8.14). Unlike the others, tacrine is associated with hepatotoxicity. B. NMDA-receptor antagonist Stimulation of glutamate receptors in the CNS appears to be critical for the formation of certain memories. However, overstimulation of glutamate receptors, particularly of the NMDA type, has been shown to result in excitotoxic effects on neurons and is suggested as a mechanism for neurodegenerative or apoptotic (programmed cell death) processes. Binding of glutamate to the NMDA receptor assists in the opening of an associated ion channel that allows Na^+ and, particularly, Ca^{2+} to enter the neuron. Unfortunately, excess intracellular Ca^{2+} can activate a number of processes that ultimately damage neurons and lead to apoptosis. Antagonists of the NMDA-glutamate receptor are often neuroprotective, preventing the loss of neurons following ischemic and other injuries. Memantine [MEM-an-teen] is a dimethyl adamantane derivative. Pharm 5th 3-21-11.indb 108 3/21/11 2:21:46 PM VIII. Drugs Used In Multiple Sclerosis 109 Memantine acts by physically blocking the NMDA receptor–associated ion channel, but, at therapeutic doses, only a fraction of these channels are actually blocked. This partial blockade may allow memantine to limit Ca^{2+} influx into the neuron, such that toxic intracellular levels are not achieved during NMDA-receptor overstimulation, while still permitting sufficient Ca^{2+} flow through unblocked channels to preserve other vital processes that depend on Ca^{2+} (or Na^+) influx through these channels. This is in contrast to psychotoxic agents such as phencyclidine, which occupy and block nearly all of these channels. In short term studies, memantine has been shown to slow the rate of memory loss in both vascular-associated and Alzheimer dementia in patients with moderate to severe cognitive losses. However, there is no evidence that memantine prevents or slows the neurodegeneration in patients with Alzheimer disease or is more effective than the AChE inhibitors. Memantine is well tolerated, with few dose-dependent adverse events. Expected side effects, such as confusion, agitation, and restlessness, are indistinguishable from the symptoms of Alzheimer disease. Given its different mechanism of action and possible neuroprotective effects, memantine is often given in combination with an AChE inhibitor. Long-term data showing a significant effect of this combination is not available. VIII. DRUGS USED IN MULTIPLE SCLEROSIS Multiple sclerosis (MS) is an autoimmune inflammatory demyelinating disease of the central nervous system (CNS). The course of MS is variable. For some, MS may consist of one or two acute neurologic episodes. In others, it is a chronic, relapsing, or progressive disease that may span 10 to 20 years. Historically, medications, such as the corticosteroids (for example, dexamethasone and prednisone), have been used to treat acute attacks of the disease. Other medications that have been used include chemotherapeutic agents, such as cyclophosphamide and azathioprine. Newer medications that have been approved for the treatment of MS include interferon β1a and interferon β1b as immune system modulators of the interferons and the T-helper cell response, which contribute to the inflammatory responses that lead to demyelination of the axon sheaths. Mitoxantrone: The cytotoxic anthracycline analog, mitoxantrone [my-toeZAN-trone], which can kill T cells, may also be used. The major target of these medications is to modify the body’s immune response through inhibition of white blood cell–mediated inflammatory processes that eventually lead to myelin sheath damage and a decreased or inappropriate axonal communication between cells. Adverse effects of these medications may include depression; local injection or infusion reactions; hepatic enzyme increases; flulike symptoms, such as fever and myalgias and leukopenia. Fingolimod is the first oral drug that can slow the progression of disability and reduce the frequency and severity of symptoms in MS, offering patients an alternative to the currently available injectable therapies. Fingolimod alters lymphocyte migration, resulting in sequestration of lymphocytes in lymph nodes. Fingolimod is effective for reducing the relapse rate in patients with MS. However, this benefit is associated with an increased risk of lifethreatening infection. Dalfampridine, a potassium channel blocker administered orally, improves walking speeds vs placebo. It is the first drug approved for this use. Currently approved MS drugs are indicated to decrease relapse rates or in some cases to prevent accumulation of disability. Pharm 5th 3-21-11.indb 109 3/21/11 2:21:47 PM 110 8. Neurodegenerative Diseases Other: Glatiramer [gluh-TEER-a-mur] is a synthetic polypeptide that resembles myelin protein and may act as a “decoy” to T-cell attack. A monoclonal antibody, natalizumab [NA-ta-LIZ-oo-mab], is also indicated for MS in patients who have failed first-line therapies. IX. DRUGS USED IN AMYOTROPHIC LATERAL SCLEROSIS Though not indicated for the treatment of Alzheimer disease, another NMDA-receptor antagonist is indicated for the management of ALS. Riluzole [RI-lu-zole] blocks glutamate, sodium channels, and calcium channels. It may improve the survival time and delay the need for ventilator support in patients suffering from ALS. Study Questions Choose the ONE best answer. 8.1 Which one of the following combinations of antiparkinson drugs is an appropriate therapy? A. Amantadine, carbidopa, and entacapone. B. Levodopa, carbidopa, and entacapone. C. Pramipexole, carbidopa, and entacapone. D. Ropinirole, selegiline, and entacapone. E. Ropinirole, carbidopa, and selegiline. 8.2 Peripheral adverse effects of levodopa, including nausea, hypotension, and cardiac arrhythmias, can be diminished by including which of the following drugs in the therapy? A. Amantadine. B. Bromocriptine. C. Carbidopa. D. Entacapone. E. Ropinirole. 8.3 Which of the following antiparkinson drugs may cause peripheral vasospasm? A. Amantadine. B. Bromocriptine. C. Carbidopa. D. Entacapone. E. Ropinirole. 8.4 Modest improvement in the memory of patients with Alzheimer’s disease may occur with drugs that increase transmission at which of the following receptors? A. Adrenergic. B. Cholinergic. C. Dopaminergic. D. GABAergic. E. Serotonergic. 08 Neurodegen 5-16-11#.indd 110 Correct answer = B. To reduce the dose of levodopa and its peripheral side effects, the peripheral decarboxylase inhibitor, carbidopa, is coadministered. As a result of this combination, more levodopa is available for metabolism by catechol-O-methyltransferase (COMT) to 3-methyldopa, which competes with dopa for the active transport processes into the central nervous system. By administering entacapone (an inhibitor of COMT), the competing product is not formed, and more dopa enters the brain. The other choices are not appropriate, because neither peripheral decarboxylase nor COMT nor monoamine oxidase metabolizes amantadine or the direct-acting dopamine agonists, ropinirole and pramipexole. Correct answer = C. Carbidopa inhibits the peripheral decarboxylation of levodopa to dopamine, thereby diminishing the gastrointestinal and cardiovascular side effects of levodopa. The other agents listed do not ameliorate levodopa’s adverse effects. Correct answer = B. Bromocriptine is a dopaminereceptor

agonist that may cause vasospasm. It is contraindicated in patients with peripheral vascular disease. Ropinirole directly stimulates dopamine receptors, but it does not cause vasospasm. The other drugs do not act directly on dopamine receptors. Correct answer = B. Acetylcholinesterase inhibitors, such as rivastigmine, increase cholinergic transmission in the CNS and may cause a modest delay in the progression of Alzheimer's disease. Increased transmission at the other types of receptors listed does not result in improved memory. 5/16/11 12:35:08 PM 9 Anxiolytic and Hypnotic Drugs I. OVERVIEW BENZODIAZEPINES Anxiety is an unpleasant state of tension, apprehension, or uneasiness (a fear that seems to arise from a unknown source). Disorders involving anxiety are the most common mental disturbances. The physical symptoms of severe anxiety are similar to those of fear (such as tachycardia, sweating, trembling, and palpitations) and involve sympathetic activation. Episodes of mild anxiety are common life experiences and do not warrant treatment. However, the symptoms of severe, chronic, debilitating anxiety may be treated with anti-anxiety drugs (sometimes called anxiolytic or minor tranquilizers) and/or some form of behavioral therapy or psychotherapy. Because many of the anti-anxiety drugs also cause some sedation, the same drugs often function clinically as both anxiolytic and hypnotic (sleep-inducing) agents. In addition, some have anticonvulsant activity. Figure 9.1 summarizes the anxiolytic and hypnotic agents. Though also indicated for certain anxiety disorders, the selective serotonin reuptake inhibitors (SSRIs) will be presented in the chapter discussing antidepressants. Alprazolam XANAX Chlordiazepoxide Librium Clonazepam KLONOPIN Clorazepate TRANXENE Diazepam VALIUM, DIASTAT Estazolam PROSOM Flurazepam DALMANE Lorazepam ATIVAN Midazolam VERSED Oxazepam SERAX Quazepam DORAL Temazepam RESTORIL Triazolam HALCION II. BENZODIAZEPINES Antidepressants various (see chapter 12) Buspirone BUSPAR Benzodiazepines are the most widely used anxiolytic drugs. They have largely replaced barbiturates and meprobamate in the treatment of anxiety, because benzodiazepines are safer and more effective (Figure 9.2). BARBITURATES A. Mechanism of action The targets for benzodiazepine actions are the γ-aminobutyric acid (GABAA) receptors. [Note: GABA is the major inhibitory neurotransmitter in the central nervous system (CNS).] These receptors are primarily composed of α, β, and γ subunit families of which a combination of five or more span the postsynaptic membrane (Figure 9.3). Depending on the types, number of subunits, and brain region localization, the activation of the receptors results in different pharmacologic effects. Benzodiazepines modulate GABA effects by binding to a specific, high-affinity site located at the interface of the α subunit and the γ2 subunit (see Figure 9.3). [Note: These binding sites are sometimes labeled “benzodiazepine receptors.” Two benzodiazepine receptor subtypes commonly found in the CNS have been designated as BZ1 and BZ2 receptors depending on whether their composition includes the α1 subunit or the α2 subunit, respectively. The benzodiazepine receptor locations in the CNS parallel those of the GABA neurons. Binding of GABA to its receptor triggers an open- Pharm 5th 3-21-11.indb 111 BENZODIAZEPINE ANTAGONIST Flumazenil Romazicon OTHER ANXIOLYTIC DRUGS Amobarbital AMYTAL Pentobarbital NEMBUTAL Phenobarbital LUMINAL SODIUM Secobarbital SECONAL Thiopental PENTOTHAL OTHER HYPNOTIC AGENTS Antihistamines various (see chapter 42) Chloral hydrate SOMNOTE, NOCTEC Eszopiclone LUNESTA Ethanol (alcohol, grain alcohol) various Ramelteon ROZEREM Zaleplon SONATA Zolpidem AMBIEN Figure 9.1 Summary of anxiolytic and hypnotic drugs. (Figure continues on next page.) 3/21/11 2:21:47 PM 112 9. Anxiolytic and Hypnotic Drugs TREATMENT OF ALCOHOL DEPENDENCE Acamprosate CAMPRAL Disulfiram ANTABUSE Naltrexone DEPADE, REVIA Figure 9.1 (continued) Summary of anxiolytic and hypnotic drugs. ing of a chloride channel, which leads to an increase in chloride conductance (see Figure 9.3). Benzodiazepines increase the frequency of channel openings produced by GABA. The influx of chloride ions causes a small hyperpolarization that moves the postsynaptic potential away from its firing threshold and, thus, inhibits the formation of action potentials. [Note: Binding of a benzodiazepine to its receptor site will increase the affinity of GABA for the GABA-binding site (and vice versa) without actually changing the total number of sites.] The clinical effects of the various benzodiazepines correlate well with each drug's binding affinity for the GABA receptor–chloride ion channel complex. B. Actions The benzodiazepines have neither antipsychotic activity nor analgesic action, and they do not affect the autonomic nervous system. All benzodiazepines exhibit the following actions to a greater or lesser extent: 1. Reduction of anxiety: At low doses, the benzodiazepines are anxiolytic. They are thought to reduce anxiety by selectively enhancing GABAergic transmission in neurons having the α2 subunit in their GABAA receptors, thereby inhibiting neuronal circuits in the limbic system of the brain. 2. Sedative and hypnotic actions: All of the benzodiazepines used to treat anxiety have some sedative properties, and some can produce hypnosis (artificially produced sleep) at higher doses. Their effects have been shown to be mediated by the α1-GABAA receptors. 3. Anterograde amnesia: The temporary impairment of memory with use of the benzodiazepines is also mediated by the α1-GABAA receptors. This also impairs a person's ability to learn and form new memories. 4. Anticonvulsant: Several of the benzodiazepines have anticonvulsant activity and some are used to treat epilepsy (status epilepticus) and other seizure disorders. This effect is partially, although not completely, mediated by α1-GABAA receptors. Benzodiazepines are relatively safe, because the lethal dose is over 1000-fold greater than the typical therapeutic dose. 5. Muscle relaxant: At high doses, the benzodiazepines relax the spasticity of skeletal muscle, probably by increasing presynaptic inhibition in the spinal cord, where the α2-GABAA receptors are largely located. Baclofen is a muscle relaxant that is believed to affect GABA receptors at the level of the spinal cord. Morphine Chlorpromazine C. Therapeutic uses Phenobarbital Ratio = Lethal dose Effective dose The individual benzodiazepines show small differences in their relative anxiolytic, anticonvulsant, and sedative properties. However, the duration of action varies widely among this group, and pharmacokinetic considerations are often important in choosing one benzodiazepine over another. Figure 9.2 Ratio of lethal dose to effective dose for morphine (an opioid, see Chapter 14), chlorpromazine (a neuroleptic, see Chapter 13), and the anxiolytic, hypnotic drugs, phenobarbital and diazepam. 1. Anxiety disorders: Benzodiazepines are effective for the treatment of the anxiety symptoms secondary to panic disorder, generalized anxiety disorder (GAD), social anxiety disorder, performance anxiety, posttraumatic stress disorder, obsessive-compulsive disorder, and the extreme anxiety sometimes encountered with specific phobias such as fear of flying. The benzodiazepines are also useful in treating the anxiety that accompanies some forms of depression and Diazepam 0 Pharm 5th 3-21-11.indb 112 20 40 1000 3/21/11 2:21:48 PM II. Benzodiazepines 113 Cl– empty A Receptor (no agonists) α B Receptor binding GABA Cl– α β γ α β Empty receptor is inactive, and the coupled chloride channel is closed. Cl– GABA Binding of GABA causes the chloride ion channel to open, leading to hyperpolarization of the cell. C Receptor binding GABA Cl– Cl– GABA Benzodiazepine and benzodiazepine Entry of Cl– hyperpolarizes the cell, making it more difficult to depolarize, and therefore reduces neural excitability. Binding of GABA is enhanced by benzodiazepine, resulting in a greater entry of chloride ion. Cl– Cl– Cl– Figure 9.3 Schematic diagram of benzodiazepine–GABA–chloride ion channel complex. GABA = γ-aminobutyric acid. schizophrenia. These drugs should not be used to alleviate the normal stress of everyday life. They should be reserved for continued severe anxiety, and then should only be used for short periods of time because of their addiction potential. The longer-acting agents, such as clonazepam [kloe-NAZ-e-pam], lorazepam [lor-AZ-e-pam], and diazepam [dye-AZ-e-pam], are often preferred in those patients with anxiety who may require treatment for prolonged periods of time. The anti-anxiety effects of the benzodiazepines are less subject to tolerance than the sedative and hypnotic effects. [Note: Tolerance (that is, decreased responsiveness to repeated doses of the drug) occurs when used for more than 1 to 2 weeks. Cross-tolerance exists among this group of agents with ethanol. It has been shown that tolerance is associated with a decrease in GABA-receptor density.] For panic disorders, alprazolam [al-PRAY-zoe-lam] is effective for shortand long-term treatment, although it may cause withdrawal reactions in about 30 percent of sufferers. 2. Muscular disorders: Diazepam is useful in the treatment of skeletal muscle spasms, such as occur in muscle strain, and in treating spasticity from degenerative disorders, such as multiple sclerosis and cerebral palsy. 3. Amnesia: The shorter-acting agents are often employed as premedication for anxiety-provoking and unpleasant procedures, such as Pharm 5th 3-21-11.indb 113 3/21/11 2:21:50 PM 114 9. Anxiolytic and Hypnotic Drugs DURATION OF ACTION OF BENZODIAZEPINES 4. Seizures: Clonazepam is occasionally used in the treatment of certain types of epilepsy, whereas diazepam and lorazepam are the drugs of choice in terminating grand mal epileptic seizures and status epilepticus (see p. 184). Due to cross-tolerance, chlordiazepoxide [klor-di-az-e-POX-ide], clorazepate [klor-AZ-e-pate], diazepam, and oxazepam [ox-AZ-e-pam] are useful in the acute treatment of alcohol withdrawal and reducing the risk of withdrawal-related seizures. Long-acting Clorazepate Chlordiazepoxide Diazepam Flurazepam Quazepam Intermediate-acting 24 6 18 12 10–20 Hours Alprazolam Estazolam Lorazepam Temazepam Short-acting 11 12 1 2 10 3 9 4 8 7 6 endoscopic, bronchoscopic, and certain dental procedures as well as angioplasty. They also cause a form of conscious sedation, allowing the person to be receptive to instructions during these procedures. Midazolam [mi-DAY-zoe-lam] is a benzodiazepine also used for the induction of anesthesia. 5 3–8 Hours Oxazepam Triazolam Figure 9.4 Comparison of the durations of action of the benzodiazepines. 5. Sleep disorders: Not all benzodiazepines are useful as hypnotic agents, although all have sedative or calming effects. They tend to decrease the latency to sleep onset and increase Stage II of nonrapid eye movement (REM) sleep. Both REM sleep and slow-wave sleep are decreased. In the treatment of insomnia, it is important to balance the sedative effect needed at bedtime with the residual sedation (“hangover”) upon awakening. Commonly prescribed benzodiazepines for sleep disorders include long-acting flurazepam [flureAZ-e-pam], intermediate-acting temazepam [te-MAZ-e-pam], and short-acting triazolam [trye-AY-zoe-lam]. a. Flurazepam: This long-acting benzodiazepine significantly reduces both sleep-induction time and the number of awakenings, and it increases the duration of sleep. Flurazepam has a longacting effect (Figure 9.4) and causes little rebound insomnia. With continued use, the drug has been shown to maintain its effectiveness for up to 4 weeks. Flurazepam and its active metabolites have a half-life of approximately 85 hours, which may result in daytime sedation and accumulation of the drug. b. Temazepam: This drug is useful in patients who experience frequent wakening. However, because the peak sedative effect occurs 1 to 3 hours after an oral dose it should be given 1 to 2 hours before the desired bedtime. c. Triazolam: This benzodiazepine has a relatively short duration of action and, therefore, is used to induce sleep in patients with recurring insomnia. Whereas temazepam is useful for insomnia caused by the inability to stay asleep, triazolam is effective in treating individuals who have difficulty in going to sleep. Tolerance frequently develops within a few days, and withdrawal of the drug often results in rebound insomnia, leading the patient to demand another prescription or higher dose. Therefore, this drug is best used intermittently rather than daily. In general, hypnotics should be given for only a limited time, usually less than 2 to 4 weeks. D. Pharmacokinetics 1. Absorption and distribution: The benzodiazepines are lipophilic. They are rapidly and completely absorbed after oral administration and distribute throughout the body. Pharm 5th 3-21-11.indb 114 3/21/11 2:21:51 PM II. Benzodiazepines 2. Durations of action: The half-lives of the benzodiazepines are very important clinically, because the duration of action may determine the therapeutic usefulness. The benzodiazepines can be roughly divided into short-, intermediate-, and long-acting groups (see Figure 9.4). The longer-acting agents form active metabolites with long half-lives. However, with some benzodiazepines, the clinical durations of action do not always correlate with actual half-lives (otherwise, a dose of diazepam could conceivably be given only every other day or even less often given its active metabolites). This may be due to receptor dissociation rates in the CNS and subsequent redistribution elsewhere. 3. Fate: Most benzodiazepines, including chlordiazepoxide and diazepam, are metabolized by the hepatic microsomal system to compounds that are also active. For these benzodiazepines, the apparent half-life of the drug represents the combined actions of the parent drug and its metabolites. The drugs' effects are terminated not only by excretion but also by redistribution. The benzodiazepines are excreted in urine as glucuronides or oxidized metabolites. All the benzodiazepines cross the placental barrier and may depress the CNS of the newborn if given before birth. Nursing infants may also become exposed to the drugs in breast milk. 115 The drugs that are more potent and rapidly eliminated (for example, triazolam) have more frequent and severe withdrawal problems. Triazolam Alprazolam Temazepam Diazepam Flurazepam -40 -20 0 20 40 60 80 Increase in total wake time from baseline (%) The less potent and more slowly eliminated drugs (for example, flurazepam) continue to improve sleep even after discontinuation. E. Dependence Psychological and physical dependence on benzodiazepines can develop if high doses of the drugs are given over a prolonged period. Abrupt discontinuation of the benzodiazepines results in withdrawal symptoms, including confusion, anxiety, agitation, restlessness, insomnia, tension, and (rarely) seizures. Because of the long half-lives of some benzodiazepines, withdrawal symptoms may occur slowly and last a number of days after discontinuation of therapy. Benzodiazepines with a short elimination half-life, such as triazolam, induce more abrupt and severe withdrawal reactions than those seen with drugs that are slowly eliminated such as flurazepam (Figure 9.5). Figure 9.5 Frequency of rebound insomnia resulting from discontinuation of benzodiazepine therapy. F. Adverse effects 1. Drowsiness and confusion: These effects are the two most common side effects of the benzodiazepines. Ataxia occurs at high doses and precludes activities that require fine motor coordination, such as driving an automobile. Cognitive impairment (decreased longterm recall and retention of new knowledge) can occur with use of benzodiazepines. Triazolam, one of the most potent oral benzodiazepines with rapid elimination, often shows a rapid development of tolerance, early morning insomnia, and daytime anxiety as well as amnesia and confusion. 2. Precautions: Benzodiazepines should be used cautiously in treating patients with liver disease. These drugs should be avoided in patients with acute narrow-angle glaucoma. Alcohol and other CNS depressants enhance the sedative-hypnotic effects of the benzodiazepines. Benzodiazepines are, however, considerably less dangerous than the older anxiolytic and hypnotic drugs. As a result, a drug overdose is seldom lethal unless other central depressants, such as alcohol, are taken concurrently. Pharm 5th 3-21-11.indb 115 3/21/11 2:21:52 PM 9. Anxiolytic and Hypnotic Drugs Daily mg dose lorazepam Initiate therapy with a benzodiazepine, such as lorazepam 1 10 Concomitant therapy with antidepressant, such as escitalopram Tapered withdrawal of benzodiazepine 0 0 14 0 Days 28 42 56 Daily mg dose escitalopram 116 Figure 9.6 Treatment guideline for persistent anxiety. III. BENZODIAZEPINE ANTAGONIST Note that buspirone shows less interference with motor functions, a benefit that is particulary important in elderly patients. 27 Nausea 17 10 Headache Decreased concentration Drowsiness 13 7 10 33 10 30 10 Fatigue 27 Buspirone IV. OTHER ANXIOLYTIC AGENTS A. Antidepressants 0 Dizziness Flumazenil [floo-MAZ-eh-nill] is a GABA-receptor antagonist that can rapidly reverse the effects of benzodiazepines. The drug is available for intravenous (IV) administration only. Onset is rapid, but duration is short, with a halflife of about 1 hour. Frequent administration may be necessary to maintain reversal of a long-acting benzodiazepine. Administration of flumazenil may precipitate withdrawal in dependent patients or cause seizures if a benzodiazepine is used to control seizure activity. Seizures may also result if the patient ingests tricyclic antidepressants (TCAs). Dizziness, nausea, vomiting, and agitation are the most common side effects. Alprazolam Many antidepressants have proven efficacy in managing the long-term symptoms of chronic anxiety disorders and should be seriously considered as first-line agents, especially in patients with concerns for addiction or dependence or a history of addiction or dependence to other substances. Selective serotonin reuptake inhibitors (SSRIs, such a escitalopram), or selective serotonin and norepinephrine reuptake inhibitors (SNRIs, such as venlafaxine) may be used alone, or prescribed in combination with a low dose of a benzodiazepine during the first weeks of treatment (Figure 9.6). After four to six weeks, when the antidepressant begins to produce an anxiolytic effect, the benzodiazepine dose can be tapered. SSRIs and SNRIs have a lower potential for physical dependence than the benzodiazepines, and have become first-line treatment for GAD. While only certain SSRIs or SNRIs have been approved by the FDA for the treatment of GAD, the efficacy of these drugs for GAD is most likely a class effect. Thus, the choice among these antidepressants can be based upon side effects and cost. Long-term use of antidepressants and benzodiazepines for anxiety disorders is often required to maintain ongoing benefit and prevent relapse. Please refer to Chapter 12 for a discussion of the antidepressant agents. B. Buspirone Figure 9.7 Comparison of common adverse effects of buspirone and alprazolam. Results are expressed as the percentage of patients showing each symptom. Pharm 5th 3-21-11.indb 116 Buspirone [byoo-SPYE-rone] is useful for the chronic treatment of GAD and has an efficacy comparable to that of the benzodiazepines. This agent is not effective for short-term or “as-needed” treatment of acute anxiety states. The actions of buspirone appear to be mediated by serotonin (5-HT1A) receptors, although other receptors could be involved, 3/21/11 2:21:53 PM V. Barbiturates because buspirone displays some affinity for DA2 dopamine receptors and 5-HT2A serotonin receptors. Thus, its mode of action differs from that of the benzodiazepines. In addition, buspirone lacks the anticonvulsant and muscle-relaxant properties of the benzodiazepines and causes only minimal sedation. However, it does cause hypothermia and can increase prolactin and growth hormone. The frequency of adverse effects is low, with the most common effects being headaches, dizziness, nervousness, and light-headedness. Sedation and psychomotor and cognitive dysfunction are minimal, and dependence is unlikely. It does not potentiate the CNS depression of alcohol. Buspirone has the disadvantage of a slow onset of action. Figure 9.7 compares some of the common adverse effects of buspirone and the benzodiazepine alprazolam. V. BARBITURATES The barbiturates were formerly the mainstay of treatment to sedate patients or to induce and maintain sleep. Today, they have been largely replaced by the benzodiazepines, primarily because barbiturates induce tolerance, drug-metabolizing enzymes, and physical dependence and are associated with very severe withdrawal symptoms. Foremost is their ability to cause coma in toxic doses. Certain barbiturates, such as the very short-acting thiopental, are still used to induce anesthesia (see p. 145). 117 DURATION OF ACTION OF BARBITURATES Long-acting A. Mechanism of action The sedative-hypnotic action of the barbiturates is due to their interaction with GABAA receptors, which enhances GABAergic transmission. The binding site is distinct from that of the benzodiazepines. Barbiturates potentiate GABA action on chloride entry into the neuron by prolonging the duration of the chloride-channel openings. In addition, barbiturates can block excitatory glutamate receptors. Anesthetic concentrations of pentobarbital also block high-frequency sodium channels. All of these molecular actions lead to decreased neuronal activity. Phenobarbital Short-acting 11 1. Depression of CNS: At low doses, the barbiturates produce sedation (have a calming effect and reduce excitement). At higher doses, the drugs cause hypnosis, followed by anesthesia (loss of feeling or sensation), and, finally, coma and death. Thus, any degree of depression of the CNS is possible, depending on the dose. Barbiturates do not raise the pain threshold and have no analgesic properties. They may even exacerbate pain. Chronic use leads to tolerance. 2. Respiratory depression: Barbiturates suppress the hypoxic and chemoreceptor response to CO_2, and overdosage is followed by respiratory depression and death. Pharm 5th 3-21-11.indb 117 1 2 3 9 4 8 B. Actions Barbiturates are classified according to their duration of action (Figure 9.8). For example, thiopental [thye-oh-PEN-tal], which acts within seconds and has a duration of action of about 30 minutes, is used in the IV induction of anesthesia. By contrast, phenobarbital [fee-noe-BAR-bital], which has a duration of action greater than a day, is useful in the treatment of seizures (see p. 187). Pentobarbital [pen-toe-BAR-bi-tal], secobarbital [see-koe-BAR-bi-tal], and amobarbital [am-oh-BAR-bi-tal] are short-acting barbiturates, which are effective as sedative and hypnotic (but not anti-anxiety) agents. 12 10 7 6 5 3–8 Hours Pentobarbital Secobarbital Amobarbital Ultra-short-acting 0 50 10 20 40 30 20 Minutes Thiopental Figure 9.8 Barbiturates classified according to their durations of action. 3/21/11 2:21:54 PM 118 9. Anxiolytic and Hypnotic Drugs Potential for addiction 3. Enzyme induction: Barbiturates induce cytochrome P450 (CYP450) microsomal enzymes in the liver. Therefore, chronic barbiturate administration diminishes the action of many drugs that are dependent on CYP450 metabolism to reduce their concentration. C. Therapeutic uses 1. Anesthesia: Selection of a barbiturate is strongly influenced by the desired duration of action. The ultrashort-acting barbiturates, such as thiopental, are used intravenously to induce anesthesia. Drowsiness Nausea 2. Anticonvulsant: Phenobarbital is used in long-term management of tonic-clonic seizures, status epilepticus, and eclampsia. Phenobarbital has been regarded as the drug of choice for treatment of young children with recurrent febrile seizures. However, phenobarbital can depress cognitive performance in children, and the drug should be used cautiously. Phenobarbital has specific anticonvulsant activity that is distinguished from the nonspecific CNS depression. 3. Anxiety: Barbiturates have been used as mild sedatives to relieve anxiety, nervous tension, and insomnia. When used as hypnotics, they suppress REM sleep more than other stages. However, most have been replaced by the benzodiazepines. D. Pharmacokinetics Vertigo Tremors Barbiturates are absorbed orally and distributed widely throughout the body. All barbiturates redistribute in the body, from the brain to the splanchnic areas, to skeletal muscle, and, finally, to adipose tissue. This movement is important in causing the short duration of action of thiopental and similar short-acting derivatives. Barbiturates readily cross the placenta and can depress the fetus. These agents are metabolized in the liver, and inactive metabolites are excreted in urine. E. Adverse effects 1. CNS: Barbiturates cause drowsiness, impaired concentration, and mental and physical sluggishness (Figure 9.9). The CNS depressant effects of barbiturates synergize with those of ethanol. P-450 P-450 P-450 Enzyme induction Figure 9.9 Adverse effect of barbiturates. 2. Drug hangover: Hypnotic doses of barbiturates produce a feeling of tiredness well after the patient wakes. This drug hangover may lead to impaired ability to function normally for many hours after waking. Occasionally, nausea and dizziness occur. 3. Precautions: As noted previously, barbiturates induce the CYP450 system and, therefore, may decrease the duration of action of drugs that are metabolized by these hepatic enzymes. Barbiturates increase porphyrin synthesis and are contraindicated in patients with acute intermittent porphyria. 4. Physical dependence: Abrupt withdrawal from barbiturates may cause tremors, anxiety, weakness, restlessness, nausea and vomiting, seizures, delirium, and cardiac arrest. Withdrawal is much more severe than that associated with opiates and can result in death. 5. Poisoning: Barbiturate poisoning has been a leading cause of death resulting from drug overdoses for many decades. Severe depression of respiration is coupled with central cardiovascular depression and Pharm 5th 3-21-11.indb 118 3/21/11 2:21:54 PM VI. Other Hypnotic Agents 119 results in a shock-like condition with shallow, infrequent breathing. Treatment includes artificial respiration and purging the stomach of its contents if the drug has been recently taken. [Note: No specific barbiturate antagonist is available.] Hemodialysis may be necessary if large quantities have been taken. Alkalinization of the urine often aids in the elimination of phenobarbital. VI. OTHER HYPNOTIC AGENTS A. Zolpidem The hypnotic zolpidem [ZOL-pi-dem] is not a benzodiazepine in structure, but it acts on a subset of the benzodiazepine receptor family, BZ1. Zolpidem has no anticonvulsant or muscle-relaxing properties. It shows few withdrawal effects and exhibits minimal rebound insomnia and little or no tolerance occurs with prolonged use. Zolpidem is rapidly absorbed from the gastrointestinal (GI) tract, and it has a rapid onset of action and short elimination half-life (about 2 to 3 hours) and provides a hypnotic effect for approximately 5 hours (Figure 9.10). [Note: An extended-release formulation is now available.] Zolpidem undergoes hepatic oxidation by the CYP450 system to inactive products. Thus, drugs such as rifampin, which induce this enzyme system, shorten the half-life of zolpidem, and drugs that inhibit the CYP3A4 isoenzyme may increase the half-life this drug. Adverse effects of zolpidem include nightmares, agitation, headache, GI upset, dizziness, and daytime drowsiness. Unlike the benzodiazepines, at usual hypnotic doses, the nonbenzodiazepine drugs, zolpidem, zaleplon, and eszopiclone, do not significantly alter the various sleep stages and, hence, are often the preferred hypnotics . This may be due to their relative selectivity for the BZ1 receptor. B. Zaleplon Zaleplon (ZAL-e-plon) is very similar to zolpidem in its hypnotic actions, but zaleplon causes fewer residual effects on psychomotor and cognitive functions compared to zolpidem or the benzodiazepines. This may be due to its rapid elimination, with a half-life of approximately 1 hour. The drug is metabolized by CYP3A4 (see p. 14). Zolpidem 30 minutes 5 hours 30 minutes Zaleplon 3 hours Eszopiclone Ramelteon Onset 20 minutes 7 hours 30 minutes 7 hours Duration Figure 9.10 Onset and duration of action of the commonly used nonbenzodiazpine hypnotic agents. C. Eszopiclone Eszopiclone [es-ZOE-pi-clone] is an oral nonbenzodiazepine hypnotic (also using the BZ1 receptor similar to zolpidem and zaleplon) and is also used for treating insomnia. Eszopiclone been shown to be effective for up to 6 months compared to a placebo. Eszopiclone is rapidly absorbed (time to peak, 1 hour), extensively metabolized by oxidation and demethylation via the CYP450 system, and mainly excreted in urine. Elimination half-life is approximately 6 hours. Adverse events reported with eszopiclone include anxiety, dry mouth, headache, peripheral edema, somnolence, and unpleasant taste. D. Ramelteon Ramelteon [ram-EL-tee-on] is a selective agonist at the MT1 and MT2 subtypes of melatonin receptors. Normally, light stimulating the retina transmits a signal to the suprachiasmatic nucleus (SCN) of the hypothalamus that, in turn, relays a signal via a lengthy nerve pathway to the pineal gland that inhibits the release of melatonin from the gland. As darkness falls and light ceases to strike the retina, melatonin release Pharm 5th 3-21-11.indb 119 3/21/11 2:21:55 PM 120 9. Anxiolytic and Hypnotic Drugs from the pineal gland is no longer inhibited, and the gland begins to secrete melatonin. Stimulation of MT1 and MT2 receptors by melatonin in the SCN is able to induce and promote sleep and is thought to maintain the circadian rhythm underlying the normal sleep–wake cycle. Ramelteon is indicated for the treatment of insomnia in which falling asleep (increased sleep latency) is the primary complaint. The potential for abuse of ramelteon is believed to be minimal, and no evidence of dependence or withdrawal effects has been observed. Therefore, ramelteon can be administered long term. Common adverse effects of ramelteon include dizziness, fatigue, and somnolence. Ramelteon may also increase prolactin levels. E. Antihistamines NAD^+ Ethanol NADH NAD^+ Acetaldehyde NADH Acetate Disulfiram Disulfiram causes accumulation of acetaldehyde, resulting in flushing, tachycardia, hyperventilation, and nausea. Figure 9.11 Metabolism of ethanol, and the effect of disulfiram. NAD^+ = oxidized form of nicotinamide-adenine dinucleotide; NADH = reduced form of nicotinamide-adenine dinucleotide. Some antihistamines with sedating properties, such as diphenhydramine, hydroxyzine and doxylamine, are effective in treating mild types of insomnia. However, these drugs are usually ineffective for all but the milder forms of situational insomnia. Furthermore, they have numerous undesirable side effects (such as anticholinergic effects) that make them less useful than the benzodiazepines. Some sedative antihistamines are marketed in numerous over-the-counter products. F. Ethanol Ethanol (ethyl alcohol) has anxiolytic and sedative effects, but its toxic potential outweighs its benefits. Ethanol [ETH-an-ol] is a CNS depressant, producing sedation and, ultimately, hypnosis with increasing dosage. Because ethanol has a shallow dose–response curve, sedation occurs over a wide dosage range. It is readily absorbed orally and has a volume of distribution close to that of total body water. Ethanol is metabolized primarily in the liver, first to acetaldehyde by alcohol dehydrogenase and then to acetate by aldehyde dehydrogenase (Figure 9.11). Elimination is mostly through the kidney, but a fraction is excreted through the lungs. Ethanol synergizes with many other sedative agents and can produce severe CNS depression when used in conjunction with benzodiazepines, antihistamines, or barbiturates. Chronic consumption can lead to severe liver disease, gastritis, and nutritional deficiencies. Cardiomyopathy is also a consequence of heavy drinking. The treatment of choice for alcohol withdrawal is the benzodiazepines. Carbamazepine is effective in treating convulsive episodes during withdrawal. G. Drugs to treat alcohol dependence 1. Disulfiram: Disulfiram [dye-SUL-fi-ram] blocks the oxidation of acetaldehyde to acetic acid by inhibiting aldehyde dehydrogenase (see Figure 9.11). This results in the accumulation of acetaldehyde in the blood, causing flushing, tachycardia, hyperventilation, and nausea. Disulfiram has found some use in the patient seriously desiring to stop alcohol ingestion. A conditioned avoidance response is induced so that the patient abstains from alcohol to prevent the unpleasant effects of disulfiram-induced acetaldehyde accumulation. 2. Naltrexone: Naltrexone [nal-TREX-own] is a long-acting opiate antagonist that should be used in conjunction with supportive psychotherapy. Naltrexone is better tolerated than disulfiram and does not produce the aversive reaction that disulfiram does. 3. Acamprosate: Acamprosate [AK-om-PRO-sate] is an agent used in alcohol dependence treatment programs with an as yet poorly Pharm 5th 3-21-11.indb 120 3/21/11 2:21:55 PM VI. Other Hypnotic Agents. 121 understood mechanism of action. This agent should also be used in conjunction with supportive psychotherapy. Figure 9.12 summarizes the therapeutic disadvantages and advantages of some of the anxiolytic and hypnotic drugs. Therapeutic Disadvantages Therapeutic Advantages Benzodiazepines Clonazepam Potential use in chronic therapy for seizures. Clorazepate Chlordiazepoxide Diazepam The benzodiazepines may disturb intellectual functioning and motor dexterity. Flurazepam The benzodiazepines have the potential for dependence, and withdrawal seizures may occur. Alprazolam Quazepam Lorazepam Temazepam Withdrawal of drug often results in rebound insomnia. No muscle relaxatio nor anticonvulsant activity. Have no anticonvulsant or musclerelaxing properties. Buspirone Do not require Phase I metabolism and, therefore, show fewer drug interactions and are safer in patients with hepatic impairment. Useful in long-term therapy for chronic anxiety with symptoms of irritability and hostility. Does not potentiate the CNS depression of alcohol. Low potential for addiction. Eszopiclone Hydroxyzine Effective for up to 6 months. Zaleplon Show minimal withdrawal effects. Zolpidem Exhibit minimal rebound insomnia. Ramelteon Little or no tolerance occurs with pronged use. Has only marginal effects on objective measures of sleep efficacy. Barbiturates The barbiturates induce tolerance, drug-metabolizing enzymes, and physical dependence, and they show severe withdrawal symptoms. Agent of choice in treating panic disorders. Triazolam Other agents Slower onset of action than benzodiazepines. These less potent and more slowly eliminated drugs show no rebound insomnia on discontinuation of treatment. The potential for abuse is minimal with minimal dependence or withdrawal effects. The drug can be administered long-term. Phenobarbital Pentobarbital Secobarbital Amobarbital Rapid onset of action. Thiopental Figure 9.12 Therapeutic disadvantages and advantages of some anxiolytic and hypnotic agents. CNS = central nervous system. Pharm 5th 3-21-11.indb 121 3/21/11 2:21:59 PM 122 9. Anxiolytic and Hypnotic Drugs Study Questions Choose the ONE best answer. 9.1 Which one of the following statements is correct? A. Benzodiazepines directly open chloride channels. B. Benzodiazepines show analgesic actions. C. Clinical improvement of anxiety requires 2 to 4 weeks of treatment with benzodiazepines. D. All benzodiazepines have some sedative effects. E. Benzodiazepines, like other central nervous system depressants, readily produce general anesthesia. 9.2 Which one of the following is a short-acting hypnotic? A. Phenobarbital. B. Diazepam. C. Chlordiazepoxide. D. Triazolam. E. Flurazepam. Correct answer = D. Although all benzodiazepines can cause sedation, the drugs labeled “benzodiazepines” in Figure 9.1 are promoted for the treatment of sleep disorder. Benzodiazepines enhance the binding of γ-aminobutyric acid to its receptor, which increases the permeability of chloride. The benzodiazepines do not relieve pain but may reduce the anxiety associated with pain. Unlike the tricyclic antidepressants and the monoamine oxidase inhibitors, the benzodiazepines are effective within hours of administration. Benzodiazepines do not produce general anesthesia and, therefore, are relatively safe drugs with a high therapeutic index. Correct answer = D. Triazolam is an ultrashort-acting drug used as an adjuvant to dental anesthesia. The other drugs listed are not as short acting. 9.3 Which one of the following statements is correct? A. Phenobarbital shows analgesic properties. B. Diazepam and phenobarbital induce the cytochrome P450 enzyme system. C. Phenobarbital is useful in the treatment of acute intermittent porphyria. D. Phenobarbital induces respiratory depression, which is enhanced by the consumption of ethanol. E. Buspirone has actions similar to those of the benzodiazepines. 9.4 A 45-year-old man who has been injured in a car accident is brought into the emergency room. His blood alcohol level on admission is 275 mg/dL. Hospital records show a prior hospitalization for alcohol-related seizures. His wife confirms that he has been drinking heavily for 3 weeks. What treatment should be provided to the patient if he goes into withdrawal? Correct answer = D. Barbiturates and ethanol are a potentially lethal combination. Phenobarbital is unable to alter the pain threshold. Only phenobarbital strongly induces the synthesis of the hepatic cytochrome P450 drug-metabolizing system. Phenobarbital is contraindicated in the treatment of acute intermittent porphyria. Buspirone lacks the anticonvulsant and muscle-relaxant properties of the benzodiazepines and causes only minimal sedation. Correct answer = B. It is important to treat the seizures associated with alcohol withdrawal. Benzodiazepines, such as chlordiazepoxide, diazepam, or the shorter-acting lorazepam, are effective in controlling this problem. They are less sedating than pentobarbital or phenytoin. A. None. B. Lorazepam. C. Pentobarbital. D. Phenytoin. E. Buspirone. Pharm 5th 3-21-11.indb 122 3/21/11 2:21:59 PM 10 CNS Stimulants I. OVERVIEW This chapter describes two groups of drugs that act primarily to stimulate the central nervous system (CNS). The first group, the psychomotor stimulants, cause excitement and euphoria, decrease feelings of fatigue, and increase motor activity. The second group, the hallucinogens, or psychotomimetic drugs, produce profound changes in thought patterns and mood, with little effect on the brainstem and spinal cord. Figure 10.1 summarizes the CNS stimulants. As a group, the CNS stimulants have diverse clinical uses and are important as drugs of abuse, as are the CNS depressants described in Chapter 9 and the narcotics described in Chapter 14 (Figure 10.2). II. PSYCHOMOTOR STIMULANTS A. Methylxanthines The methylxanthines include theophylline [thee-OFF-i-lin], which is found in tea; theobromine [thee-o-BRO-min], found in cocoa; and caffeine [kaf-EEN]. Caffeine, the most widely consumed stimulant in the world, is found in highest concentration in coffee, but it is also present in tea, cola drinks, chocolate candy, and cocoa. 1. Mechanism of action: Several mechanisms have been proposed for the actions of methylxanthines, including translocation of extracellular calcium, increase in cyclic adenosine monophosphate and cyclic guanosine monophosphate caused by inhibition of phosphodiesterase, and blockade of adenosine receptors. The latter most likely accounts for the actions achieved by the usual consumption of caffeine-containing beverages. PSYCHOMOTOR STIMULANTS Amphetamine ADDERALL Armodafinil NUVIGIL Atomoxetine STRATTERA Caffeine CAFCIT, NO DOZ, VIVARIN Cocaine Dexmethylphenidate FOCALIN Dextroamphetamine DEXEDRINE, DEXTROSTAT Lisdexamfetamine VYVANSE Methylphenidate RITALIN, CONCERTA, DAYTRANA Modafinil PROVIGIL Nicotine COMMIT, NICODERM CQ, NICORETTE Theophylline ELIXOPHYLLIN, THEO-24, THEOCHRON, UNIPHYL Varenicline CHANTIX HALLUCINOGENS Dronabinol MARINOL Lysergic acid diethylamide (LSD) Phencyclidine (PCP) Tetrahydrocannabinol (THC) Figure 10.1 Summary of central nervous system (CNS) stimulants. 2. Actions: a. CNS: The caffeine contained in one to two cups of coffee (100– 200 mg) causes a decrease in fatigue and increased mental alertness as a result of stimulating the cortex and other areas of the brain. Consumption of 1.5 g of caffeine (12 to 15 cups of coffee) produces anxiety and tremors. The spinal cord is stimulated only by very high doses (2–5 g) of caffeine. Tolerance can rapidly develop to the stimulating properties of caffeine, and withdrawal consists of feelings of fatigue and sedation. b. Cardiovascular system: A high dose of caffeine has positive inotropic and chronotropic effects on the heart. [Note: Increased contractility can be harmful to patients with angina Pharm 5th 3-21-11.indb 123 3/21/11 2:22:00 PM 124 10. CNS Stimulants pectoris. In others, an accelerated heart rate can trigger premature ventricular contractions.] CNS STIMULANTS Caffeine c. Diuretic action: Caffeine has a mild diuretic action that increases urinary output of sodium, chloride, and potassium. Nicotine Cocaine d. Gastric mucosa: Because all methylxanthines stimulate secretion of hydrochloric acid from the gastric mucosa, individuals with peptic ulcers should avoid foods and beverages containing methylxanthines. Amphetamines HALLUCINOGENS LSD 3. Therapeutic uses: Caffeine and its derivatives relax the smooth muscles of the bronchioles. [Note: Previously the mainstay of asthma therapy, theophylline has been largely replaced by other agents, such as β2 agonists and corticosteroids.] Cannabis Phencyclidine CNS DEPRESSANTS 4. Pharmacokinetics: The methylxanthines are well absorbed orally. Caffeine distributes throughout the body, including the brain. These drugs cross the placenta to the fetus and are secreted into the mother's milk. All the methylxanthines are metabolized in the liver, generally by the CYP1A2 pathway, and the metabolites are then excreted in the urine. Ethanol Barbiturates Benzodiazepines NARCOTICS Morphine Heroin Low High Figure 10.2 Relative potential for physical dependence on commonly abused substances. LSD = lysergic acid diethylamide. Low doses of nicotine Arousal and relaxation High doses of nicotine Respiratory paralysis Figure 10.3 Actions of nicotine on the central nervous system. Pharm 5th 3-21-11.indb 124 5. Adverse effects: Moderate doses of caffeine cause insomnia, anxiety, and agitation. A high dosage is required for toxicity, which is manifested by emesis and convulsions. The lethal dose is 10 g of caffeine (about 100 cups of coffee), which induces cardiac arrhythmias. Death from caffeine is, therefore, highly unlikely. Lethargy, irritability, and headache occur in users who routinely consumed more than 600 mg of caffeine per day (roughly six cups of coffee per day) and then suddenly stop. B. Nicotine Nicotine [NIK-o-teen] is the active ingredient in tobacco. Although this drug is not currently used therapeutically (except in smoking cessation therapy), nicotine remains important because it is second only to caffeine as the most widely used CNS stimulant, and it is second only to alcohol as the most abused drug. In combination with the tars and carbon monoxide found in cigarette smoke, nicotine represents a serious risk factor for lung and cardiovascular disease, various cancers, and other illnesses. Dependency on the drug is not easily overcome. 1. Mechanism of action: In low doses, nicotine causes ganglionic stimulation by depolarization. At high doses, nicotine causes ganglionic blockade. Nicotine receptors exist at a number of sites in the CNS, which participate in the stimulant attributes of the drug. 2. Actions: a. CNS: Nicotine is highly lipid soluble and readily crosses the bloodbrain barrier. Cigarette smoking or administration of low doses of nicotine produces some degree of euphoria and arousal as well as relaxation. It improves attention, learning, problem solving, and reaction time. High doses of nicotine result in central respiratory paralysis and severe hypotension caused by medullary paralysis (Figure 10.3). Nicotine is also an appetite suppressant. 3/21/11 2:22:01 PM II. Psychomotor Stimulants b. Peripheral effects: The peripheral effects of nicotine are complex. Stimulation of sympathetic ganglia as well as the adrenal medulla increases blood pressure and heart rate. Thus, use of tobacco is particularly harmful in hypertensive patients. Many patients with peripheral vascular disease experience an exacerbation of symptoms with smoking. For example, nicotineinduced vasoconstriction can decreased coronary blood flow, adversely affecting a patient with angina. Stimulation of parasympathetic ganglia also increases motor activity of the bowel. At higher doses, blood pressure falls, and activity ceases in both the gastrointestinal (GI) tract and bladder musculature as a result of a nicotine-induced block of parasympathetic ganglia. 3. Pharmacokinetics: Because nicotine is highly lipid soluble, absorption readily occurs via the oral mucosa, lungs, GI mucosa, and skin. Nicotine crosses the placental membrane and is secreted in the milk of lactating women. By inhaling tobacco smoke, the average smoker takes in 1 to 2 mg of nicotine per cigarette (most cigarettes contain 6 to 8 mg of nicotine). The acute lethal dose is 60 mg. More than 90 percent of the nicotine inhaled in smoke is absorbed. Clearance of nicotine involves metabolism in the lung and the liver and urinary excretion. Tolerance to the toxic effects of nicotine develops rapidly, often within days after beginning usage. 125 Potential for Addiction Nicotine Figure 10.4 Nicotine has potential for addiction. 20 4. Adverse effects: The CNS effects of nicotine include irritability and tremors. Nicotine may also cause intestinal cramps, diarrhea, and increased heart rate and blood pressure. In addition, cigarette smoking increases the rate of metabolism for a number of drugs. C. Varenicline Varenicline [ver-EN-ih-kleen] is a partial agonist at neuronal nicotinic acetylcholine receptors in the CNS. Because varenicline is only a partial agonist at these receptors, it produces less euphoric effects than those produced by nicotine itself (nicotine is a full agonist at these receptors). Thus, it is useful as an adjunct in the management of smoking cessation in patients with nicotine withdrawal symptoms. Additionally, varenicline tends to attenuate the rewarding effects of nicotine if a person relapses and uses tobacco. Patients should be monitored for suicidal thoughts, vivid nightmares, and mood changes. Pharm 5th 3-21-11.indb 125 10 5 Blood nicotine concentration (ng/mL) 5. Withdrawal syndrome: As with the other drugs in this class, nicotine is an addictive substance, and physical dependence develops rapidly and can be severe (Figure 10.4). Withdrawal is characterized by irritability, anxiety, restlessness, difficulty concentrating, headaches, and insomnia. Appetite is affected, and GI pain often occurs. [Note: Smoking cessation programs that combine pharmacologic and behavioral therapy are the most successful in helping individuals to stop smoking.] The transdermal patch and chewing gum containing nicotine have been shown to reduce nicotine withdrawal symptoms and to help smokers stop smoking. For example, the blood concentration of nicotine obtained from nicotine chewing gum is typically about one-half the peak level observed with smoking (Figure 10.5). Bupropion, an antidepressant (see p. 155), can reduce the craving for cigarettes. CIGARETTES 15 11/3 cigarettes 0 20 NICOTINE GUM 15 10 5 0 Two pieces of gum -10 0 30 60 90 120 20 TRANSDERMAL PATCH 15 10 5 0 Patch in place -10 0 30 60 90 Minutes 120 600 Figure 10.5 Blood concentrations of nicotine in individuals who smoked cigarettes, chewed nicotine gum, or received nicotine by transdermal patch. 3/21/11 2:22:01 PM 126 10. CNS Stimulants D. Cocaine Cocaine [KOE-kane] is a widely available and highly addictive drug that is currently abused daily by more than 3 million people in the United States. Because of its abuse potential, cocaine is classified as a Schedule II drug by the U.S. Drug Enforcement Agency. NEURON Norepinephrine Serotonin Dopamine Cocaine INCREASED RESPONSE Figure 10.6 Mechanism of action of cocaine. Potential for addiction Cocaine Amphetamine Figure 10.7 Cocaine and amphetamine have potential for addiction. 1. Mechanism of action: The primary mechanism of action underlying the central and peripheral effects of cocaine is blockade of reuptake of the monoamines (norepinephrine, serotonin, and dopamine) into the presynaptic terminals from which these neurotransmitters are released (Figure 10.6). This blockade is caused by cocaine binding to the monoaminergic reuptake transporters, and, thus, potentiates and prolongs the CNS and peripheral actions of these monoamines. In particular, the prolongation of dopaminergic effects in the brain's pleasure system (limbic system) produces the intense euphoria that cocaine initially causes. Chronic intake of cocaine depletes dopamine. This depletion triggers the vicious cycle of craving for cocaine that temporarily relieves severe depression (Figure 10.7). 2. Actions: a. CNS: The behavioral effects of cocaine result from powerful stimulation of the cortex and brainstem. Cocaine acutely increases mental awareness and produces a feeling of wellbeing and euphoria similar to that caused by amphetamine. Like amphetamine, cocaine can produce hallucinations and delusions of paranoia or grandiosity. Cocaine increases motor activity, and, at high doses, it causes tremors and convulsions, followed by respiratory and vasomotor depression. b. Sympathetic nervous system: Peripherally, cocaine potentiates the action of norepinephrine, and it produces the “fight-orflight” syndrome characteristic of adrenergic stimulation. This is associated with tachycardia, hypertension, pupillary dilation, and peripheral vasoconstriction. Recent evidence suggests that the ability of baroreceptor reflexes to buffer the hypertensive effect may be impaired. c. Hyperthermia: Cocaine is unique among illicit drugs in that death can result not only as a function of dose, but also from the drug's propensity to cause hyperthermia. [Note: Mortality rates for cocaine overdose rise in hot weather.] Even a small dose of intranasal cocaine impairs sweating and cutaneous vasodilation. Perception of thermal discomfort is also decreased. 3. Therapeutic uses: Cocaine has a local anesthetic action that represents the only current rationale for the therapeutic use of cocaine. For example, cocaine is applied topically as a local anesthetic during eye, ear, nose, and throat surgery. Whereas the local anesthetic action of cocaine is due to a block of voltage-activated sodium channels, an interaction with potassium channels may contribute to the ability of cocaine to cause cardiac arrhythmias. [Note: Cocaine is the only local anesthetic that causes vasoconstriction. This effect is responsible for the necrosis and perforation of the nasal septum seen in association with chronic inhalation of cocaine powder.] Pharm 5th 3-21-11.indb 126 3/21/11 2:22:02 PM II. Psychomotor Stimulants 127 4. Pharmacokinetics: Cocaine is often self-administered by chewing, intranasal snorting, smoking, or intravenous (IV) injection. The peak effect occurs 15 to 20 minutes after intranasal intake of cocaine powder, and the “high” disappears in 1 to 1.5 hours. Rapid but short-lived effects are achieved following IV injection of cocaine or by smoking the freebase form of the drug (“crack”). Because the onset of action is most rapid, the potential for overdosage and dependence is greatest with IV injection and crack smoking. Cocaine is rapidly de-esterified and demethylated to benzoylecgonine, which is excreted in the urine. Detection of this substance in the urine identifies a user. Euphoria Tachycardia Respiration rate 5. Adverse effects: a. Anxiety: The toxic response to acute cocaine ingestion can precipitate an anxiety reaction that includes hypertension, tachycardia, sweating, and paranoia. [Note: Little tolerance to the toxic CNS effects of cocaine (for example, convulsions) occurs with prolonged use.] Because of the irritability, many users take cocaine with alcohol. A product of cocaine metabolites and ethanol is cocaethylene, which is also psychoactive and believed to contribute to cardiotoxicity. b. Depression: As with all stimulant drugs, cocaine stimulation of the CNS is followed by a period of mental depression. Addicts withdrawing from cocaine exhibit physical and emotional depression as well as agitation. The latter symptom can be treated with benzodiazepines or phenothiazines. c. Toxic effects: Cocaine can induce seizures as well as fatal cardiac arrhythmias (Figure 10.8). Use of IV diazepam may be required to control cocaine-induced seizures. The incidence of myocardial infarction in cocaine users is unrelated to dose, to duration of use, or to route of administration. There is no marker to identify those individuals who may have life-threatening cardiac effects after taking cocaine. Agitation Hypertension BP Dyspnea Seizure Arrhythmias E. Amphetamine Amphetamine [am-FET-a-meen] is a sympathetic amine that shows neurologic and clinical effects quite similar to those of cocaine. Dextroamphetamine [dex-troe-am-FET-a-meen] is the major member of this class of compounds. Methamphetamine [meth-am-FET-a-mine] (also known as “speed”) is a derivative of amphetamine available for prescription use. It can also be smoked and is preferred by many abusers. 3,4-Methylenedioxymethamphetamine (also known as MDMA, or Ecstasy), a synthetic derivative of methamphetamine with both stimulant and hallucinogenic properties, is discussed on p. 537 1. Mechanism of action: As with cocaine, the effects of amphetamine on the CNS and peripheral nervous system are indirect. That is, both depend upon an elevation of the level of catecholamine neurotransmitters in synaptic spaces. Amphetamine, however, achieves this effect by releasing intracellular stores of catecholamines (Figure 10.9). Because amphetamine also inhibits monoamine oxidase (MAO), high levels of catecholamines are readily released into synaptic spaces. Despite different mechanisms of action, the behavioral Pharm 5th 3-21-11.indb 127 Respiratory failure R.I.P. Figure 10.8 Major effects of cocaine use. 3/21/11 2:22:03 PM 128 10. CNS Stimulants A No amphetamine effects of amphetamine and its derivatives are similar to those of cocaine. 2. Actions: Norepinephrine Serotonin Dopamine RESPONSE B With amphetamine + Amphetamine Norepinephrine Serotonin Dopamine INCREASED RESPONSE Figure 10.9 Mechanism of action of amphetamine. Pharm 5th 3-21-11.indb 128 a. CNS: The major behavioral effects of amphetamine result from a combination of its dopamine and norepinephrine releaseenhancing properties. Amphetamine stimulates the entire cerebrospinal axis, cortex, brainstem, and medulla. This leads to increased alertness, decreased fatigue, depressed appetite, and insomnia. These CNS stimulant effects of amphetamine and its derivatives have led to their use in therapy for hyperactivity in children, for narcolepsy, and for appetite control. At high doses, psychosis and convulsions can ensue. b. Sympathetic nervous system: In addition to its marked action on the CNS, amphetamine acts on the adrenergic system, indirectly stimulating the receptors through norepinephrine release. 3. Therapeutic uses: Factors that limit the therapeutic usefulness of amphetamine include psychological and physiological dependence similar to those with cocaine and, with chronic use, the development of tolerance to the euphoric and anorectic effects. a. Attention deficit hyperactivity disorder (ADHD): Some young children are hyperkinetic and lack the ability to be involved in any one activity for longer than a few minutes. Dextroam phetamine and the amphetamine derivative methylphenidate [meth-ill-FEN-ih-date] can help improve attention spans and alleviate many of the behavioral problems associated with this syndrome, in addition to reducing the hyperkinesia that such children demonstrate. Lisdexamfetamine [lis-dex-am-FET-ameen] is a prodrug that is converted to the active component dextroamphetamine after GI absorption and metabolism. Lisdexamfetamine prolongs the patient's span of attention, allowing better function in a school atmosphere. Atomoxetine [AT-oh-MOX-ih-teen] is a nonstimulant drug approved for ADHD in children and adults. [Note: This drug should not be taken by individuals on MAO inhibitors and by patients with narrow-angle glaucoma.] Unlike methylphenidate, which blocks dopamine reuptake, atomoxetine is a norepinephrine-reuptake inhibitor. Therefore, it is not habit forming and is not a controlled substance. b. Narcolepsy: Narcolepsy is a relatively rare sleep disorder that is characterized by uncontrollable bouts of sleepiness during the day. It is sometimes accompanied by catalepsy, a loss in muscle control, and even paralysis brought on by strong emotions such as laughter. However, it is the sleepiness for which the patient is usually treated with drugs, such as amphetamine or methylphenidate. Recently, a newer drug, modafinil [moe-DA-fi-nil], and its R-enantiomer derivative, armodafinil [ahr-moe-DA-fi-nil], have become available to treat narcolepsy. Modafinil produces fewer psychoactive and euphoric effects as well as fewer alterations in mood, perception, thinking, and feelings typical of other CNS stimulants. It does promote wakefulness. The mechanism of action remains unclear, but may involve the adrenergic and 3/21/11 2:22:04 PM II. Psychomotor Stimulants 129 dopaminergic systems, although it has been shown to differ from that of amphetamine. Modafinil is effective orally. It is well distributed throughout the body and undergoes extensive hepatic metabolism. The metabolites are excreted in urine. Headaches, nausea, and rhinitis are the primary adverse effects. There is some evidence to indicate the potential for abuse and physical dependence with modafinil. 4. Pharmacokinetics: Amphetamine is completely absorbed from the GI tract, metabolized by the liver, and excreted in the urine. [Note: Administration of urinary alkalinizing agents will increase the nonionized species of the drug and decrease its excretion.] Amphetamine abusers often administer the drugs by IV injection and/or by smoking. The euphoria caused by amphetamine lasts 4 to 6 hours, or fourto eightfold longer than the effects of cocaine. 5. Adverse effects: The amphetamines may cause addiction, leading to dependence, tolerance, and drug-seeking behavior. In addition, they have the following undesirable effects. a. CNS effects: Undesirable side effects of amphetamine usage include insomnia, irritability, weakness, dizziness, tremor, and hyperactive reflexes (Figure 10.10). Amphetamine can also cause confusion, delirium, panic states, and suicidal tendencies, especially in mentally ill patients. Chronic amphetamine use produces a state of “amphetamine psychosis” that resembles the psychotic episodes associated with schizophrenia. Whereas long-term amphetamine use is associated with psychic and physical dependence, tolerance to its effects may occur within a few weeks. Overdoses of amphetamine are treated with chlorpromazine or haloperidol, which relieve the CNS symptoms as well as the hypertension because of their α-blocking effects. The anorectic effect of amphetamine is due to its action in the lateral hypothalamic feeding center. b. Cardiovascular effects: In addition to its CNS effects, amphetamine causes palpitations, cardiac arrhythmias, hypertension, anginal pain, and circulatory collapse. Headache, chills, and excessive sweating may also occur. Because of its cardiovascular effects, amphetamine should not be given to patients with cardiovascular disease and those receiving MAO inhibitors. c. GI system effects: Amphetamine acts on the GI system, causing anorexia, nausea, vomiting, abdominal cramps, and diarrhea. Administration of sodium bicarbonate will increase the reabsorption of dextroamphetamine from the renal tubules into the bloodstream. d. Contraindications: Neither patients with hypertension, cardiovascular disease, hyperthyroidism, or glaucoma should be treated with this drug, nor should patients with a history of drug abuse, nor anyone taking MAO inhibitors. Vertigo Hypertension BP Insomnia Confusion Potential for addiction Nausea Diarrhea Figure 10.10 Adverse effects of amphetamines. F. Methylphenidate Methylphenidate has CNS-stimulant properties similar to those of amphetamine and may also lead to abuse, although its addictive poten- Pharm 5th 3-21-11.indb 129 3/21/11 2:22:05 PM 130 10. CNS Stimulants tial is controversial. It is a Schedule II drug. It is presently one of the most prescribed medications in children. It is estimated that 4 to 6 million children in the United State take methylphenidate daily for ADHD. The pharmacologically active isomer, dexmethylphenidate, has also been approved in the United States for the treatment of ADHD. 1. Mechanism of action: Children with ADHD may produce weak dopamine signals, which suggests that once-interesting activities provide fewer rewards to these children. Methylphenidate is a dopamine transport inhibitor and may act by increasing dopamine in the synaptic space. [Note: Methylphenidate may have less potential for abuse than cocaine, because it enters the brain much more slowly than cocaine and, thus, does not increase dopamine levels as rapidly.] 2. Therapeutic uses: Methylphenidate has been used for several decades in the treatment of ADHD in children ages 6 to 16 years. It is also effective in the treatment of narcolepsy. Unlike methylphenidate, dexmethylphenidate is not indicated in the treatment of narcolepsy. 3. Pharmacokinetics: Both methylphenidate and dexmethylphenidate are readily absorbed upon oral administration. Methylphenidate is available in extended release capsules and as a transdermal patch. The de-esterified product, ritalinic acid, is excreted in urine. 4. Adverse reactions: GI effects are the most common and include abdominal pain and nausea. Other reactions include anorexia, insomnia, nervousness, and fever. In seizure patients, methylphenidate seems to increase the seizure frequency, especially if the patient is taking antidepressants. Methylphenidate is contraindicated in patients with glaucoma. 5. Drug interactions: Studies have shown that methylphenidate can interfere in the metabolism of warfarin, phenytoin, phenobarbital, primidone, and the tricyclic antidepressants. III. HALLUCINOGENS A few drugs have, as their primary action, the ability to induce altered perceptual states reminiscent of dreams. Many of these altered states are accompanied by visions of bright, colorful changes in the environment and by a plasticity of constantly changing shapes and color. The individual under the influence of these drugs is incapable of normal decision-making because the drug interferes with rational thought. These compounds are known as hallucinogens or psychotomimetic drugs. A. Lysergic acid diethylamide Multiple sites in the CNS are affected by lysergic acid diethylamide (LSD). The drug shows serotonin (5-HT) agonist activity at presynaptic 5-HT1 receptors in the midbrain, and it stimulates 5-HT2 receptors. Activation of the sympathetic nervous system occurs, which causes pupillary dilation, increased blood pressure, piloerection, and increased body temperature. Taken orally, low doses of LSD can induce hallucinations with brilliant colors. Mood alteration also occurs. Tolerance and physical dependence have occurred, but true dependence is rare. Adverse effects include hyperreflexia, nausea, and muscular weakness. High doses may produce long-lasting psychotic changes in susceptible indi- Pharm 5th 3-21-11.indb 130 3/21/11 2:22:05 PM III. Hallucinogens 131 GABA or glutamate 4 PRESYNAPTIC NEURON 3 Activated receptor modulates release of inhibitory neurotransmitters, such as GABA. Presynaptic cannabinoid receptor Endocannabinoids bind to the cannabinoid receptors on the presynaptic neuron that form synapses with the stimulated neuron. 1 Excitation of postsynaptic neuron causes its depolarization and an influx of Ca^{2+}. 2 Elevated Ca^{2+} levels stimulate the synthesis and release of endocannabinoids. Ca^{2+} Endocannabinoids + POSTSYNAPTIC NEURON Ca^{2+} GABA or glutamate receptor Figure 10.11 Cannabinoid receptor. GABA = γ-aminobutyric aid. viduals. Haloperidol and other neuroleptics can block the hallucinatory action of LSD and quickly abort the syndrome. B. Tetrahydrocannabinol The main psychoactive alkaloid contained in marijuana is Δ9-tetrahydrocannabinol [tet-ra-HY-dro-can-NAB-i-nol] (THC), which is available as dronabinol [droe-NAB-i-nol]. This product is prescribed to treat emesis and to stimulate the appetite. Depending on the social situation, THC can produce euphoria, followed by drowsiness and relaxation. In addition to adversely affecting short-term memory and mental activity, THC decreases muscle strength and impairs highly skilled motor activity such as that required to drive a car. Its wide range of effects includes appetite stimulation, xerostomia, visual hallucinations, delusions, and enhancement of sensory activity. THC receptors, designated CB1 receptors, have been found on inhibitory presynaptic nerve terminals that interact synaptically with pyramidal neurons. CB1 is coupled to a G protein. Interestingly, like the endogenous ligands of the opioid system, endocannabinoids have been identified in the CNS. These compounds, which bind to the CB1 receptors, are membrane derived and synthesized on demand, and they may act as local neuromodulators (Figure 10.11). The action of THC is believed to be mediated through the CB1 receptors, but this is still under investigation. The effects of THC appear immediately after the drug is smoked, but maximum effects take about 20 minutes. By 3 hours, the effects largely disappear. Dronabinol is administered orally and has a peak effect in 2 to 4 hours. Its psychoactive effects can last up to 6 hours, but its appetite-stimulant effects may persist for 24 hours. It is highly lipid soluble and has a large volume of distribution. THC itself is extensively metabolized by the mixed-function oxidases. Elimination is largely through the biliary route. Adverse effects include increased heart rate, decreased blood pressure, and reddening of the conjunctiva. At high doses, a toxic psychosis develops Pharm 5th 3-21-11.indb 131 Tachycardia Hypertension BP Hallucinations Figure 10.12 Adverse effects of tetrahydrocannabinol. 3/21/11 2:22:06 PM 132 10. CNS Stimulants (Figure 10.12). Tolerance and mild physical dependence occur with continued, frequent use of the drug. Dronabinol is indicated as an appetite stimulant for patients with acquired immunodeficiency syndrome who are losing weight. It is also sometimes given for the severe emesis caused by some cancer chemotherapeutic agents. The CB1-receptor antagonist, rimonabant [ri-MOH-nah-bant], is effective in the treatment of obesity and has been found to decrease appetite and body weight in humans. Rimonabant is not currently available in the United States because, during clinical trials, it was found to induce psychiatric disturbances, such as anxiety and depression, which may limit its use. C. Phencyclidine Phencyclidine [fen-SYE-kli-deen] (also known as PCP, or “angel dust”) inhibits the reuptake of dopamine, 5-HT, and norepinephrine. Phencyclidine has anticholinergic activity but, surprisingly, produces hypersalivation. Phencyclidine, an analog of ketamine, causes dissociative anesthesia (insensitivity to pain without loss of consciousness) and analgesia. In this state, it produces numbness of extremities, staggered gait, slurred speech, and muscular rigidity. Sometimes, hostile and bizarre behavior is seen. At increased dosages, anesthesia, stupor, and coma may result but, strangely, the eyes may remain open. Increased sensitivity to external stimuli results, and the CNS actions may persist for a week. Tolerance often develops with continued use. Phencyclidine has no therapeutic applications, and manufacture of the drug in the United States is illegal. Study Question Choose the ONE best answer. 10.1 A very agitated young male was brought to the emergency room by the police. Psychiatric examination revealed that he had snorted cocaine several times in the past few days, the last time being 10 hours previously. He was given a drug that sedated him, and he fell asleep. The drug that was used to counter this patient's apparent cocaine withdrawal was very likely: A. Phenobarbital. B. Lorazepam. C. Cocaine. D. Hydroxyzine. E. Fluoxetine. Pharm 5th 3-21-11.indb 132 Correct answer = B. The anxiolytic properties of benzodiazepines, such as lorazepam, make them the drugs of choice in treating the anxiety and agitation of cocaine withdrawal. Lorazepam also has hypnotic properties. Phenobarbital has hypnotic properties, but its anxiolytic properties are inferior to those of the benzodiazepines. Cocaine itself could counteract the agitation of withdrawal, but its use would not be proper therapy. Hydroxyzine, an antihistamine, is effective as a hypnotic, and it is sometimes used to deal with anxiety, especially if emesis is a problem. Fluoxetine is an antidepressant with no immediate effects on anxiety. 3/21/11 2:22:07 PM Anesthetics 11 I. OVERVIEW PREANESTHETIC MEDICATIONS General anesthesia is a reversible state of central nervous system (CNS) depression, resulting in loss of response to and perception of external stimuli. For patients undergoing surgical and other medical procedures, anesthesia provides these five important benefits: • Sedation and reduction of anxiety • Lack of awareness and amnesia • Skeletal muscle relaxation • Suppression of undesirable reflexes • Analgesia Because no single agent provides all desirable properties, several categories of drugs are used in combination to produce optimal anesthesia (Figure 11.1). Preanesthetic medications serve to calm the patient, relieve pain, and protect against undesirable effects of subsequently administered anesthetics or the surgical procedure itself. Skeletal muscle relaxants facilitate intubation of the trachea and suppress muscle tone to the degree required for surgery. Potent general anesthetics are delivered via inhalation and/or intravenous (IV) injection. With the exception of nitrous oxide, modern inhaled anesthetics are all volatile, halogenated hydrocarbons. IV anesthetic agents consist of a number of chemically unrelated drug types that are commonly used for the rapid induction of anesthesia. II. PATIENT FACTORS IN SELECTION OF ANESTHESIA During preoperative planning, drugs are selected that will provide a safe and efficient anesthetic regimen based on the nature of the surgical or diagnostic procedure and the patient's physiologic, pathologic, and pharmacologic state. A. Status of organ systems 1. Cardiovascular system: Anesthetic agents suppress cardiovascular function to varying degrees. Ischemic injury to tissues throughout the body may follow reduced perfusion pressure if a hypotensive episode develops during anesthesia. Treatment with vasoactive substances may be necessary. Some anesthetics, such as halothane, may sensitize the heart to the arrhythmogenic effects of sympathomimetic agents. Pharm 5th 3-21-11.indb 133 Antacids Anticholinergics Antiemetics Antihistamines Benzodiazepines Opioids GENERAL ANESTHETICS: INHALED Desflurane SUPRANE Halothane FLUOTHANE Isoflurane FORANE Nitrous oxide NITROUS OXIDE Sevoflurane ULTANE GENERAL ANESTHETICS: INTRAVENOUS Barbiturates Benzodiazepines Dexmedetomidine PRECEDEX Etomidate AMIDATE Ketamine KETALAR Opioids Propofol DIPRIVAN NEUROMUSCULR BLOCKERS (see Ch.5) Cisatracurium, pancuronium, rocuronium, succinylcholine, vecuronium LOCAL ANESTHETICS: AMIDES Bupivacaine MARCAINE Lidocaine XYLOCAINE Mepivacaine CARBOCAINE Ropivacaine NAROPIN LOCAL ANESTHETICS: ESTERS Chloroprocaine NESACAINE Procaine NOVOCAINE Tetracaine PONTOCAINE Figure 11.1 Summary of common drugs used for anesthesia. See chapter 5 for summary of neuromuscular blocking agents 3/21/11 2:22:07 PM 134 11. Anesthetics Some functions of adjuncts to anesthesia Relieve anxiety (benzodiazepines) Prevent gastric acid secretion (H2 blockers) Prevent allergic reactions (antihistamines) Prevent aspiration of stomach contents and postsurgical nausea and vomiting (antiemetics) Provide analgesia (opioids) Prevent bradycardia and secretion of fluids into the respiratory tract (anticholinergic drugs) Facilitate intubation and relaxation (neuromuscular blocking agents) Figure 11.2 Components of balanced anesthesia. Pharm 5th 3-21-11.indb 134 2. Respiratory system: The condition of the patient's respiratory system must be considered for all anesthetics. For example, asthma and ventilation or perfusion abnormalities complicate control of an inhalation anesthetic. Inhaled

anesthetics depress the respiratory system and act as bronchodilators. IV anesthetic agents and opioids suppress respiration. These effects on pulmonary function may influence the ability to provide adequate ventilation and oxygenation during surgery and postoperatively. 3. Liver and kidney: Because the liver and kidney influence the longterm distribution and clearance of anesthetic agents and may also be the target organs for toxic effects, the physiologic status of these organs must be considered. The release of fluoride, bromide, and other metabolic products of the halogenated hydrocarbons can affect these organs, especially if the metabolites accumulate with repeated anesthetic administration over a short period of time. 4. Nervous system: The existence of neurologic disorders (for example, epilepsy, myasthenia gravis, neuromuscular disease, and compromised cerebral circulation) influences the selection of an anesthetic, as would a patient history suggestive of a genetically determined sensitivity to malignant hyperthermia (see p. 140). 5. Pregnancy: Special precautions should be kept in mind when anesthetics and adjunct drugs are administered to a pregnant woman. In early pregnancy, potential effects on organogenesis in the fetus are a major concern. Transient use of nitrous oxide has been reported to cause aplastic anemia in the unborn child. Oral clefts have occurred in the fetuses of women who have received benzodiazepines during early pregnancy. Benzodiazepines should not be used routinely during labor, because of resultant temporary hypotonia and altered thermoregulation in the newborn. B. Concomitant use of drugs 1. Multiple adjunct agents: Commonly, surgical patients receive one or more of the following preanesthetic medications: H_2 blockers, such as famotidine or ranitidine to reduce gastric acidity; benzodiazepines, such as midazolam or diazepam to allay anxiety and facilitate amnesia; opioids such as fentanyl for analgesia; antihistamines such as diphenhydramine for prevention of allergic reactions; antiemetics such as ondansetron to prevent nausea and the possible aspiration of stomach contents; and/or anticholinergics such as glycopyrrolate to prevent bradycardia and secretion of fluids into the respiratory tract (Figure 11.2). These agents facilitate smooth induction of anesthesia and, when administered concurrently, also lower the dose of anesthetic required to maintain the desired level of surgical anesthesia. However, such coadministration can also enhance undesirable anesthetic effects (for example, hypoventilation), and may produce negative effects that are not observed when each drug is given individually. 2. Concomitant use of additional nonanesthetic drugs: Surgical patients may be chronically exposed to agents for the treatment of underlying diseases, as well as to drugs of abuse that alter their response to anesthetics. For example, alcoholics have elevated levels of hepatic microsomal enzymes involved in the metabolism of anesthetics, and drug abusers may be overly tolerant of opioids. 3/21/11 2:22:07 PM III. Stages And Depth Of Anesthesia 135 III. STAGES AND DEPTH OF ANESTHESIA General anesthesia can be divided into three stages: induction, maintenance, and recovery. Induction is defined as the period of time from the onset of administration of the potent anesthetic to the development of effective surgical anesthesia in the patient. Maintenance provides a sustained surgical anesthesia. Recovery is the time from discontinuation of administration of anesthesia until consciousness and protective physiologic reflexes are regained. Induction of anesthesia depends on how fast effective concentrations of the anesthetic drug reach the brain, whereas recovery is essentially the reverse of induction and depends on how fast the anesthetic drug diffuses from the brain. Depth of anesthesia is the degree to which the CNS is depressed and is a useful parameter for individualizing anesthesia. A. Induction General anesthesia in adults is normally induced with an IV anesthetic like propofol, which produces unconsciousness within 30–40 seconds after injection. At that time, additional inhalation and/or IV drugs comprising the selected anesthetic combination may be given to produce the desired depth of surgical (Stage III, see below) anesthesia. [Note: This often includes coadministration of an IV skeletal muscle relaxant such as rocuronium, vecuronium, or succinylcholine to facilitate intubation and muscle relaxation.] For children without IV access, inhalation induction is used with nonpungent agents, such as halothane or sevoflurane, to induce general anesthesia. B. Maintenance of anesthesia Maintenance is the period during which the patient is surgically anesthetized. After administering the selected anesthetic mixture, the patient's vital signs and response to various stimuli are monitored continuously throughout the surgical procedure to carefully balance the amount of drug inhaled and/or infused with the depth of anesthesia. Anesthesia is commonly maintained by the administration of volatile anesthetics, which offer good control over the depth of anesthesia. Opioids such as fentanyl are often used for pain relief along with inhalation agents, because the latter are not good analgesics. IV infusions of various drugs may also be used during the maintenance phase. I Loss of pain sensation PAIN II Combative behavior C. Recovery Postoperatively, the anesthetic admixture is withdrawn, and the patient is monitored for the return of consciousness. For most anesthetic agents, recovery is the reverse of induction. That is, redistribution from the site of action (rather than metabolism of the anesthetic) underlies recovery. If skeletal muscle relaxants have not been fully metabolized, reversal agents may be used. The anesthesiologist continues to monitor the patient to be sure that he or she is fully recovered, with normal physiologic functions (for example, spontaneous respiration, acceptable blood pressure and heart rate, intact reflexes, etc.). Patients are observed for delayed reactions such as respiratory depression from opioids administered for postoperative pain control. D. Depth of anesthesia The depth of anesthesia has traditionally been divided into four sequential stages. Each stage is characterized by increased CNS depression, which is caused by accumulation of the anesthetic drug in the brain (Figure 11.3). [Note: These stages were discerned and defined with the Pharm 5th 3-21-11.indb 135 III Surgical anesthesia O.R. Z Z Z Z ZZ IV Medullary paralysis and death Figure 11.3 Stages of anesthesia. O.R. = operating room. 3/21/11 2:22:08 PM 136 11. Anesthetics original anesthetic ether, which produces a slow onset of anesthesia. With commonly used modern anesthetics, the stages are difficult to characterize clearly because of the rapid onset of surgical anesthesia.] 1. Stage I—Analgesia: Loss of pain sensation results from interference with sensory transmission in the spinothalamic tract. The patient progresses from conscious and conversational to drowsy. Amnesia and reduced awareness of pain occur as Stage II is approached. 2. Stage II—Excitement: The patient experiences delirium and possibly combative behavior. There is a rise and irregularity in blood pressure and respiration as well as a risk of laryngospasm. To shorten or eliminate this stage of anesthesia, a rapid acting agent, such as propofol, is given intravenously before inhalation anesthesia is administered. 3. Stage III—Surgical anesthesia: There is gradual loss of muscle tone and reflexes as the CNS is further depressed. Regular respiration and relaxation of skeletal muscles with eventual loss of spontaneous movement occur in this stage. This is the ideal stage of anesthesia for surgery. Continuous careful monitoring is required to prevent undesired progression into Stage IV. 4. Stage IV—Medullary paralysis: Severe depression of the respiratory and vasomotor centers occur during this stage. Death can rapidly ensue unless measures are taken to maintain circulation and respiration. IV. INHALATION ANESTHETICS Inhaled gases are a mainstay of anesthesia and are used primarily for the maintenance of anesthesia after administration of an IV agent. No single anesthetic is superior to another under all circumstances. One advantage of inhalation anesthetics is that the depth of anesthesia can be rapidly altered by changing the inhaled concentration of the drug. Inhalational general anesthetics have very steep dose-response curves. In addition, they have a very narrow therapeutic index (generally from 2 to 4), so the difference in drug concentrations causing no effect, surgical anesthesia, and severe cardiac and respiratory depression is small. No antagonists exist. To minimize waste and decrease cost, potent inhaled anesthetic agents are delivered in a recirculation system containing absorbents that remove carbon dioxide and allow re-breathing of the inhaled anesthetic. A. Common features of inhalation anesthetics Modern inhalation anesthetics are nonflammable, nonexplosive agents that include the gas nitrous oxide as well as a number of volatile, halogenated hydrocarbons. As a group, these agents decrease cerebrovascular resistance, resulting in increased perfusion of the brain. They also cause bronchodilation and decrease both spontaneous minute ventilation (volume of air per unit time moved into or out of the lungs) and hypoxic pulmonary vasoconstriction (increased pulmonary vascular resistance in poorly aerated regions of the lungs, which allows redirection of pulmonary blood flow to regions that are richer in oxygen content). The movement of these agents from the lungs to the different body compartments depends upon their solubility in blood and tissues as well as on blood flow. These factors play a role not only in induction, but also in recovery. Pharm 5th 3-21-11.indb 136 3/21/11 2:22:08 PM IV. Inhalation Anesthetics 137 B. Potency The potency of inhaled anesthetics is defined quantitatively as the minimum alveolar concentration (MAC). This is the end-tidal concentration of anesthetic gas needed to eliminate movement among 50 percent of patients challenged by a standardized skin incision. [Note: MAC is the median effective dose (ED_{50}) of the anesthetic.] MAC is usually expressed as the percentage of gas in a mixture required to achieve the effect. Numerically, MAC is small for potent anesthetics, such as sevoflurane, and large for less potent agents, such as nitrous oxide (N_2O). Therefore, the inverse of MAC is an index of the potency of the anesthetic. MAC values are useful in comparing pharmacologic effects of different anesthetics, because a high MAC equals low potency (Figure 11.4). Note that nitrous oxide alone cannot produce complete anesthesia, because an admixture with sufficient oxygen cannot approach its MAC value. The more lipid soluble an anesthetic, the lower the concentration of anesthetic needed to produce anesthesia and, thus, the higher the potency of the anesthetic. Factors that can increase MAC (and make the patient less sensitive) include hyperthermia (greater than 42° C), drugs that increase CNS catecholamines, and chronic ethanol abuse. Factors that can decrease MAC (and make the patient more sensitive) include increased age, hypothermia, pregnancy, sepsis, acute ethanol intoxication, concurrent administration of IV anesthetics, and α_2-adrenergic receptor agonists (such as clonidine and dexmedetomidine). Halothane 0.75% Isoflurane 1.2% 2% Sevoflurane 6% Desflurane Nitrous oxide 105% 0 2 4 6 100 MAC Percentage anesthetic gases Figure 11.4 Minimal alveolar concentrations (MAC) for anesthetic gases. C. Uptake and distribution of inhalation anesthetics The principal objective of inhalation anesthesia is to achieve a constant and optimal brain partial pressure (Pbr) of the inhaled anesthetic (partial pressure equilibrium between alveoli [PA] and brain [Pbr]). Thus, the alveoli are the "windows to the brain" for inhaled anesthetics. The partial pressure of an anesthetic gas at the origin of the respiratory pathway is the driving force that moves the anesthetic into the alveolar space and, thence, into the blood, which delivers the drug to the brain and various other body compartments. Because gases move from one compartment to another within the body according to partial pressure gradients, a steady state is achieved when the partial pressure in each of these compartments is equivalent to that in the inspired mixture. [Note: At equilibrium, alveolar partial pressure = arterial partial pressure = brain partial pressure, or PA = Pa = Pbr.] The time course for attaining this steady state is determined by the following factors: 1. Alveolar wash-in: This term refers to the replacement of the normal lung gases with the inspired anesthetic mixture. The time required for this process is directly proportional to the functional residual capacity of the lung (the volume of gas remaining in the lungs at the end of a normal expiration) and inversely proportional to the ventilatory rate. It is independent of the physical properties of the gas. As the partial pressure builds within the lung, anesthetic transfer from the lung begins. 2. Anesthetic uptake: Anesthetic uptake is the product of gas solubility in the blood, cardiac output, and the anesthetic gradient between alveolar and blood partial pressure gradients. a. Solubility in the blood: This is determined by a physical property of the anesthetic molecule called the blood/gas partition coeffi cient, which is the ratio of the concentration of an anesthetic in the blood phase to the concentration of the anesthetic in the gas Pharm 5th 3-21-11.indb 137 3/21/11 2:22:08 PM 138 11. Anesthetics Most soluble in blood Halothane 2.4 Isoflurane 1.4 Sevoflurane Nitrous Des0.65 oxide flurane 0.47 0.42 Blood/gas partition coefficient Figure 11.5 Blood/gas partition coefficients for some inhalation anesthetics. phase when the anesthetic is in equilibrium between the two phases (Figure 11.5). For inhaled anesthetics, think of the blood as a pharmacologically inactive reservoir. Drugs with low versus high solubility in blood differ in their speed of induction of anesthesia. For example, when an anesthetic gas with low blood solubility, such as nitrous oxide, diffuses from the alveoli into the circulation, little of the anesthetic dissolves in the blood. Therefore, the equilibrium between the inhaled anesthetic and arterial blood occurs rapidly, and relatively few additional molecules of anesthetic are required to raise arterial anesthetic partial pressure, thereby rapidly achieving a steady state. Agents with low solubility in blood, thus, quickly saturate the blood. In contrast, an anesthetic gas with high blood solubility, such as halothane, dissolves more completely in the blood, and greater amounts of the anesthetic and longer periods of time are required to raise blood partial pressure. This results in increased times of induction and recovery and slower changes in the depth of anesthesia in response to alterations in the concentration of the inhaled drug. The solubility in blood is ranked in the following order: halothane > isoflurane > sevoflurane > nitrous oxide > desflurane. b. Cardiac output : Cardiac output (CO) affects removal of anesthetic to peripheral tissues, which are not the site of action. For inhaled anesthetics, higher CO removes anesthetic from the alveoli faster (because of increased blood flow through the lungs) and thus slows the rate of rise in the alveolar concentration of the gas. It will therefore take longer for the gas to reach equilibrium between the alveoli and the site of action in the brain. Thus, for inhaled anesthetics, higher CO = slower induction. Again, for inhaled anesthetics, think of the blood as a pharmacologically inactive reservoir. A low CO (shock) speeds the rate of rise of the alveolar concentration of the gas, since there is less uptake (removal to peripheral tissues) to oppose input. [Note: For intravenous anesthetics see p. 144 for an explanation of effects of CO.] c. Alveolar to venous partial pressure gradient of the anesthetic: This is the driving force of anesthetic delivery. For all practical purposes, the pulmonary end-capillary anesthetic partial pressure may be considered equal to the alveolar anesthetic partial pressure if the patient does not have severe lung diffusion disease. The arterial circulation distributes the anesthetic to various tissues, and the pressure gradient drives free anesthetic gas into tissues. As the venous circulation returns blood depleted of anesthetic to the lung, more gas moves into the blood from the lung according to the partial pressure difference. The greater is the difference in anesthetic concentration between alveolar (arterial) to venous blood, the higher the uptake and the slower the induction. Over time, the partial pressure in the venous blood closely approximates the partial pressure in the inspired mixture. That is, no further net anesthetic uptake from the lung occurs. 3. Effect of different tissue types on anesthetic uptake: The time required for a particular tissue to achieve a steady state with the partial pressure of an anesthetic gas in the inspired mixture is inversely proportional to the blood flow to that tissue (that is, faster flow results in a more rapidly achieved steady state). It is also directly proportional to the capacity of that tissue to store anesthetic (that is, a Pharm 5th 3-21-11.indb 138 3/21/11 2:22:09 PM IV. Inhalation Anesthetics b. Skeletal muscles: These are poorly perfused during anesthesia. This, and the fact that they have a large volume, prolongs the time required to achieve steady state. c. Fat: This tissue is also poorly perfused. However, potent volatile general anesthetics are very lipid soluble. Therefore, fat has a large capacity to store anesthetic. This combination of slow delivery to a high-capacity compartment prolongs the time required to achieve steady state in that tissue. d. Bone, ligaments, and cartilage: These are poorly perfused and have a relatively low capacity to store anesthetic. Therefore, these tissues have only a slight impact on the time course of anesthetic distribution in the body. 4. Washout: When the administration of an inhalation anesthetic is discontinued, the body becomes the "source" that drives the anesthetic into the alveolar space. The same factors that influence attainment of steady state with an inspired anesthetic determine the time course of clearance of the drug from the body. Thus, nitrous oxide exits the body faster than halothane (Figure 11.6). D. Mechanism of action No specific receptor has been identified as the locus of general anesthetic action. Indeed, the fact that chemically unrelated compounds produce the anesthetic state argues against the existence of such a receptor. The focus is now on interactions of the inhaled anesthetics with proteins comprising ion channels. For example, the general anesthetics increase the sensitivity of the γ-aminobutyric acid ($GABA_A$) receptors to the neurotransmitter, GABA, at clinically effective concentrations of the drug. This causes a prolongation of the inhibitory chloride ion current after a pulse of GABA release. Postsynaptic neuronal excitability is, thus, diminished (Figure 11.7). Other receptors are also affected by volatile anesthetics. For example, the activity of the inhibitory glycine receptors in the spinal motor neurons is increased. In addition, the inhalation anesthetics block the excitatory postsynaptic current of the nicotinic receptors. The mechanism by which the anesthetics perform these modulatory roles is not understood. Alveolar concentration (percentage of inspired concentration) a. Brain, heart, liver, kidney, and endocrine glands: These highly perfused tissues rapidly attain a steady state with the partial pressure of anesthetic in the blood. Induction Nitrous oxide 100 Desflurane Sevoflurane Isoflurane 50 Halothane 0 0 10 20 30 Min Recovery 100 Percentage of initial alveolar concentration larger capacity results in a longer time required to achieve steady state). Capacity, in turn, is directly proportional to the tissue's volume and the tissue/blood solubility coefficient of the anesthetic molecules. Four major tissue compartments determine the time course of anesthetic uptake: 139 50 Halothane Isoflurane Sevoflurane Nitrous oxide Desflurane 0 0 10 20 30 Min Figure 11.6 Changes in the alveolar blood concentrations of some inhalation anesthetics over time. E. Halothane This agent is the prototype to which newer inhalation anesthetics have been compared. When halothane (HAL-oh-thane) was introduced, its ability to induce the anesthetic state rapidly and to allow quick recovery (and the fact that it was nonexplosive) made it an anesthetic of choice. However, with the recognition of the adverse effects discussed below and the availability of other anesthetics that cause fewer complications, halothane has largely been replaced in the United States. Pharm 5th 3-21-11.indb 139 3/21/11 2:22:09 PM 140 11. Anesthetics A No anesthetic Binding of GABA causes the chloride ion channel to open, leading to hyperpolarization of the cell. Cl– GABA Cl– In presence of B inhaled anesthetic Binding of GABA is enhanced by inhaled anesthetics, resulting in a greater entry of chloride ion. 1. Therapeutic uses: Halothane is a potent anesthetic but a relatively weak analgesic. Thus, halothane is usually coadministered with nitrous oxide, opioids, or local anesthetics. It is a potent bronchodilator. Halothane relaxes both skeletal and uterine muscle, and it can be used in obstetrics when uterine relaxation is indicated. Halothane is not hepatotoxic in pediatric patients (unlike its potential effect on adults, see below), and combined with its pleasant odor, this makes it suitable in children for inhalation induction, although sevoflurane is now the agent of choice for inhalation induction if cost is not a factor. 2. Pharmacokinetics: Halothane is oxidatively metabolized in the body to tissue-toxic hydrocarbons (for example, trifluoroethanol) and bromide ion. These substances may be responsible for the toxic reaction that some patients (especially females) develop after halothane anesthesia. This reaction begins as a fever, followed by anorexia, nausea, and vomiting, and patients may exhibit signs of hepatitis. [Note: Although the incidence of this reaction is low (approximately 1 in 10,000 individuals) 50 percent of affected patients may die of hepatic necrosis. To avoid this condition, halothane anesthesia is not repeated at intervals of less than 2 to 3 weeks. All halogenated inhalation anesthetics have been reported to cause hepatitis, but at a much lower incidence than with halothane. For example, isoflurane does so in 1 in 500,000 individuals.] 3. Adverse effects: Cl– GABA Cl– Entry of Cl- hyperpolarizes cell, making it more difficult to depolarize, and therefore reduces neural excitability. Figure 11.7 An example of modulation of a ligand-gated membrane channel modulated by inhaled anesthetics. GABA = γ-aminobutyric acid. Cl– = chloride ion. Pharm 5th 3-21-11.indb 140 a. Cardiac effects: Like other halogenated hydrocarbons, halothane is vagomimetic and causes atropine-sensitive bradycardia. In addition, halothane has the undesirable property of causing cardiac arrhythmias. [Note: These are especially serious if hypercapnia (increased arterial carbon dioxide partial pressure) develops due to reduced alveolar ventilation or an increase in the plasma concentration of catecholamines.] Halothane, like the other halogenated anesthetics, produces concentrationdependent hypotension. Should it become necessary to counter excessive hypotension during halothane anesthesia, it is recommended that a direct-acting vasoconstrictor, such as phenylephrine, be given. b. Malignant hyperthermia (MH): In a very small percentage of susceptible patients, exposure to any of the halogenated hydrocarbon anesthetics, as well as the neuromuscular blocking agent succinylcholine, has the potential to induce MH, a rare life-threatening condition. In susceptible individuals, these drugs can induce a drastic and uncontrolled increase in skeletal muscle oxidative metabolism, which overwhelms the body's capacity to supply oxygen, remove carbon dioxide, and regulate body temperature, eventually leading to circulatory collapse and death if not treated immediately. Recent investigations have identified a dramatic increase in the myoplasmic calcium ion concentration. Strong evidence indicates that MH is due to an excitation–contraction coupling defect. Burn victims and individuals with Duchenne muscular dystrophy, myotonia, osteogenesis imperfecta, and central-core disease are susceptible to MH. Susceptibility to MH is often inherited as an autosomal dominant disorder. Should a patient exhibit the characteristic symptoms of MH, dantrolene is given as the anesthetic mixture is withdrawn. Therefore, dantrolene should always be available 3/21/11 2:22:10 PM IV. Inhalation Anesthetics 141 for emergency use. The patient must be carefully monitored and supported for respiratory, circulatory, and renal problems. Use of dantrolene and the avoidance of triggering agents (for example, volatile halogenated anesthetics and succinylcholine) in susceptible individuals have markedly reduced the mortality from this condition. F. Isoflurane This halogenated anesthetic has been widely used in the United States. It is a very stable molecule that undergoes little metabolism and is not, therefore, toxic to the liver or kidney. Isoflurane (eye-soe-FLUR-ane) does not induce cardiac arrhythmias and does not sensitize the heart to the action of catecholamines. However, like the other halogenated gases, it produces dose-dependent hypotension due to peripheral vasodilation. It has a pungent odor and stimulates respiratory reflexes (for example, breath-holding, salivation, coughing, and laryngospasm) and is, therefore, not used for inhalation induction. With higher blood solubility than desflurane and sevoflurane, isoflurane is typically used now only when cost is a factor. G. Desflurane Desflurane [DES-flure-ane] provides very rapid onset and recovery due to its low blood solubility, the lowest of all the volatile anesthetics. The rapidity with which desflurane causes anesthesia and emergence has made it a popular anesthetic for outpatient surgery. However, desflurane has a low volatility and, thus, must be delivered using a special heated vaporizer. Like isoflurane, it decreases vascular resistance and perfuses all major tissues very well. Because it is irritating to the airway and can cause laryngospasm, coughing, and excessive secretions, desflurane is not used for inhalation inductions. Because it is relatively expensive, it is often not used for maintenance during extended anesthesia. Its degradation is minimal, and, therefore, tissue toxicity is rare. H. Sevoflurane Sevoflurane [see-voe-FLOOR-ane] has low pungency, allowing rapid induction without irritating the airway, thus making it suitable for inhalation induction in pediatric patients. It is replacing halothane for this purpose. This agent has rapid onset and recovery due to low blood solubility. Sevoflurane is metabolized by the liver, and compounds formed in the anesthesia circuit may be nephrotoxic if fresh gas flow is too low. I. Nitrous oxide Nitrous oxide [NYE-truss-OX-ide] ("laughing gas"), is non-irritating and a potent analgesic but a weak general anesthetic. For example, nitrous oxide is frequently employed at concentrations of 30–50 percent in combination with oxygen for analgesia, particularly in dental surgery. However, nitrous oxide at 80 percent (without adjunct agents) cannot produce surgical anesthesia. Therefore, it is commonly combined with other, more potent agents to attain pain-free anesthesia. Nitrous oxide is poorly soluble in blood and other tissues, allowing it to move very rapidly in and out of the body. [Note: Nitrous oxide, because of its fast uptake from the alveolar gas, can concentrate the halogenated anesthetics in the alveoli when they are concomitantly administered. This phenomenon is known as the "second gas effect."] Within closed body compartments, nitrous oxide can increase the volume (for example, causing a pneumothorax) or increase the pressure (for example, in the sinuses), because it replaces nitrogen in the various air spaces faster Pharm 5th 3-21-11.indb 141 3/21/11 2:22:11 PM 142 11. Anesthetics Halothane Isoflurane Desflurane Sevoflurane Increased Arrhythmias Dopamine + Norepinephrine + Epinephrine Increased Sensitivity to catecholamines Decreased Cardiac output Blood pressure Decreased to a lesser extent than halothane Decreased to a lesser extent than halothane Dose dependent decreased Dose dependent decreased Dose dependent decreased Dose dependent decreased Inhibited Initial stimulation Initial stimulation Inhibited Some risk Low risk Low risk Low risk Low risk Low risk Low risk Some risk Respiratory reflexes Hepatic toxicity Decreased to a lesser extent than halothane Renal toxicity Figure 11.8 Characteristics of some inhalation anesthetics. Pharm 5th 3-21-11.indb 142 3/21/11 2:22:12 PM V. Intravenous Anesthetics 143 than the nitrogen leaves. Furthermore, its speed of movement allows nitrous oxide to retard oxygen uptake during recovery, thereby causing "diffusion hypoxia," which can be overcome by administering significant concentrations of inspired oxygen during recovery. This anesthetic does not depress respiration, and it does not produce muscle relaxation. Under the usual circumstances of coadministration with other anesthetics, it also has moderate to no effect on the cardiovascular system or on increasing cerebral blood flow, and it is the least hepatotoxic of the inhalation anesthetics. Therefore, it is probably the safest of these anesthetics, provided that at least 20-percent oxygen is administered simultaneously. Some characteristics of the inhalation anesthetics are summarized in Figure 11.8. V. INTRAVENOUS ANESTHETICS IV anesthetics cause the rapid induction of anesthesia. This is often described as occurring within one "arm-brain circulation time," or the time it takes the drug to travel from the site of injection (usually the arm) to the brain, where it has its effect. Anesthesia may then be maintained with an appropriate inhalation agent. IV anesthetics may be used as the sole agents for short procedures or administered as infusions to help maintain anesthesia during longer procedures. In lower doses, they may be used to provide sedation. A. Induction After entering the blood stream, a percentage of the drug binds to the plasma proteins, and the rest remains unbound or "free." The degree of protein binding depends upon the physical characteristics of the particular drug, such as degree of ionization and lipid solubility. The drug is carried by venous blood to the right side of the heart, through the pulmonary circulation, and via the left side of the heart into the systemic circulation. The majority of the CO (70 percent) flows to the brain, liver, and kidney ("vessel-rich organs"). Thus, a high proportion of the initial drug bolus is delivered to the cerebral circulation and then passes along a concentration gradient from the blood into the brain. The rate of this transfer is dependent on the arterial concentration of the unbound free drug, the lipid solubility of the drug, and the degree of ionization. Unbound, lipid-soluble, non-ionized molecules cross the blood-brain barrier most quickly. Once the drug has penetrated the CNS tissue, it exerts its effects. Like the inhalation anesthetics, the exact mode of action of the IV anesthetic drugs is unknown. B. Recovery Recovery from IV anesthetics is due to redistribution from sites in the CNS. Following the initial flooding of the CNS and other vessel-rich tissues with non-ionized molecules, the drug starts to diffuse into other tissues with a lesser blood supply. With secondary tissue uptake, predominantly by skeletal muscle, the plasma concentration of the drug falls, allowing it to diffuse out of the CNS, down the resulting reverse concentration gradient. This initial redistribution of drug into other tissues leads to the rapid recovery seen after a single dose of an induction drug. Metabolism and plasma clearance become important only following infusions and repeat doses of a drug. Adipose tissue makes little contribution to the early redistribution of free drug following a bolus, due to its poor blood supply. However, following repeat doses or infusions, equilibration with fat tissue forms a drug reservoir, often leading to delayed recovery. Pharm 5th 3-21-11.indb 143 3/21/11 2:22:12 PM 144 11. Anesthetics C. Effect of reduced cardiac output (CO) In circumstances in which CO is reduced (for example, in patients in shock, the elderly, cardiac disease, etc.), the body compensates by diverting an increased proportion of the CO to the cerebral circulation to preserve cerebral blood flow. A greater proportion of any given drug will enter the cerebral circulation under these circumstances. As a result, the dose of induction drug must be reduced. Further, a decrease in CO leads to prolonged circulation time. That is, as global CO is reduced, the time taken for an induction drug to reach the brain and exert its effect is prolonged. The slow titration of a reduced dose of IV drug is key to a safe induction in patients with reduced CO. D. Propofol Propofol [PROPE-o-fol] is an IV sedative/hypnotic used in the induction or maintenance of anesthesia. Propofol is widely used and has replaced thiopental as the first choice for anesthesia induction and sedation, because it produces a euphoric feeling in the patient and does not cause postanesthetic nausea and vomiting. 1. Onset: The induction of anesthesia is smooth and occurs within about 30–40 seconds of administration. Following an IV bolus, there is rapid equilibration between the plasma and the highly perfused tissue of the brain, as described earlier. Plasma levels decline rapidly as a result of redistribution, followed by a more prolonged period of hepatic metabolism and renal clearance. The initial redistribution half-life is between 2 and 4 minutes. The pharmacokinetics of propofol are not altered by moderate hepatic or renal failure. 2. Actions: Supplementation with narcotics for analgesia is required. Whereas propofol facilitates depression in the CNS, it is occasionally accompanied by excitatory phenomena, such as muscle twitching, spontaneous movement, and hiccups. Propofol decreases blood pressure without depressing the myocardium. It also reduces intracranial pressure, mainly due to systemic vasodilation. It has much less of a depressant effect than the volatile anesthetics on CNS-evoked potentials such as somatosensory evoked potentials. This makes propofol useful for such surgeries as resection of spinal tumors, in which somatosensory evoked potentials are monitored to assess spinal cord functions. Propofol is commonly infused in lower doses to provide sedation for outpatient procedures. The incidence of postoperative nausea and vomiting is very low with the use of propofol. E. Fospropofol Fospropofol [PHOS-propofol] is a new, water-soluble drug approved only for sedation. Fospropofol is metabolized to propofol in the body, and the pharmacological effects of fospropofol are attributed to propofol (thus, fospropofol is a "prodrug" of propofol). Therefore, blood levels of propofol after the administration of a bolus of fospropofol reach lower peak levels than for an equipotent dose of propofol, and its clinical effect is more sustained. Because fospropofol is water soluble, the problems associated with lipid-formulated propofol (such as pain at the IV injection site and increased chance for bacterial contamination) are expected to be less frequent. Following the administration of fospropofol, loss of consciousness takes about 4 minutes, compared to one circulatory time with propofol. Pharm 5th 3-21-11.indb 144 3/21/11 2:22:12 PM V. Intravenous Anesthetics 145 Thiopental [thio-PENT-awl] is a potent anesthetic but a weak analgesic. It is an ultrashort-acting barbiturate with high lipid solubility. When agents such as thiopental and methohexital [meth-oh-HEX-i-tal] are administered intravenously, they quickly enter the CNS and depress function, often in less than 1 minute. However, diffusion out of the brain can also occur very rapidly because of redistribution of the drug to other body tissues, including skeletal muscle and, ultimately, adipose tissue (Figure 11.9). The short duration of anesthetic action is due to the decrease of barbiturate concentration in the brain to a level below that necessary to produce anesthesia. These drugs may remain in the body for relatively long periods of time after their administration, because only about 15 percent of the dose of barbiturates entering the circulation is metabolized by the liver per hour. Thus, metabolism of thiopental is much slower than its tissue redistribution. The barbiturates are not significantly analgesic and, therefore, require some type of supplementary analgesic administration during anesthesia to avoid objectionable changes in blood pressure and autonomic function. Thiopental has minor effects on the cardiovascular system, but it may contribute to severe hypotension in patients with hypovolemia or shock. All barbiturates can cause apnea, coughing, chest wall spasm, laryngospasm, and bronchospasm. [Note: The latter is of particular concern for asthmatic patients.] Barbiturates are contraindicated in patients with acute intermittent or variegate porphyria. Thiopental concentration (percentage of initial dose) F. Barbiturates 100 50 0 Blood Brain 1 Muscle 10 Adipose tissue 100 1000 Minutes Figure 11.9 Redistribution of thiopental from brain to muscle and adipose tissue. G. Benzodiazepines The benzodiazepines are used in conjunction with anesthetics to sedate the patient. The most commonly used is midazolam [mi-DAZ-o-lam]. Diazepam [dye-AZ-uh-pam] and lorazepam [lore-AZ-uh-pam] are alternatives. All three facilitate amnesia while causing sedation, enhancing the inhibitory effects of various neurotransmitters, particularly GABA. Minimal cardiovascular depressant effects are seen, but all are potential respiratory depressants (especially when administered intravenously). They are metabolized by the liver with variable elimination half-lives, and erythromycin may prolong their effects. Benzodiazepines can induce a temporary form of anterograde amnesia in which the patient retains memory of past events, but new information is not transferred into long-term memory. Therefore, important treatment information should be repeated to the patient after the effects of the drug have worn off. H. Opioids Because of their analgesic property, opioids are commonly used with anesthetics, such as in combination with nitrous oxide or volatile halogenated anesthetics. The choice of opioid used perioperatively is based primarily on the duration of action needed. The most commonly used opioids are fentanyl [FEN-ta-nil] and its congeners, sufentanil [SOO-fenta-nil] and remifentanil [REMI-fen-ta-nil], because they induce analgesia more rapidly than morphine does. They may be administered either intravenously, epidurally, or intrathecally (into the cerebrospinal fluid). Opioids are not good amnesics, and they can all cause hypotension, respiratory depression, and muscle rigidity as well as postanesthetic nausea and vomiting. Opioid effects can be antagonized by naloxone (see p. 178). Pharm 5th 3-21-11.indb 145 3/21/11 2:22:13 PM 146 11. Anesthetics I. Etomidate Etomidate (ee-TOM-uh-date) is used to induce anesthesia. It is a hypnotic agent but lacks analgesic activity. Its water solubility is poor, so etomidate is formulated in a propylene glycol solution. Induction is rapid, and the drug is short acting. It is usually only used for patients with coronary artery disease or cardiovascular dysfunction such as shock. Etomidate is hydrolyzed in the liver. Among its benefits are little to no effect on the heart and circulation. Its adverse effects include a decrease in plasma cortisol and aldosterone levels, which can persist for up to 8 hours. This is apparently due to inhibition of 11-β-hydroxylase.1 Etomidate should not be infused for an extended time, because prolonged suppression of these hormones can be hazardous. Venous pain can occur on injection, and involuntary skeletal muscle movements are not uncommon. The latter are managed by administration of benzo diazepines and opioids. J. Ketamine Ketamine [KET-a-meen], a short-acting, nonbarbiturate anesthetic, induces a dissociated state in which the patient is unconscious (but may appear to be awake) and does not feel pain. This dissociative anesthesia provides sedation, amnesia, and immobility. Ketamine interacts with the N-methyl-D-aspartate receptor. It also stimulates the central sympathetic outflow, which, in turn, causes stimulation of the heart with increased blood pressure and CO. This property is especially beneficial in patients with either hypovolemic or cardiogenic shock as well as in patients with asthma. Therefore, ketamine is used when circulatory depression is undesirable. On the other hand, these effects preclude the use of ketamine in hypertensive or stroke patients. The drug is lipophilic and enters the brain circulation very quickly. Like the barbiturates, it redistributes to other organs and tissues. It is metabolized in the liver, but small amounts can be excreted unchanged. Ketamine is used mainly in children and elderly adults for short procedures. However, it is not widely used, because it increases cerebral blood flow and induces postoperative hallucinations ("nightmares"), particularly in adults. K. Dexmedetomidine Dexmedetomidine [dex-med-eh-TOM-uh-deen] is a sedative medication used by intensive care units and anesthesiologists. It is relatively unique in its ability to provide sedation without causing respiratory depression. Like clonidine, its mechanism of action is agonism of α_2 receptors in certain parts of the brain. Dexmedetomidine has sedative, analgesic, sympatholytic, and anxiolytic effects that blunt many of the cardiovascular responses in the perioperative period. It reduces the volatile anesthetic, sedative and analgesic requirements of the patient without causing significant respiratory depression. Some therapeutic advantages and disadvantages of the anesthetic agents are summarized in Figure 11.10. VI. PARALYTICS / NEUROMUSCULAR BLOCKERS Neuromuscular blockers are used to abolish reflexes to facilitate tracheal intubation, and to provide muscle relaxation as needed for certain types of surgery. Their mechanism of action is blockade of the nicotinic acetylcholine receptors in the neuromuscular junction. These agents, which include cisatracurium, pancuronium, rocuronium, succinylcholine, and vecuronium, are described on pp. 64–67. Pharm 5th 3-21-11.indb 146 3/21/11 2:22:13 PM VII. Local Anesthetics 147 Therapeutic Disadvantages be delivered using a • Must special vaporizer • Incomplete anesthesia • No muscle relaxation be used with other • Must anesthetics for surgical anesthesia hepatic and renal • Reduces blood flow • Lowers blood pressure myocardium to • Sensitizes actions of catecholamines • Hepatic toxicity • Arrhythmias renal toxicity • Potential at low flows • Poor analgesia • Causes significant nausea • Little muscle relaxation • Laryngospasm • Poor analgesia Therapeutic Advantages Inhalation anesthetics Desflurane Nitrous oxide Halothane Isoflurane Sevoflurane Intravenous anesthetics Thiopental Ketamine Fentanyl Propofol Dexmedetomidine • Good analgesia • Rapid onset/recovery • Safe, nonirritating • Good muscle relaxation • Rapid recovery • Stability of cardiac output not raise • Does intracranial pressure sensitization of • No heart to epinephrine smooth muscle • Bronchial relaxation good for patients • • with asthma Rapid onset/recovery Not irritating; useful in children • Rapid onset of action • Potent anesthesia • Good analgesia • Not likely to cause nausea onset • Rapid • Lowers intracranial pressure respiratory depression • No undesirable cardio• Blunts vascular reflexes Figure 11.10 Therapeutic disadvantages and advantages of some anesthetic agents. VII. LOCAL ANESTHETICS Local anesthetics abolish sensation and, in higher concentrations, motor activity in a limited area of the body. They are applied or injected to block nerve conduction of sensory impulses from the periphery to the CNS. Local anesthesia is induced when propagation of action potentials is prevented, so that sensation cannot be transmitted from the source of stimulation to the brain. Local anesthetics work by blocking sodium ion channels to prevent the transient increase in permeability of the nerve membrane to sodium that is required for an action potential to occur. Delivery techniques include topical administration, infiltration, ring blocks, peripheral nerve blocks, and neuraxial (spinal, epidural, or caudal) blocks. The small, unmyelinated nerve fibers that conduct impulses for pain, temperature, and autonomic activity are most sensitive to the action of local anesthetics. Structurally, local anesthetics have fundamental features in common. These include a lipophilic group, joined by an amide or ester linkage to a carbon chain, which, Pharm 5th 3-21-11.indb 147 Ester linkage O H 2N C O (CH 2) 2 N Procaine Amide linkage O NH C CH 2 N Lidocaine C 2H 5 C 2H 5 C 2H 5 C 2H 5 Figure 11.11 Representative structures of ester and amide anesthetics. 3/21/11 2:22:18 PM 148 11. Anesthetics in turn, is joined to a hydrophilic group (Figure 11.11). The most widely used of the local anesthetic compounds are bupivacaine [byoo-PIV-ah-kane], lidocaine [LYE-doe-kane], mepivacaine [muh-PIV-a-kane], procaine [PROkane], ropivacaine [roe-PIV-a-kane], and tetracaine [TET-tra-kane]. Of these, lidocaine is probably the most commonly used. Bupivacaine is noted for its cardiotoxicity. Mepivacaine should not be used in obstetric anesthesia due to its increased toxicity to the neonate. A. Metabolism Biotransformation of amides occurs primarily in the liver. Prilocaine is also metabolized in the plasma and kidney, and one of its metabolites may lead to methemoglobinemia. Esters are biotransformed by plasma cholinesterase (pseudocholinesterase). Patients with pseudocholinesterase deficiency may be expected to metabolize ester local anesthetics more slowly. However, at normal doses, this has little clinical effect. Reduced hepatic function predisposes the patient to toxic effects but should not significantly increase the duration of action of local anesthetics. B. Onset and duration of action Onset and duration of action of local anesthetics are influenced by several factors. These include tissue pH, pKa of the drug, nerve morphology, concentration, and lipid solubility of the drug. Of these, the most important are pH of the tissue and pKa of the drug. At physiologic pH, these compounds are charged. The ionized form interacts with the protein receptor of the sodium channel to inhibit its function and, thereby, achieve local anesthesia. The pH may drop in sites of infection, which causes onset to be delayed or even prevented. Within limits, higher concentration and greater lipid solubility improve onset to some degree. Duration of action depends on the length of time the drug can stay in the nerve to block sodium channels. C. Actions Local anesthetics cause vasodilation, which leads to rapid diffusion away from the site of action and results in a short duration of action when these drugs are administered alone. By adding the vasoconstrictor epinephrine to the local anesthetic, the rate of local anesthetic diffusion and absorption is decreased. This both minimizes systemic toxicity and increases the duration of action. Hepatic function does not affect the duration of action of local anesthesia, which is determined by redistribution and not biotransformation. Some of these local anesthetics agents confer additional benefits such as the antiarrhythmic effect of lidocaine when administered intravenously. D. Allergic reactions Patient reports of allergic reactions to local anesthetics are fairly common, but investigation shows that most of these are of psychogenic origin. Psychogenic reactions are often misdiagnosed as allergic reactions and may also mimic them, with signs such as urticaria, edema, and bronchospasm. True allergy to an amide is exceedingly rare, whereas the ester procaine is somewhat more allergenic. An allergy to one ester rules out use of another ester, because the allergenic component is the breakdown product para-aminobenzoic acid, and metabolism of all esters yields this compound. In contrast, an allergy to one amide does not rule out use of another amide. A patient may be allergic to other compounds in the local anesthetic, such as preservatives in multidose vials. Pharm 5th 3-21-11.indb 148 3/21/11 2:22:19 PM VII. Local Anesthetics 149 E. Administration to children and the elderly Before administering local anesthetic to a child, the maximum dose based on the child's weight should be calculated to help prevent inadvertent overdose. There are no significant differences in the response to local anesthetics between younger and older adults, and the doses required for each block are the same regardless of patient age. However, it is prudent to stay well below the maximum recommended doses in elderly patients who often have some compromise in liver function. Because some degree of cardiovascular compromise may also be expected in elderly patients, reducing the dose of epinephrine may be prudent. Previous recommendations, now known to be wrong, precluded the use of specific local anesthetics in patients who are susceptible to MH. Today, it is well accepted that all local anesthetics are safe for these patients. F. Systemic local anesthetic toxicity Toxic blood levels of the drug may be due to repeated injections or could result from a single inadvertent IV injection. Aspiration before every injection is paramount to safety. The signs, symptoms, and timing of local anesthetic systemic toxicity are unpredictable. The most important step in treating local anesthetic toxicity is to consider the diagnosis in any patient with altered mental status or cardiovascular instability following injection of local anesthetic. CNS symptoms (either excitation or depression of the CNS) may be apparent but may also be subtle, nonspecific, or absent. Treatment for systemic local anesthetic toxicity includes airway management, support of breathing and circulation, seizure suppression, and, if needed, cardiopulmonary resuscitation. Administering a 20-percent lipid emulsion infusion (lipid rescue therapy) is a promising asset in treating local anesthetic toxicity. See Figure 11.12 for a summary of pharmacologic properties of some local anesthetics. Metabolism Rapid by plasma cholinesterase • Lidocaine • Mepivacaine • Bupivacaine, • Prilocaine • Ropivacaine Slow, hepatic Systemic toxicity Less likely More likely Allergic reaction Possible- PABA derivatives form Very rare Stability in solution Breaks down in ampules (heat, sun) Very stable chemically Onset of action Slow as a general rule Moderate to fast pKa's Higher than physiologic pH (8.5–8.9) Close to physiologic pH (7.6–8.1) CHARACTERISTIC DRUG • Procaine • Tetracaine • Chloroprocaine • Cocaine ESTERS POTENCY AMIDES ONSET DURATION Procaine Low Rapid Short Chloroprocaine Low Rapid Short Tetracaine High Slow Long (spinal) Lidocaine Low Rapid Intermediate Mepivacaine Low Moderate Intermediate Bupivacaine High Slow Long Ropivacaine High Moderate Long Figure 11.12 Summary of pharmacologic properties of some local anesthetics. PABA = para-aminobenzoic acid. Pharm 5th 3-21-11.indb 149 3/21/11 2:22:19 PM 150 11. Anesthetics Study Questions Choose the ONE best answer. 11.1 Which of the following is a potent analgesic but a weak anesthetic? A. Etomidate. B. Halothane. C. Midazolam. D. Nitrous oxide. E. Thiopental. 11.2 The potency of inhaled anesthetics is defined quantitatively as: A. Blood/gas partition coefficient. B. Cerebrovascular resistance. C. Minimum alveolar concentration. D. Volatility index. E. Sensitivity factor. 11.3 Recovery from IV induction agents is due to: A. Liver metabolism. B. Protein binding. C. Ionization. D. Redistribution from sites in the CNS. E. Plasma clearance. 11.4 Which one of the following is a potent intravenous anesthetic but a weak analgesic? A. Propofol. B. Benzodiazepines. C. Ketamine. D Etomidate. E. Isoflurane. 11.5 Local anesthetics A. Affect only small, unmyelinated nerve fibers. B. Have either a lipophilic or a hydrophilic group. C. Have either an amide or an ester linkage. D. Are unaffected by pH of the tissue and pKa of the drug. E. In their ionized form interact with the protein receptor of calcium channels. 11 Anesthetics 5-16-11#.indd 150 Correct answer = D. Etomidate is a hypnotic agent but lacks analgesic activity. Midazolam is a common sedative / amnestic. Halothane and thiopental are potent anesthetics with weak analgesic properties. Nitrous oxide provides good analgesia but is a weak anesthetic that must be combined with other agents to provide complete anesthesia. Correct answer = C. Potency of inhaled anesthetics is defined by MAC, equivalent to the median effective dose (ED_{50}) of the anesthetic. Blood/gas partition coefficient determines solubility of the gas in blood. Cerebrovascular resistance is decreased by inhalation anesthetics. Volatility index and sensitivity factor are not terms associated with inhalation anesthetics. Correct answer = D. Following initial flooding of the CNS with non-ionized molecules, the drug diffuses into other tissues. With secondary tissue uptake, plasma concentration falls, allowing the drug to diffuse out of the CNS. This initial redistribution of drug into other tissues leads to the rapid recovery seen after a single dose of an IV induction drug. Protein binding, ionization, and lipid solubility affect rate of transfer. Correct answer = A. Propofol is a potent anesthetic but a weak analgesic. It is the most widely used intravenously administered general anesthetic. It has a high lipid solubility. The other choices do not fit this profile. Correct answer = C. The small, unmyelinated nerve fibers that conduct impulses for pain, temperature, and autonomic activity are most sensitive to the action of local anesthetics, but other nerve fibers are affected also. Local anesthetics have a lipophilic group, joined by either an amide or ester linkage to a carbon chain which, in turn, is joined to a hydrophilic group. Onset and duration of action of local anesthetics are influenced by both pH of the tissue and pKa of the drug. Local anesthetics work by blocking sodium ion channels. 5/16/11 12:38:06 PM Antidepressants I. OVERVIEW The symptoms of depression are intense feelings of sadness, hopelessness, and despair as well as the inability to experience pleasure in usual activities, changes in sleep patterns and appetite, loss of energy, and suicidal thoughts. Mania is characterized by the opposite behavior: enthusiasm, rapid thought and speech patterns, extreme self-confidence, and impaired judgment. [Note: Depression and mania are different from schizophrenia (see p. 161), which produces disturbances in thought.] II. MECHANISM OF ANTIDEPRESSANT DRUGS Most clinically useful antidepressant drugs potentiate, either directly or indirectly, the actions of norepinephrine and/or serotonin in the brain. (See Figure 12.1 for a summary of the antidepressant agents.) This, along with other evidence, led to the biogenic amine theory, which proposes that depression is due to a deficiency of monoamines, such as norepinephrine and serotonin, at certain key sites in the brain. Conversely, the theory proposes that mania is caused by an overproduction of these neurotransmitters. However, the amine theory of depression and mania is overly simplistic. It fails to explain why the pharmacologic effects of any of the antidepressant and anti-mania drugs on neurotransmission occur immediately, whereas the time course for a therapeutic response occurs over several weeks. Furthermore, the potency of the antidepressant drugs in blocking neurotransmitter uptake often does not correlate with clinically observed antidepressant effects. This suggests that decreased uptake of the neurotransmitter is only an initial effect of the drugs, which may not be directly responsible for the antidepressant effects. It has been proposed that presynaptic inhibitory receptor densities in the brain decrease over a 2 to 4 week period with antidepressant drug use. This down-regulation of inhibitory receptors permits greater synthesis and release of neurotransmitters into the synaptic cleft and enhanced signaling in the postsynaptic neurons, presumably leading to a therapeutic response. III. SELECTIVE SEROTONIN REUPTAKE INHIBITORS The selective serotonin reuptake inhibitors (SSRIs) are a group of chemically diverse antidepressant drugs that specifically inhibit serotonin reuptake, having 300- to 3000-fold greater selectivity for the serotonin transporter, as compared to the norepinephrine transporter. This contrasts with the tricyclic antidepressants (TCAs, see p. 155) that nonselectively inhibit the uptake of norepinephrine and serotonin (Figure 12.2). Both of these antidepressant drug classes exhibit little ability to block the dop- Pharm 5th 3-21-11.indb 151 12 SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRIs) Citalopram CELEXA Escitalopram LEXAPRO Fluoxetine PROZAC Fluvoxamine LUVOX CR Paroxetine PAXIL Sertraline ZOLOFT SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS (SNRIs) Desvenlafaxine Pristiq Duloxetine CYMBALTA Venlafaxine EFFEXOR ATYPICAL ANTIDEPRESSANTS Bupropion WELLBUTRIN, ZYBAN Mirtazapine REMERON Nefazodone SERZONE Trazodone DESYREL TRICYCLIC ANTIDEPRESSANTS (TCAs) Amitriptyline ELAVIL Amoxapine ASENDIN Clomipramine ANAFRANIL Desipramine NORPRAMIN Doxepin SINEQUAN Imipramine TOFRANIL Maprotiline LUDIOMIL Nortriptyline PALMELOR Protriptyline VIVACTIL Trimipramine SURMONTIL MONOAMINE OXIDASE INHIBITORS (MAOIs) Isocarboxazid Marplan Phenelzine NARDIL Selegiline ELDEPRYL Tranylcypromine PARNATE Figure 12.1 Summary of antidepressants. (Continued on next page) 3/21/11 2:22:19 PM 152 12. Antidepressants DRUGS USED TO TREAT MANIA and BIPOLAR DISORDER Carbamazepine TEGRETOL, EQUETRO, CARBATROL Lithium ESKALITH Valprioc acid DEPAKENE, DEPAKOTE Figure 12.1 (continued) Summary of antidepressants. DRUG UPTAKE INHIBITION Norepinephrine Selective serotonin reuptake inhibitor Fluoxetine Selective serotonin/ norepinephrine reuptake inhibitors Venlafaxine Duloxetine Tricyclic antidepressant Imipramine 0 Serotonin ++++ ++* ++++ ++++ ++++ ++++ +++ Figure 12.2 Relative receptor specificity of some antidepressant drugs. *Venlafaxine inhibits norepinephrine reuptake only at high doses. ++++ = very strong affinity; +++ = strong affinity; ++ = moderate affinity; + = weak affinity; 0 = little or no affinity. Administration of antidepressant Depression amine transporter. Moreover, the SSRIs have little blocking activity at muscarinic, α-adrenergic, and histaminic H_1 receptors. Therefore, common side effects associated with TCAs, such as orthostatic hypotension, sedation, dry mouth, and blurred vision, are not commonly seen with the SSRIs. Because they have fewer adverse effects and are relatively safe even in overdose, the SSRIs have largely replaced TCAs and monoamine oxidase inhibitors (MAOIs) as the drugs of choice in treating depression. SSRIs include fluoxetine [floo-OX-e-teen] (the prototypic drug), citalopram [sye-TAL-oh-pram], escitalopram [es-sye-TAL-oh-pram], fluvoxamine [floo-VOX-e-meen], paroxetine [pa-ROX-e-teen], and sertraline [SER-tra-leen]. Both citalopram and fluoxetine are racemic mixtures, of which the respective S-enantiomers are the more potent inhibitors of the serotonin reuptake pump. Escitalopram is the pure S-enatiomer of citalopram. A. Actions The SSRIs block the reuptake of serotonin, leading to increased concentrations of the neurotransmitter in the synaptic cleft and, ultimately, to greater postsynaptic neuronal activity. Antidepressants, including SSRIs, typically take at least 2 weeks to produce significant improvement in mood, and maximum benefit may require up to 12 weeks or more (Figure 12.3). However, none of the antidepressants are uniformly effective. Approximately 40 percent of depressed patients treated with adequate doses for 4 to 8 weeks do not respond to the antidepressant agent. Patients who do not respond to one antidepressant may respond to another, and approximately 80 percent or more will respond to at least one antidepressant drug. [Note: These drugs do not usually produce central nervous system (CNS) stimulation or mood elevation in normal individuals.] B. Therapeutic uses The primary indication for SSRIs is depression, for which they are as effective as the TCAs. A number of other psychiatric disorders also respond favorably to SSRIs, including obsessive-compulsive disorder, panic disorder, generalized anxiety disorder, posttraumatic stress disorder, social anxiety disorder, premenstrual dysphoric disorder, and bulimia nervosa (only fluoxetine is approved for this last indication). C. Pharmacokinetics Onset of action 2 to 12 weeks Antidepressant effects Figure 12.3 Onset of therapeutic effects of the major antidepressant drugs requires several weeks. Pharm 5th 3-21-11.indb 152 All of the SSRIs are well absorbed after oral administration. Peak levels are seen in approximately 2 to 8 hours on average. Food has little effect on absorption (except with sertraline, for which food increases its absorption). Only sertraline undergoes significant first-pass metabolism. The majority of SSRIs have plasma half-lives that range between 16 and 36 hours. Metabolism by cytochrome P450 (CYP450)-dependent enzymes and glucuronide or sulfate conjugation occur extensively. [Note: These metabolites do not generally contribute to the pharmacologic activity.] Fluoxetine differs from the other members of the class in two respects. First, it has a much longer half-life (50 hours) and is available as a sustained-release preparation allowing once-weekly dosing. Second, the metabolite of the S-enantiomer, S-norfluoxetine, is as potent as the parent compound. The half-life of the metabolite is quite long, averaging 10 days. Fluoxetine and paroxetine are potent inhibitors of a hepatic CYP450 isoenzyme (CYP2D6) responsible for the elimination of TCAs, neuroleptic drugs, and some antiarrhythmic and β-adrenergic antagonist drugs. [Note: About 7 percent of the Caucasian population 3/21/11 2:22:20 PM III. Selective Serotonin Reuptake Inhibitors lacks this P450 enzyme and, therefore, metabolize fluoxetine and other substrates of this enzyme very slowly. These individuals may be referred to in the literature as "poor metabolizers."] Other cytochrome enzymes (CYP2C9/19, CYP3A4, CYP1A2) are involved with SSRI metabolism and may also be inhibited to various degrees by the SSRIs. Thus, they may affect the metabolism of multiple medications. Excretion of the SSRIs is primarily through the kidneys, except for paroxetine and sertraline, which also undergo fecal excretion (35 and 50 percent, respectively). Dosages of all of these drugs should be adjusted downward in patients with hepatic impairment. 153 Nausea Anxiety D. Adverse effects Although the SSRIs are considered to have fewer and less severe adverse effects than the TCAs and MAOIs, the SSRIs are not without troublesome adverse effects, such as headache, sweating, anxiety and agitation, gastrointestinal (GI) effects (nausea, vomiting, diarrhea), weakness and fatigue, sexual dysfunction, changes in weight, sleep disturbances (insomnia and somnolence), and the above-mentioned potential for drug-drug interactions (Figure 12.4). 1. Sleep disturbances: Paroxetine and fluvoxamine are generally more sedating than activating, and they may be useful in patients who have difficulty sleeping. Conversely, patients who are fatigued or complaining of excessive somnolence may benefit from one of the more activating antidepressants, such as fluoxetine or sertraline. 2. Sexual dysfunction: Loss of libido, delayed ejaculation, and anorgasmia are underreported side effects often noted by clinicians, but these are not prominently featured in the list of standard side effects. One option for managing SSRI-induced sexual dysfunction is to replace the offending antidepressant with an antidepressant having fewer sexual side effects, such as bupropion or mirtazapine. Alternatively, the dose of the drug may be reduced. In men with erectile dysfunction and depression, treatment with sildenafil, vardenafil, or tadalafil (see p. 363) may improve sexual function. 3. Use in children and teenagers: Antidepressants should be used cautiously in children and teenagers, because about 1 out of 50 children report suicidal ideation as a result of SSRI treatment. Pediatric patients should be observed for worsening depression and suicidal thinking whenever any antidepressant is started or its dose is increased or decreased. Fluoxetine, sertraline, and fluvoxamine are U.S. Food and Drug Administration (FDA)-approved for use in children to treat obsessive-compulsive disorder, and fluoxetine is approved to treat childhood depression. Drowsiness Insomnia Sexual dysfunction Drug interactions Figure 12.4 Some commonly observed adverse effects of selective serotonin reuptake inhibitors. 4. Overdoses: Large intakes of SSRIs do not usually cause cardiac arrhythmias (compared to the arrhythmia risk for the TCAs), but seizures are a possibility because all antidepressants may lower the seizure threshold. All SSRIs have the potential to cause a serotonin syndrome that may include the symptoms of hyperthermia, muscle rigidity, sweating, myoclonus (clonic muscle twitching), and changes in mental status and vital signs when used in the presence of a MAOI or other highly serotonergic drug. Therefore, extended periods of washout for each drug class should occur prior to the administration of the other class of drugs. Pharm 5th 3-21-11.indb 153 3/21/11 2:22:21 PM 154 12. Antidepressants Antidepressant drug blocks reuptake of the neurotransmitter. 5. Discontinuation syndrome: Whereas all of the SSRIs have the potential for causing a discontinuation syndrome after their abrupt withdrawal, the agents with the shorter half-lives and having inactive metabolites have a higher risk for such an adverse reaction. Fluoxetine has the lowest risk of causing an SSRI discontinuation syndrome. Possible signs and symptoms of such a serotonin-related discontinuation syndrome include headache, malaise and flu-like symptoms, agitation and irritability, nervousness, and changes in sleep pattern. PRESYNAPTIC NEURON Serotonin Norepinephrine IV. SEROTONIN/NOREPINEPHRINE REUPTAKE INHIBITORS Venlafaxine Duloxetine POSTSYNAPTIC NEURON SYNAPTIC CLEFT Postsynaptic response Figure 12.5 Proposed mechanism of action of selective serotonin/norepinephrine reuptake inhibitor antidepressant drugs. Venlafaxine [VEN-la-fax-een], desvenlafaxine [dez-VEN-la-fax-een], and duloxetine (doo-LOX-e-teen) inhibit the reuptake of both serotonin and norepinephrine (Figure 12.5). These agents, termed selective serotonin/norepinephrine reuptake inhibitors (SNRIs), may be effective in treating depression in patients in whom SSRIs are ineffective. Furthermore, depression is often accompanied by chronic painful symptoms, such as backache and muscle aches, against which SSRIs are also relatively ineffective. This pain is, in part, modulated by serotonin and norepinephrine pathways in the CNS. Both SNRIs and TCAs, with their dual actions of inhibiting both serotonin and norepinephrine reuptake, are sometimes effective in relieving physical symptoms of neuropathic pain such as diabetic peripheral neuropathy. However, the SNRIs, unlike the TCAs, have little activity at adrenergic, muscarinic, or histamine receptors and, thus, have fewer of these receptor-mediated adverse effects than the TCAs (see Figure 12.2). Venlafaxine, desvenlafaxine, and duloxetine may precipitate a discontinuation syndrome if treatment is abruptly stopped. A. Venlafaxine and desvenlafaxine Venlafaxine is a potent inhibitor of serotonin reuptake and, at medium to higher doses, is an inhibitor of norepinephrine reuptake. It is also a mild inhibitor of dopamine reuptake at high doses. Venlafaxine has minimal inhibition of the CYP450 isoenzymes and is a substrate of the CYP2D6 isoenzyme. The half-life of the parent compound plus its active metabolite is approximately 11 hours. Desvenlafaxine is the active, demethylated, metabolite of the parent compound venlafaxine. The most common side effects of venlafaxine are nausea, headache, sexual dysfunction, dizziness, insomnia, sedation, and constipation. At high doses, there may be an increase in blood pressure and heart rate. Desvenlafaxine is not considered to have a significantly different clinical or adverse effect profile compared to venlafaxine. B. Duloxetine Duloxetine inhibits serotonin and norepinephrine reuptake at all doses. It is extensively metabolized in the liver to numerous metabolites. Duloxetine should not be administered to patients with hepatic insufficiency. Metabolites are excreted in the urine, and the use of duloxetine is not recommended in patients with end-stage renal disease. Food delays the absorption of the drug. The half-life is approximately 12 hours. GI side effects are common with duloxetine, including nausea, dry mouth, and constipation. Diarrhea and vomiting are seen less often. Insomnia, dizziness, somnolence, and sweating are also seen. Sexual dysfunction also occurs along with the possible risk for an increase in either blood pressure or heart rate. Duloxetine is a moderate inhibitor of CYP2D6 and CYP3A4 isoenzymes. Pharm 5th 3-21-11.indb 154 3/21/11 2:22:21 PM VI. Tricyclic Antidepressants 155 V. ATYPICAL ANTIDEPRESSANTS The atypical antidepressants are a mixed group of agents that have actions at several different sites. This group includes bupropion [byoo-PROE-peeon], mirtazapine [mir-TAZ-a-peen], nefazodone [nef-AY-zoe-done], and trazodone [TRAZ-oh-done]. They are not any more efficacious than the TCAs or SSRIs, but their side effect profiles are different. A. Bupropion This drug acts as a weak dopamine and norepinephrine reuptake inhibitor to alleviate the symptoms of depression. Its short half-life may require more than once-a-day dosing or the administration of an extended-release formulation. Bupropion also assists in decreasing the craving and attenuating the withdrawal symptoms for nicotine in tobacco users trying to quit smoking. Side effects may include dry mouth, sweating, nervousness, tremor, a very low incidence of sexual dysfunction, and an increased risk for seizures at high doses. Bupropion is metabolized by the CYP2B6 pathway and is considered to have a relatively low risk for drug-drug interactions. The daily dose of bupropion should be within the manufacturer's recommendations to minimize the risk of seizures that may occur in above recommended doses. Its use should also be avoided in patients at risk for seizures or who have eating disorders (such as bulimia). B. Mirtazapine This drug enhances serotonin and norepinephrine neurotransmission via mechanisms related to its ability to block presynaptic α_2 receptors. Additionally, it may owe at least some of its antidepressant activity to its ability to block 5-HT2 receptors. It is a sedative because of its potent antihistaminic activity, but it does not cause the antimuscarinic side effects of the TCAs, or interfere with sexual functioning, as do the SSRIs. Increased appetite and weight gain frequently occur (Figure 12.6). Mirtazapine is markedly sedating, which may be an advantage in depressed patients having difficulty sleeping. Weight gain ZZ Z Sedation C. Nefazodone and trazodone These drugs are weak inhibitors of serotonin reuptake. Their therapeutic benefit appears to be related to their ability to block postsynaptic 5-HT2A receptors. With chronic use, these agents may desensitize 5-HT1A presynaptic autoreceptors and, thereby, increase serotonin release. Both agents are sedating, probably because of their potent H_1-blocking activity. Trazodone has been associated with causing priapism, and nefazodone has been associated with the risk for hepatotoxicity. Both agents also have mild to moderate α_1-receptor antagonism contributing to orthostasis and dizziness. Figure 12.6 Some commonly observed adverse effects of mirtazapine. VI. TRICYCLIC ANTIDEPRESSANTS The TCAs block norepinephrine and serotonin reuptake into the neuron and, thus, if discovered today, might have been referred to as SNRIs except for their differences in adverse effects relative to this newer class of antidepressants. The TCAs include the tertiary amines imipramine [ee-MIP-ra-meen] (the prototype drug), amitriptyline [aye-mee-TRIP-ti-leen], clomipramine [kloe-MIP-ra-meen], doxepin [DOX-e-pin], and trimipramine [trye-MIP-rameen]. The TCAs also include the secondary amines desipramine [dess-IP-rameen] and nortriptyline [nor-TRIP-ti-leen] (the respective N-demethylated Pharm 5th 3-21-11.indb 155 3/21/11 2:22:22 PM 156 12. Antidepressants Weight gain Dry mouth metabolites of imipramine and amitriptyline) and protriptyline [proe-TRIPti-leen]. Maprotiline [ma-PROE-ti-leen] and amoxapine [a-MOX-a-peen] are related "tetracyclic" antidepressant agents and are commonly included in the general class of TCAs. All have similar therapeutic efficacy, and the specific choice of drug may depend on such issues as patient tolerance to side effects, prior response, preexisting medical conditions, and duration of action. Patients who do not respond to one TCA may benefit from a different drug in this group. These drugs are a valuable alternative for patients who do not respond to SSRIs. A. Mechanism of action Constipation Urinary retention Blurred vision Tachycardia Arrhythmias Nausea Drowsiness 1. Inhibition of neurotransmitter reuptake: TCAs and amoxapine are potent inhibitors of the neuronal reuptake of norepinephrine and serotonin

into presynaptic nerve terminals. At therapeutic concentrations, they do not block dopamine transporters. By blocking the major route of neurotransmitter removal, the TCAs cause increased concentrations of monoamines in the synaptic cleft, ultimately resulting in antidepressant effects. Maprotiline and desipramine are relatively selective inhibitors of norepinephrine reuptake. 2. Blocking of receptors: TCAs also block serotonergic, α-adrenergic, histaminic, and muscarinic receptors (see Figure 12.3). It is not known if any of these actions produce TCAs' therapeutic benefit. However, actions at these receptors are likely responsible for many of the adverse effects of the TCAs. Amoxapine also blocks 5-HT2 and D2 receptors. B. Actions The TCAs elevate mood, improve mental alertness, increase physical activity, and reduce morbid preoccupation in 50 to 70 percent of individuals with major depression. The onset of the mood elevation is slow, requiring 2 weeks or longer (see Figure 12.3). These drugs do not commonly produce CNS stimulation or mood elevation in normal individuals. Physical and psychological dependence has been rarely reported, however, this necessitates slow withdrawal to minimize discontinuation syndromes and cholinergic rebound effects. These drugs, like all of the antidepressants, can be used for prolonged treatment of depression. C. Therapeutic uses The TCAs are effective in treating moderate to severe depression. Some patients with panic disorder also respond to TCAs. Imipramine has been used to control bed-wetting in children (older than age 6 years) by causing contraction of the internal sphincter of the bladder. At present, it is used cautiously because of the inducement of cardiac arrhythmias and other serious cardiovascular problems. The TCAs, particularly amitriptyline, have been used to treat migraine headache and chronic pain syndromes (for example, neuropathic pain) in a number of conditions for which the cause of the pain is unclear. Low doses of TCAs, especially doxepin, can be used to treat insomnia. D. Pharmacokinetics Figure 12.7 Some commonly observed adverse effects of tricyclic antidepressants. Pharm 5th 3-21-11.indb 156 TCAs are well absorbed upon oral administration. Because of their lipophilic nature, they are widely distributed and readily penetrate into the CNS. This lipid solubility also causes these drugs to have variable halflives (for example, 4 to 17 hours for imipramine). As a result of their variable first-pass metabolism in the liver, TCAs have low and inconsis- 3/21/11 2:22:26 PM VII. Monoamine Oxidase Inhibitors tent bioavailability. Therefore, the patient's response and plasma levels can be used to adjust dosage. The initial treatment period is typically 4 to 8 weeks. The dosage can be gradually reduced to improve tolerability, unless relapse occurs. These drugs are metabolized by the hepatic microsomal system (and, thus, may be sensitive to agents that induce or inhibit the CYP450 isoenzymes) and conjugated with glucuronic acid. Ultimately, the TCAs are excreted as inactive metabolites via the kidney. E. Adverse effects Blockade of muscarinic receptors leads to blurred vision, xerostomia (dry mouth), urinary retention, sinus tachycardia, constipation, and aggravation of narrow-angle glaucoma (Figure 12.7). These agents also affect cardiac conduction similarly to quinidine, which may precipitate life-threatening arrhythmias should an overdose of one of these drugs be taken. The TCAs also block α-adrenergic receptors, causing orthostatic hypotension, dizziness, and reflex tachycardia. In clinical practice, this is the most serious problem in elderly adults. Imipramine is the most likely, and nortriptyline the least likely, to cause orthostatic hypotension. Sedation may be prominent, especially during the first several weeks of treatment, and is related to the ability of these drugs to block histamine H1 receptors. Weight gain is a common adverse effect of the TCAs. Sexual dysfunction, as evidenced by erectile dysfunction in men and anorgasmia in women, occurs in a significant minority of patients, but the incidence is still considered to be lower than the incidence of sexual dysfunction associated with the SSRIs. 1. Precautions : TCAs (like all antidepressants) should be used with caution in patients with bipolar disorder, even during their depressed state, because antidepressants may cause a switch to manic behavior. The TCAs have a narrow therapeutic index (for example, five- to sixfold the maximal daily dose of imipramine can be lethal). Depressed patients who are suicidal should be given only limited quantities of these drugs and be monitored closely. Drug interactions with the TCAs are shown in Figure 12.8. The TCAs may exacerbate certain medical conditions, such as unstable angina, benign prostatic hyperplasia, epilepsy, and preexisting arrhythmias. Caution should be exercised with their use in very young or very old patients as well. 157 Mutual enhancement: hypertension, hyperpyrexia, convulsions, and coma MAO inhibitors Potentiate effects of biogenic amine drugs by preventing their removal from the synaptic cleft Direct-acting adrenergic drugs Tricyclic antidepressants Indirect-acting adrenergic drugs Ethanol Other CNS depressants Toxic sedation Block effects of indirect-acting sympathomimetic drugs by preventing the drugs from reaching their intracelluar sites of action Figure 12.8 Drugs interacting with tricyclic antidepressants. CNS = central nervous system; MAO = monoamine oxidase. VII. MONOAMINE OXIDASE INHIBITORS Monoamine oxidase (MAO) is a mitochondrial enzyme found in nerve and other tissues, such as the gut and liver. In the neuron, MAO functions as a "safety valve" to oxidatively deaminate and inactivate any excess neuro transmitter molecules (norepinephrine, dopamine, and serotonin) that may leak out of synaptic vesicles when the neuron is at rest. The MAO inhibitors (MAOIs) may irreversibly or reversibly inactivate the enzyme, permitting neurotransmitter molecules to escape degradation and, therefore, to both accumulate within the presynaptic neuron and leak into the synaptic space. This is believed to cause activation of norepinephrine and serotonin receptors, and it may be responsible for the indirect antidepressant action of these drugs. Four MAOIs are currently available for treatment of depression: phenelzine [FEN-el-zeen]; tranylcypromine [tran-il-SIP-roe-meen]; isocarboxazid [eye-soe-car-BOX-ih-zid]; and the agent that was prior-approved for Parkinson disease, but is now also approved for depression, selegiline, which is the first antidepressant available in a transdermal delivery system. Use of MAOIs is now limited due to the complicated dietary restrictions required of patients taking them. Pharm 5th 3-21-11.indb 157 3/21/11 2:22:27 PM 158 12. Antidepressants A Normal monoamine transmission Synaptic vesicle MAO inactivates monoamines (norepinephrine, serotonin, and dopamine) that leak from a synaptic vesicle. MAO POSTSYNAPTIC NEURON B Synaptic vesicle SYNAPTIC CLEFT Postsynaptic response Effect of MAOIs MAOIs prevent inactivation of monoamines within a neuron, causing excess neurotransmitter to diffuse into the synaptic space. Inactive metabolites C. Therapeutic uses The MAOIs are indicated for depressed patients who are unresponsive or allergic to TCAs or who experience strong anxiety. Patients with low psychomotor activity may benefit from the stimulant properties of the MAOIs. These drugs are also useful in the treatment of phobic states. A special subcategory of depression, called atypical depression, may respond preferentially to MAOIs. Atypical depression is characterized by labile mood, rejection sensitivity, and appetite disorders. Because of their risk for drug-drug and drug-food interactions, the MAOIs are considered to be last-line agents in many treatment venues. D. Pharmacokinetics E. Adverse effects Norepinephrine Serotonin Dopamine SYNAPTIC CLEFT Postsynaptic response Figure 12.9 Mechanism of action of monoamine oxidase inhibitors (MAOIs). Pharm 5th 3-21-11.indb 158 Although MAO is fully inhibited after several days of treatment, the antidepressant action of the MAOIs, like that of the SSRIs and TCAs, is delayed several weeks. Selegiline and tranylcypromine have an amphetamine-like stimulant effect that may produce agitation or insomnia. These drugs are well absorbed after oral administration, but antidepressant effects require at least 2 to 4 weeks of treatment. Enzyme regeneration, when irreversibly inactivated, varies, but it usually occurs several weeks after termination of the drug. Thus, when switching antidepressant agents, a minimum of 2 weeks of delay must be allowed after termination of MAOI therapy and the initiation of another antidepressant from any other class. MAOIs are metabolized and excreted rapidly in urine. MAO POSTSYNAPTIC NEURON Most MAOIs, such as phenelzine, form stable complexes with the enzyme, causing irreversible inactivation. This results in increased stores of norepinephrine, serotonin, and dopamine within the neuron and subsequent diffusion of excess neurotransmitter into the synaptic space (Figure 12.9). These drugs inhibit not only MAO in the brain, but also MAO in the liver and gut that catalyze oxidative deamination of drugs and potentially toxic substances, such as tyramine, which is found in certain foods. The MAOIs, therefore, show a high incidence of drug-drug and drug-food interactions. Selegiline administered as the transdermal patch may produce less inhibition of gut and hepatic MAO at low doses because it avoids first-pass metabolism. B. Actions Inactive metabolites Norepinephrine Serotonin Dopamine A. Mechanism of action Severe and often unpredictable side effects, due to drug-food and drug-drug interactions, limit the widespread use of MAOIs. For example, tyramine, which is contained in certain foods, such as aged cheeses and meats, chicken liver, pickled or smoked fish (such as anchovies or herring), and red wines, is normally inactivated by MAO in the gut. Individuals receiving a MAOI are unable to degrade tyramine obtained from the diet. Tyramine causes the release of large amounts of stored catecholamines from nerve terminals, resulting in what is termed a "hypertensive crisis," with signs and symptoms such as occipital headache, stiff neck, tachycardia, nausea, hypertension, cardiac arrhythmias, seizures, and, possibly, stroke. Patients must, therefore, be educated to avoid tyramine-containing foods. Phentolamine and prazosin are helpful in the management of tyramine-induced hypertension. 3/21/11 2:22:29 PM VIII. Treatment Of Mania And Bipolar Disorder [Note: Treatment with MAOIs may be dangerous in severely depressed patients with suicidal tendencies. Purposeful consumption of tyramine-containing foods is a possibility.] Other possible side effects of treatment with MAOIs include drowsiness, orthostatic hypotension, blurred vision, dry mouth, dysuria, and constipation. MAOIs and SSRIs should not be coadministered due to the risk of the life-threatening "serotonin syndrome." Both types of drugs require washout periods of at least 2 weeks before the other type is administered, with the exception of fluoxetine, which should be discontinued at least 6 weeks before a MAOI is initiated. Combination of MAOIs and bupropion can produce seizures. Figure 12.10 summarizes the side effects of the antidepressant drugs. VIII. TREATMENT OF MANIA AND BIPOLAR DISORDER The treatment of bipolar disorder has increased in recent years, partly due to the increased recognition of the disorder and also due to the increase in the number of medications FDA-approved for the treatment of mania. A. Lithium Lithium salts are used prophylactically for treating manic-depressive patients and in the treatment of manic episodes and, thus, are considered "mood stabilizers." Lithium is effective in treating 60 to 80 percent of patients exhibiting mania and hypomania. Although many cellular processes are altered by treatment with lithium salts, the mode of action is unknown. [Note: Lithium is believed to attenuate signaling via receptors coupled to the phosphatidylinositol bisphosphate (PIP2) secondmessenger system. Lithium interferes with the resynthesis (recycling) of PIP2, leading to its relative depletion in neuronal membranes of the CNS. PIP2 levels in peripheral membranes are unaffected by lithium.] Lithium is given orally, and the ion is excreted by the kidney. Lithium salts can be toxic. Their safety factor and therapeutic index are extremely low and comparable to those of digoxin. Common adverse effects may include headache, dry mouth, polydipsia, polyuria, polyphagia, GI distress (give lithium with food), fine hand tremor, dizziness, fatigue, dermatologic reactions, and sedation. Adverse effects due to higher plasma levels may include ataxia, slurred speech, coarse tremors, confusion, and convulsions. [Note: The diabetes insipidus that results from taking lithium can be treated with amiloride.] Thyroid function may be decreased and should be monitored. Lithium causes no noticeable effect on normal individuals. It is not a sedative, euphoriant, or depressant. B. Other drugs Several antiepileptic drugs, including, most notably, carbamazepine, valproic acid, and lamotrigine, have been identified and FDA approved as mood stabilizers, being used successfully in the treatment of bipolar disorder. Other agents that may improve manic symptoms include the older (for example, chlorpromazine and haloperidol) and newer antipsychotics. The atypical antipsychotics (risperidone, olanzapine, ziprasidone, aripiprazole, asenapine, and quetiapine) have also received FDA approval for the management of mania. Benzodiazepines are also frequently used as adjunctive treatments for the acute stabilization of patients with mania. (See the respective chapters on these psychotropics for a more detailed description). Pharm 5th 3-21-11.indb 159 159 Gastrointestinal distress Sedating; may be useful for agitation SELECTIVE SEROTONIN RE-UPTAKE INHIBITORS Citalopram Escitalopram Fluoxetine Fluvoxamine Paroxetine Sertraline SEROTONIN/ NOREPINEPHRINE REUPTAKE INHIBITORS Duloxetine Venlafaxine Desvenlafaxine ATYPICAL ANTIDEPRESSANTS Bupropion Mirtazapine Nefazodone Trazodone TRICYCLIC/POLYCYCLIC ANTIDEPRESSANTS Amitriptyline Amoxapine Clomipramine Desipramine Doxepin Imipramine Maprotiline Nortriptyline Protriptyline Trimipramine MONOAMINE OXIDASE INHIBITORS Phenelzine Tranylcypromine High potential for orthostatic hypotension Weight gain Figure 12.10 Side effects of some drugs used to treat depression. 3/21/11 2:22:29 PM 160 12. Antidepressants Study Questions Choose the ONE best answer. 12.1 A 55-year-old teacher began to experience changes in mood. He was losing interest in his work and lacked the desire to play his daily tennis match. He was preoccupied with feelings of guilt, worthlessness, and hopelessness. In addition to the psychiatric symptoms, the patient complained of muscle aches throughout his body. Physical and laboratory tests were unremarkable. After 6 weeks of therapy with fluoxetine, the patient's symptoms resolved. However, the patient complains of sexual dysfunction. Which of the following drugs might be useful in this patient? Correct answer = D. Mirtazapine is largely free from sexual side effects. However, sexual dysfunction commonly occurs with selective serotonin reuptake inhibitors (fluvoxamine, sertraline, and citalopram) as well as with tricyclic antidepressants, and serotonin/ norepinephrine reuptake inhibitors. Lithium is used for the treatment of mania and bipolar disorder. A. Fluvoxamine. B. Sertraline. C. Citalopram. D. Mirtazapine. E. Lithium. 12.2 A 25-year-old woman has a long history of depressive symptoms accompanied by body aches. Physical and laboratory tests are unremarkable. Which of the following drugs might be useful in this patient? A. Fluoxetine. B. Sertraline. C. Phenelzine. D. Mirtazapine. E. Duloxetine. 12.3 A 51-year-old woman with symptoms of major depression also has narrow-angle glaucoma. Which of the following antidepressants should be avoided in this patient? A. Amitriptyline. B. Sertraline. C. Bupropion. D. Mirtazapine. E. Fluvoxamine. 12.4 A 36-year-old man presents with symptoms of compulsive behavior. If anything is out of order, he feels that "work will not be accomplished effectively or efficiently." He realizes that his behavior is interfering with his ability to accomplish his daily tasks but cannot seem to stop himself. Which of the following drugs would be most helpful to this patient? Correct answer = E. Duloxetine is a serotonin/norepinephrine reuptake inhibitor that can be used for depression accompanied by neuropathic pain. Selective serotonin reuptake inhibitors (fluoxetine and sertraline), monoamine oxidase inhibitors (phenelzine), and atypical antidepressants (mirtazapine) have little activity against neuropathic pain. Correct answer = A. Because of its potent antimuscarinic activity, amitriptyline should not be given to patients with glaucoma because of the risk of acute increases in ocular pressure. The other antidepressants all lack antagonist activity at the muscarinic receptor. Correct answer = B. Selective serotonin reuptake inhibitors are particularly effective in treating obsessive-compulsive disorder and fluvoxamine is approved for this condition. The other drugs are ineffective in the treatment of obsessive-compulsive disorder. A. Imipramine. B. Fluvoxamine. C. Amitriptyline. D. Tranylcypromine. E. Lithium. Pharm 5th 3-21-11.indb 160 3/21/11 2:22:30 PM Antipsychotic Drugs 13 I. OVERVIEW The antipsychotic drugs (also called neuroleptics or major tranquilizers) are used primarily to treat schizophrenia, but they are also effective in other psychotic states, including manic states with psychotic symptoms such as grandiosity, paranoia, and hallucinations, and delirium. The use of antipsychotic medications involves a difficult trade-off between the benefit of alleviating psychotic symptoms and the risk of wide variety of troubling adverse effects. Antipsychotic drugs are not curative and do not eliminate the chronic thought disorder, but they often decrease the intensity of hallucinations and delusions and permit the person with schizophrenia to function in a supportive environment. II. SCHIZOPHRENIA Schizophrenia is a particular type of psychosis (that is, a mental disorder caused by some inherent dysfunction of the brain). It is characterized by delusions, hallucinations (often in the form of voices), and thinking or speech disturbances. This mental disorder is a common affliction, occurring in about 1 percent of the population. The illness often initially affects people during late adolescence or early adulthood and is a chronic and disabling disorder. Schizophrenia has a strong genetic component and probably reflects some fundamental biochemical abnormality, possibly a dysfunction of the mesolimbic or mesocortical dopaminergic neuronal pathways. III. ANTIPSYCHOTIC DRUGS FIRST-GENERATION ANTIPSYCHOTIC (low potency) Chlorpromazine THORAZINE Prochlorperazine COMPAZINE Thioridazine MELLARIL FIRST-GENERATION ANTIPSYCHOTIC (high potency) Fluphenazine PROLIXIN Haloperidol HALDOL Pimozide ORAP Thiothixene NAVANE SECOND GENERATION ANTIPSYCHOTIC Aripiprazole ABILIFY Asenapine SAPHRIS Clozapine CLOZARIL Iloperidone FANAPT Lurasidone LATUDA Olanzapine ZYPREXA Quetiapine SEROQUEL Paliperidone INVEGA Risperidone RISPERDAL Ziprasidone GEODON Figure 13.1 Summary of neuroleptic agents. The antipsychotic drugs are divided into first- and second-generation agents. The first-generation drugs are further classified as "low-potency" or "high-potency," not to indicate the drugs' clinical effectiveness, but rather to indicate their affinity for the dopamine D2 receptor, which, in turn, influences the adverse effect profile of the drug. A. First-generation antipsychotics The first-generation antipsychotic drugs (also called conventional, typical, or traditional antipsychotics) are competitive inhibitors at a variety of receptors, but their antipsychotic effects reflect competitive blocking of D2 dopamine receptors. First-generation antipsychotics are more likely to be associated with movement disorders, particularly for drugs that bind tightly to dopaminergic neurorecep- Pharm 5th 3-21-11.indb 161 3/21/11 2:22:30 PM 162 13. Neuroleptics Dopamine tors, such as haloperidol, and less true of medications that bind weakly, such as chlorpromazine. No one drug is clinically more effective than another. B. Second-generation antipsychotic drugs The second generation antipsychotic drugs (also referred to as "atypical" antipsychotics) have fewer extrapyramidal symptoms (EPS) than the first-generation agents, but are associated with a higher risk of metabolic side effects, such as diabetes, hypercholesterolemia, and weight gain. The second-generation drugs appear to owe their unique activity to blockade of both serotonin and dopamine (and, perhaps, other) receptors. Antipsychotic drugs Dopamine Dopamine receptor blocked DECREASED INTRACELLULAR RESPONSE Figure 13.2 Dopamine-blocking actions of neuroleptic drugs. 1. Drug selection: Current antipsychotic therapy commonly comprises second-generation agents to minimize the risk of debilitating movement disorders associated with the first-generation drugs that act primarily at the D2 dopamine receptor. All of the second-generation antipsychotics exhibit an efficacy that is equivalent to, and occasionally exceeds, that of the first-generation antipsychotic agents. However, consistent differences in therapeutic efficacy among the individual second-generation drugs have not been established, and individual patient response and comorbid conditions must often be used as a guide in drug selection. Further, second-generation antipsychotics should not be considered interchangeable because patients may respond differently to each drug in this class. 2. Refractory patients: Approximately 20% of patients with schizophrenia will have an insufficient response to all first- and secondgeneration antipsychotics. For these patients, clozapine has shown to be an effective antipsychotic with minimal risk of EPS. However, its clinical use is limited to refractory patients because of serious side effects. Clozapine can produce bone marrow suppression, seizures, and cardiovascular side effects. The risk of severe agranulocytosis necessitates frequent monitoring of white blood cell counts. C. Mechanism of action 1. Dopamine receptor–blocking activity in the brain: All of the firstgeneration and most of the second-generation antipsychotic drugs block dopamine receptors in the brain and the periphery (Figure 13.2). The clinical efficacy of the typical antipsychotic drugs correlates closely with their relative ability to block D2 receptors in the mesolimbic system of the brain. The actions of the antipsychotic drugs are antagonized by agents that raise synaptic dopamine concentrations (for example, levodopa and amphetamines) or mimic dopamine at post-synaptic binding sites (for example, bromocriptine). 2. Serotonin receptor–blocking activity in the brain: Most of the second-generation agents appear to exert part of their unique action through inhibition of serotonin receptors (5-HT), particularly 5-HT2A receptors. Thus, clozapine has high affinity for D1, D4, 5-HT2, muscarinic, and α-adrenergic receptors, but it is also a weak dopamine D2-receptor antagonist (Figure 13.3). Risperidone [ris-PEAR-ihdohn] blocks 5-HT2A receptors to a greater extent than it does D2 receptors, as does olanzapine [oh-LANZ-ih-peen]. The second-generation antipsychotic aripiprazole [a-rih-PIP-ra-zole] is a partial agonist at D2 and 5-HT1A receptors as well as a blocker of 5-HT2A recep- Pharm 5th 3-21-11.indb 162 3/21/11 2:22:30 PM III. Antipsychotic Drugs 163 tors. Quetiapine [qwe-TY-ih-peen] blocks D2 receptors more potently than 5HT2A receptors but is relatively weak at blocking either receptor, and its low risk for EPS may also be related to the relatively short period of time it binds to the D2 receptor. Relative affinities at D2 receptors Clozapine Chlorpromazine Haloperidol B. Actions The antipsychotic actions of antipsychotic drugs appear to reflect a blockade at dopamine and/or serotonin receptors. However, many of these agents also block cholinergic, adrenergic, and histaminergic receptors (Figure 13.4). It is unknown what role, if any, these actions have in alleviating the symptoms of psychosis. The undesirable side effects of these agents, however, are often a result of actions at these other receptors. 1. Antipsychotic actions: All of the antipsychotic drugs can reduce the hallucinations and delusions associated with schizophrenia (the so-called "positive" symptoms) by blocking dopamine receptors in the mesolimbic system of the brain. The "negative" symptoms, such as blunted affect, anhedonia (not getting pleasure from normally pleasurable stimuli), apathy, and impaired attention, as well as cognitive impairment, are not as responsive to therapy, particularly with the first-generation antipsychotics. Many second-generation agents, such as clozapine, ameliorate the negative symptoms to some extent. All of the drugs also have a calming effect and reduce spontaneous physical movement. In contrast to the central nervous system (CNS) depressants, such as barbiturates, the antipsychotics do not depress the intellectual functioning of the patient as much, and motor coordination difficulties are minimal. The antipsychotic effects usually take several days to weeks to occur, suggesting that the therapeutic effects are related to secondary changes in the corticostriatal pathways. Low affinity High affinity Most neuroleptic drugs have affinities at D2-dopaminergic receptors that parallel clinical potency. Clozapine differs from typical neuroleptic drugs in having a similar affinity for both D1- and D2-dopaminergic receptors. Relative affinities at D1 receptors Clozapine Chlorpromazine Haloperidol High affinity Low affinity Figure 13.3 Relative affinity of clozapine, chlorpromazine, and haloperidol at D1and D2-dopaminergic receptors. 2. Extrapyramidal effects: Dystonias (sustained contraction of muscles leading to twisting, distorted postures), Parkinson-like symptoms, akathisia (motor restlessness), and tardive dyskinesia ANTIPSYCHOTIC DRUGS Particularly thioridazine, chlorpromazine Particularly chlorpromazine Cholinergic (muscarinic) receptor All, but particularly haloperidol, fluphenazine, thiothixene α- Adrenergic receptor Dopamine receptor Risperidone, clozapine Serotonin receptor Particularly chlorpromazine, clozapine H1 Histamine receptor GABA receptor Figure 13.4 Antipsychotic drugs block at dopaminergic and serotonergic receptors as well as at adrenergic, cholinergic, and histamine-binding receptors. GABA = γ-aminobutyric acid. Pharm 5th 3-21-11.indb 163 3/21/11 2:22:31 PM 164 13. Neuroleptics Meclizine Dimenhydrinate For nausea due to . . . Vertigo Scopolamine Promethazine For nausea due to . . . Motion sickness Domperidone Haloperidol Metoclopramide Prochlorperazine For nausea due to . . . Cancer chemotherapy (involuntary movements of the tongue, lips, neck, trunk, and limbs) occur with chronic treatment. Blocking of dopamine receptors in the nigrostriatal pathway probably causes these unwanted movement symptoms. The second-generation antipsychotics exhibit a lower incidence of these symptoms. 3. Antiemetic effects: With the exception of aripiprazole, most of the antipsychotic drugs have antiemetic effects that are mediated by blocking D2-dopaminergic receptors of the chemoreceptor trigger zone of the medulla. (See p. 357 for a discussion of emesis.) Figure 13.5 summarizes the antiemetic uses of antipsychotic agents, along with the therapeutic applications of other drugs that combat nausea. [Note: The second-generation antipsychotic drugs are not used as antiemetics.] 4. Anticholinergic effects: Some of the antipsychotics, particularly thioridazine, chlorpromazine, clozapine, and olanzapine, produce anticholinergic effects, including blurred vision; dry mouth (the exception is clozapine, which increases salivation); confusion; and inhibition of gastrointestinal and urinary tract smooth muscle, leading to constipation and urinary retention. This anticholinergic property may actually assist in reducing the risk of EPS with these agents. 5. Other effects: Blockade of α-adrenergic receptors causes orthostatic hypotension and light-headedness. The antipsychotics also alter temperature-regulating mechanisms and can produce poikilothermia (condition in which body temperature varies with the environment). In the pituitary, antipsychotics block D2 receptors, leading to an increase in prolactin release. Second-generation antipsychotics are less likely to produce prolactin elevations. Sedation occurs with those drugs that are potent antagonists of the H1-histamine receptor, including chlorpromazine, olanzapine, quetiapine, and clozapine. Sexual dysfunction may also occur with the antipsychotics due to various receptor-binding characteristics. C. Therapeutic uses Thiethylperazine Domperidone For nausea due to . . . Radiation therapy Figure 13.5 Therapeutic application of antiemetic agents. Pharm 5th 3-21-11.indb 164 1. Treatment of schizophrenia: The antipsychotics are considered to be the only efficacious treatment for schizophrenia. Not all patients respond, and complete normalization of behavior is seldom achieved. The first-generation antipsychotics are most effective in treating positive symptoms of schizophrenia (delusions, hallucinations, thought processing, and agitation). The newer agents with 5-HT2A receptor-blocking activity may be effective in many patients who are resistant to the traditional agents, especially in treating the negative symptoms of schizophrenia (social withdrawal, blunted emotions, ambivalence, and reduced ability to relate to people). However, even the second-generation antipsychotics do not consistently improve the negative symptoms of schizophrenia more than the older agents do. 2. Prevention of severe nausea and vomiting: The older antipsychotics (most commonly, prochlorperazine [PROE-clor-PEAR-a-zeen]) are useful in the treatment of drug-induced nausea (see p. 358). However, nausea arising from motion should be treated with sedatives, antihistamines, and anticholinergics, rather than with the powerful antipsychotic drugs. [Note: Transdermal scopolamine is a drug of choice for treatment of motion sickness.] 3/21/11 2:22:33 PM III. Antipsychotic Drugs 165 3. Other uses: The antipsychotic drugs can be used as tranquilizers to manage agitated and disruptive behavior, secondary to other disorders. Antipsychotics are used in combination with narcotic analgesics for treatment of chronic pain with severe anxiety. Chlorpromazine is used to treat intractable hiccups. Although promethazine [proeMETH-a-zeen] is not an effective antipsychotic drug, this agent is used in treating pruritus because of its antihistaminic properties. Pimozide [PI-moe-zide] is primarily indicated for treatment of the motor and phonic tics of Tourette disorder. However, risperidone and haloperidol are also commonly prescribed for this tic disorder. Also, risperidone and aripiprazole are now approved for the management of the disruptive behavior and irritability secondary to autism. Urinary retention Weight Gain D. Absorption and metabolism After oral administration, the antipsychotics show variable absorption that is unaffected by food (except for ziprasidone [zi PRAY si done] and paliperidone [pal-ih-PEAR-ih-dohn], the absorption of which is increased with food). These agents readily pass into the brain, have a large volume of distribution, bind well to plasma proteins, and are metabolized to many different substances, usually by the cytochrome P450 system in the liver, particularly the CYP2D6, CYP1A2, and CYP3A4 isoenzymes. Some metabolites are active. Fluphenazine decanoate, haloperidol decanoate, risperidone microspheres, paliperidone palmitate, and olanzapine pamoate are long-acting injectable (LAI) formulations of antipsychotics that are administered via deep gluteal intramuscular injection or deltoid injection. These formulations have a therapeutic duration of action of up to 2 to 4 weeks and, therefore, are often used to treat outpatients and individuals who are noncompliant with oral medications. However, patients may still develop EPS, but the risk of EPS is lower with these LAI formulations compared to their respective oral formulations. The antipsychotic drugs produce some tolerance but little physical dependence. E. Adverse effects Adverse effects of the antipsychotic drugs can occur in practically all patients and are significant in about 80 percent (Figure 13.6). Although antipsychotic drugs have an array of adverse effects, their therapeutic index is high. 1. Extrapyramidal side effects: The inhibitory effects of dopaminergic neurons are normally balanced by the excitatory actions of cholinergic neurons in the striatum. Blocking dopamine receptors alters this balance, causing a relative excess of cholinergic influence, which results in extrapyramidal motor effects. The maximal risk of appearance of the movement disorders is time and dose dependent, with dystonias occurring within a few hours to days of treatment, followed by akathisias (the inability to remain seated due to motor restlessness) occurring within days to weeks. Parkinson-like symptoms of bradykinesia, rigidity, and tremor usually occur within weeks to months of initiating treatment. Tardive dyskinesia, which can be irreversible, may occur after months or years of treatment. a. Effect of anticholinergic drugs : If cholinergic activity is also blocked, a new, more nearly normal balance is restored, and extrapyramidal effects are minimized. This can be achieved by administration of an anticholinergic drug, such as benztropine. The therapeutic trade-off will be fewer EPS in exchange for the Pharm 5th 3-21-11.indb 165 Seizure ZZ Z Sedation Extrapyramidal symptoms BP Postural hypotension Sexual dysfunction Arrhythmias and sudden cardiac death Dry mouth Figure 13.6 Adverse effects observed in individuals treated with antipsychotic drugs. 3/21/11 2:22:33 PM 166 13. Neuroleptics side effect of muscarinic-receptor blockade. [Note: Sometimes, the parkinsonian symptoms and akathisias persist despite the use of anticholinergic drugs.] Those drugs that exhibit strong anticholinergic activity, such as thioridazine, show fewer extrapyramidal disturbances, because the cholinergic activity is strongly dampened. This contrasts with haloperidol and fluphenazine, which have low anticholinergic activity and produce extrapyramidal effects more frequently because of the preferential blocking of dopaminergic transmission without the blocking of cholinergic activity. Akathisia may respond better to β blockers or benzodiazepines rather than anticholinergic medications. 2. Tardive dyskinesia: Long-term treatment with antipsychotics can cause this motor disorder. Patients display involuntary movements, including bilateral and facial jaw movements and "fly-catching" motions of the tongue. A prolonged holiday from antipsychotics may cause the symptoms to diminish or disappear within a few months. However, in many individuals, tardive dyskinesia is irreversible and persists after discontinuation of therapy. Tardive dyskinesia is postulated to result from an increased number of dopamine receptors that are synthesized as a compensatory response to long-term dopamine-receptor blockade. This makes the neuron supersensitive to the actions of dopamine, and it allows the dopaminergic input to this structure to overpower the cholinergic input, causing excess movement in the patient. Traditional anti-EPS medications do not generally improve tardive dyskinesia and may actually worsen this condition. 3. Antipsychotic malignant syndrome: This potentially fatal reaction to antipsychotic drugs is characterized by muscle rigidity, fever, altered mental status and stupor, unstable blood pressure, and myoglobinemia. Treatment necessitates discontinuation of the antipsychotic agent and supportive therapy. Administration of dantrolene or bromocriptine may be helpful. 4. Other effects: Drowsiness occurs due to CNS depression and antihistaminic effects, usually during the first few weeks of treatment. Confusion sometimes results. Those antipsychotic agents with potent antimuscarinic activity often produce dry mouth, urinary retention, constipation, and loss of accommodation. Others may block α-adrenergic receptors, resulting in lowered blood pressure and orthostatic hypotension. The antipsychotics depress the hypothalamus, affecting thermoregulation and causing amenorrhea, galactorrhea, gynecomastia, infertility, and impotence. Significant weight gain is often a reason for noncompliance. It is also recommended that glucose and lipid profiles be monitored in patients taking antipsychotics due to the potential for the second-generation agents to increase these laboratory parameters and the possible exacerbation of preexisting diabetes mellitus or hyperlipidemia. 5. Cautions and contraindications: Acute agitation accompanying withdrawal from alcohol or other drugs may be aggravated by the antipsychotics. Stabilization with a simple sedative, such as a benzodiazepine, is the preferred treatment. All antipsychotics may lower the seizure threshold and should be used cautiously in patients with seizure disorders. Therefore, the antipsychotics can also aggravate pre- Pharm 5th 3-21-11.indb 166 3/21/11 2:22:34 PM III. Antipsychotic Drugs 167 F. Maintenance treatment Patients who have had two or more psychotic episodes, secondary to schizophrenia, should receive maintenance therapy for at least 5 years, and some experts prefer indefinite therapy. There has been a greater emphasis in research and practice on identifying and aggressively managing first-episode psychosis to determine the benefits of antipsychotic agents in this population. Low doses of antipsychotic drugs are not as effective as higher-dose maintenance therapy in preventing relapse. The rate of relapse may be lower with second generation drugs (Figure 13.7). Figure 13.8 summarizes the therapeutic uses of some of the antipsychotic drugs. DRUG Patients receiving the atypical neuroleptic risperidone show fewer relapses than those treated with haloperidol, a highpotency, typical neuroleptic. 100 Relapse free (%) existing epilepsy and should be used with caution in patients with epilepsy. The high incidence of agranulocytosis with clozapine may limit its use to patients who are resistant to other drugs. All of the second-generation antipsychotics also carry the warning of increased risk for mortality when used in elderly patients with dementiarelated behavioral disturbances and psychosis. Antipsychotics used in patients with mood disorders should also be monitored for worsening of mood and suicidal ideation or behaviors. Risperidone Haloperidol 0 0 Days 800 Figure 13.7 Rates of relapse among patients with schizophrenia after maintenance therapy with either risperidone or haloperidol. THERAPEUTIC NOTES First generation Chlorpromazine Moderate to high potential for EPS; moderate to high potential for weight gain, orthostasis, sedation, antimuscarinic effects. Fluphenazine Oral formulation has a high potential for EPS; low potential for weight gain, sedation, and orthostasis; low to moderate potential for anti-muscarinic effects; common use is in the LAI formulation administered every 2-3 weeks in patients with schizophrenia and a history of non-compliance with oral antipsychotic regimens. Haloperidol High potential for EPS; low potential for anti-adrenergic (orthostasis) or anti-muscarinic adverse events; low potential for weight gain or sedation; available in a LAI formulation administered every 4 weeks. Second generation Aripiprazole Low potential for EPS; low potential for weight gain; low potential for sedation and anti-muscarinic effects; also approved for the treatment of bipolar disorder; also approved for autistic disorder in children, and as an adjunctive treatment for major depression. Asenapine Low potential for EPS; low potential for weight gain; low to moderate potential for sedation; low potential for orthostasis; also approved for the treatment of bipolar disorder; available as a sublingual formulation. Clozapine Very low potential for EPS; risk for blood dyscrasias (eg. agranulocytosis = ~1%); risk for seizures; risk for myocarditis; high potential for the following: sialorrhea, weight gain, anti-muscarinic effects, orthostasis, and sedation. Low potential for EPS; moderate to high potential for weight gain and sedation; low potential for orthostasis; also approved for the treatment of bipolar disorder; available as a LAI formulation administered every 2-4 weeks. Olanzapine Paliperidone Low to moderate potential for EPS; low potential for weight gain; low potential for sedation; available as a LAI formulation administered every 4 weeks; also approved for use in schizo-affective disorder. Quetiapine Low potential for EPS; moderate potential for weight gain; moderate potential for orthostasis; moderate to high potential for sedation; also approved for the treatment of bipolar disorder and as an adjunctive treatment for major depression. Risperidone Low to moderate potential for EPS; low to moderate potential for weight gain; low to moderate potential for orthostasis; low to moderate potential for sedation; also approved for the treatment of bipolar disorder; also approved for autistic disorder in children; available as a LAI formulation administered every 2 weeks. Ziprasidone Low potential for extrapyramidal effects; contraindicated in patients with history of cardiac arrhythmias; minimal weight gain. Used in treatment of bipolar depression. Figure 13.8 Summary of antipsychotic agents commonly used to treat schizophrenia. EPS = extrapryamidal effects; LAI = long-acting injectable. Pharm 5th 3-21-11.indb 167 3/21/11 2:22:34 PM 168 13. Neuroleptics Study Questions Choose the ONE best answer. 13.1 An adolescent male is newly diagnosed with schizophrenia. Which of the following neuroleptic agents may improve his apathy and blunted affect? A. Chlorpromazine. B. Fluphenazine. C. Haloperidol. D. Risperidone. E. Thioridazine. 13.2 Which one of the following neuroleptics has been shown to be a partial agonist at the D2 receptor? A. Aripiprazole. B. Clozapine. C. Haloperidol. D. Risperidone. E. Thioridazine. 13.3 A 21-year-old male has recently begun pimozide therapy for Tourette disorder. His parents bring him to the emergency department. They describe that he has been having "different-appearing tics" than before, such as prolonged contraction of the facial muscles. While being examined, he experiences opisthotonus (type of extrapyramidal spasm of the body in which the head and heels are bent backward and the body is bowed forward). Which of the following drugs would be beneficial in reducing these symptoms? Correct answer = D. Risperidone is the only neuroleptic on the list that has some benefit in improving the negative symptoms of schizophrenia. All of the agents have the potential to diminish the hallucinations and delusional thought processes. Correct answer = A. Aripiprazole is the agent that acts as a partial agonist at D2 receptors. Theoretically, the drug would enhance action at these receptors when there is a low concentration of dopamine and would block the actions of high concentrations of dopamine. All of the other drugs are only antagonistic at D2 receptors, with haloperidol being particularly potent. Correct answer = A. The patient is experiencing extrapyramidal symptoms due to pimozide, and a muscarinic antagonist such as benztropine would be effective in reducing the symptoms. The other drugs would have no effect or, in the case of prochlorperazine, might increase the symptoms. A. Benztropine. B. Bromocriptine. C. Lithium. D. Prochlorperazine. E. Risperidone. 13.4 A 28-year-old woman with schizoid affective disorder and difficulty sleeping would be most benefited by which of the following drugs? A. Aripiprazole. B. Chlorpromazine. C. Haloperidol. D. Risperidone. E. Ziprasidone. Pharm 5th 3-21-11.indb 168 Correct answer = B. Chlorpromazine has significant sedative activity as well as antipsychotic properties. Of the choices, it is the drug most likely to alleviate this patient's major complaints, including her insomnia. 3/21/11 2:22:35 PM 14 Opioids I. OVERVIEW Management of pain is one of clinical medicine's greatest challenges. Pain is defined as an unpleasant sensation that can be either acute or chronic and is a consequence of complex neurochemical processes in the peripheral and central nervous system (CNS). It is subjective, and the physician must rely on the patient's perception and description of his or her pain. Alleviation of pain depends on the specific type of pain, nociceptive or neurogenic pain. In many cases, for example, with mild to moderate arthritic pain (nociceptive pain), nonsteroidal anti-inflammatory agents (NSAIDs, see Chapter 42) are effective. Neurogenic pain responds best to anticonvulsants (for example, pregabalin, see p. 188), tricyclic antidepressants (for example, amitriptyline, see p. 155), or serotonin/norepinephrine reuptake inhibitors (for example, duloxetine, see p. 154) rather than NSAIDs or opioids. However, for severe or chronic malignant or nonmalignant pain, opioids are usually the drugs of choice. Opioids are natural or synthetic compounds that produce morphine-like effects. [Note: The term "opiate" is reserved for drugs, such as morphine and codeine, obtained from the juice of the opium poppy.] All drugs in this category act by binding to specific opioid receptors in the CNS to produce effects that mimic the action of endogenous peptide neurotransmitters (for example, endorphins, enkephalins, and dynorphins). Although the opioids have a broad range of effects, their primary use is to relieve intense pain, whether that pain is from surgery or a result of injury or disease such as cancer. However, their widespread availability has led to abuse of those opioids with euphoric properties. Antagonists that can reverse the actions of opioids are also very important clinically for use in cases of overdose. Figure 14.1 lists the opioid agonists and antagonists discussed in this chapter. II. OPIOID RECEPTORS Opioids interact stereospecifically with protein receptors on the membranes of certain cells in the CNS, on nerve terminals in the periphery, and on cells of the gastrointestinal (GI) tract and other anatomic regions. The major effects of the opioids are mediated by three major receptor families. These are designated by the Greek letters μ (mu), κ (kappa), and δ (delta). Each receptor family exhibits a different specificity for the drug(s) it binds. The analgesic properties of the opioids are primarily mediated by the μ receptors. However, the κ receptors in the dorsal horn also contribute (for example, butorphanol and nalbuphine) primarily owe their analgesic effect to κ-receptor activation. The enkephalins interact more selectively with the δ receptors in the periphery. All three opioid receptors are members of the G protein–coupled receptor family and inhibit adenylyl cyclase. They Pharm 5th 3-21-11.indb 169 STRONG AGONISTS Alfentanil ALFENTA Fentanyl ACTIQ, DURAGESIC, FENTORA Heroin Hydrocodone various Hydromorphone DILAUDID Meperidine DEMEROL Methadone DOLOPHINE Morphine ROXANOL, CONTIN, ORAMORPH, KADIAN, AVINZA Oxycodone OXYCONTIN Oxymorphone OPANA Remifentanil ULTIVA Sufentanil SUFENTA Tapentadol NUCYNTA MODERATE/LOW AGONISTS Codeine MIXED AGONIST-ANTAGONISTS AND PARTIAL AGONISTS Buprenorphine BUPRENEX, SUBUTEX Butorphanol STADOL Nalbuphine NUBAIN Pentazocine TALWIN ANTAGONISTS Nalmefene REVEX Naloxone NARCAN Naltrexone DEPADE, REVIA, VIVITROL OTHER ANALGESICS Tramadol ULTRAM Figure 14.1 Summary of opioid analgesics and antagonists. 3/21/11 2:22:35 PM 170 14. Opioids Activation of the opioid receptor decreases Ca^{2+} influx in response to incoming action potential. This decreases release of excitatory neurotransmitters, such as glutamate. are also associated with ion channels, increasing postsynaptic K^{+} efflux (hyperpolarization) or reducing presynaptic Ca^{2+} influx, thus impeding neuronal firing and transmitter release (Figure 14.2). III. STRONG AGONISTS Morphine [MOR-feen] is the major analgesic drug contained in crude opium and is the prototype strong agonist. Codeine is present in crude opium in lower concentrations and is inherently less potent, making codeine the prototype of the weak opioid agonists. Morphine and several other opioids have high affinity for μ receptors, whereas other agents have varying affinities for δ and κ receptors. PRESYNAPTIC NEURON Opioid receptor A. Morphine Synaptic vesicle Ca^{2+} Ca^{2+} Glutamate 1. Mechanism of action: Opioids exert their major effects by interacting with opioid receptors in the CNS and in other anatomic structures, such as the GI tract and the urinary bladder. Opioids cause hyperpolarization of nerve cells, inhibition of nerve firing, and presynaptic inhibition of transmitter release. Morphine acts at κ receptors in laminae I and II of the dorsal horn of the spinal cord, and it decreases the release of substance P, which modulates pain perception in the spinal cord. Morphine also appears to inhibit the release of many excitatory transmitters from nerve terminals carrying nociceptive (painful) stimuli. 2. Actions: K^{+} + K^{+} Excitatory response Opioid receptor Activation of the opioid receptor increases K^{+} efflux and decreases the response of the postsynaptic neuron to excitatory neurotransmitters. POSTSYNAPTIC NEURON Figure 14.2 Mechanism of action of μ-opioid receptor agonists in the spinal cord. a. Analgesia: Morphine causes analgesia (relief of pain without the loss of consciousness). Opioids relieve pain both by raising the pain threshold at the spinal cord level and, what is more important, by altering the brain's perception of pain. Patients treated with morphine are still aware of the presence of pain, but the sensation is not unpleasant. However, when given to an individual free of pain, its effects may be unpleasant and may cause nausea and vomiting. The maximum analgesic efficacy for representative agonists is shown in Figure 14.3. b. Euphoria: Morphine produces a powerful sense of contentment and well-being. Euphoria may be caused by disinhibition of the dopamine-containing neurons of the ventral tegmentum. c. Respiration: Morphine causes respiratory depression by reduction of the sensitivity of respiratory center neurons to carbon dioxide. This can occur with ordinary doses of morphine in patients who are opioid-naïve and can be accentuated as the dose is increased until, ultimately, respiration ceases. Respiratory depression is the most common cause of death in acute opioid overdoses. Tolerance to this effect does develop quickly with repeated dosing, which allows the safe use of morphine for the treatment of pain when the dose is correctly titrated. d. Depression of cough reflex: Both morphine and codeine have antitussive properties. In general, cough suppression does not correlate closely with the analgesic and respiratory depressant properties of opioid drugs. The receptors involved in the antitussive action appear to be different from those involved in analgesia. e. Miosis: The pinpoint pupil, characteristic of morphine use, results from stimulation of μ and κ receptors. Morphine excites Pharm 5th 3-21-11.indb 170 3/21/11 2:22:36 PM III. Strong Agonists the Edinger-Westphal nucleus of the oculomotor nerve, which causes enhanced parasympathetic stimulation to the eye (Figure 14.4). There is little tolerance to the effect, and all morphine abusers demonstrate pinpoint pupils. [Note: This is important diagnostically, because many other causes of coma and respiratory depression produce dilation of the pupil.] f. Emesis: Morphine directly stimulates the chemoreceptor trigger zone in the area postrema that causes vomiting. g. GI tract: Morphine relieves diarrhea and dysentery by decreasing the motility and increasing the tone of the intestinal circular smooth muscle. Morphine also increases the tone of the anal sphincter. Overall, morphine and other narcotics produce constipation, with little tolerance developing. [Note: A nonprescription laxative combination of the stool softener docusate with the stimulant laxative senna has been used successfully to treat this opioid-induced constipation.] Morphine can also increase biliary tract pressure due to contraction of the gallbladder and constriction of the biliary sphincter. h. Cardiovascular: Morphine has no major effects on the blood pressure or heart rate except at large doses, at which hypotension and bradycardia may occur. Because of respiratory depression and carbon dioxide retention, cerebral vessels dilate and increase cerebrospinal fluid (CSF) pressure. Therefore, morphine is usually contraindicated in individuals with head or severe brain injury. 171 Afentanil Fentanyl Hydrocodone Meperidine Methadone Morphine Oxycodone Remifentanil Sufentanil Buprenorphine Nalbuphine Pentazocine Codeine High Moderate Low Low High Figure 14.3 A comparison of the maximum efficacy of commonly used narcotic analgesics. i. Histamine release: Morphine releases histamine from mast cells, causing urticaria, sweating, and vasodilation. Because it can cause bronchoconstriction, asthmatics should not receive the drug. j. Hormonal actions: Morphine increases growth hormone release and enhances prolactin secretion. It increases antidiuretic hormone and, thus, leads to urinary retention. [Note: Because it also can inhibit the urinary bladder voiding reflex, catheterization may be required.] k. Labor: Morphine may prolong the second stage of labor by transiently decreasing the strength, duration, and frequency of uterine contractions. 3. Therapeutic uses: a. Analgesia: Despite intensive research, few other drugs have been developed that are as effective as morphine in the relief of pain. Opioids induce sleep, and in clinical situations when pain is present and sleep is necessary, opiates may be used to supplement the sleep-inducing properties of benzodiazepines such as temazepam. [Note: The sedative-hypnotic drugs are not usually analgesic, and they may have diminished sedative effect in the presence of pain.] b. Treatment of diarrhea: Morphine decreases the motility and increases the tone of intestinal circular smooth muscle. [Note: This can cause constipation. Morphine products such as tincture of opium and camphorated tincture of opium (paregoric) have been used to treat diarrhea.] Pharm 5th 3-21-11.indb 171 Figure 14.4 Morphine causes enhanced parasympathetic stimulation to the eye, resulting in pinpoint pupils. 3/21/11 2:22:37 PM 172 Hypotension 14. Opioids c. Relief of cough: Although morphine suppresses the cough reflex, codeine or dextromethorphan are more widely used for this purpose. Codeine has greater antitussive action than morphine. BP d. Treatment of acute pulmonary edema: Intravenous (IV) morphine dramatically relieves dyspnea caused by pulmonary edema associated with left ventricular failure, possibly by its vasodilatory effect. Dysphoria (anxiety, depression, or unease) 4. Pharmacokinetics: ZZ Sedation Z Constipation Urinary retention Nausea Potential for addiction Respiratory depression Figure 14.5 Adverse effects commonly observed in individuals treated with opioids. Pharm 5th 3-21-11.indb 172 a. Administration: Because significant first-pass metabolism of morphine occurs in the liver, intramuscular, subcutaneous, and IV injections produce the most reliable responses. Absorption of morphine from the GI tract is slow and erratic. When used orally, morphine is commonly administered in an extended-release form to provide more consistent plasma levels. It is important to note that morphine has a linear pharmacokinetic profile. This pharmacokinetic trait allows dosing to be more predictable and more flexible. [Note: In cases of chronic pain associated with neoplastic disease, it has become common practice to use either the extended-release tablets orally or pumps that allow the patient to control the pain through self-administration.] b. Distribution: Morphine rapidly enters all body tissues, including the fetuses of pregnant women, and should not be used for analgesia during labor. Infants born of addicted mothers show physical dependence on opiates and exhibit withdrawal symptoms if opioids are not administered. Only a small percentage of morphine crosses the blood-brain barrier, because morphine is the least lipophilic of the common opioids. This contrasts with the more fat-soluble opioids, such as fentanyl and methadone, which readily penetrate into the brain. c. Fate: Morphine is conjugated with glucuronic acid in the liver. Morphine-6-glucuronide is a very potent analgesic, whereas the conjugate at position 3 (morphine-3-glucuronide) has been found not to have opioid activity, but is believed to cause the neuro-excitatory effects seen with high doses of morphine. The conjugates are excreted primarily in urine, with small quantities appearing in bile. The duration of action of morphine is 4 to 6 hours when administered systemically to morphine-naïve individuals but considerably longer when injected epidurally, because its low lipophilicity prevents redistribution from the epidural space. [Note: A patient's age can influence the response to morphine. Elderly patients are more sensitive to the analgesic effects of the drug, possibly due to decreased metabolism or other factors, such as decreased lean body mass, renal function, etc. They should be treated with lower doses. Neonates should not receive morphine because of their low conjugating capacity.] 5. Adverse effects: Severe respiratory depression can occur and result in death from acute opioid poisoning. A serious effect of the drug is stoppage of respiratory exchange in patients with emphysema or cor pulmonale. [Note: If used in such individuals, respiration must be carefully monitored.] Other effects include vomiting, dysphoria, and histamine-enhanced hypotensive effects (Figure 14.5). The ele- 3/21/11 2:22:38 PM III. Strong Agonists vation of intracranial pressure, particularly in head injury, can be serious. Morphine enhances cerebral and spinal ischemia. In benign prostatic hyperplasia, morphine may cause acute urinary retention. Patients with adrenal insufficiency or myxedema may experience extended and increased effects from the opioids. Morphine should be used cautiously in patients with bronchial asthma, liver failure, or impaired renal function. 173 Absolute contraindication to meperidine and relative contraindication to other narcotic analgesics Increased CNS because of high depression, incidence of hyperparticularly pyrexic coma respiratory depression 6. Tolerance and physical dependence: Repeated use produces tolerance to the respiratory depressant, analgesic, euphoric, and sedative effects of morphine. However, tolerance usually does not develop to the pupil-constricting and constipating effects of the drug. Physical and psychological dependence readily occur with morphine and with some of the other agonists (see Figure 14.3). Withdrawal produces a series of autonomic, motor, and psychological responses that incapacitate the individual and cause serious (almost unbearable) symptoms. However, it is very rare that the effects are so profound as to cause death. [Note: Detoxification of morphine-dependent individuals is usually accomplished through the oral administration of methadone, buprenorphine (see below), or clonidine.] 7. Drug interactions: Drug interactions with morphine appear to be rare, although the depressant actions of morphine are enhanced by phenothiazines, monoamine oxidase inhibitors (MAOIs), and tricyclic antidepressants (Figure 14.6). B. Meperidine Meperidine [me-PER-i-deen] is a synthetic opioid structurally unrelated to morphine. It is used for acute pain. 1. Mechanism of action: Meperidine binds to opioid receptors, particularly μ receptors. It also binds well to κ receptors. 2. Actions: Meperidine causes a depression of respiration similar to that of morphine, but it has no significant cardiovascular action when given orally. On IV administration, meperidine produces a decrease in peripheral resistance and an increase in peripheral blood flow, and it may cause an increase in cardiac rate. As with morphine, meperidine dilates cerebral vessels, increases CSF pressure, and contracts smooth muscle (the latter to a lesser extent than does morphine). Meperidine does not cause pinpoint pupils but, rather, causes the pupils to dilate because of an anticholinergic action. 3. Therapeutic uses: Meperidine provides analgesia but is not recommended for long-term use due to its active metabolite, normeperidine, which has significant neurotoxic properties. Unlike morphine, meperidine is not clinically useful in the treatment of diarrhea or cough. Meperidine produces less of an increase in urinary retention than does morphine. 4. Pharmacokinetics: Meperidine is well absorbed from the GI tract, and is available for oral administration. However, meperidine is most often administered parenterally. The drug has a duration of action of 2 to 4 hours, which is shorter than that of morphine (Figure 14.7). Meperidine is N-demethylated to normeperidine in the liver and is excreted in urine. Pharm 5th 3-21-11.indb 173 Sedativehypnotics MAO inhibitors Narcotic analgesics Tricyclic antidepressants Antipsychotic drugs Increased sedation; variable effects on respiratory depression Figure 14.6 Drugs interacting with narcotic analgesics. CNS = central nervous system; MAO = monoamine oxidase. Key Morphine Meperidine Fentanyl Time to peak effect Duration of action 20 minutes 4 hours 15 minutes 2–4 hours 5 minutes 15–30 minutes Figure 14.7 Time to peak effect and duration of action of several opioids administered intravenously. 3/21/11 2:22:39 PM 174 14. Opioids 5. Adverse effects: Large or repetitive doses of meperidine can cause anxiety, tremors, muscle twitches, and, rarely, convulsions, due to the accumulation of normeperidine. The drug differs from opioids in that, when given in large doses, it dilates the pupil and causes hyperactive reflexes. Severe hypotension can occur when the drug is administered postoperatively. Due to its antimuscarinic (anticholinergic) action, patients may experience dry mouth and blurred vision. When used with major antipsychotic drugs, depression is greatly enhanced. Administration to patients taking MAOIs or dextromethorphan can provoke severe reactions, such as convulsions and hyperthermia. Meperidine is considered to be inappropriate for use in geriatric patients and patients with impaired renal function, due to the accumulation of normeperidine. Due to toxicities associated with meperidine use in elderly populations, this medication has been included on the Beers list, which was developed to identify those medications that should be avoided in elderly patients. Adverse effects associated with normeperidine are not reversible by administration of naloxone. C. Methadone Methadone [METH-a-done] is a synthetic, orally effective opioid which has variable equianalgesic potency compared to that of morphine and the conversion between the two products is not linear. Methadone induces less euphoria and has a somewhat longer duration of action. Severity of withdrawal Buprenorphine is used in opiate detoxification, because it has a less severe and shorter duration of withdrawal symptoms compared to methadone. 1. Mechanism of action: The actions of methadone are mediated by μ receptors. In addition, methadone is an antagonist of the N-methylD-aspartate (NMDA) receptor, which is useful in the treatment of neurogenic pain. Heroin Buprenorphine Methadone 0 5 10 Days since last drug dose 15 Symptoms last longest with methadone, but are less severe than those of heroin withdrawal. Figure 14.8 Severity of opioid-withdrawal symptoms after abrupt withdrawal of equivalent doses of heroin, buprenorphine, and methodone. Pharm 5th 3-21-11.indb 174 2. Actions: Methadone is well absorbed when administered orally, unlike morphine, which is only partially absorbed from the GI tract. Like morphine, methadone increases biliary pressure and is also constipating (but less so than morphine). 3. Therapeutic uses: Methadone is used as an analgesic in nociceptive and neurogenic pain as well as in the controlled withdrawal of dependent abusers from heroin and morphine. Orally administered, methadone is substituted for the injected opioid. The patient is then slowly weaned from methadone. Methadone causes a withdrawal syndrome that is milder but more protracted (days to weeks) than that of other opioids (Figure 14.8). 4. Pharmacokinetics: Methadone is readily absorbed following oral administration. The drug is biotransformed in the liver and is excreted almost exclusively in feces. It is important to understand the pharmacokinetics of methadone when using this medication, due to multiple variables associated with it. Methadone is very lipophilic, leading to accumulation in the fat tissues. The slow release from these fat tissues causes the half-life to range from 12 to 40 hours and has been reported to extend up to 150 hours. The actual duration of analgesia ranges from 4 to 8 hours. Upon repetitive dosing, methadone levels can accumulate due to this long terminal half-life, thereby leading to toxicity. The metabolism is variable because it relies on multiple cytochrome P450 (CYP450) enzymes, some of which are affected by known genetic polymorphisms and are susceptible to many drugdrug interactions. 3/21/11 2:22:40 PM III. Strong Agonists 175 5. Adverse effects: Methadone can produce physical dependence like that of morphine but has less neurotoxicity than what is seen with morphine due to the lack of active metabolites. Methadone can cause torsades de pointes in certain situations. Overdosing is possible when prescribers are not aware of the incomplete cross-tolerance between methadone and other opioids, the long half-life associated with methadone and the proper titration guidelines to avoid its accumulation, and the multiple drug-drug interactions that can occur with this agent. D. Fentanyl Fentanyl [FEN-ta-nil], which is chemically related to meperidine, has 100-fold the analgesic potency of morphine and is used in anesthesia. The drug is highly lipophilic and has a rapid onset and short duration of action (15–30 minutes). It is usually administered IV, epidurally, or intrathecally. Epidural fentanyl is used to induce anesthesia (see p. 145) and for analgesia postoperatively and during labor. An oral transmucosal preparation and a transdermal patch are also available. The transmucosal preparation is used in the treatment of cancer patients with breakthrough pain who are tolerant to opioids (Figure 14.9). The transdermal patch must be used with caution, because death resulting from hypoventilation has been known to occur. [Note: The transdermal patch creates a reservoir of the drug in the skin. Hence, the onset is delayed 12 hours, and the offset is prolonged.] Fentanyl is often used during cardiac surgery because of its negligible effects on myocardial contractility. Muscular rigidity, primarily of the abdomen and chest wall, is often observed with fentanyl use in anesthesia. Fentanyl is metabolized to inactive metabolites by the CYP450 3A4 system, and drugs that inhibit this isozyme can potentiate the effect of fentanyl. Most of the drug and metabolites are eliminated through the urine. Adverse effects of fentanyl are similar to those of other μ-receptor agonists. Because of life-threatening hypoventilation, the fentanyl patch is contraindicated in the management of acute and postoperative pain and in pain that can be ameliorated with other analgesics. Unlike meperidine, it causes pupillary constriction. E. Sufentanil, alfentanil, and remifentanil Three drugs related to fentanyl, sufentanil [soo-FEN-ta-nil], alfentanil [alFEN-ta-nil], and remifentanil [rem-ih-FEN-ta-nil], differ in their potency and metabolic disposition. Sufentanil is even more potent than fentanyl, whereas the other two are less potent and shorter acting. F. Heroin Heroin [HAIR-o-in] does not occur naturally. It is produced by diacetylation of morphine, which leads to a threefold increase in its potency. Its greater lipid solubility allows it to cross the blood-brain barrier more rapidly than morphine, causing a more exaggerated euphoria when the drug is injected. Heroin is converted to morphine in the body, but its effects last about half as long. It has no accepted medical use in the United States but is used therapeutically in other countries for the severe pain of cancer. Transmucosal form of fentanyl is delivered to the buccal mucosa in lozenge form that the patient sucks on. Matrix containing fentanyl Matrix containing fentanyl Saliva Oral mucosa Vascular tissue Figure 14.9 Transmucosal delivery of fentanyl. Lozenges are used only in opioidtolerant patients, such as cancer patients who experience breakthrough pain. Absorption of the transmucosal form provides a rapidly absorbed dose from the buccal mucosa and a more prolonged effect that is delivered to the gastrointestinal system after swallowing. G. Oxycodone and oxymorphone Oxycodone [ok-see-KOE-done] is a semisynthetic derivative of morphine. It is orally active and is sometimes formulated with aspirin or acetamin- Pharm 5th 3-21-11.indb 175 3/21/11 2:22:40 PM 176 14. Opioids ophen. It is used to treat moderate to severe pain and has many properties in common with morphine. Its oral analgesic effect is approximately twice that of morphine. Oxycodone is metabolized via CYP450 2D6 and 3A4 enzyme systems. Excretion is via the kidney. Abuse of the sustained-release preparation (ingestion of crushed tablets) has been implicated in many deaths. It is important that the higher-dosage forms of the latter preparation be used only by patients who are tolerant to opioids. Oxymorphone [ox-ee-MOR-fone] is a narcotic analgesic with a potency similar to that of hydromorphone (see below). It is available in both immediate-acting and extended-release formulations. There are not any clinically relevant drug-drug interactions associated with the CYP450 enzyme system compared to oxycodone. H. Hydromorphone and hydrocodone Pain Analgesia Hydromorphone [hye-droe-MORE-fone] and hydrocodone [hye-droeKOE-done] are orally active, semisynthetic analogues of morphine and codeine, respectively. Oral hydromorphone is approximately eight to ten times more potent than oral morphine as an analgesic and is used most often to treat severe pain. Hydromorphone is preferred over morphine in patients with renal dysfunction due to less accumulation of active metabolites compared to morphine. Hydrocodone is the methyl ether of hydromorphone, but is much weaker an analgesic than hydromorphone. The analgesic potency of oral hydrocodone is approximately that of morphine. Hydrocodone is often combined with acetaminophen or ibuprofen to treat moderate-to-severe pain. It is also used as an antitussive. Hydrocodone is metabolized in the liver to several metabolites, one of which is hydromorphone via the actions of CYP450 2D6, which can be affected by drug-drug interactions. IV. MODERATE/LOW AGONIST ZZ Z Sedation Euphoria Dry cough Figure 14.10 Some actions of codeine. Pharm 5th 3-21-11.indb 176 A. Codeine The analgesic actions of codeine [KOE-deen] derive from its conversion to morphine by the CYP450 2D6 enzyme system, whereas the drug's antitussive effects are due to codeine itself. Thus, codeine is a much less potent analgesic than morphine. Codeine's analgesic potency is approximately 30 percent that of morphine. Codeine shows good antitussive activity at doses that do not cause analgesia. At commonly used doses, the drug has a lower potential for abuse than morphine. Codeine is often used in combination with aspirin or acetaminophen. [Note: In most nonprescription cough preparations, codeine has been replaced by drugs such as dextromethorphan, a synthetic cough depressant that has relatively no analgesic action and a relatively low potential for abuse in usual antitussive doses.] Figure 14.10 shows some of the actions of codeine. V. MIXED AGONIST-ANTAGONISTS AND PARTIAL AGONISTS Drugs that stimulate one receptor but block another are termed mixed agonist-antagonists. The effects of these drugs depend on previous exposure to opioids. In individuals who have not recently received opioids (naïve patients), mixed agonist-antagonists show agonist activity and are used to relieve pain. In the patient with opioid dependence, the agonist-antagonist 3/21/11 2:22:41 PM V. Mixed Agonist-Antagonists And Partial Agonists 177 drugs may show primarily blocking effects (that is, produce withdrawal symptoms). A. Pentazocine Buprenorphine [byoo-pre-NOR-feen] is classified as a partial agonist, acting at the μ receptor. It acts like morphine in naïve patients, but it can also precipitate withdrawal in morphine users. A major use is in opiate detoxification, because it has a less severe and shorter duration of withdrawal symptoms compared to methadone (see Figures 14.8 and 14.11). It causes little sedation, respiratory depression, and hypotension, even at high doses. In contrast to methadone, which is available only at specialized clinics, buprenorphine is approved for office-based detoxification or maintenance. Buprenorphine is administered sublingually, parenterally, or transdermally and has a long duration of action because of its tight binding to the μ receptor. The tablets are indicated for the treatment of opioid dependence and are available in buprenorphine alone (Subutex) and also in a combination product

containing buprenorphine and naloxone (Suboxone). Naloxone was added to buprenorphine to prevent the abuse of buprenorphine via IV administration. There is no clinical effect seen with oral naloxone, but, upon IV administration, opioid antagonism will occur, and the patient will experience withdrawal. The injectable form and the once weekly transdermal patch are indicated for the relief of moderate to severe pain. It is metabolized by the liver and excreted in bile and urine. Adverse effects include respiratory depression that cannot easily be reversed by naloxone and decreased (or, rarely, increased) blood pressure, nausea, and dizziness. C. Nalbuphine and butorphanol Nalbuphine [NAL-byoo-feen] and butorphanol [byoo-TOR-fa-nole], like pentazocine, play a limited role in the treatment of chronic pain. Neither is available for oral use. Their propensity to cause psychotomimetic (actions mimicking the symptoms of psychosis) effects is less than that of pentazocine. Nalbuphine does not affect the heart or increase blood pressure, in contrast to pentazocine and butorphanol. A benefit of all three medications is that they exhibit a ceiling effect for respiratory depression. Pharm 5th 3-21-11.indb 177 Opiate craving Score Placebo 50 0 Buprenorphine 0 1 2 Weeks 3 4 Subject's impression of overall status B 100 Score B. Buprenorphine A 100 50 0 0 1 2 Weeks 3 4 Clinicians' impression of overall status C 100 Score Pentazocine [pen-TAZ-oh-seen] acts as an agonist on κ receptors and is a weak antagonist at μ and δ receptors. Pentazocine promotes analgesia by activating receptors in the spinal cord, and it is used to relieve moderate pain. It may be administered either orally or parenterally. Pentazocine produces less euphoria compared to morphine. In higher doses, the drug causes respiratory depression and decreases the activity of the GI tract. High doses increase blood pressure and can cause hallucinations, nightmares, dysphoria, tachycardia, and dizziness. The latter properties have led to its decreased use. In angina, pentazocine increases the mean aortic pressure and pulmonary arterial pressure and, thus, increases the work of the heart. The drug decreases renal plasma flow. Despite its antagonist action, pentazocine does not antagonize the respiratory depression of morphine, but it can precipitate a withdrawal syndrome in a morphine abuser. Tolerance and dependence develop on repeated use. 50 Weeks 0 0 1 2 3 4 Figure 14.11 Scores for opiate craving and overall status in opioid-addicted patients assigned to office-based treatment with buprenorphine or placebo. 3/21/11 2:22:41 PM 178 14. Opioids VI. OTHER ANALGESICS A. Tramadol Tramadol (TRA-ma-dole) is a centrally acting analgesic that binds to the μ-opioid receptor. The drug undergoes extensive metabolism via CYP450 2D6, leading to an active metabolite that has a much higher affinity for the μ receptor than the parent compound. In addition, it weakly inhibits reuptake of norepinephrine and serotonin. It is used to manage moderate to moderately severe pain. Its respiratory-depressant activity is less than that of morphine. Naloxone (see below) can only partially reverse the analgesia produced by tramadol or its active metabolite. Anaphylactoid reactions have been reported. Toxicity through drug-drug interactions with medications, such as selective serotonin reuptake inhibitors and tricyclic antidepressants, or in overdose, leads to CNS excitation and seizures. Tramadol should also be avoided in patients taking MAOIs. B. Tapentadol Opioid agonists Naloxone Tapentadol (ta-PEN-ta-dol) is a centrally acting analgesic that binds the μ-opioid receptor and is also a norepinephrine reuptake inhibitor that is believed to create an additive effect to the opioid actions. It has been used to manage moderate to severe pain, both chronic and acute. Limited drug-drug interactions have been seen with tapentadol due to the pharmacokinetic profile. Tapentadol does not appear to inhibit or induce the CYP450 enzyme system because it is mainly metabolized by glucuronidation. Because tapentadol does not produce active metabolites, dosing adjustment is not necessary in mild to moderate renal impairment. Tapentadol should be avoided in patients currently taking MAOIs and those who have taken MAOIs within the last 14 days. Tapentadol is currently available in an immediate-release formulation. VII. ANTAGONISTS Opioid receptor The opioid antagonists bind with high affinity to opioid receptors but fail to activate the receptor-mediated response. Administration of opioid antagonists produces no profound effects in normal individuals. However, in patients dependent on opioids, antagonists rapidly reverse the effect of agonists, such as morphine or any full μ-agonist, and precipitate the symptoms of opiate withdrawal. A. Naloxone Opioid receptor Binding of naloxone does not activate the receptor. Therefore, naloxone reverses the effects of opioid agonists, such as morphine and heroin. Figure 14.12 Competition of naloxone with opioid agonists. Pharm 5th 3-21-11.indb 178 Naloxone [nal-OX-own] is used to reverse the coma and respiratory depression of opioid overdose. It rapidly displaces all receptor-bound opioid molecules and, therefore, is able to reverse the effect of a morphine overdose (Figure 14.12). Within 30 seconds of IV injection of naloxone, the respiratory depression and coma characteristic of high doses of morphine are reversed, causing the patient to be revived and alert. Naloxone has a half-life of 30 to 81 minutes. [Note: Because of its relatively short duration of action, a depressed patient who has been treated and recovered may lapse back into respiratory depression.] Naloxone is a competitive antagonist at μ, κ, and δ, receptors, with a tenfold higher affinity for μ than for κ receptors. This may explain why naloxone readily reverses respiratory depression with only minimal reversal of the analgesia that results from agonist stimulation of κ receptors in the spinal cord. Naloxone produces no pharmacologic effects in normal 3/21/11 2:22:42 PM VII. Antagonists 179 individuals, but it precipitates withdrawal symptoms in opioid abusers. Figure 14.13 summarizes some of the signs and symptoms of opiate withdrawal. There is no clinical effect seen with oral naloxone, but, upon IV administration, opioid antagonism will occur, and the patient will experience withdrawal. This is why naloxone has been combined with oral opioids to deter IV drug abuse. B. Naltrexone Naltrexone [nal-TREX-own] has actions similar to those of naloxone. It has a longer duration of action than naloxone, and a single oral dose of naltrexone blocks the effect of injected heroin for up to 48 hours. Naltrexone in combination with clonidine (and, sometimes, with buprenorphine) is used for rapid opioid detoxification. Although it may also be beneficial in treating chronic alcoholism by an unknown mechanism, benzodiazepines and clonidine are preferred. Naltrexone can lead to hepatotoxicity. Stage I: Up to 8 hours Stage II: 8–24 hours Anxiety Anxiety Insomnia Drug craving GI disturbance Rhinorrhea Mydriasis Diaphoresis Stage III: Up to 3 days 98.6 BP Tachycardia Nausea, vomiting Chills Hypertension Tremors Diarrhea Seizure Fever Muscle spasms Figure 14.13 Opiate withdrawal syndrome. GI = gastrointestinal. Pharm 5th 3-21-11.indb 179 3/21/11 2:22:44 PM 180 14. Opioids Study Questions Choose the ONE best answer. 14.1 A young man is brought into the emergency room. He is unconscious, and he has pupillary constriction and depressed respiration. You note needle marks on his legs. You administer naltrexone, and he awakens. This agent was effective because: A. The patient was suffering from an overdose of a benzodiazepine. B. Naltrexone antagonizes opiates at the receptor site. C. Naltrexone is a stimulant of the central nervous system. D. Naltrexone binds to the opioid and inactivates it. E. The patient was was suffering from an overdose of meperidine. 14.2 A heroin addict has entered a rehabilitation program that requires that she take methadone. Methadone is effective in this situation because it: A. Is an antagonist at the morphine receptors. B. Is a non-narcotic. C. Is longer acting than heroin, conferring milder withdrawal than with the latter drug. D. Does not cause constipation. E. Is nonaddictive. 14.3 Which of the following statements about morphine is correct? A. It is used therapeutically to relieve pain caused by severe head injury. B. Its withdrawal symptoms can be relieved by naloxone. C. It causes diarrhea. D. It is most effective by oral administration. E. It rapidly enters all body tissues, including the fetus. 14.4 The pain of a patient with bone cancer has been managed with a morphine pump. However, he has become tolerant to morphine. Which of the following might be indicated to ameliorate his pain? A. Meperidine. B. Codeine. C. Fentanyl. D. Methadone. E. Buprenorphine. Pharm 5th 3-21-11.indb 180 Correct answer = B. The indications are that the patient is suffering from an overdose of an opioid such as heroin. Naltrexone antagonizes the opioid by displacing it from the receptor. It is used in preference to naloxone, because it is longer acting and, thus, can act as long as the opiate is in the body. Meperidine causes the pupils to dilate. Correct answer = C. Methadone is used in rehabilitation programs as a substitute for heroin. It has similar euphorigenic and analgesic activity, is orally active, and can be easily controlled. Most important, it is long acting, and the withdrawal the patient undergoes as she is being weaned off the drug is much milder than would be the case with heroin. Methadone is a synthetic, orally effective opioid that acts at the μ receptors. It does cause constipation and can be addictive. Correct answer = E. Morphine causes increased cerebrospinal fluid pressure secondary to dilation of cerebral vasculature and is contraindicated in severe head injury. Naloxone is an opioid antagonist and can precipitate withdrawal symptoms in morphineaddicted individuals. Morphine is administered parenterally, because absorption from the gastrointestinal tract is unreliable. It causes constipation. Correct answer= C. Fentanyl is used in anesthesia. It produces analgesia and is usually injected epidurally. However, its analgesic action is also beneficial in cancer patients. It is available as a transdermal patch and an oral transmucosal preparation. Meperidine and codeine show cross-tolerance with morphine and, thus, would not be effective. Buprenorphine, like methadone, is used in opiate detoxification and could precipitate withdrawal. 3/21/11 2:22:44 PM Epilepsy I. OVERVIEW Epilepsy affects approximately 3 percent of individuals by the time they are 80 years old. About 10 percent of the population will have at least one seizure in their lifetime. Globally, epilepsy is the third most common neurologic disorder after cerebrovascular and Alzheimer disease. Epilepsy is not a single entity. Instead it is, an assortment of different seizure types and syndromes originating from several mechanisms that have in common the sudden, excessive, and synchronous discharge of cerebral neurons. This abnormal electrical activity may result in a variety of events, including loss of consciousness, abnormal movements, atypical or odd behavior, and distorted perceptions that are of limited duration but recur if untreated. The site of origin of the abnormal neuronal firing determines the symptoms that are produced. For example, if the motor cortex is involved, the patient may experience abnormal movements or a generalized convulsion. Seizures originating in the parietal or occipital lobe may include visual, auditory, and olfactory hallucinations. Medication or vagal nerve stimulator therapy is the most widely effective mode for the treatment of patients with epilepsy. It is expected that seizures can be controlled completely in approximately 70 to 80 percent percent of patients with one medication. It is estimated that approximately 10 to 15 percent of patients will require more than one drug, and perhaps about 10 percent may not achieve complete seizure control. A summary of antiseizure drugs is shown in Figure 15.1. II. IDIOPATHIC AND SYMPTOMATIC SEIZURES In most cases, epilepsy has no identifiable cause. Focal areas that are functionally abnormal may be triggered into activity by changes in physiologic factors, such as an alteration in blood gases, pH, electrolytes, and blood glucose level and changes in environmental factors, such as sleep deprivation, alcohol intake, and stress. The neuronal discharge in epilepsy results from the firing of a small population of neurons in some specific area of the brain that is referred to as the "primary focus." Anatomically, this focal area may appear to be normal. However, advances in technology have improved the ability to detect abnormalities. Neuroimaging techniques, such as magnetic resonance imaging (MRI), positron-emission tomography (PET) scans, and single-photon-emission coherence tomography (SPECT) may identify areas of concern (Figure 15.2). Epilepsy can be labeled idiopathic if the etiology is unknown or symptomatic if it is secondary to an identifiable condition. Though multiple specific epilepsy syndromes that include symptoms other than seizures have been classified, a discussion of these syndromes is beyond the scope of this chapter. Pharm 5th 3-21-11.indb 181 15 Carbamazepine TEGRETOL Diazepam VALIUM Divalproex DEPAKOTE Ethosuximide ZARONTIN Felbamate FELBATOL Gabapentin NEURONTIN Lacosamide VIMPAT Lamotrigine LAMICTAL Levetiracetam KEPPRA Lorazepam ATIVAN Oxcarbazepine TRILEPTAL Phenobarbital LUMINAL Phenytoin DILANTIN Fosphenytoin CEREBYX Primidone MYSOLINE Rufinamide BANZEL Tiagabine GABITRIL Topiramate TOPAMAX Vigabatrin SABRIL Zonisamide ZONEGRAN Figure 15.1 Summary of agents used in the treatment of epilepsy. Drugs arranged alphabetically. 3/21/11 2:22:44 PM 182 15. Epilepsy Single-photon-emission-coherence tomography (SPECT) can be used to measure regional blood flow in the brain. The image shows an increased blood flow in the left temporal lobe associated with the onset of a seizure in the same area. A. Idiopathic epilepsy When no specific anatomic cause for the seizure, such as trauma or neoplasm, is evident, a patient may be diagnosed with idiopathic or cryptogenic (primary) epilepsy. These seizures may result from an inherited abnormality in the central nervous system (CNS). Patients are treated chronically with antiseizure drugs or vagal nerve stimulation. Most cases of epilepsy are idiopathic. B. Symptomatic epilepsy Figure 15.2 Region of the brain in a person with epilepsy showing increased blood flow during a seizure. A number of causes, such as illicit drug use, tumor, head injury, hypoglycemia, meningeal infection, and the rapid withdrawal of alcohol from an alcoholic, can precipitate seizures. When two or more seizures occur, the patient may be diagnosed with symptomatic (secondary) epilepsy. Chronic treatment with antiseizure medications, vagal nerve stimulation, and surgery are all appropriate treatments and may be used alone or in combination. In some cases when the cause of a single seizure can be determined and corrected, therapy may not necessary. For example, a seizure that is caused by transient hypotension or is due to a drug reaction is not epilepsy and does not require chronic therapy. In other situations, antiseizure drugs may be given until the primary cause of the seizures can be corrected. III. CLASSIFICATION OF SEIZURES SEIZURES Partial (consciousness preserved) Simple (conscioune normal) Complex (consciousness altered/ no memory) Generalized (consciousness lost/no memory) Tonic-clonic Absence Myoclonic Infantile spasm Status epilepticus Generalized Status Epilepticus (convulsive or non-consvulsive) Partial Status Epilepticus (consciousness lost/no memory) Figure 15.3 Classification of epilepsy. Pharm 5th 3-21-11.indb 182 It is important to correctly classify seizures to determine appropriate treatment. Seizures have been categorized by site of origin, etiology, electrophysiologic correlation, and clinical presentation. The International League Against Epilepsy (ILAE) developed a nomenclature for describing seizures. This classification is considered the standard way to describe seizures and epilepsy syndromes (Figure 15.3). Seizures have been classified into two broad groups: partial (or focal), and generalized. A diagnosis may include classifying the seizure as partial or generalized epilepsy depending on the onset. A. Partial Partial seizures involve only a portion of the brain, typically part of one lobe of one hemisphere. The symptoms of each seizure type depend on the site of neuronal discharge and on the extent to which the electrical activity spreads to other neuron777777777777s in the brain. Consciousness is usually preserved. Partial seizures may progress to become generalized tonic-clonic seizures. 1. Simple partial: These seizures are caused by a group of hyperactive neurons exhibiting abnormal electrical activity, which are confined to a single locus in the brain. The electrical discharge does not spread, and the patient does not lose consciousness. The patient often exhibits abnormal activity of a single limb or muscle group that is controlled by the region of the brain experiencing the disturbance. The patient may also show sensory distortions. This activity may spread. Simple partial seizures may occur at any age. 2. Complex partial: These seizures exhibit complex sensory hallucinations and mental distortion. Motor dysfunction may involve chewing movements, diarrhea, and/or urination. Consciousness is altered. Simple partial seizure activity may spread to become complex and then spread to a secondary generalized convulsion. Complex partial seizures may occur at any age. 3/21/11 2:22:46 PM IV. Drug Choice 183 B. Generalized Generalized seizures may begin locally and then progress to include abnormal electrical discharges throughout both hemispheres of the brain. Primary generalized seizures may be convulsive or nonconvulsive, and the patient usually has an immediate loss of consciousness. 1. Tonic-clonic: These seizures result in loss of consciousness, followed by tonic (continuous contraction) and clonic (rapid contraction and relaxation) phases. The seizure may be followed by a period of confusion and exhaustion due to the depletion of glucose and energy stores. 2. Absence: These seizures involve a brief, abrupt, and self-limiting loss of consciousness. The onset generally occurs in patients at 3 to 5 years of age and lasts until puberty or beyond. The patient stares and exhibits rapid eye-blinking, which lasts for 3 to 5 seconds. An absence seizure has a very distinct three-per-second spike and wave discharge seen on electroencephalogram. 3. Myoclonic: These seizures consist of short episodes of muscle contractions that may recur for several minutes. They generally occur after wakening and exhibit as brief jerks of the limbs. Myoclonic seizures occur at any age but usually begin around puberty or early adulthood. 4. Febrile seizures: Young children may develop seizures with illness accompanied by high fever. This tendency may run in siblings. Febrile seizures consist of generalized tonic-clonic convulsions of short duration and do not necessarily lead to a diagnosis of epilepsy. 5. Status epilepticus: In status epilepticus, two or more seizures occur without recovery of full consciousness between them. These may be partial or primary generalized, convulsive or nonconvulsive. Status epilepticus is life-threatening and requires emergency treatment. C. Mechanism of action of antiepileptic drugs Drugs reduce seizures through such mechanisms as blocking voltagegated channels (Na+ or Ca2+), enhancing inhibitory γ-aminobutyric acid (GABA)-ergic impulses, and interfering with excitatory glutamate transmission. Some antiepileptic drugs appear to have multiple targets within the CNS, whereas the mechanism of action for some agents is poorly defined. Antiepilepsy drugs suppress seizures but do not "cure" or "prevent" epilepsy. IV. DRUG CHOICE Choice of drug treatment is based on the classification of the seizures, patient-specific variables (for example, age, comorbid medical conditions, lifestyle, and personal preference), and characteristics of the drug (such as cost and interactions with other medications). For example, partial onset seizures are treated with a different set of medications than primary generalized seizures, although the list of effective agents overlaps. Several of the antiseizure drugs may be equally effective. The toxicity of the agent and characteristics of the patient are major considerations in drug selection and treatment plan. In newly diagnosed patients, monotherapy is instituted with a single agent until seizures are controlled or toxicity occurs (Figure 15.4). Compared to those receiving combination therapy, patients receiving monotherapy exhibit better adherence and fewer side effects. If seizures are Pharm 5th 3-21-11.indb 183 Newly diagnosed epilepsy Consider starting therapy after the second seizure. • First-choice drug drug appropriate for the patient's • Choose type of seizure. • —Consider toxicity of the agent —Consider characteristics of the patient Gradually titrate the dosage to that which is maximally tolerated and/or produces optimal seizure control. Seizures persist Seizure free Second-choice drug The second drug is titrated to a therapeutic level that controls seizures before tapering and discontinuing the original antiseizure agent. If the first drug is associated with significant adverse effects, it should be tapered while the second drug is added. • • Seizures persist Seizure free Rational combination of two drugs Alternative drug therapy Seizures persist Seizure free Consider vagal nerve stimulation Figure 15.4 Therapeutic strategies for managing newly diagnosed epilepsy. 3/21/11 2:22:47 PM 184 15. Epilepsy Key: Drug name Drug name Consider first based on patient characteristics, diagnosis and symptoms, and concurrent medical problems. Vagal stimulator Drug name Consider next if seizures persist or adverse effects of first drug limit therapy. Consider as alternative if seizures persist or adverse effects limit therapy. Consider when adherence, drug interaction, or adverse effects limit drug therapy. PARTIAL EPILEPSY Simple partial, complex partial with or without secondary generalization Elderly patients Lamotrigine Levetiracetam Topiramate Lamotrigine Carbamazepine Lacosamide Pregabalin Zonisamide Divalproex Gabapentin Oxcarbazepine Vagal stimulator Phenytoin Tiagabine Gabapentin Carbamazepine Topiramate Ethosuximide Lamotrigine Benzodiazepines Vagal stimulator PRIMARY GENERALIZED EPILEPSY Absence Divalproex Lamotrigine Myoclonic Divalproex Levetiracetam Lamotrigine Tonic-clonic Levetiracetam Topiramate Status epilepticus Benzodiazepines Fosphenytoin Topiramate Zonisamide Divalproex Vagal stimulator Zonisamide Barbiturates EPILEPSY SYNDROME Benign rolandic Infantile spasms (West syndrome) Gabapentin Lamotrigine Corticotropin Vigabatrin Divalproex Lennox-Gastaut Lamotrigine Topiramate Carbamazepine Levetiracetam Topiramate Benzodiazepines Divalproex Topiramate Divalproex Oxcarbazepine Lamotrigine Zonisamide Levetiracetam Rufinamide Benzodiazepines Vigabatrin Felbamate Vagal stimulator Zonisamide Figure 15.5 Therapeutic indications for the anticonvulsant agents. Benzodiazepines = diazepam and lorazepam not controlled with the first drug, monotherapy with an alternate antiepileptic drug or drugs should be considered. Failing that, consider vagal nerve stimulation (Figure 15.5). Awareness of the antiepileptic drugs available and their mechanisms of action, pharmacokinetics, potential for drug–drug interactions, and adverse effects is essential for successful treatment of the patient. There will be patients who require a combination of medications to control their seizures. Pharm 5th 3-21-11.indb 184 3/21/11 2:22:49 PM V. Primary Antiepileptic Drugs 185 V. PRIMARY ANTIEPILEPTIC DRUGS Nausea and vomiting During the past 20 years, the Food and Drug Administration (FDA) has approved many new antiepileptic drugs. Some of these agents seemed to show potential advantages over drugs approved prior to 1990 in terms of pharmacokinetics, tolerability, and reduced risk for drug–drug interactions. The list of drugs approved since 1990 includes felbamate, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, rufinamide, tiagabine, topiramate, vigabatrin, and zonisamide. These are labeled "second generation" when compared with older antiepileptics, such as carbamazepine, divalproex, ethosuximide, phenobarbital, phenytoin, and valproic acid. However, several studies have failed to provide sufficient evidence that the second-generation drugs are significantly better than the older agents in terms of efficacy and lack of adverse effects. For that reason, the most commonly used antiepileptic drugs are described in alphabetic order, rather than attempting to rank them by efficacy. Figure 15.6 shows common adverse effects of the antiepileptic drugs. Those drugs with an increased risk of suicidal behavior and suicidal ideation require an FDA black box warning on the label. Sedation Ataxia A. Benzodiazepines Benzodiazepines bind to GABA inhibitory receptors to reduce firing rate. Diazepam and lorazepam are most often used as an adjunctive therapy for myoclonic as well as for partial and generalized tonic-clonic seizures. Lorazepam (see p. 114) has a shorter pharmacokinetic half-life but stays in the brain longer than diazepam. Diazepam is available for rectal administration to avoid or interrupt prolonged generalized tonicclonic seizures or clusters. Other benzodiazepines may be used in the treatment of various epilepsies but should be considered for use only after trials with monotherapy or combinations of most other medications for treatment of seizures fail. Rash Na+ Hyponatremia B. Carbamazepine Carbamazepine [kar-ba-MAZ-a peen] reduces the propagation of abnormal impulses in the brain by blocking sodium channels, thereby inhibiting the generation of repetitive action potentials in the epileptic focus and preventing their spread. Carbamazepine is effective for treatment of partial seizures and, secondarily, generalized tonic-clonic seizures. It is also used to treat trigeminal neuralgia and bipolar disorder. Carbamazepine is absorbed slowly and erratically following oral administration and may vary from generic to generic, resulting in large variations in serum concentrations of the drug. It induces its own drug metabolism and has an active metabolite. It is a substrate for CYP3A4 with minor metabolism by CYP1A2 and CYC2C8. The epoxide metabolite accounts for 25 percent of the dose, is active, and can be inhibited by drugs that inhibit UDP glucuronosyltransferase (UGT), leading to toxicity (Figure 15.7). Carbamazepine is an inducer of the isozyme families CYP1A2, CYP2C, and CYP3A and UGT enzymes, which may increase the clearance and reduce the efficacy of drugs that they metabolize. It is not as well tolerated by the elderly as are other available antiseizure medications. Hyponatremia may be noted in some patients, especially the elderly, and could indicate a need for change of therapy. A characteristic rash may develop early in therapy but may not require a change in treatment. Carbamazepine should not be prescribed for patients with absence seizures because it may cause an increase in seizures. Pharm 5th 3-21-11.indb 185 Weight gain or weight loss Teratogenicity Osteoporosis Figure 15.6 Notable adverse effects of antiseizure medications. 3/21/11 2:22:50 PM 186 15. Epilepsy C. Ethosuximide CYP1A2 Carbamazepine CYP2C8 Carbamazepine CYP2C9 Ethosuximide [eth-oh-SUX-i-mide] reduces propagation of abnormal electrical activity in the brain, most likely by inhibiting T-type calcium channels. It is effective in treating only primary generalized absence seizures (see Figure 15.5). Use of ethosuximide is limited because of this very narrow spectrum of activity. D. Felbamate Carbamazepine Divalproex Phenobarbital Phenytoin CYP2C19 Divalproex Felbamate Phenobarbital Phenytoin Zonisamide Felbamate [FEL-ba-mate] has a broad spectrum of anticonvulsant action. The drug has multiple proposed mechanisms including 1) blocking voltage-dependent sodium channels, 2) competing with the glycine-coagonist binding site on the N-methyl-D-aspartate (NMDA) glutamate receptor, 3) blocking calcium channels, and 4) potentiating the action of GABA. It is an inhibitor of drugs metabolized by CYP2C19 and β-oxidation (Figure 15.7), and induces drugs metabolized by CYP3A4. It is reserved for use in refractory epilepsies (particularly Lennox-Gastaut syndrome) because of the risk of aplastic anemia (about 1:4000) and hepatic failure. E. Gabapentin CYP3A4 Carbamazepine Ethosuximide Tiagabine Zonisamide UDP-glucuronsyltransferases Divalproex Lamotrigine Lorazepam Figure 15.7 CYP metabolism of the antiepileptic drugs. Gabapentin [GA-ba-pen-tin] is an analog of GABA. However, it does not act at GABA receptors, and it neither enhances GABA actions nor is converted to GABA. Its precise mechanism of action is not known. It is approved as adjunct therapy for partial seizures and for treatment of postherpetic neuralgia. Gabapentin exhibits nonlinear pharmacokinetics (see p. 14) due to its uptake by a saturable transport system from the gut. Gabapentin does not bind to plasma proteins and is excreted unchanged through the kidneys. Reduced dosing is required in renal disease. Gabapentin has been shown to be well tolerated by the elderly population with partial seizures due to its relatively mild adverse effects. It may also be a good choice for the older patient because there are limited or no reported associated pharmacokinetic drug interactions. F. Lacosamide Lacosamide [la-KOE-sa-mide] in vitro affects voltage-gated sodium channels, resulting in stabilization of hyperexcitable neuronal membranes and inhibition of repetitive neuronal firing. Lacosamide binds to collapsin response mediator protein-2 (CRMP-2), a phosphoprotein mainly expressed in the nervous system and involved in neuronal differentiation and control of axonal outgrowth. The role of CRMP-2 binding in seizure control is unknown. Lacosamide is approved for adjunctive treatment of partial seizures. In clinical trials, the drug caused euphoria similar to that produced by alprazolam and is labeled as a controlled substance (Schedule V). It is available in an injectable formulation. The most common adverse events that limit treatment include dizziness, headache, and fatigue. G. Lamotrigine Lamotrigine [la-MOE-tri-jeen] blocks sodium channels as well as high voltage–dependent calcium channels. Lamotrigine is effective in a wide variety of seizure types, including partial seizures, generalized seizures, and typical absence seizures and in the Lennox-Gastaut syndrome. It is approved for use in bipolar disorder as well. Lamotrigine is metabolized primarily to the N-2 glucuronide through the UGT pathway. The half-life of lamotrigine (24–35 hours) is decreased by enzyme-inducing drugs (for Pharm 5th 3-21-11.indb 186 3/21/11 2:22:50 PM V. Primary Antiepileptic Drugs 187 example, carbamazepine and phenytoin) and increased by greater than 50 percent with the addition of valproate. Lamotrigine dosages should be reduced when adding valproate to therapy unless the valproate is being added in a small dose to provide a boost to the lamotrigine serum concentration. Rapid titration to high serum concentrations of lamotrigine have been reported to cause a rash, which in some patients may progress to a serious, life-threatening reaction. Lamotrigine has also been shown to be well tolerated by the elderly population with partial seizures due to its relatively minor adverse effects. H. Levetiracetam Levetiracetam [lee-ve-tye-RA-se-tam] is approved for adjunct therapy of partial onset seizures, myoclonic seizures, and primary generalized tonic-clonic seizures in adults and children. The exact mechanism of anticonvulsant action is unknown. It demonstrates high affinity for a synaptic vesicle protein (SV2A). In mice, this was associated with potent antiseizure action. The drug is well absorbed orally and excreted in urine mostly (66 percent) unchanged. The drug does not interact with CYP or UGT metabolism systems. Side effects most often reported include dizziness, sleep disturbances, headache, and weakness. I. Oxcarbazepine Oxcarbazepine [ox-kar-BAY-zeh-peen] is a prodrug that is rapidly reduced to the 10-monohydroxy (MHD) metabolite responsible for its anticonvulsant activity. MHD blocks sodium channels, preventing the spread of the abnormal discharge. It is also thought to modulate calcium channels. It is approved for use in adults and children with partial onset seizures. Oxcarbazepine is a less potent inducer of CYP3A4 and UGT than carbamazepine. The adverse effects profile is similar to that of other antiepileptic drugs. It can cause nausea, vomiting, headache, and visual disturbances. J. Phenobarbital K. Phenytoin and fosphenytoin Phenytoin [FEN-i-toin] blocks voltage-gated sodium channels by selectively binding to the channel in the inactive state and slowing its rate of recovery. At very high concentrations, phenytoin can also block voltagedependent calcium channels and interfere with the release of monoaminergic neurotransmitters. Phenytoin is effective for treatment of partial seizures and generalized tonic-clonic seizures and in the treatment of status epilepticus (see Figure 15.5). The drug is 90 percent bound to plasma albumin. Phenytoin induces drugs metabolized by the CYP2C and CYP3A families and the UGT enzyme system. Phenytoin exhibits saturable enzyme metabolism at a low serum concentration. Therefore, knowledge of zero-order pharmacokinetics and population parameters is important for dosing adjustment. Small increases in a daily dose can produce large increases in the plasma concentration, resulting in drug induced toxicity (Figure 15.8). Depression of the CNS occurs particularly in the cerebellum and vestibular system, causing nystagmus and ataxia. Pharm 5th 3-21-11.indb 187 Plasma concentration (μg/mL) Phenobarbital [fee-noe-BAR-bih-tal] was synthesized in 1902 and brought to the market in 1912 by Bayer. Its primary mechanism of action is enhancing the inhibitory effects of GABA-mediated neurons (see p. 113). Phenobarbital in epilepsy should be used primarily in the treatment of status epilepticus. When the hepatic hydroxylation system becomes saturated, small increases in the dose of phenytoin cause a large increase in the plasma concentration of the drug. 30 20 10 0 0 400 800 Phenytoin dosage (mg/day) Figure 15.8 Nonlinear effect of phenytoin dosage on the plasma concentration of the drug. 3/21/11 2:22:51 PM 188 15. Epilepsy The elderly are highly susceptible to this effect. Gingival hyperplasia may cause the gums to grow over the teeth (Figure 5.9). Long-term use may lead to development of peripheral neuropathies and osteoporosis. Although phenytoin is the drug used most commonly worldwide for epilepsy due to its low cost per tablet, the cost of therapy may be much higher when the potential for serious toxicity and adverse effects is weighed. Figure 15.9 Gingival hyperplasia in patient treated with phenytoin. Fosphenytoin [FOS-phen-i-toin] is a prodrug and is rapidly converted to phenytoin in the blood, reaching high levels within minutes. Fosphenytoin may also be administered intramuscularly (IM). However, phenytoin sodium should never be given IM because it can cause tissue damage and necrosis. Fosphenytoin is the drug of choice and standard of care for IV and IM administration. Because of sound-alike and lookalike trade names, there is a risk for prescribing errors. The trade name of fosphenytoin is Cerebyx®, which is easily confused with Celebrex®, the cyclooxygenase-2 inhibitor, and Celexa®, the antidepressant. L. Pregabalin Pregabalin [pree-GABA-lin] binds to the α2-δ site, an auxiliary subunit of voltage-gated calcium channels in the CNS, inhibiting excitatory neurotransmitter release. The exact role this plays in treatment is not known, but the drug has proven effects on partial onset seizures, neuropathic pain associated with diabetic peripheral neuropathy, postherpetic neuralgia, and fibromyalgia. More than 90 percent of pregabalin is eliminated renally, with no indication of CYP involvement. Drowsiness, blurred vision, weight gain, and peripheral edema have been reported. M. Rufinamide Rufinamide [roo-FIN-a-mide] in vitro acts at the sodium channels. It is approved for the adjunctive treatment of seizures associated with Lennox-Gastaut syndrome in children over age 4 years and in adults. Rufinamide is a weak inhibitor of CYP2E1 and a weak inducer of CYP3A4 enzymes. Food increases absorption and peak serum concentrations. Serum concentrations of rufinamide are affected by other antiseizure medications. It is induced by carbamazepine and phenytoin and inhibited when given with valproate. Women taking birth control tablets should be counseled that they may not be effective when used concurrently with rufinamide. Adverse effects include the potential for shortened QT intervals. Patients with familial short QT syndrome should not be treated with rufinamide. N. Tiagabine Tiagabine [ty-AG-a-been] blocks GABA uptake into presynaptic neurons, permitting more GABA to be available for receptor binding, and therefore, to enhanced inhibitory activity. Tiagabine is effective in decreasing the number of seizures in patients with partial onset epilepsy. Binding to albumin and α1-acid glycoprotein is greater than 95 percent. Metabolism is mainly completed by the CYP3A family of enzymes. Adverse effects include fatigue, dizziness, and gastrointestinal upset. There is some indication in postmarketing surveillance that seizures have occurred in patients using tiagabine who did not have epilepsy. Tiagabine has not been approved for and should not be used for any other indication. Pharm 5th 3-21-11.indb 188 3/21/11 2:22:51 PM V. Primary Antiepileptic Drugs 189 O. Topiramate Topiramate [toe-PEER-a-mate] has several actions that are believed to contribute to its broad spectrum of antiseizure activity. Topiramate blocks voltage-dependent sodium channels, and it has been shown to increase the frequency of chloride channel opening by binding to the GABAA receptor. High-voltage calcium currents (L type) are reduced by topiramate. It is a carbonic anhydrase inhibitor and may act at glutamate (NMDA) sites. Topiramate is effective and approved for use in partial and primary generalized epilepsy. It is also approved for treatment of migraine. Topiramate is eliminated renally, but it also has inactive metabolites. It inhibits CYP2C19 and is induced by phenytoin and carbamazepine. Lamotrigine is reported to cause an increase in topiramate concentration. Coadministration of topiramate reduces ethinyl estradiol. Therefore, women taking the drug should be counseled to use additional methods of birth control. Adverse effects include somnolence, weight loss, and paresthesias. Renal stones are reported to occur at a higher incidence than in a nontreated population. Glaucoma, oligohidrosis, and hyperthermia have also been reported. The latter are specifically related to the carbonic anhydrase activity. P. Valproic acid and divalproex Valproic acid is available as a free acid. Divalproex sodium is a combination of sodium valproate and valproic acid that is converted to valproate when it reaches the gastrointestinal tract. It was developed to improve gastrointestinal tolerance of valproic acid. All of the available salt forms are equivalent in efficacy (valproic acid and valproate sodium). Commercial products are available in multiple-salt dosage forms and extended-release formulations. Therefore, the risk for medication errors is high, and it is essential to be familiar with all preparations. Possible mechanisms of action include sodium channel blockade, blockade of GABA transaminase, and action at the T-type calcium channels. These varied mechanisms provide a broad spectrum of activity against seizures. is the drugs are effective for the treatment of partial and primary generalized epilepsies. Valproate inhibits metabolism of the CYP2C9, UGT, and epoxide hydrolase systems (see Figure 15.7). Valproate is bound to albumin (greater than 90 percent), which can cause significant interactions with other highly protein-bound drugs. Rare hepatic toxicity may cause a rise in hepatic enzymes in plasma, which should be monitored frequently. Teratogenicity is also of great concern. Therefore, all women of childbearing age should be placed on other therapies and counseled about the potential for birth defects, including cognitive (Figure 15.10) and behavioral abnormalities and neural tube defects. Q. Vigabatrin Vigabatrin [vyeGA-ba-trin] acts as an irreversible inhibitor of γ-aminobutyric acid transaminase (GABA-T). GABA-T is the enzyme responsible for metabolism of GABA. Vigabatrin is associated with adverse effects resulting in visual field loss ranging from mild to severe in 30 percent or more of patients. Vigabatrin is only available through pharmacies that participate in the SHARE program (1-888-45-SHARE). Physicians must be registered with SHARE to prescribe vigabatrin. Mean IQ 97 Carbamazepine Lamotrigine 100 Phenytoin 98 Valproate 87 80 85 90 95 100 105 Mean IQ at age 3 years In utero exposure to valproate, when compared with other commonly used antiepileptic drugs, is associated with an increased risk of impaired cognitive function at 3 years of age. Valproate should not be used in women of childbearing potential. Figure 15.10 Cognitive function at 3 years of age after fetal exposure to high doses of antiepileptic drugs. The means (black squares) and 95% confidence intervals (horizontal lines) are given for the children's IQ as a function of the antiepileptic drugs. R. Zonisamide Zonisamide [zoe-NIS-a-mide] is a sulfonamide derivative that has a broad spectrum of action. The compound has multiple effects on Pharm 5th 3-21-11.indb 189 3/21/11 2:22:52 PM 190 15. Epilepsy A 1 An implanted pulse generator connects to electrodes that coil around the vagus nerve. 2 The vagal nerve stimulator generates an electrical pulse that stimulates the vagus nerve. euronal systems thought to be involved in seizure generation. These n include blockade of both voltage-gated sodium channels and T-type calcium currents. It has a limited amount of carbonic anhydrase activity. Cross reactivity with other sulfonamides should be reviewed. Its use should be monitored in patients with reported allergies. Zonisamide is approved for use in patients

barrier IV Metabolites appear in the urine Chloramphenicol Figure 32.18 Administration and fate of chloramphenicol. Chlorpropamide Phenytoin Tolbutamide Warfarin - Serum concentration increases Chloramphenicol P450 Metabolites Figure 32.19 Inhibition of the cytochrome P450 system by chloramphenicol. Adequate levels of clindamycin are not achieved in the brain Metabolites of clindamycin are excreted in the bile and urine Clindamycin Figure 32.20 Administration and fate of clindamycin. 3/21/11 2:27:58 PM 406 32. Protein Synthesis Inhibitors VIII. QUINUPRISTIN/DALFOPRISTIN Quinupristin/ dalfopristin does not reach therapeutic levels in CSF IV IM Metabolites of quinupristin/ dalfopristin are primarily excreted via bile Quinupristin/dalfopristin [KWIN-yoo-pris-tin/DAL-foh-pris-tin] is a mixture of two streptogramins in a ratio of thirty to seventy, respectively. They are derived from a streptomycete and then chemically modified. The drug is normally reserved for the treatment of vancomycin-resistant Enterococcus faecium (VRE). A. Mechanism of action Each component of this combination drug binds to a separate site on the 50S bacterial ribosome, forming a stable ternary complex. Thus, they synergistically interrupt protein synthesis. The combination drug is bactericidal and has a long postantibiotic effect. B. Resistance Quinupristin/dalfopristin Figure 32.21 Administration and fate of quinupristin/dalfopristin. CSP = cerebrospinal fuid. Cyclosporine Nifedipine Verapamil Diltiazem Nevirapine Indinavir Ritonavir Midazolam Carbamazepine P450 Enzymatic processes commonly account for resistance to these agents. For example, the presence of a ribosomal enzyme that methylates the target bacterial 23S ribosomal RNA site can interfere in quinupristin binding. In some cases, the enzymatic modification can change the action from bactericidal to bacteriostatic. Plasmid-associated acetyltransferase inactivates dalfopristin. An active efflux pump can also decrease levels of the antibiotics in bacteria. C. Antibacterial spectrum Serum concentration increases Quinupristin/ dalfopristin Metabolites Figure 32.22 Inhibition of the cytochrome P450 system by quinupristin/dalfopristin. The combination drug is active primarily against gram-positive cocci, including those resistant to other antibiotics (for example, methicillinresistant staphylococci). Its primary use is in the treatment of E. faecium infections, including VRE strains. [Note: In the latter case, the effect is bacteriostatic rather than bactericidal.] The drug is not effective against Enterococcus faecalis. D. Pharmacokinetics Quinupristin/dalfopristin is injected intravenously (the drug is incompatible with a saline medium). The combination drug penetrates macrophages and polymorphonucleocytes, a property that is important, because VRE are intracellular. Levels in the CSF are low. Both compounds undergo metabolism. The products are less active than the parent in the case of quinupristin and are equally active in the case of dalfopristin. Most of the parent drugs and metabolites are cleared through the liver and eliminated via the bile into the feces (Figure 32.21). Urinary excretion is secondary. E. Adverse effects 1. Venous irritation: This commonly occurs when quinupristin/dalfopristin is administered through a peripheral rather than a central line. 2. Arthralgia and myalgia: These have been reported when higher levels of the drugs are employed. 3. Hyperbilirubinemia: Total bilirubin is elevated in about 25 percent of patients, resulting from a competition with the antibiotic for excretion. 4. Interactions: Because of the ability of quinupristin/dalfopristin to inhibit the cytochrome P450 (CYP3A4) isozyme, concomitant admin- Pharm 5th 3-21-11.indb 406 3/21/11 2:28:00 PM IX. Linezolid 407 istration with drugs that are metabolized by this pathway may lead to toxicities (Figure 32.22). A drug interaction with digoxin appears to occur by the same mechanism as that caused by erythromycin. fMet 3' 5' IX. LINEZOLID UAC Linezolid [lih-NEH-zo-lid] was introduced to combat resistant gram-positive organisms, such as methicillin- and vancomycin-resistant Staphylococcus aureus, vancomycin-resistant E. faecium and E. faecalis, and penicillin-resistant streptococci. Linezolid is a synthetic oxazolidinone. AUG UUU 5' AAG Linezolid 50S B. Resistance fMet Linezolid is completely absorbed on oral administration and this formulation can be considered for treatment of bacteremia caused by VRE. An intravenous preparation is also available. The drug is widely distributed throughout the body, having a volume of distribution of 40 to 50 liters. Two metabolites that are oxidation products have been identified, one of which has antimicrobial activity. However, cytochrome P450 enzymes are not involved in their formation. The drug is excreted both by renal and nonrenal routes. E. Adverse effects Linezolid is well-tolerated, with some reports of gastrointestinal upset, nausea, and diarrhea, as well as headaches and rash. Thrombocytopenia was found to occur in about 2 percent of patients who were on the drug for longer than 10 days. Although no reports have appeared that linezolid inhibits monoamine oxidase activity, patients are cautioned not to consume large quantities of tyramine-containing foods. Early oxazolidinones had been shown to inhibit monoamine oxidase activity, and can precipitate serotonin syndrome in patients concomitantly taking SSRIs. The condition was reversible when the drug was suspended. Irreversible peripheral neuropathies and optic neuritis (causing blindness) is associated with greater than 28 days of use. Pharm 5th 3-21-11.indb 407 3' 5' 70S C. Antibacterial spectrum D. Pharmacokinetics 3' Formation of initiation complex The drug inhibits bacterial protein synthesis by inhibiting the formation of the 70S initiation complex. Linezolid binds to a site on the 50S subunit near the interface with the 30S subunit (Figure 32.23). The antibacterial action of linezolid is directed primarily against grampositive organisms, such as staphylococci, streptococci, and enterococci, as well as Corynebacterium species and Listeria monocytogenes (Figure 32.24). It is also moderately active against Mycobacterium tuberculosis. However, its main clinical use is against the resistant organisms mentioned above. Like other agents that interfere with bacterial protein synthesis, linezolid is bacteriostatic. However, it is cidal against streptococci and Clostridium perfringens. At this time, linezolid is considered non-inferior to vancomycin for the treatment of MRSA pneumonia. Linezolid is an alternative to daptomycin for infections caused by VRE. Linezolid should not be used for the treatment of MRSA bacteremia. UAA mRNA A. Mechanism of action Decreased binding to the target site confers resistance on the organism. Cross-resistance with other antibiotics does not occur. CGG 30S UAC 5' AUG UUU AAG CGG UAA 3' mRNA Figure 32.23 Mechanism of action of linezolid. Gram (+) cocci Enterococcus faecalis (including vancomycin-resistant strains) Enterococcus faecium (vancomycin-resistant strains) Staphylococcus epidermidis (including methicillin-resistant strains) Staphylococcus haemolyticus Streptococcus pneumoniae (penicillin-resistant strains) Viridans group streptococci Gram (+) bacilli Corynebacterium species Listeria monocytogenes Gram (–) cocci Gram (–) rods Anaerobic organisms Clostridium perfringens Spirochetes Mycoplasma Chlamydia Other Mycobacterium tuberculosis Figure 32.24 Antimicrobial spectrum of linezolid. 3/21/11 2:28:01 PM 408 32. Protein Synthesis Inhibitors Study Questions Choose the ONE best answer. 32.1 A patient with a gunshot wound to the abdomen, which has resulted in spillage of intestinal contents, is brought to the emergency room. Which antibiotic would you select to effectively treat an infection due to Bacteroides fragilis? A. Aztreonam. B. Clindamycin. C. Gentamicin. D. Azithromycin. E. Doxycycline. 32.2 A pregnant woman was hospitalized and catheterized with a Foley catheter. She developed a urinary tract infection caused by Pseudomonas aeruginosa and was treated with gentamicin. Which of the following adverse effects was a risk to the fetus when the woman was on gentamicin? B. Bacteroides fragilis is an anaerobic organism. The only drug on the list that is effective against it is clindamycin. Aztreonam is effective against aerobic, not anaerobic organisms. Gentamicin works against Francisella tularensis, a gram-negative organism rarely causing infection, and in combination with penicillin G against Enterococci. Azithromycin is used for respiratory infections. The only anaerobic organisms that tetracyclines (doxyxycline) are effective against are Clostridium perfringens and Clostridium tetani. Correct answer = B. Gentamicin can cross the placental barrier and cause hearing loss in the newborns of mothers who have received it. The other adverse effects are not risks with gentamicin. A. Skeletal deformity. B. Hearing loss. C. Teratogenesis. D. Blindness. E. Mental retardation. 32.3 Children younger than 8 years of age should not receive tetracyclines because these agents: A. Cause rupture of tendons. B. Do not cross into the cerebrospinal fluid. C. Are not bactericidal. D. Deposit in tissues undergoing calcification. E. Can cause aplastic anemia. 32.4 A 46-year-old woman is in the intensive care unit for treatment of a vancomycin-resistant strain of Enterococcus faecium–caused bacteremia. She is receiving five other medications. To limit the risk of drug interactions in this woman, which one of the following antibiotics should be used? A. Azithromycin. B. Clindamycin. C. Doxycycline. D. Linezolid. E. Quinupristin/dalfopristin. Pharm 5th 3-21-11.indb 408 Correct answer = D. Although it is true that tetracyclines are not bactericidal, they are contraindicated in this age group because they are deposited in tissues undergoing calcification, such as teeth and bone, and can stunt growth. Ciprofloxacin can interfere in cartilage formation and cause rupture of tendons and is also contraindicated in children, but it is a fluoroquinolone. Tetracyclines can cross into the cerebrospinal fluid. They do not cause aplastic anemia, a property usually associated with chloramphenicol. Correct answer = D. Azithromycin, clindamycin, and doxycycline do not have significant activity against this organism. Both linezolid and quinupristin/dalfopristin have activity against vancomycin-resistant Enterococcus faecium, but the latter antibiotic is a potent inhibitor of cytochrome CYP3A4 isozymes. Linezolid is not an inhibitor of these isozymes and would be less likely to have interactions with other drugs. 3/21/11 2:28:01 PM Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics I. FLUOROQUINOLONES 33 FLUOROQUINOLONES 1st GEN. Naladixic acid is the predecessor to all fluoroquinolones. Introduction of the first fluorinated quinolone, norfloxacin, was rapidly followed by development of other members of this group, such as ciprofloxacin, which has had wide clinical application. Today, over 10,000 analogs have been synthesized. Newer fluorinated quinolones offer greater potency, a broader spectrum of antimicrobial activity, greater in vitro efficacy against resistant organisms, and in some cases, a better safety profile than older quinolones and other antibiotics. Compared to ciprofloxacin, the new compounds are more active against gram-positive organisms, yet retain favorable activity against gram-negative microorganisms. It seems likely that the number of drugs in this class of antibiotics will increase due to its wide antibacterial spectrum, favorable pharmacokinetic properties, and relatively infrequent adverse event profile. Unfortunately, their overuse has already led to the emergence of resistance, resulting in limitations to their clinical usefulness. The fluoroquinolones and other antibiotics discussed in this chapter are listed in Figure 33.1. Nalidixic acid NEGGRAM A. Mechanism of action Pyrimethamine DARAPRIM Trimethoprim PROLOPRIM The fluoroquinolones enter the bacterium by passive diffusion through water-filled protein channels (porins) in the outer membrane. Once inside the cell, they inhibit the replication of bacterial DNA by interfering with the action of DNA gyrase (topoisomerase II) and topoisomerase IV during bacterial growth and reproduction. [Note: Topoisomerases are enzymes that change the configuration or topology of DNA by a nicking, pass-through, and resealing mechanism. They do not change the DNA’s primary sequence (Figure 33.2).] Binding of the quinolone to both the enzyme and the DNA forms a ternary complex that inhibits the resealing step, and can cause cell death by inducing cleavage of the DNA. Because DNA gyrase is a bacteriospecific target for antimicrobial therapy, cross-resistance with other, more commonly used antimicrobial drugs is rare, but this is increasing in the case of multidrug-resistant organisms. The second site blocked by the fluoroquinolones—topoisomerase IV—is required by bacteria for cell division. It has been implicated in the process of segregating newly replicated DNA. In gram-negative organisms (for example, Escherichia coli), the inhibition of DNA gyrase is more significant than that of topoisomerase IV, whereas in gram-positive organisms (for example, the streptococci), the opposite is true. Pharm 5th 3-21-11.indb 409 FLUOROQUINOLONES 2nd GEN. Ciprofloxacin CIPRO Norfloxacin NOROXIN Ofloxacin FLOXIN FLUOROQUINOLONES 3rd GEN. Levofloxacin LEVAQUIN FLUOROQUINOLONES 4th GEN. Moxifloxacin AVELOX INHIBITORS OF FOLATE SYNTHESIS Mafenide SULFAMYLON Silver sulfadiazine SILVADENE Sulfasalazine AZULFIDINE Sulfisoxazole GANTRISIN INHIBITORS OF FOLATE REDUCTION COMBINATION OF INHIBITORS OF FOLATE SYNTHESIS AND REDUCTION Cotrimoxazole (trimethoprim + sulfamethoxazole) BACTRIM URINARY TRACT ANTISEPTICS Methenamine MANDELAMINE, HIPREX Nitrofurantoin MACROBID 33.1 Summary of drugs described in this chapter. 3/21/11 2:28:02 PM 410 33. Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics B. Antimicrobial spectrum Left half of circle folds over right half Back half of helix is cleaved Fluoroquinolones Front half of helix passes through break, which is resealed Figure 33.2 Action of Type II DNA topoisomerase. Fluoroquinolones are bactericidal and exhibit AUC/MIC dependent killing. Bactericidal activity becomes more pronounced as the serum drug concentration increases to approximately 30-fold the minimum inhibitory concentration. In general, they are effective against gramnegative organisms such as the Enterobacteriaceae, Pseudomonas species, Haemophilus influenzae, Moraxella catarrhalis, Legionellaceae, chlamydia, mycoplasma and some mycobacteria. They are effective in the treatment of gonorrhea but not syphilis. The newer agents (for example, levofloxacin and moxifloxacin) also have good activity against some gram-positive organisms, such as Streptococcus pneumoniae. Moxifloxacin has activity against many anaerobes. If used prophylactically before transurethral surgery, fluoroquinolones lower the incidence of postsurgical urinary tract infections (UTIs). It has become common practice to classify the fluoroquinolones into “generations,” based on their antimicrobial targets (Figure 33.3). The nonfluorinated quinolone nalidixic acid is considered to be first generation, with a narrow spectrum of susceptible organisms usually confined to the urinary tract. Ciprofloxacin and norfloxacin are assigned to the second generation because of their activity against aerobic gram-negative and atypical bacteria. In addition, these fluoroquinolones exhibit significant intracellular penetration, allowing therapy for infections in which a bacterium spends part or all of its life cycle inside a host cell (for example, chlamydia, mycoplasma, and legionella). Levofloxacin is classified as third generation because of its increased activity against gram-positive bacteria. Lastly, the fourth generation includes only moxifloxacin because of its activity against anaerobic, as well as, gram-positive organisms. C. Examples of clinically useful fluoroquinolones 1. Ciprofloxacin: The serum levels of ciprofloxacin [sip-row-FLOX-asin] that are achieved are effective against many systemic infections, with the exception of serious infections caused by methicillin-resistant Staphylococcus aureus (MRSA), the enterococci, and pneumococci (Figure 33.4). Ciprofloxacin is particularly useful in treating infections caused by many Enterobacteriaceae and other gram-negative bacilli. For example, traveler’s diarrhea caused by E. coli can be effectively treated. It is the most potent of the fluoroquinolones for Pseudomonas aeruginosa infections and, therefore, is used in the treatment of pseudomonal infections associated with cystic fibrosis. The drug is also used as an alternative to more toxic drugs, such as the aminoglycosides. It may act synergistically with β-lactams and is also of benefit in treating resistant tuberculosis. Ciprofloxacin is also commonly used to treat typhoid fever in third-world countries. 2. Norfloxacin: Norfloxacin (nor-FLOX-a-sin) is effective against both gram-negative (including P. aeruginosa) and gram-positive organisms in treating complicated and uncomplicated UTIs, prostatitis and traveler's diarrhea (unlabeled use). It is not effective in systemic infections. 3. Levofloxacin: Levofloxacin [leave-oh-FLOX-a-sin] is an isomer of ofloxacin [oh-FLOX-a-sin] and has largely replaced it clinically. It can be used in the treatment of prostatitis due to E. coli and of sexually transmitted diseases, with the exception of syphilis. It may be used as alternative therapy in patients with gonorrhea. Additionally, Pharm 5th 3-21-11.indb 410 3/21/11 2:28:02 PM I. Fluoroquinolones 411 First Generation Gram (+) cocci Gram (+) bacilli Gram (–) cocci Gram (–) rods Anaerobic organisms Spirochetes Mycoplasma Chlamydia Other Third Generation Second Generation Gram (+) cocci Gram (+) bacilli Gram (–) cocci Gram (–) rods Anaerobic organisms Spirochetes Mycoplasma Chlamydia Other First-generation quinolones, which are used less often today, have moderate gram-negative activity. They achieve minimal serum concentrations and are restricted to the treatment of uncomplicated urinary tract infections. Third-generation fluoroquinolones retain expanded gram-negative activity and show improved activity against atypical organisms and specific gram-positive bacteria. Fourth Generation Second-generation fluoroquinolones have expanded gram-negative activity and also have some activity against gram-positive and atypical organisms, such as Mycoplasma pneumoniae and Chlamydia pneumoniae. Gram (+) cocci Gram (+) bacilli Gram (–) cocci Gram (–) rods Anaerobic organisms Spirochetes Mycoplasma Chlamydia Other Fourth-generation fluoroquinolones shows improved gram-positive coverage, maintains gram-negative activity, and gains anaerobic coverage. Figure 33.3 Summary of antimicrobial spectrum of quinolones. [Note: The antimicrobial spectrum of specific agents may differ from the generalizations shown in this figure.] ANTHRAX Ciprofloxacin is the drug of choice for postexposure prophylaxis and for treatment of anthrax. Alternate agents include doxycycline. Gram (+) cocci Streptococus pneumoniae Gram (+) bacilli Bacillus anthracis Gram (–) cocci Gram (–) rods URINARY TRACT INFECTIONS Ciprofloxacin and levofloxacin are effective in treating uncomplicated and complicated urinary tract infections. Enterobacter species Escherichia coli Haemophilus influenzae Klebsiella pneumoniae Legionella pneumophila Proteus mirabilis Pseudomonas aeruginosa Serratia marcescens Shigella species Anaerobic organisms Spirochetes Mycoplasma Chlamydia Other RESISTANT RESPIRATORY INFECTIONS Levofloxacin is often effective in treating infections unresponsive to β-lactam antibiotics, such as amoxacillin-clavulanic acid. Ciprofloxacin is not the drug of first choice for pneumonia or sinusitis, because it has weak activity against Streptococcus pneumoniae, a common causative agent. Levofloxacin and moxifloxacin are known as “respiratory fluoroquinolones” due to their activity versus Streptococcus pneumoniae GASTROINTESTINAL TRACT INFECTIONS Ciprofloxacin is highly efficacious in treating acute diarrheal illnesses due to enteric pathogens. Figure 33.4 Typical therapeutic applications of fluoroquinolones. due to its broad spectrum of activity, levofloxacin is utilized in a wide range of infections, including skin infections, acute sinusitis, acute exacerbation of chronic bronchitis, community-acquired pneumonia, as well as nosocomial pneumonia. Levofloxacin has excellent activity against S. pneumoniae respiratory infections Pharm 5th 3-21-11.indb 411 3/21/11 2:28:05 PM 412 33. Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics Ciprofloxacin Levofloxacin Moxifloxacin Norfloxacin Ofloxacin 4. Moxifloxacin: Moxifloxacin [moxie-FLOX-a-sin] not only has enhanced activity against gram-positive organisms (for example, S. pneumoniae) but also has excellent activity against many anaerobes. It has very poor activity against P. aeruginosa. Moxifloxacin does not concentrate in urine and is not indicated for the treatment of UTIs. Ciprofloxacin Levofloxacin D. Resistance IV When the fluoroquinolones were first introduced, there was optimism that resistance would not develop. Although no plasmid-mediated resistance has been reported, resistant MRSA, pseudomonas, coagulasenegative staphylococci, and enterococci have unfortunately emerged due to chromosomal mutations. Cross-resistance exists among the quinolones. The mechanisms responsible for this resistance include the following. Metabolites appear in bile 1. Altered target: Mutations in the bacterial DNA gyrase have been associated with a decreased affinity for fluoroquinolones. Topoisomerase IV also undergoes mutations. Resistance is frequently associated with mutations in both DNA gyrase and topoisomerase IV. Metabolites appear in urine Fluoroquinolones Figure 33.5 Administration and fate of the fluoroquinolones. 2. Decreased accumulation: Reduced intracellular concentration of the drugs in the bacterial cell is linked to two mechanisms. One involves a decreased number of porin proteins in the outer membrane of the resistant cell, thereby impairing access of the drugs to the intracellular topoisomerases. The other mechanism is associated with an energy-dependent efflux system in the cell membrane. Plasma ciprofloxacin (μg/mL) E. Pharmacokinetics 1. Absorption: Only 35 to 70 percent of orally administered norfloxacin is absorbed, compared with 85 to 95 percent of the other fluoroquinolones (Figure 33.5). Intravenous preparations of ciprofloxacin and levofloxacin are available. Ingestion of the fluoroquinolones with sucralfate, antacids containing aluminum or magnesium, or dietary supplements containing iron or zinc can interfere with the absorption of these antibacterial drugs. Calcium and other divalent cations have also been shown to interfere with the absorption of these agents (Figure 33.6). The fluoroquinolones with the longest half-lives (levofloxacin and moxifloxacin) permit once-daily dosing. Ciprofloxacin, 500 mg 3 + water + milk + yogurt 2 2. Elimination: Binding to plasma proteins ranges from 10 to 40 per1 0 0 2 4 6 Time (hours) 8 10 Figure 33.6 Effect of dietary calcium on the absorption of ciprofloxacin. Pharm 5th 3-21-11.indb 412 24 cent. [Note: Achieved plasma levels of free norfloxacin are insufficient for treatment of systemic infections.] All the fluoroquinolones distribute well into all tissues and body fluids. Levels are high in bone, urine (except moxifloxacin), kidney, and prostatic tissue (but not prostatic fluid), and concentrations in the lung exceed those in serum. Penetration into cerebrospinal fluid is relatively low except for ofloxacin, for which concentrations can be as high as 90 percent of those in the serum. The fluoroquinolones also accumulate in macrophages and polymorphonuclear leukocytes, thus being effective against intracellular organisms such as Legionella pneumophila. Most fluoroquinolones are excreted renally, therefore, the dose needs to be adjusted when renal function changes. Moxifloxacin, on the other hand, is excreted primarily by the liver, and no dose adjustment is required with decreased renal functioning. 3/21/11 2:28:07 PM II. Overview Of The Folate Antagonists 413 F. Adverse reactions In general, these agents are very well tolerated. Toxicities similar to those for nalidixic acid have been reported for the fluoroquinolones (Figure 33.7). Diarrhea 1. Gastrointestinal: The most common adverse effects of the fluoroquinolones are nausea, vomiting, and diarrhea, which occur in three to six percent of patients. 2. Central nervous system problems: The most prominent central nervous system (CNS) effects of fluoroquinolone treatment are headache and dizziness or light-headedness. Thus, patients with CNS disorders, such as epilepsy, should be treated cautiously with these drugs. [Note: Ciprofloxacin interferes in the metabolism of theophylline and may evoke seizures.] 3. Phototoxicity: Patients taking fluoroquinolones are advised to avoid excessive sunlight and to apply sunscreens. However, the latter may not protect completely. Thus, it is advisable that the drug should be discontinued at the first sign of phototoxicity. 4. Connective tissue problems: Fluoroquinolones should be avoided in pregnancy, in nursing mothers, and in children under 18 years of age, because articular cartilage erosion (arthropathy) occurs in immature experimental animals. [Note: Careful monitoring is indicated in children with cystic fibrosis, who receive fluoroquinolones for acute pulmonary exacerbations.] In 2008, FDA added a Black Box Warning to fluoroquinolones about increased risk of tendinitis or tendon rupture that may occur with systemic fluoroquinolone use, not with ophthalmic or otic use. The Achilles tendon is the most frequent tendon associated with the occurrence of tendinitis and tendon rupture. The adverse event can occur during fluoroquinolone treatment, or up to several months after completion of therapy. The risk of developing tendinitis or tendon rupture associated with fluoroquinolone use is increased in patients over 60 years of age, those receiving concomitant corticosteroid therapy, and in patients with kidney, heart, or lung transplants. 5. Contraindications: Moxifloxacin and other fluoroquinolones, may prolong the QTc interval and, thus, should not be used in patients who are predisposed to arrhythmias or are taking antiarrhythmic medications and not being actively monitored. 6. Drug interactions: The effect of antacids and cations on the absorption of these agents was considered above. Ciprofloxacin and ofloxacin can increase the serum levels of theophylline by inhibiting its metabolism (Figure 33.8). This is not the case with the third- and fourth-generation fluoroquinolones, which may raise the serum levels of warfarin, caffeine, and cyclosporine. Nausea Headache Dizziness Nephrotoxicity Figure 33.7 Some adverse reactions to fluoroquinolones. Theophylline Warfarin Cyclosporine P-450 - Serum concentration increases Ciprofloxacin Ofloxacin II. OVERVIEW OF THE FOLATE ANTAGONISTS Metabolites Enzymes requiring folate-derived cofactors are essential for the synthesis of purines and pyrimidines (precursors of RNA and DNA) and other compounds necessary for cellular growth and replication. Therefore, in the absence of folate, cells cannot grow or divide. To synthesize the critical folate derivative, Pharm 5th 3-21-11.indb 413 Figure 33.8 Drug interactions with fluoroquinolones. 3/21/11 2:28:08 PM 414 33. Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics H2 N COOH Pteridine precursor + p-Aminobenzoic acid (PABA) III. SULFONAMIDES Microorganisms Sulfanilamide (and other sulfonamides) - tetrahydrofolic acid, humans must first obtain preformed folate in the form of folic acid as a vitamin from the diet. In contrast, many bacteria are impermeable to folic acid and other folates and, therefore, must rely on their ability to synthesize folate de novo. The sulfonamides (sulfa drugs) are a family of antibiotics that inhibit this de novo synthesis of folate. A second type of folate antagonist—trimethoprim—prevents microorganisms from converting dihydrofolic acid to tetrahydrofolic acid, with minimal effect on a human cell’s ability to make this conversion. Thus, both sulfonamides and trimethoprim interfere with the ability of an infecting bacterium to divide. Combining the sulfonamide, sulfamethoxazole, with trimethoprim (the generic name for the combination is cotrimoxazole) provides a synergistic combination that is used as effective treatment of a variety of bacterial infections. Dihydropteroate synthetase The sulfa drugs are seldom prescribed alone except in developing countries, where they are still employed because of their low cost and their efficacy in certain bacterial infections, such as trachoma and those of the urinary tract. However, when cotrimoxazole was introduced in the mid-1970s, there was a renewed interest in the sulfonamides. Sulfa drugs differ from each other not only in their chemical and physical properties, but also in their pharmacokinetics. A. Mechanism of action Glutamate In many microorganisms, dihydrofolic acid is synthesized from p-amino benzoic acid (PABA), pteridine, and glutamate (Figure 33.9). All the sulfonamides currently in clinical use are synthetic analogs of PABA. Because of their structural similarity to PABA, the sulfonamides compete with this substrate for the bacterial enzyme, dihydropteroate synthetase. They thus inhibit the synthesis of bacterial dihydrofolic acid and, thereby, the formation of its essential cofactor forms. The sulfa drugs, including cotrimoxazole, are bacteriostatic. Dihydrofolic acid Humans and microorganisms 2 NADPH +2H Trimethoprim - Dihydrofolate reductase 2 NADP Purine synthesis Sulfa drugs are active against selected Enterobacteria in the urinary tract and Nocardia. In addition, sulfadiazine [sul-fa-DYE-a-zeen], in combination with the dihydrofolate reductase inhibitor pyrimethamine [pyri-METH-a-meen], is the preferred form of treatment for toxoplasmosis. C. Resistance Tetrahydrofolic acid Amino acid synthesis B. Antibacterial spectrum Thymidine synthesis Figure 33.9 Inhibition of tetrahydrofolate synthesis by sulfonamides and trimethoprim. Only organisms that synthesize their folate requirements de novo are sensitive to the sulfonamides. Thus, humans, who synthesize critical folate cofactors from dietary folic acid, are not affected, and bacteria that can obtain folates from their environment are naturally resistant to these drugs. Acquired bacterial resistance to the sulfa drugs can arise from plasmid transfers or random mutations. [Note: Organisms resistant to one member of this drug family are resistant to all.] Resistance is generally irreversible and may be due to 1) an altered dihydropteroate synthetase, 2) decreased cellular permeability to sulfa drugs, or 3) enhanced production of the natural substrate, PABA. D. Pharmacokinetics 1. Administration: After oral administration, most sulfa drugs are well absorbed via the small intestine (Figure 33.10). An exception is sulfasalazine [sul-fa-SAL-a-zeen]. It is not absorbed when administered orally or as a suppository and, therefore, is reserved for treatment of Pharm 5th 3-21-11.indb 414 3/21/11 2:28:09 PM III. Sulfonamides chronic inflammatory bowel disease (for example, Crohn’s disease or ulcerative colitis). [Note: Local intestinal flora split sulfasalazine into sulfapyridine and 5-aminosalicylate, with the latter exerting the antiinflammatory effect. Absorption of the sulfapyridine can lead to toxicity in patients who are slow acetylators (see below).] Intravenous sulfonamides are generally reserved for patients who are unable to take oral preparations. Because of the risk of sensitization, sulfas are not usually applied topically. However, in burn units, creams of silver sulfadiazine or mafenide [mah-FEN-ide] acetate (α-amino-p-toluenesulfonamide) have been effective in reducing burn-associated sepsis because they prevent colonization of bacteria. Superinfections with resistant bacteria or fungi may still occur. [Note: Silver sulfadiazine is preferred because mafenide produces pain on application. Furthermore, mafenide can be absorbed in burn patients, causing an increased risk of acid-base imbalance.] 2. Distribution: Sulfa drugs are bound to serum albumin in the circulation, where the extent of binding depends on the particular agent’s pKa. In general, the smaller the pKa value, the greater the binding. Sulfa drugs distribute throughout the body’s water and penetrate well into cerebrospinal fluid—even in the absence of inflammation. They can also pass the placental barrier and enter fetal tissues. 415 Drug crosses blood-brain barrier IV Topical Unchanged drug and acetylated metabolites appear in the urine urine Suppository Sulfonamides Figure 33.10 Administration and fate of the sulfonamides. 3. Metabolism: The sulfa drugs are acetylated, primarily in the liver. The product is devoid of antimicrobial activity, but retains the toxic potential to precipitate at neutral or acidic pH. This causes crystalluria (“stone formation”; see below) and, therefore, potential damage to the kidney. Crystalluria E. Adverse effects A A A 4. Excretion: Sulfa drugs are eliminated by glomerular filtration and require dose adjustments for renal dysfunction. Depressed kidney function causes accumulation of both the parent compounds and their metabolites necessitating dose adjustment. The sulfonamides may also be eliminated in breast milk. Hypersensitivity 1. Crystalluria: Nephrotoxicity develops as a result of crystalluria (Figure 33.11). Adequate hydration and alkalinization of urine prevent the problem by reducing the concentration of drug and promoting its ionization. Agents, such as sulfisoxazole [sul-fi-SOX-a-zole] and sulfamethoxazole [sul-fa-meth-OX-a-zole] are more soluble at urinary pH than are the older sulfonamides (for example, sulfadiazine) and are less liable to cause crystalluria. Hemolytic anemia 2. Hypersensitivity: Hypersensitivity reactions, such as rashes, angioedema, and Stevens-Johnson syndrome, are potential problems. The latter occurs more frequently with the longer-acting agents. When patients report previous sulfa allergy, it is paramount to acquire a description of the reaction to direct appropriate therapy. 3. Hemopoietic disturbances: Hemolytic anemia is encountered in patients with glucose 6-phosphate dehydrogenase deficiency. Granulocytopenia and thrombocytopenia can also occur. 4. Kernicterus: This disorder may occur in newborns, because sulfa drugs displace bilirubin from binding sites on serum albumin. The bilirubin is then free to pass into the CNS, because the baby’s bloodbrain barrier is not fully developed (see below). Pharm 5th 3-21-11.indb 415 Kernicterus Bilirubin Figure 33.11 Some adverse reactions to sulfonamides. 3/21/11 2:28:12 PM 416 33. Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics Sulfonamides Contraindicated Methenamine Figure 33.12 Contraindication for sulfonamide treatment. 5. Drug potentiation: Transient potentiation of the anticoagulant effect of warfarin results from their displacement from binding sites on serum albumin. Free methotrexate levels may also rise through displacement. 6. Contraindications: Due to the danger of kernicterus, sulfa drugs should be avoided in newborns and infants less than 2 months of age as well as in pregnant women at term. Because sulfonamides condense with formaldehyde, they should not be given to patients receiving methenamine for UTIs (Figure 33.12). IV. TRIMETHOPRIM Trimethoprim [trye METH-oh-prim], a potent inhibitor of bacterial dihydrofolate reductase, exhibits an antibacterial spectrum similar to that of the sulfonamides. Trimethoprim is most often compounded with sulfamethoxazole, producing the combination called cotrimoxazole. A. Mechanism of action The active form of folate is the tetrahydro-derivative that is formed through reduction of dihydrofolic acid by dihydrofolate reductase. This enzymatic reaction (see Figure 33.9) is inhibited by trimethoprim, leading to a decreased availability of the tetrahydrofolate coenzymes required for purine, pyrimidine, and amino acid synthesis. The bacterial reductase has a much stronger affinity for trimethoprim than does the mammalian enzyme, which accounts for the drug’s selective toxicity. [Note: Examples of other drugs that function as folate reductase inhibitors include pyrimethamine, which is used with sulfonamides in treating parasitic infections, and methotrexate, which is used in the treatment of cancer, rheumatoid arthritis, and psoriasis]. B. Antibacterial spectrum The antibacterial spectrum of trimethoprim is similar to that of sulfamethoxazole. However, trimethoprim is 20- to 50-fold more potent than the sulfonamide. Trimethoprim may be used alone in the treatment of acute UTIs and in the treatment of bacterial prostatitis (although fluoroquinolones are preferred) and vaginitis. C. Resistance Resistance in gram-negative bacteria is due to the presence of an altered dihydrofolate reductase that has a lower affinity for trimethoprim. Overproduction of the enzyme may also lead to resistance, because this can decrease drug permeability. D. Pharmacokinetics The half-life of trimethoprim is similar to that of sulfamethoxazole. However, because the drug is a weak base, higher concentrations of trimethoprim are achieved in the relatively acidic prostatic and vaginal fluids. The drug also penetrates the cerebrospinal fluid. Trimethoprim undergoes some O-demethylation, but most of it is excreted unchanged through the kidney. E. Adverse effects Trimethoprim can produce the effects of folic acid deficiency. These effects include megaloblastic anemia, leukopenia, and granulocyto Pharm 5th 3-21-11.indb 416 3/21/11 2:28:13 PM V. Cotrimoxazole 417 penia, especially in pregnant patients and those having very poor diets. These blood disorders can be reversed by the simultaneous administration of folinic acid, which does not enter bacteria. Trimethoprim and sulfamethoxazole together (cotrimoxazole) show greater inhibition of bacterial growth. The combination of trimethoprim with sulfamethoxazole, called cotrimoxazole [co-try-MOX-a-zole], shows greater antimicrobial activity than equivalent quantities of either drug used alone (see Figure 33.13). The combination was selected because of their synergistic activity and the similarity in the half-lives of the two drugs. A. Mechanism of action The synergistic antimicrobial activity of cotrimoxazole results from its inhibition of two sequential steps in the synthesis of tetrahydrofolic acid: sulfamethoxazole inhibits the incorporation of PABA into dihydrofolic acid precursors, and trimethoprim prevents reduction of dihydrofolate to tetrahydrofolate (see Figure 33.9). Number of bacteria (arbitrary units) V. COTRIMOXAZOLE No drug 100 Trimethoprim alone 50 Sulfamethoxazole alone Both drugs 0 0 5 10 Hours B. Antibacterial spectrum Cotrimoxazole has a broader spectrum of antibacterial action than the sulfa drugs (Figure 33.14). It is effective in treating UTIs and respiratory tract infections as well as in Pneumocystis jiroveci pneumonia and ampicillin- or chloramphenicol-resistant systemic salmonella infections. It has activity versus MRSA, and can be particularly useful for community acquired skin and soft tissue infections caused by this organism. It is the drug of choice for infections caused by susceptible Nocardia species and Stenotrophamonas maltophilia. Figure 33.13 Synergism between trimethoprim and sulfamethoxazole inhibits growth of Escherichia coli. LISTERIOSIS RESPIRATORY INFECTIONS Cotrimoxazole is effective against Haemophilis influenzae. Cotrimoxazole is an alternative treatment for Legionella pneumophilia. PNEUMOCYSTIS JIROVECI PNEUMONIA This is a common opportunistic infection complicating AIDS. Cotrimoxazole is the most effective therapy. Prophylaxis with cotrimoxazole is recommended for HIV-infected patients with fewer than 200 CD4+ cells/mL. Gram (+) cocci Ampicillin or cotrimoxazole is effective in treating the septicemia and meningitis caused by Listeria monocytogenes. Gram (+) bacilli Listeria monocytogenes Gram (–) cocci Gram (–) rods Escherichia coli Haemophilus influenzae Legionella pneumophila Proteus mirabilis Salmonella typhi Shigella species Anaerobic organisms Spirochetes Mycoplasma Chlamydia Other Pneumocystis jiroveci PROSTATE AND URINARY TRACT INFECTIONS Trimethoprim concentrates in prostatic and vaginal fluids, making it effective in treating infections at these sites. Chronic urinary tract infections respond to cotrimoxazole. GASTROINTESTINAL INFECTIONS Cotrimoxazole is useful in the treatment of shigellosis and nontyphoid salmonella. The drug is also effective in the management of carriers of Salmonella typhi. Figure 33.14 Typical therapeutic applications of cotrimoxazole (sulfamethoxazole plus trimethoprim). Pharm 5th 3-21-11.indb 417 3/21/11 2:28:18 PM 418 33. Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics C. Resistance Drug crosses blood-brain barrier very slowly IV Resistance to the trimethoprim-sulfamethoxazole combination is less frequently encountered than resistance to either of the drugs alone, because it would require that the bacterium have simultaneous resistance to both drugs. D. Pharmacokinetics Unchanged drug and metabolites appear in urine the urine Cotrimoxazole Figure 33.15 Administration and fate of cotrimoxazole. Trimethoprim is more lipid soluble than sulfamethoxazole and has a greater volume of distribution. Administration of one part trimethoprim to five parts of the sulfa drug produces a ratio of the drugs in the plasma of twenty parts sulfamethoxazole to one part trimethoprim. This ratio is optimal for the antibiotic effect. Cotrimoxazole is generally administered orally (Figure 33.15). Exceptions involve intravenous administration to patients with bloodstream infections or severe pneumonia caused by P. jiroveci, or to patients who cannot take the drug by mouth. Both agents distribute throughout the body. Trimethoprim concentrates in the relatively acidic milieu of prostatic and vaginal fluids, and it accounts for the use of the trimethoprim-sulfamethoxazole combination in infections at these sites. Both parent drugs and their metabolites are excreted in the urine. E. Adverse effects 1. Dermatologic: Reactions involving the skin are very common and may be severe in the elderly (Figure 33.16). Skin rash Nausea 2. Gastrointestinal: Nausea, vomiting, as well as, glossitis and stomatitis are not unusual. 3. Hematologic: Megaloblastic anemia, leukopenia, and thrombocytopenia may occur. All these effects may be reversed by the concurrent administration of folinic acid, which protects the patient and does not enter the microorganism. Hemolytic anemia may occur in patients with glucose 6-phosphate dehydrogenase deficiency due to the sulfamethoxazole. 4. Patients infected with human immunodeficiency virus: Immunocompromised patients with P. jiroveci pneumonia frequently show drug-induced fever, rashes, diarrhea, and/or pancytopenia. Hematologic toxicities 5. Drug interactions: Prolonged prothrombin times (increased INR) in patients receiving both sulfamethoxazole and warfarin have been reported. The plasma half-life of phenytoin may be increased due to an inhibition of its metabolism. Methotrexate levels may rise due to displacement from albumin-binding sites by sulfamethoxazole. VI. URINARY TRACT ANTISEPTICS/ANTIMICROBIALS Figure 33.16 Some adverse reactions to cotrimoxazole. Pharm 5th 3-21-11.indb 418 Urinary tract infections (most commonly uncomplicated acute cystitis and pyelonephritis) in women of child-bearing age and in the elderly are one of the most common problems seen by primary care physicians. Escherichia coli is the most common pathogen, causing about 80 percent of uncomplicated upper and lower UTIs. Staphylococcus saprophyticus is the second most common bacterial pathogen causing UTIs, with other common causes including Klebsiella pneumoniae and Proteus mirabilis. These infections may be treated with any one of a group of agents called urinary tract antiseptics, including methenamine, nitrofurantoin, and the quinolone nalidixic 3/21/11 2:28:21 PM VI. Urinary Tract Antiseptics/Antimicrobials 419 acid. These drugs do not achieve antibacterial levels in the circulation, but because they are concentrated in the urine, microorganisms at that site can be effectively eradicated. A. Methenamine 1. Mechanism of action: To act, methenamine [meth-EN-a-meen] must decompose at an acidic pH of 5.5 or less in the urine, thus producing formaldehyde, which acts locally and is toxic to most bacteria (Figure 33.17). Methenamine should not be used in patients with indwelling catheters. Bacteria do not develop resistance to formaldehyde. [Note: Methenamine is frequently formulated with a weak acid, such as mandelic acid or hippuric acid. Ascorbic acid (vitamin C), and cranberry juice have been used to reduce urinary pH. Non-prescription antacids, such as sodium bicarbonate should be avoided.] 2. Antibacterial spectrum: Methenamine is primarily used for chronic suppressive therapy. Urea-splitting bacteria that alkalinize the urine, such as Proteus species, are usually resistant to the action of methenamine. Methenamine is used to treat lower UTIs but is not effective in upper UTIs. It is most useful when the causative organism is E. coli, however it can suppress other organisms. N CH 2 CH 2 Kills bacteria CH 2 N N CH 2 CH 2 N HCHO CH 2 Methenamine 6 H 2O 6 Formaldehyde + 4 NH4 Decomposition to formaldehyde occurs at low pH of urine. Figure 33.17 Formation of formaldehyde from methenamine at acid pH. 3. Pharmacokinetics: Methenamine is administered orally. In addi- tion to formaldehyde, ammonium ion is produced in the bladder. Because the liver rapidly metabolizes ammonia to form urea, methenamine is contraindicated in patients with hepatic insufficiency, in which elevated levels of circulating ammonium ions would be toxic to the CNS. Methenamine is distributed throughout the body fluids, but no decomposition of the drug occurs at pH 7.4. Thus, systemic toxicity does not occur and the drug is eliminated in the urine. 4. Adverse effects: The major side effect of methenamine treatment is gastrointestinal distress, although at higher doses, albuminuria, hematuria, and rashes may develop. Methenamine mandelate is contraindicated in patients with renal insufficiency, because mandelic acid may precipitate. [Note: Sulfonamides, such as cotrimoxazole, react with formaldehyde and must not be used concomitantly with methenamine. The combination increases the risk of crystalluria and mutual antagonism.] B. Nitrofurantoin Nitrofurantoin [nye-troe-FYOOR-an-toyn] sensitive bacteria reduce the drug to a highly active intermediate that inhibits various enzymes and damages bacterial DNA. Bacteria that are susceptible rarely become resistant during therapy. Antibiotic activity is greater in acidic urine. It is useful against E. coli, but other common urinary tract gram-negative bacteria may be resistant. Gram-positive cocci are susceptible. Hemolytic anemia is encountered in patients with glucose 6-phosphate dehydrogenase deficiency. Other adverse effects include gastrointestinal disturbances, acute pneumonitis, and neurologic problems. Interstitial pulmonary fibrosis has occurred in patients who take nitrofurantoin chronically. This is of critical importance, especially in the elderly. Contraindications: Anuria, oliguria, significant impairment of renal function (not to be used in patients with creatinine clearance less than 60 mL/min or significantly elevated serum creatinine), pregnancy at term or ≥ 38 weeks pregnant. Pharm 5th 3-21-11.indb 419 3/21/11 2:28:22 PM 420 33. Quinolones, Folic Acid Antagonists, and Urinary Tract Antiseptics Study Questions Choose the ONE best answer. 33.1 A 30-year-old male is diagnosed to be human immunodeficiency virus (HIV) positive. His CD4+ count is 200 cells/mm3 and his viral load is 10,000 copies/ mL. In addition to receiving antiviral therapy, which of the following is indicated to protect him against pneumonia due to Pneumocystis jiroveci? A. Trimethoprim. B. Ciprofloxacin. C. Cotrimoxazole. D. Clindamycin. E. Sulfamethoxazole. 33.2 A 26-year-old young man presents with the symptoms of gonorrhea. Because this condition is often associated with an infection due to Chlamydia trachomatis, which of the following quinolones would be the best choice for treating him? A. Ciprofloxacin. B. Nalidixic acid. C. Norfloxacin. D. Levofloxacin. E. Moxifloxacin. 33.3 In which one of the following infections is cipro floxacin ineffective? A. Urinary tract infections due to a β-lactamase producing strain of Klebsiella. B. Pneumonia due to Streptococcus pneumoniae. C. Exacerbation of chronic bronchitis due to Morax ella catarrhalis. D. Urinary tract infection due to Escherichia coli. E. Urinary tract infection due to Pseudomonas aeruginosa. 33.4 Sulfonamides increase the risk of neonatal kernicterus, because they: A. Diminish the production of plasma albumin. B. Increase the turnover of red blood cells. C. Inhibit the metabolism of bilirubin. D. Compete for bilirubin-binding sites on plasma albumin. E. Depress the bone marrow. Pharm 5th 3-21-11.indb 420 Correct answer = C. Prophylaxis with cotrimoxazole is the standard treatment for patients with human immunodeficiency virus with CD4+ counts at 200 cells/mm3 or lower. Trimethoprim and sulfamethoxazole are not effective as monotherapy. It can be used in combination with dapsone. Clindamycin is effective in pneumonia, which has already developed due to this organism, but is not used prophylactically because of its adverse effect on the gastrointestinal tract. Ciprofloxacin lacks activity against this organism. Correct answer = D. Levofloxacin, a third-generation fluoroquinolone, shows increased activity against both gonorrheal and chlamydial infections compared to the second-generation examples, ciprofloxacin and norfloxacin. Nalidixic acid, a first-generation fluoroquinolone, lacks activity in these conditions. Moxifloxacin, a fourth-generation fluoroqinolone, also does not affect these atypical organisms. Correct answer = B. Ciprofloxacin does not have sufficient activity against S. pneumoniae to be effective. Because it is not a β-lactam, ciprofloxacin is effective in treating UTIs caused by β-lactamase producing organisms. Ciprofloxacin is indicated for treatment of the other infections listed. Correct answer = D. Increased release of albuminbound bilirubin increases the plasma concentration of free bilirubin, which can penetrate the central nervous system.The sulfonamides do not cause the other effects on this list. 3/21/11 2:28:22 PM Antimycobacterials I. OVERVIEW Mycobacteria are slender, rod-shaped bacteria with lipid-rich cell walls that stain poorly with the Gram stain, but once stained, the walls cannot be easily decolorized by treatment with acidified organic solvents. Hence, they are termed “acid-fast.” The most widely encountered mycobacterial infection is tuberculosis—the leading cause worldwide of death from infection. Members of the genus Mycobacterium also cause leprosy, as well as, several tuberculosis-like human infections. Mycobacterial infections are intracellular and, generally, result in the formation of slow-growing granulomatous lesions that are responsible for major tissue destruction. Diagnostic testing for tuberculosis can be accomplished via the standard tuberculin skin test with purified protein derivative (PPD) or by an interferon-gamma release assay (IGRA) blood test, Quantiferon-TB Gold, approved by the FDA in 2005. The advantages that the blood test offers is that it requires only a single test visit, and it is less susceptible to falsepositive results due to BCG vaccination or to infection with mycobacteria other than Mycobacterium tuberculosis. However, the cost of the blood test is more than that of the skin test, yet it reduces the expense of follow-up x-rays and lab tests needed with a tuberculin skin test. There are four currently recommended first-line agents utilized for antituberculosis therapy (Figure 34.1). Second-line medications are either less effective, more toxic, or have not been studied as extensively. They are useful in patients who cannot tolerate the first-line drugs or who are infected with myobacteria that are resistant to the first-line agents. 34 DRUGS USED TO TREAT TUBERCULOSIS Ethambutol MYAMBUTOL Isoniazid (INH) NYDRAZID, others Pyrazinamide PYRAZINAMIDE Rifamycins RIFADIN DRUGS USED TO TREAT TUBERCULOSIS (2nd line) Aminoglycosides Aminosalicylic acid PASER Capreomycin CAPASTAT SULFATE Cycloserine SEROMYCIN Ethionamide TRECATOR Fluoroquinolones Macrolides DRUGS USED TO TREAT LEPROSY Clofazimine LAMPRENE Dapsone DAPSONE Rifampin (Rifampicin) RIFADIN Figure 34.1 Summary of drugs used to treat mycobacterial infections. II. CHEMOTHERAPY FOR TUBERCULOSIS Mycobacterium tuberculosis, one of a number of mycobacteria, can lead to serious infections of the lungs, genitourinary tract, skeleton, and meninges. Treating tuberculosis as well as other mycobacterial infections presents therapeutic problems. The organism grows slowly; thus, are difficult to culture and may have to be treated for 6 months to 2 years. Resistant organisms readily emerge, particularly in patients who have had prior therapy or who fail to adhere to the treatment protocol. It is currently estimated that about one-third of the world’s population is infected with M. tuberculosis, with 30 million people having active disease. Worldwide, 9 million new cases occur, and approximately 2 million people die of the disease each year. Pharm 5th 3-21-11.indb 421 3/21/11 2:28:23 PM 422 34. Antimycobacterials Percentage resistant A. Strategies for addressing drug resistance 100 50 0 80 40 0 120 Days after initiation of treatment Figure 34.2 Cumulative percentage of strains of Mycobacterium tuberculosis showing resistance to streptomycin. Intensive phase Continuation phase Isoniazid Rifampin Pyrazinamide Ethambutol 0 1 2 3 4 Months 5 6 Figure 34.3 One of several recommended multidrug schedules for the treatment of tuberculosis. Strains of M. tuberculosis that are resistant to a particular agent emerge during treatment with a single drug. For example, Figure 34.2 shows that resistance rapidly develops in patients given only streptomycin. Therefore, multidrug therapy is employed when treating tuberculosis in an effort to delay or prevent the emergence of resistant strains. Isoniazid, rifampin (or rifabutin or rifapentine), ethambutol, and pyrazinamide are the principal or so-called “first-line” drugs because of their efficacy and acceptable degree of toxicity. Today, however, because of poor patient compliance and other factors, the number of multidrug-resistant organisms has risen. Some bacteria have been identified that are resistant to as many as seven antitubercular agents. Therefore, although treatment regimens vary in duration and in the agents employed, they always include a minimum of two drugs, preferably with both being bactericidal (see p. 370) The combination of drugs should prevent the emergence of resistant strains. The multidrug regimen is continued well beyond the disappearance of clinical disease to eradicate any persistent organisms. For example, the initial short-course chemotherapy for tuberculosis includes isoniazid, rifampin, ethambutol, and pyrazinamide for 2 months and then isoniazid and rifampin for the next 4 months (the “continuation phase”; Figure 34.3). Before susceptibility data are available, more drugs may be added to the first-line agents for patients who have previously had tuberculosis or those in whom multidrug-resistant tuberculosis is suspected. The added drugs normally include an aminoglycoside (streptomycin, kanamycin, or amikacin) or capreomycin (injectable agents), a fluoroquinolone, and perhaps a second-line antituberculosis agent such as cycloserine, ethionamide, or p-aminosalicylic acid. Once susceptibility data are available, the drug regimen can be individually tailored to the patient. Patient compliance is often low when multidrug schedules last for 6 months or longer. One successful strategy for achieving better treatment completion rates is “directly observed therapy,” also known as DOT, in which patients take their medication while being supervised and observed. DOT has been shown to decrease drug resistance as well as relapse and mortality rates and to improve cure rates. Most local and state health departments offer DOT services. B. Isoniazid Isoniazid [eye-soe-NYE-a-zid], the hydrazide of isonicotinic acid, is a synthetic analog of pyridoxine. It is the most potent of the antitubercular drugs, but is never given as a single agent in the treatment of active tuberculosis. Its introduction revolutionized the treatment of tuberculosis. 1. Mechanism of action: Isoniazid, often referred to as INH, is a pro drug that is activated by a mycobacterial catalase-peroxidase (KatG). Genetic and biochemical evidence has implicated at least two different target enzymes for isoniazid within the unique Type II fatty acid synthase system involved in the production of mycolic acids. [Note: Mycolic acid is a unique class of very-long-chain, β-hydroxylated fatty acids found in mycobacterial cell walls. Decreased mycolic acid synthesis corresponds with the loss of acid-fastness after exposure to isoniazid.] The targeted enzymes are enoyl acyl carrier protein reductase (InhA) and a β-ketoacyl-ACP synthase (KasA). The activated drug covalently binds to and inhibits these enzymes, which are essential for the synthesis of mycolic acid. Pharm 5th 3-21-11.indb 422 3/21/11 2:28:23 PM II. Chemotherapy For Tuberculosis 3. Resistance: This is associated with several different chromosomal mutations, each of which results in one of the following: mutation or deletion of KatG (producing mutants incapable of prodrug activation), varying mutations of the acyl carrier proteins, or over expression of InhA. Cross-resistance does not occur between isoniazid and other antitubercular drugs. In rapid acetylators, isoniazid has a short half-life (1 hr) Number of subjects 2. Antibacterial spectrum: For bacilli in the stationary phase, isoniazid is bacteriostatic, but for rapidly dividing organisms, it is bactericidal. It is effective against intracellular bacteria. Isoniazid is specific for treatment of M. tuberculosis, although Mycobacterium kansasii (an organism that causes three percent of the clinical illness known as tuberculosis) may be susceptible at higher drug levels. When it is used alone, resistant organisms rapidly emerge. 423 In slow acetylators, isoniazid has a long half-life (3 hrs) 20 10 0 50 100 150 200 250 Half-life (min) 4. Pharmacokinetics: Orally administered isoniazid is readily absorbed. Absorption is impaired if isoniazid is taken with food, particularly carbohydrates, or with aluminum-containing antacids. The drug diffuses into all body fluids, cells, and caseous material (necrotic tissue resembling cheese that is produced in tubercles). Drug levels in the cerebrospinal fluid (CSF) are about the same as those in the serum. The drug readily penetrates host cells and is effective against bacilli growing intracellularly. Infected tissue tends to retain the drug longer. Isoniazid undergoes N-acetylation and hydrolysis, resulting in inactive products. [Note: Acetylation is genetically regulated, with the fast acetylator trait being autosomally dominant. A bimodal distribution of fast and slow acetylators exists (Figure 34.4).] Chronic liver disease decreases metabolism, and doses must be reduced. Excretion is through glomerular filtration, predominantly as metabolites (Figure 34.5). Slow acetylators excrete more of the parent compound. Severely depressed renal function results in accumulation of the drug, primarily in slow acetylators. Figure 34 .4 Bimodal distribution of isoniazid half-lives caused by rapid and slow acetylation of the drug. 5. Adverse effects: The incidence of adverse effects is fairly low. Except for hypersensitivity, adverse effects are related to the dosage and duration of administration. Isoniazid a. Peripheral neuritis: Peripheral neuritis (manifesting as paresthesias of the hands and feet), which is the most common adverse effect, appears to be due to a relative pyridoxine deficiency. Most of the toxic reactions are corrected by supplementation of 25 to 50 mg per day of pyridoxine (vitamin B6). [Note: Isoniazid can achieve levels in breast milk that are high enough to cause a pyridoxine deficiency in the infant unless the mother is supplemented with the vitamin.] b. Hepatitis and idiosyncratic hepatotoxicity: Potentially fatal hepatitis is the most severe side effect associated with isoniazid. It has been suggested that this is caused by a toxic metabolite of monoacetylhydrazine, formed during the metabolism of isoniazid. The incidence increases among patients with increasing age, among patients who also take rifampin, or among those who drink alcohol daily. c. Drug interactions: Because isoniazid inhibits metabolism of phenytoin (Figure 34.6), isoniazid can potentiate the adverse effects of that drug (for example, nystagmus and ataxia). Slow acetylators are particularly at risk. Pharm 5th 3-21-11.indb 423 Metabolites appear in the urine urine Figure 34.5 Administration and fate of isoniazid. Phenytoin P-450 Isoniazid Metabolites Figure 34.6 Isoniazid potentiates the adverse effects of phenytoin. 3/21/11 2:28:25 PM 424 34. Antimycobacterials d. Other adverse effects: Mental abnormalities, convulsions in patients prone to seizures, and optic neuritis have been observed. Hypersensitivity reactions include rashes and fever. C. Rifamycins: Rifampin, rifabutin and rifapentine Rifampin, rifabutin, and rifapentine are all considered to be rifamycins, a group of structurally similar macrocyclic antibiotics, which are first-line drugs for tuberculosis. Any of these rifamycins must always be used in conjunction with at least one other antituberculosis drug to which the isolate is susceptible. 1. Rifampin: Rifampin [rif-AM-pin], which is derived from the soil mold Streptomyces, has a broader antimicrobial activity than isoniazid and has found application in the treatment of a number of different bacterial infections. Because resistant strains rapidly emerge during therapy, it is never given as a single agent in the treatment of active tuberculosis. a. Mechanism of action: Rifampin blocks transcription by interacting with the β subunit of bacterial, but not human, DNAdependent RNA polymerase. [Note: The drug is thus specific for prokaryotes.] Rifampin inhibits mRNA synthesis by suppressing the initiation step. b. Antimicrobial spectrum: Rifampin is bactericidal for both intracellular and extracellular mycobacteria, including M. tuberculosis, and atypical mycobacteria, such as M. kansasii. It is effective against many gram-positive and gram-negative organisms and is used prophylactically for individuals exposed to meningitis caused by meningococci or Haemophilus influenzae. Rifampin is the most active antileprosy drug at present, but to delay the emergence of resistant strains, it is usually given in combination with other drugs. Rifabutin, an analog of rifampin, has some activity against Mycobacterium avium-intracellulare complex, but is less active against tuberculosis. c. Resistance: Resistance to rifampin can be caused by a mutation in the affinity of the bacterial DNA-dependent RNA polymerase for the drug, or by decreased permeability. Metabolites appear in the bile One-third of dose appears in urine Rifampin Figure 34.7 Administration and fate of rifampin. [Note: Patient should be warned that urine and tears may turn orange-red in color.] Pharm 5th 3-21-11.indb 424 d. Pharmacokinetics: Absorption is adequate after oral administration. Distribution of rifampin occurs to all body fluids and organs. Adequate levels are attained in the CSF even in the absence of inflammation. The drug is taken up by the liver and undergoes enterohepatic cycling. Rifampin itself can induce the hepatic mixed-function oxidases (see p. 14), leading to a shortened half-life and numerous drug interactions. Elimination of metabolites and the parent drug is via the bile into the feces or via the urine (Figure 34.7). [Note: Urine and feces, as well as, other secretions have an orange-red color; patients should be forewarned. Tears may permanently stain soft contact lenses orange-red.] e. Adverse effects: Rifampin is generally well tolerated. The most common adverse reactions include nausea, vomiting, and rash. Hepatitis and death due to liver failure is rare; however, the drug should be used judiciously in patients who are alcoholic, elderly, 3/21/11 2:28:26 PM II. Chemotherapy For Tuberculosis or have chronic liver disease due to the increased incidence of severe hepatic dysfunction when rifampin is administered alone or concomitantly with isoniazid. Often, when rifampin is dosed intermittently, or in daily doses of 1.2 grams or greater, a flu-like syndrome is associated with fever, chills, and myalgias and sometimes is associated with acute renal failure, hemolytic anemia, and shock. f. Drug interactions: Because rifampin can induce a number of cytochrome P450 enzymes (see p. 14), it can decrease the halflives of other drugs that are coadministered and metabolized by this system (Figure 34.8). This may lead to higher dosage requirements for these agents. 2. Rifabutin: Rifabutin [rif-a-BYOO-tin], a derivative of rifampin, is the preferred drug for use in tuberculosis-infected patients with the human immunodeficiency virus (HIV), who are concomitantly treated with protease inhibitors or nonnucleoside reverse transcriptase inhibitors, because it is a less potent inducer of cytochrome P450 enzymes. Rifabutin has adverse effects similar to those of rifampin, but can also cause uveitis, skin hyperpigmentation, and neutropenia. 3. Rifapentine: Rifapentine [rih-fa-PEN-teen] has activity comparable to that of rifampin but has a longer half-life than rifampin and rifabutin, which permits weekly dosing. However, for the intensive phase (initial 2 months) of the short-course therapy for tuberculosis, rifapentine is given twice weekly. In the subsequent phase, rifapentine is dosed once per week for 4 months. To avoid resistance issues, rifapentine should not be used alone but, rather, be included in a three to four-drug regimen. 425 Clofibrate Digitoxin Ketoconazole Methadone Oral contraceptives Prednisone Propranolol Quinidine Sulfonylureas Warfarin Rifampin P450 P450 P450 Enzyme induction Metabolite P450 Metabolites Figure 34.8 induces cytochrome P450, which can decrease the half-lives of coadministered drugs that are metabolized by this system. D. Pyrazinamide Pyrazinamide [peer-a-ZIN-a-mide] is a synthetic, orally effective, bactericidal, antitubercular agent used in combination with isoniazid, rifampin, and ethambutol. It is bactericidal to actively dividing organisms, but the mechanism of its action is unknown. Pyrazinamide must be enzymatically hydrolyzed to pyrazinoic acid, which is the active form of the drug. Some resistant strains lack the pyrazinamidase. Pyrazinamide is active against tubercle bacilli in the acidic environment of lysosomes, as well as, in macrophages. Pyrazinamide distributes throughout the body, penetrating the CSF. It undergoes extensive metabolism. About one to five percent of patients taking isoniazid, rifampin, and pyrazinamide may experience liver dysfunction. Urate retention can also occur, and may precipitate a gouty attack (Figure 34.9). Pyrazinamide Ethambutol Uric acid Figure 34.9 Pyrazinamide and ethambutol may cause urate retention and gouty attacks. E. Ethambutol Ethambutol [e-THAM-byoo-tole] is bacteriostatic and specific for most strains of M. tuberculosis and M. kansasii. Ethambutol inhibits ara binosyl transferase—an enzyme that is important for the synthesis of the mycobacterial arabinogalactan cell wall. Resistance is not a serious problem if the drug is employed with other antitubercular agents. Ethambutol can be used in combination with pyrazinamide, isoniazid, and rifampin to treat tuberculosis. Absorbed on oral administration, ethambutol is well distributed throughout the body. Penetration into the central nervous system (CNS) is therapeutically adequate in tuber- Pharm 5th 3-21-11.indb 425 3/21/11 2:28:28 PM 426 34. Antimycobacterials DRUG ADVERSE EFFECTS COMMENTS Ethambutol Optic neuritis with blurred vision, red-green color blindness Establish baseline visual acuity and color vision; test monthly. Isoniazid Hepatic enzyme elevation, hepatitis, peripheral neuropathy Take baseline hepatic enzyme measurements; repeat if abnormal or patient is at risk or symptomatic. Clinically significant interation with phenytoin and antifungal agents (azoles). Pyrazinamide Nausea, hepatitis, hyperuricemia, rash, joint ache, gout (rare) Take baseline hepatic enzymes and uric acid measurements; repeat if abnormal or patient is at risk or symptomatic. Rifampin Hepatitis, GI upset, rash, flu-like syndrome, significant interaction with several drugs Take baseline hepatic enzyme measurements and CBC; repeat if abnormal or patient is at risk or symptomatic. Warn patient that urine and tears may turn red-orange in color. Figure 34.10 Some characteristics of first-line drugs used in treating tuberculosis. CBC = complete blood count. GI = gastrointestinal. culous meningitis. Both parent drug and metabolites are excreted by glomerular filtration and tubular secretion. The most important adverse effect is optic neuritis, which results in diminished visual acuity and loss of ability to discriminate between red and green. Visual acuity should be periodically examined. Discontinuation of the drug results in reversal of the optic symptoms. In addition, urate excretion is decreased by the drug; thus, gout may be exacerbated (see Figure 34.9). Figure 34.10 summarizes some of the characteristics of first-line drugs. F. Alternate second-line drugs A number of drugs—streptomycin, [strep-toe-MY-sin], para-aminosalicylic acid [a-mee-noe-sal-i-SIL-ik], ethionamide [e-thye-ON-am-ide], cycloserine [sye-kloe-SER-een], capreomycin [kap-ree-oh-MYE sin], fluoroquinolones, and macrolides—are considered to be second-line drugs, either because they are no more effective than the first-line agents and their toxicities are often more serious, or because they are particularly active against atypical strains of mycobacteria. 1. Streptomycin: This is the first antibiotic effective in the treatment of tuberculosis and is discussed with the aminoglycosides (see p. 399). Its action is directed against extracellular organisms. Infections due to streptomycin-resistant organisms may be treated with kanamycin or amikacin, to which these bacilli remain sensitive. Isoniazid Aminosalicylic acid Ethionamide Acetylated isoniazid Figure 34.11 Aminosalicylic acid and ethionamide can inhibit the acetylation of isoniazid. Pharm 5th 3-21-11.indb 426 2. Capreomycin: This is a peptide that inhibits protein synthesis. It is administered parenterally. Capreomycin is primarily reserved for the treatment of multidrug-resistant tuberculosis. Careful monitoring of the patient is necessary to prevent its nephrotoxicity and ototoxicity. 3. Cycloserine is an orally effective, tuberculostatic agent that appears to antagonize the steps in bacterial cell wall synthesis involving D-alanine. It distributes well throughout body fluids, including the CSF. Cycloserine is metabolized, and both parent and metabolite are excreted in urine. Accumulation occurs with renal insufficiency. Adverse effects involve CNS disturbances, and epileptic seizure activity may be exacerbated. Peripheral neuropathies are also a problem, but they respond to pyridoxine. 3/21/11 2:28:29 PM 4. Ethionamide: This is a structural analog of isoniazid, but it is not believed to act by the same mechanism. Ethionamide can inhibit acetylation of isoniazid (Figure 34.11). It is effective after oral administration and is widely distributed throughout the body, including the CSF. Metabolism is extensive, and the urine is the main route of excretion. Adverse effects that limit its use include gastric irritation, hepatotoxicity, peripheral neuropathies, and optic neuritis. Supplementation with vitamin B6 (pyridoxine) may lessen the severity of the neurologic side effects. 5. Fluoroquinolones: The fluoroquinolones, specifically, ciprofloxacin, moxifloxacin and levofloxacin have an important place in the treatment of multidrug-resistant tuberculosis. Some atypical strains of mycobacteria are also susceptible. These drugs are discussed in detail in Chapter 33. 6. Macrolides: The macrolides, such as azithromycin and clarithromycin, are part of the regimen that includes ethambutol and rifabutin used for the treatment of infections by M. avium-intracellulare complex. Azithromycin is preferred for HIV-infected patients because it is least likely to interfere with the metabolism of antiretroviral drugs. Details about the pharmacology of macrolides are found in Chapter 32. 427 Cases, millions III. Chemotherapy For Leprosy 6 5 4 211,903 3 in 2010 2 1 0 1985 1989 1993 1997 2001 2005 2010 Year Figure 34.12 Reported prevalence of leprosy worldwide. A III. CHEMOTHERAPY FOR LEPROSY Leprosy (or, as it is specified by the U.S. Public Health Service, Hansen’s disease) is rare in the United States, but a small number of cases, both imported and domestically acquired, are reported each year. Worldwide, it is a much larger problem (Figure 34.12). Approximately 70 percent of all cases in the world are located in India. Bacilli from skin lesions or nasal discharges of infected patients enter susceptible individuals via abraded skin or the respiratory tract. The World Health

Organization recommends the triple-drug regimen of dapsone, clofazimine, and rifampin for 6 to 24 months. Figure 34.13 shows the effects of multi-drug therapy. A. Dapsone Dapsone [DAP-sone] is structurally related to the sulfonamides and similarly inhibits folate synthesis via dihydropteroate synthetase inhibiton. It is bacteriostatic for Mycobacterium leprae, but resistant strains are encountered. Dapsone is also employed in the treatment of pneumonia caused by Pneumocystis jiroveci in patients infected with HIV. The drug is well absorbed from the gastrointestinal tract and is distributed throughout the body, with high levels concentrated in the skin. The parent drug enters the enterohepatic circulation and undergoes hepatic acetylation. Both parent drug and metabolites are eliminated through the urine. Adverse reactions include hemolysis, especially in patients with glucose 6-phosphate dehydrogenase deficiency, as well as methemoglobinemia, peripheral neuropathy, and the possibility of developing erythema nodosum leprosum (a serious and severe skin complication of leprosy). [Note: The latter is treated with corticosteroids or thalidomide.] B. Clofazimine Clofazimine [kloe-FA-zi-meen] is a phenazine dye that binds to DNA and prevents it from serving as a template for future DNA replication. Its redox properties may lead to the generation of cytotoxic oxygen Pharm 5th 3-21-11.indb 427 B Figure 34.13 Leprosy patient. A. Before therapy. B. After 6 months of multidrug therapy. 3/21/11 2:28:30 PM 428 34. Antimycobacterials r adicals that are also toxic to the bacteria. Clofazimine is bactericidal to M. leprae and has some activity against M. avium-intracellulare complex. Following oral absorption, the drug accumulates in tissues, allowing intermittent therapy, but it does not enter the CNS. Patients may develop a red-brown discoloration of the skin. Eosinophilic enteritis has been reported as an adverse effect. The drug also has some anti-inflammatory activity; thus, erythema nodosum leprosum does not develop. Study Questions Choose the ONE best answer. 34.1 A 31-year-old white intravenous drug user was admitted to the hospital with a 4-week history of cough and fever. A chest radiograph showed left upper lobe cavitary infiltrate. Cultures of sputum yielded M. tuberculosis susceptible to all antimycobacterial drugs. The patient received isoniazid, rifampin, and pyrazinamide. The patient's sputum remained culture-positive for the subsequent 4 months. Which one of the following is the most likely cause of treatment failure? Correct answer = D. Although malabsorption of the drugs and the emergence of drug resistance are possibilities, the most common cause of treatment failure is nonadherence to the treatment protocol. Better treatment completion rates occur with "directly observed therapy." False-positive cultures is a possible but unlikely explanation. A. False-positive cultures. B. Maladsorption of the medications. C. Concomitant infection with HIV. D. Noncompliance by the patient. E. Drug resistance. 34.2 A 40-year-old man has been on primary therapy for active pulmonary tuberculosis for the past 2 months. At his regular clinic visit, he complains of a "pins and needles" sensation in his feet. You suspect that he might be deficient in which one of the following vitamins? A. Ascorbic acid. B. Niacin. C. Pyridoxine. D. Calcitriol. E. Folic acid. 34.3 A 35-year-old male, formerly a heroin abuser, has been on methadone maintenance for the last 13 months. Two weeks ago, he had a positive tuberculosis skin test (PPD test), and a chest radiograph showed evidence of right upper lobe infection. He was started on standard antimycobacterial therapy. He has come to the emergency department complaining of "withdrawal symptoms." Which of the following antimycobacterial drugs is likely to have caused this patient's acute withdrawal reaction? A. Ethambutol. B. Isoniazid. C. Pyrazinamide. D. Rifampin. E. Streptomycin. Pharm 5th 3-21-11.indb 428 Correct answer = C. Primary therapy for active pulmonary tuberculosis includes isoniazid. Isoniazid causes peripheral neuropathies with symptoms including paresthesias, such as "pins and needles" and numbness. This relative deficiency of pyridoxine appears to be due to the interference of isoniazid with its activation and enhancement of the excretion of pyridoxine. Concurrent administration of 100 mg of pyridoxine prevents the neuropathic actions of isoniazid. Deficiencies of any of the other vitamins would not cause peripheral neuropathies. Correct answer = D. Rifampin is a potent inducer of cytochrome P450–dependent drug-metabolizing enzymes. The duration of action of methadone is dependent upon hepatic clearance, so enhanced drug metabolism will shorten the duration and increase the risk of withdrawal symptoms in individuals on methadone maintenance. None of the other drugs listed induce cytochrome P450 enzymes. 3/21/11 2:28:31 PM Antifungal Drugs 35 I. OVERVIEW Infectious diseases caused by fungi are called mycoses, and they are often chronic in nature.1 Some mycotic infections are superficial and some involve the skin (cutaneous mycoses extending into the epidermis), but fungi may also penetrate the skin, causing subcutaneous infections. The fungal infections that are most difficult to treat are the systemic mycoses, which are often life threatening. Unlike bacteria, fungi are eukaryotic. They have rigid cell walls composed largely of chitin (a polymer of N-acetylglucosamine) rather than peptidoglycan (a characteristic component of most bacterial cell walls). The fungal cell membrane contains ergosterol rather than the cholesterol found in mammalian membranes. These chemical characteristics are useful in targeting chemotherapeutic agents against fungal infections. Fungal infections are generally resistant to antibiotics used in the treatment of bacterial infections, and, conversely, bacteria are resistant to the antifungal agents. The last two decades have seen a rise in the incidence of fungal infections such that candidemia is a significant cause of septicemia. This increased incidence of fungal infections is associated with greater numbers of patients with chronic immune suppression following organ transplant, from undergoing chemotherapy for myelogenous and solid tumors, or from the human immunodeficiency virus (HIV). During this same period, there have been significant changes in the therapeutic options available to the clinician, including new azoles and echinocandins. Figure 35.1 lists clinically useful agents for subcutaneous and systemic mycoses as well as cutaneous mycoses. II. DRUGS FOR SUBCUTANEOUS AND SYSTEMIC MYCOTIC INFECTIONS DRUGS FOR SUBCUTANEOUS AND SYSTEMIC MYCOSES Amphotericin B AMBISOME Anidulafungin ERAXIS Caspofungin CANCIDAS Fluconazole DIFLUCAN Flucytosine ANCOBON Itraconazole SPORANOX Ketoconazole NIZORAL Micafungin MYCAMINE Posaconazole NOXAFIL Voriconazole VFEND DRUGS FOR CUTANEOUS MYCOSES Butenafine LOTRIMIN ULTRA Clotrimazole, LOTRIMIN AF Ciclopirox PENLAC Econazole ECONAZOLE NITRATE Griseofulvin GRIFULVIN V, GRIS-PEG Miconazole FUNGOID, MICATIN, MONISTAT Naftifine NAFTIN Nystatin MYCOSTATIN Oxiconazole OXISTAT Sertaconazole ERTACZO Sulconazole EXELDERM Terbinafine LAMISIL Terconazole TERAZOL Tioconazole VAGISTAT-1 Tolnaftate TINACTIN A. Amphotericin B Amphotericin [am-foe-TER-i-sin] B is a naturally occurring polyene macrolide antibiotic produced by Streptomyces nodosus. In spite of its toxic potential, amphotericin B is the drug of choice for the treatment of life-threatening systemic mycoses. [Note: Conventional amphotericin (amphotericin B deoxycholate, the nonlipid formulation) has undergone several formulation improvements to reduce the incidence of side effects, particularly nephrotoxicity.] The drug is also sometimes used in combination with flucytosine to achieve more rapid sterilization of the cerebrospinal fluid (CSF). INFO LINK Pharm 5th 3-21-11.indb 429 Figure 35.1 Summary of antifungal drugs. 1 See Chapter 20 in Lippincott's Illustrated Reviews: Microbiology for a discussion of fungal infections. 3/21/11 2:28:31 PM 430 35. Antifungal Drugs 1 Amphotericin B interacts hydrophobically with ergosterol in the fungal cell membrane, forming a pore. K+ Amphotericin B pore FUNGAL CELL K+ and other small molecules 2 Potassium and other small molecules are lost through the pore, causing cell death. Figure 35.2 Model of a pore formed by amphotericin B in the lipid bilayer membrane. Minimal penetration into the CNS, vitreous humor, amniotic fluid IV Some elimination via the bile Topical Part of dose appears in urine over a long period of time Amphotericin B Figure 35.3 Administration and fate of amphotericin B. CNS = central nervous system. Pharm 5th 3-21-11.indb 430 1. Mechanism of action: Several amphotericin B molecules bind to ergosterol in the plasma membranes of sensitive fungal cells. There, they form pores (channels) that require hydrophobic interactions between the lipophilic segment of the polyene antibiotic and the sterol (Figure 35.2). The pores disrupt membrane function, allowing electrolytes (particularly potassium) and small molecules to leak from the cell, resulting in cell death. [Note: Because the polyene antibiotics bind preferentially to ergosterol rather than to cholesterol (the sterol found in mammalian membranes) a relative (but not absolute) specificity is conferred.] 2. Antifungal spectrum: Amphotericin B is either fungicidal or fungistatic, depending on the organism and the concentration of the drug. It is effective against a wide range of fungi, including Candida albicans, Histoplasma capsulatum, Cryptococcus neoformans, Coccidioides immitis, Blastomyces dermatitidis, and many strains of Aspergillus. [Note: Amphotericin B is also used in the treatment of the protozoal infection leishmaniasis.] 3. Resistance: Fungal resistance, although infrequent, is associated with decreased ergosterol content of the fungal membrane. 4. Pharmacokinetics: Amphotericin B is administered by slow, intravenous (IV) infusion (Figure 35.3). Amphotericin B is insoluble in water, and injectable preparations require the addition of sodium deoxycholate, which produces a soluble colloidal dispersion. The more dangerous intrathecal route is sometimes chosen for the treatment of meningitis caused by fungi that are sensitive to the drug. Amphotericin B has also been formulated with a variety of artificial lipids that form liposomes. The three amphotericin B lipid formulations marketed in the United States are AMPHOTEC, ABELCET, and AMBISOME. For example, the simplest and smallest of the liposome preparations, AMBISOME, is produced by the incorporation of amphotericin B into a single liposomal bilayer composed of phospholipids and cholesterol (Figure 35.4). These liposomal preparations have the primary advantage of reduced renal and infusion toxicity. However, because of their high cost, liposomal preparations are reserved mainly as salvage therapy for those individuals who cannot tolerate conventional amphotericin B. Amphotericin B is extensively bound to plasma proteins and is distributed throughout the body, becoming highly tissue bound. Inflammation favors penetration into various body fluids, but little of the drug is found in the cerebrospinal fluid (CSF), vitreous humor, or amniotic fluid. However, amphotericin B does cross the placenta. Low levels of the drug and its metabolites appear in the urine over a long period of time, and some are also eliminated via the bile. Dosage adjustment is not required in patients with compromised hepatic function, but when conventional amphotericin B causes renal dysfunction, the total daily dose is decreased by 50 percent. To minimize nephrotoxicity, alternatives including sodium loading with infusions of normal saline and the lipid-based amphotericin B products are used. 5. Adverse effects: Amphotericin B has a low therapeutic index. The total adult daily dose should not exceed 1.5 mg/kg. Small test doses may be administered to assess the degree of negative responses, such as anaphylaxis or convulsions. Other toxic manifestations include the following (Figure 35.5). 3/21/11 2:28:35 PM II. Drugs For Subcutaneous And Systemic Mycotic Infections B A 431 Coventional amphotericin B Key: Liposomal amphotericin B Phospholipid bilayer Survival at 7 days Nephrotoxicity (elevated serum creatinine levels) Patient survival is similar with conventional and liposomal preparations, but liposomal amphotericin B shows lower toxicity. Hypokalemia Amphotericin B molecules 0 50 Percentage of patients 100 Figure 35.4 A. Amphotericin B intercalated between the phospholipids of a spherical liposome (AmBisome®). B. Outcomes of antifungal therapy in febrile, neutropenic cancer patients treated with conventional amphotericin B and liposomal amphotericin B. a. Fever and chills: These occur most commonly 1 to 3 hours after starting the IV administration, but they usually subside with repeated administration of the drug. Premedication with a corticosteroid or an antipyretic helps to prevent this problem. 98.6 b. Renal impairment: Despite the low levels of the drug excreted in the urine, patients may exhibit a decrease in glomerular filtration rate and renal tubular function. Creatinine clearance can drop, and potassium and magnesium are lost. [Note: Nephrotoxicity may be potentiated by sodium depletion. A bolus infusion of normal saline before and after amphotericin B infusion may reduce the incidence of drug-induced nephrotoxicity.] Normal renal function usually returns with suspension of the drug, but residual damage is likely at high doses. Azotemia (elevated blood urea) is exacerbated by other nephrotoxic drugs, such as aminoglycosides, cyclosporine, and pentamidine, although adequate hydration can decrease its severity. c. Hypotension: A shock-like fall in blood pressure accompanied by hypokalemia may occur, requiring potassium supplementation. Care must be exercised in patients taking digoxin. d. Anemia: Normochromic, normocytic anemia caused by a reversible suppression of erythrocyte production may occur. This may be exacerbated in patients infected with HIV who are taking zidovudine. Fever Chills Kidney failure BP Hypotension Anemia e. Neurologic effects: Intrathecal administration can cause a variety of serious neurologic problems. f. Thrombophlebitis: Adding heparin to the infusion can alleviate this problem. Pharm 5th 3-21-11.indb 431 Figure 35.5 Adverse effects of amphotericin B. 3/21/11 2:28:37 PM 432 35. Antifungal Drugs B. Flucytosine NH2 F N H O Flucytosine + Amphotericin B 1. Mechanism of action: 5-FC enters fungal cells via a cytosinespecific permease, which is an enzyme not found in mammalian cells. 5-FC is then converted by a series of steps to 5-fluorodeoxyuridine 5'-monophosphate. This false nucleotide inhibits thymidylate synthase, thereby depriving the organism of thymidylic acid, an essential DNA component (Figure 35.6). The unnatural mononucleotide is further metabolized to a trinucleotide (5-fluorodeoxyuridine 5'-triphosphate) and is incorporated into fungal RNA, where it disrupts nucleic acid and protein synthesis. [Note: Amphotericin B increases cell permeability, allowing more 5-FC to penetrate the cell. Thus, 5-FC and amphotericin B are synergistic (Figure 35.7).] Permease FUNGAL CELL NH2 N O F N H Cytosine deaminase H2 O NH3 5-Flurouracil 2. Antifungal spectrum: 5-FC is fungistatic. It is effective in combination with itraconazole for treating chromoblastomycosis and in combination with amphotericin B for treating candidiasis and cryptococcosis. 5-FdUMP dUMP dTMP Thymidylate synthase Flucytosine [floo-SYE-toe-seen] (5-FC) is a synthetic pyrimidine antimetabolite that is oft en used in combination with amphotericin B. This combination of drugs is administered for the treatment of systemic mycoses and for meningitis caused by Cryptococcus neoformans and Candida albicans. DNA Decreased dTMP leads to inhibition of DNA synthesis and cell division. Figure 35.6 Mode of action of flucytosine. 5-FdUMP = 5-fluorodeoxyuridine 5'-monophosphate; dTMP = deoxythymidine 5'-monophosphate. Flucytosine 3. Resistance: Resistance due to decreased levels of any of the enzymes in the conversion of 5-FC to 5-fluorouracil (5-FU) and beyond or from increased synthesis of cytosine can develop during therapy. This is the primary reason that 5-FC is not used as a single antimycotic drug. The rate of emergence of resistant fungal cells is lower with a combination of 5-FC plus a second antifungal agent than it is with 5-FC alone. 4. Pharmacokinetics: 5-FC is well absorbed by the oral route. It distributes throughout the body water and penetrates well into the CSF. 5-FU is detectable in patients and is probably the result of metabolism of 5-FC by intestinal bacteria. Excretion of both the parent drug and its metabolites is by glomerular filtration, and the dose must be adjusted in patients with compromised renal function. 5. Adverse effects: 5-FC causes reversible neutropenia, thrombocytopenia, and dose-related bone marrow depression. Caution must be exercised in patients undergoing radiation or chemotherapy with drugs that depress bone marrow. Reversible hepatic dysfunction with elevation of serum transaminases and alkaline phosphatase may occur. Gastrointestinal disturbances, such as nausea, vomiting, and diarrhea, are common, and severe enterocolitis may also occur. [Note: Some of these adverse effects may be related to 5-FU formed by intestinal organisms from 5-FC.] C. Ketoconazole Amphotericin B Figure 35.7 Synergism between flucytosine and amphotericin B. Pharm 5th 3-21-11.indb 432 Ketoconazole [kee-toe-KON-a-zole] was the first orally active azole available for the treatment of systemic mycoses. 1. Mechanism of action: Azoles are predominantly fungistatic. They inhibit C-14 α-demethylase (a cytochrome P450 [CYP450] enzyme), thereby blocking the demethylation of lanosterol to ergosterol, the 3/21/11 2:28:39 PM II. Drugs For Subcutaneous And Systemic Mycotic Infections principal sterol of fungal membranes (Figure 35.8). This inhibition disrupts membrane structure and function, which, in turn, inhibits fungal cell growth. [Note: Unfortunately, as is often the case for the initial member of a class of drugs, the selectivity of ketoconazole toward its target is not as precise as those of later azoles. For example, in addition to blocking fungal ergosterol synthesis, the drug also inhibits human gonadal and adrenal steroid synthesis, leading to decreased testosterone and cortisol production. In addition, ketoconazole inhibits CYP450-dependent hepatic drug-metabolizing enzymes.] 2. Antifungal spectrum: Oral ketoconazole is active against many fungi, including Histoplasma, Blastomyces, Candida, and Coccidioides, but not aspergillus species. Itraconazole has largely replaced ketoconazole in the treatment of most mycoses because of its broader spectrum, greater potency, and fewer adverse effects. As a second-line drug, oral ketoconazole is a less-expensive alternative for the treatment of mucocutaneous candidiasis. However, strains of several fungal species that are resistant to ketoconazole have been identified. Topical ketoconazole is used to treat tinea corporis, tinea cruris, and tinea pedis caused by Trichophyton rubrum, Trichophyton mentagrophytes, and Epidermophyton floccosum. Also, topical ketoconazole is used to treat tinea versicolor caused by Malassezia furfur, cutaneous candidiasis caused by Candida species. It is also used topically in the treatment of seborrheic dermatitis and dandruff. 3. Resistance: This is becoming a significant clinical problem, particularly in the protracted therapy required for those with advanced HIV infection. Identified mechanisms of resistance include mutations in the C-14 α-demethylase gene, which cause decreased azole binding. Additionally, some strains of fungi have developed the ability to pump the azole out of the cell. 4. Pharmacokinetics: When ketoconazole is administered orally (Figure 35.9), it requires gastric acid for dissolution and is absorbed through the intestinal mucosa. Drugs that raise gastric pH, such as antacids, or that interfere with gastric acid secretion, such as H2-histamine– receptor blockers and proton-pump inhibitors, impair absorption. Administering acidifying agents, such as cola drinks, before taking the drug can improve absorption in patients with achlorhydria. Ketoconazole is extensively bound to plasma proteins. Although penetration into tissues is limited, it is effective in the treatment of histoplasmosis in lung, bone, skin, and soft tissues. The drug does not enter the CSF. Extensive metabolism occurs in the liver, and excretion is primarily through the bile. Levels of parent drug in the urine are too low to be effective against mycotic infections of the urinary tract. 433 Lanosterol Ketoconazole P450 C H3 Ergosterol Ergosterol Ergosterol Inhibition of ergosterol synthesis disrupts membrane function and increases permeability Figure 35.8 Mode of action of ketoconazole. Elimination via bile Ketoconazole Figure 35.9 Administration and fate of ketoconazole. 5. Adverse effects: In addition to allergies, dose-dependent gastrointestinal disturbances, including nausea, anorexia, and vomiting, are the most common adverse effects of ketoconazole treatment. Endocrine effects, such as gynecomastia, decreased libido, impotence, and menstrual irregularities, result from the blocking of androgen and adrenal steroid synthesis by ketoconazole. Transient increases in serum transaminases occur in 2 to 10 percent of patients receiving ketoconazole. Frank hepatitis occurs rarely, but requires Pharm 5th 3-21-11.indb 433 3/21/11 2:28:40 PM 434 35. Antifungal Drugs Cyclosporine Phenytoin Triazolam Warfarin Serum concentration increases Ketoconazole P450 Metabolites Figure 35.10 By inhibiting cytochrome P450, ketoconazole can potentiate the toxicities of other drugs. Ketoconazole Contraindicated Amphotericin B Figure 35.11 Ketoconazole and amphotericin B should not be used together. immediate cessation of ketoconazole treatment. [Note: Ketoconazole may accumulate in patients with hepatic dysfunction. Plasma concentrations of the drug should be monitored in these individuals.] 6. Drug interactions and contraindications: By inhibiting CYP450, ketoconazole can potentiate the toxicities of drugs such as cyclosporine, phenytoin, triazolam, and warfarin, among others (Figure 35.10). Rifampin, an inducer of the CYP450 system, can shorten the duration of action of ketoconazole and the other azoles. Drugs that decrease gastric acidity, such as H2-receptor blockers, antacids, proton-pump inhibitors, and sucralfate, can decrease absorption of ketoconazole. Ketoconazole and amphotericin B should not be used together, because the decrease in ergosterol in the fungal membrane reduces the fungicidal action of amphotericin B (Figure 35.11). Finally, ketoconazole is teratogenic in animals, and it should not be given during pregnancy. D. Fluconazole Fluconazole [floo-KON-a-zole] is a member of the triazole class of antifungal products. It is clinically important because of its lack of the endocrine side effects of ketoconazole and its excellent penetrability into the CSF of both normal and inflamed meninges. Fluconazole is employed prophylactically, with some success, for reducing fungal infections in recipients of bone marrow transplants. It inhibits the synthesis of fungal membrane ergosterol in the same manner as ketoconazole and is the drug of choice for Cryptococcus neoformans after therapy with amphotericin B, for most candidemias, and for coccidioidomycosis. Fluconazole is effective against most forms of mucocutaneous candidiasis. [Note: Treatment failures due to resistance have been reported in some HIVinfected patients.] Fluconazole is administered orally or intravenously. For the treatment of vaginal candidiasis, the dose is 150 mg as a single oral dose. Its absorption is excellent and, unlike that of ketoconazole, is not dependent on gastric acidity. Binding to plasma proteins is minimal. Unlike ketoconazole, fluconazole is poorly metabolized. The drug is excreted via the kidney, and doses must be reduced in patients with compromised renal function. The adverse effects caused by fluconazole treatment are less of a problem than those with ketoconazole. Fluconazole has no endocrinologic effects because it does not inhibit the CYP450 system responsible for the synthesis of androgens. However, it can inhibit the P450 cytochromes that metabolize other drugs listed in Figure 35.10. Nausea, vomiting, and rashes are a problem. There is a caution for patients with liver dysfunction. Fluconazole is teratogenic, as are other azoles, and should not be used in pregnancy. E. Itraconazole Itraconazole [it-ra-KON-a-zole] is an antifungal agent with a broad antifungal spectrum. Like fluconazole, it is a synthetic triazole and also lacks the endocrinologic side effects of ketoconazole. Its mechanism of action is the same as that of the other triazoles. Itraconazole is the drug of choice for the treatment of blastomycosis, sporotrichosis, paracoccidioidomycosis, and histoplasmosis. Unlike ketoconazole, it is effective in acquired immunodeficiency syndrome–associated histoplasmosis. Itraconazole is well absorbed orally, but it requires acid for dissolution. Food increases the bioavailability of some preparations. The drug is extensively bound to plasma proteins and distributes well throughout Pharm 5th 3-21-11.indb 434 3/21/11 2:28:42 PM II. Drugs For Subcutaneous And Systemic Mycotic Infections 435 most tissues, including bone and adipose tissues. However, therapeutic concentrations are not attained in the CSF. Like ketoconazole, itraconazole is extensively metabolized by the liver, but it does not inhibit androgen synthesis. Its major metabolite, hydroxyitraconazole, is biologically active, with a similar antifungal spectrum. Little of the parent drug appears in the urine, eliminating the need for dose reduction with renal failure. Adverse effects include nausea and vomiting, rash (especially in immunocompromised patients), hypokalemia, hypertension, edema, and headache. Itraconazole should be avoided in pregnancy. Itraconazole inhibits the metabolism of many drugs, including oral anticoagulants, statins, and quinidine. Inducers of the CYP450 system increase the metabolism of itraconazole. The capsules should not be taken by patients with evidence of ventricular dysfunction, such as congestive heart failure (CHF) or a history of CHF. F. Voriconazole Voriconazole [vor-i-KON-a-zole], a triazole, has the advantage of being a broad-spectrum antifungal agent. It is available for both IV and oral administration and is approximately 96 percent bioavailable. Voriconazole is approved for the treatment of invasive aspergillosis and has replaced amphotericin B as the treatment of choice for this indication. Voriconazole is also approved for treatment of serious infections caused by Scedosporium apiospermum and Fusarium species. Voriconazole penetrates tissues well, including the CNS. Elimination is primarily by metabolism through the CYP450 2C19, 2C9, and 3A4 enzymes. The significant number of drug interactions due to its metabolism through the various hepatic enzymes may limit its use. Side effects are similar to those of the other azoles. High trough concentrations are associated with visual and auditory hallucinations. G. Posaconazole Posaconazole [poe-sa-KONE-a-zole], a triazole, is a new oral, broadspectrum antifungal agent with a chemical structure similar to that of itraconazole. It was approved in 2006 to prevent Candida and Aspergillus infections in severely immunocompromised patients and for the treatment of oropharyngeal candidiasis. Due to its spectrum of activity, posaconazole could possibly be used in the treatment of fungal infections caused by Mucor species and other zygomycetes. To date, amphotericin B formulations are the only other antifungal agents available for treatment of zygomycete infections. Overall, posaconazole is relatively well tolerated. The most common side effects observed were gastrointestinal issues (nausea, vomiting, diarrhea, and abdominal pain) and headaches. Like other azoles, posaconazole can cause an elevation of the liver function tests, causing elevated serum levels of hepatic transaminases. Additionally, in patients who are receiving concomitant cyclosporine or tacrolimus for management of transplant rejection, rare cases of hemolytic uremic syndrome, thrombotic thrombocytopenic purpura, and pulmonary embolus have been reported. Due to its inhibition of CYP450 3A4 enzymes, posaconazole may increase the effect and toxicity of many drugs, including cyclosporine, tacrolimus, and sirolimus. Concomitant use of posaconazole with ergot alkaloids, pimozide, and quinidine is contraindicated. To be effective, posaconazole must be administered with a high fat meal. Posaconazole may be given two or four times daily for a total daily dose of 800 mg. Pharm 5th 3-21-11.indb 435 3/21/11 2:28:42 PM 436 35. Antifungal Drugs KETOCONAZOLE FLUCONAZOLE VORICONAZOLE POSACONAZOLE SPECTRUM Narrow Expanded Expanded Expanded ROUTE(S) OF ADMINISTRATION Oral Oral, IV Oral, IV Oral t1/2 (HOURS) 6–9 30 6–24 20–66 CSF PENETRATION No Yes Yes Yes RENAL EXCRETION No Yes No No INTERACTION WITH OTHER DRUGS Frequent Occasional Frequent Frequent INHIBITION OF MAMMALIAN STEROL SYNTHESIS Dose-dependent inhibitory effect No inhibition No inhibition No inhibition Figure 35.12 Summary of some azole fungistatic drugs. CSF = cerebrospinal fluid. Figures 35.12 and 35.13 summarize the azole antifungal agents. H. Echinocandins Echinocandins interfere with the synthesis of the fungal cell wall by inhibiting the synthesis of β(1,3)-D-glucan, leading to lysis and cell death. Caspofungin, micafungin, and anidulafungin are available for IV adminstration once daily. Micafungin does not require a loading dose. 1. Caspofungin: Caspofungin [kas-poh-FUN-jin] is the first approved member of the echinocandins class of antifungal drugs. Caspofungin has activity against Aspergillus and most Candida species, including those species resistant to azoles. Adverse effects include fever, rash, nausea, and phlebitis. Flushing occurs, which is probably due to the release of histamine from mast cells. The dose of caspofungin does not need to be adjusted in renal impairment but is warranted with moderate hepatic dysfunction. Concomitant administration of caspofungin with CYP450 enzyme inducers may require an increase in the daily dose administered. Caspofungin should not be coadministered with cyclosporine due to the high incidence of elevation of hepatic transaminases with concurrent use. Caspofungin is a second-line antifungal for those who have failed or cannot tolerate amphotericin B or an azole. 2. Micafungin and anidulafungin: Micafungin (mi-ka-FUN-gin) and anidulafungin (ay-nid-yoo-la-FUN-jin) are the newer members of the echinocandins class of antifungal drugs. Micafungin and anidulafungin have similar efficacy against Candida species, but the efficacy for treatment of other fungal infections has not been established. The dose of micafungin and anidulafungin does not need to be adjusted in renal impairment or mild-to-moderate hepatic dysfunction. No studies have been done with the use of micafungin in severe hepatic dysfunction, but andulafungin can be administered in this condition. Also, they are not substrates for CYP450 enzymes and do not have any associated drug interactions. III. DRUGS FOR CUTANEOUS MYCOTIC INFECTIONS Mold-like fungi that cause cutaneous skin infections are called dermatophytes or tinea. These tinea infections are classified by the site of their infec- Pharm 5th 3-21-11.indb 436 3/21/11 2:28:43 PM III. Drugs For Cutaneous Mycotic Infections INTERACTING DRUG 437 DRUG EFFECT ON DRUG EXPOSURE MAIN CLINICAL CONSEQUENCE OF INTERACTION Astemizole, bepridil, cisapride, halofantrine, pimozide, quinidine, sertindole, terfenadine Itraconazole, fluconazole, voriconazole, posaconazole* exposure to interacting drugs QT interval prolongation with risk of torsade de pointes Carbamazepine Voriconazole exposure to voriconazole Treatment failure of voriconazole Efavirenz Voriconazole exposure to voriconazole Treatment failure of voriconazole exposure to efavirenz Risk of efavirenz toxicity Ergot alkaloids Itraconazole, fluconazole, voriconazole, posaconazole* exposure to ergot alkaloid Ergotism Lovastatin, simvastatin Itraconazole exposure to HMGCoA reductase inhibitor Risk of rhabdomyolysis Midazolam, triazolam Itraconazole exposure to benzodiazepine Sleepiness Rifabutin Voriconazole exposure to voriconazole Treatment failure of voriconazole exposure to rifabutin Uveitis Rifampicin (rifampin) Voriconazole exposure to voriconazole Treatment failure of voriconazole High-dose ritonavir (400 mg twice daily) Voriconazole exposure to voriconazole Treatment failure of voriconazole Vincristine-vinblastine Itraconazole exposure to vinca alkaloids Neurotoxicity Sirolimus Voriconazole exposure to sirolimus Risk of sirolimus toxicity Figure 35.13 Major or life-threatening drug interactions of azole fungistatic drugs. indicates increased; indicates decreased. * Where an interaction has been reported for one triazole, the contraindication has been extended to all others. tion, such as tinea pedis, which refers to an infection of the feet. Common dermatomycoses, such as tinea infections that appear as rings or round red patches with clear centers, are often referred to as "ringworm." This is a misnomer, because fungi rather than worms cause the disease. The three different fungi that cause the majority of cutaneous infections are Trichophyton, Microsporum, and Epidermophyton. These pathogens have a high affinity for keratinized tissue such as skin, hair, and nails. The drugs used in the treatment of cutaneous mycoses are listed in Figure 35.1. A. Squalene epoxidase inhibitors These agents act by inhibiting squalene epoxidase, resulting in the blocking of the biosynthesis of ergosterol, an essential component of fungal cell membrane. 1. Terbinafine: Oral terbinafine [TER-bin-a-feen] is the drug of choice for treating dermatophytoses and, especially, onychomycoses (fungal infections of nails). It is better tolerated, requires shorter duration of therapy, and is more effective than either itraconazole or griseofulvin. Pharm 5th 3-21-11.indb 437 3/21/11 2:28:44 PM 438 35. Antifungal Drugs a. Mechanism of action: Terbinafine inhibits fungal squalene epoxidase, thereby decreasing the synthesis of ergosterol (Figure 35.14). This plus the accumulation of toxic amounts of squalene result in the death of the fungal cell. [Note: Significantly higher concentrations of terbinafine are needed to inhibit human squalene epoxidase, an enzyme required for the cholesterol synthetic pathway.] Fungal cell death Toxic products Toxic products Squalene Squalene epoxidase Terbinafine Naftifine Butenafine Ergosterol Ergosterol Ergosterol Fungal cell death Figure 35.14 Mode of action of squalene epoxidase inhibitors. Metabolites excreted in urine Terbinafine Figure 35.15 Administration and fate of terbinafine. b. Antifungal spectrum: The drug is primarily fungicidal. Topical terbinafine is active against Trichophyton rubrum and Trichophyton mentagrophytes . It may also be effective against Candida albicans, Epidermophyton floccosum, and Scopulariopsis brevicaulis, but the safety and efficacy in treating clinical infections due to these pathogens has not been established. Topical terbinafine 1% cream and solution are used to treat tinea pedis, tinea corporis, and tinea cruris. Therapy is prolonged (usually about 3 months) but considerably shorter than that with griseofulvin. c. Pharmacokinetics: Terbinafine is available for oral and topical administration, although its bioavailability is only 40 percent due to first-pass metabolism. Absorption is not significantly enhanced by food. Terbinafine is greater than 99 percent bound to plasma proteins. It is deposited in the skin, nails, and fat. Terbinafine accumulates in breast milk and should not be given to nursing mothers. A prolonged terminal half-life of 200 to 400 hours may reflect the slow release from these tissues. Oral terbinafine is extensively metabolized prior to urinary excretion (Figure 35.15). Patients with either moderate renal impairment or hepatic cirrhosis have reduced clearance. d. Adverse effects: The most common adverse effects from terbinafine are gastrointestinal disturbances (diarrhea, dyspepsia, and nausea), headache, and rash. Taste and visual disturbances have been reported as well as transient elevations in serum liver enzyme levels. All adverse effects resolve upon drug discontinuation. Rarely, terbinafine may cause hepatotoxicity and neutropenia. Although terbinafine is extensively metabolized, there does not seem to be a significant risk of reduced clearance of other drugs. Rifampin decreases blood levels of terbinafine, whereas cimetidine increases blood levels. 2. Naftifine: Naftifine [NAF-ti-feen] is active against Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans, and Epidermophyton floccosum. Naftifine 1% cream and gel is used for topical treatment of tinea corporis, tinea cruris, and tinea pedis. 3. Butenafine: Butenafine [byoo-TEN-a-feen] is active against Trichophyton rubrum, Trichophyton mentagrophytes, Trichophyton tonsurans, Epidermophyton floccosum, and Malassezia furfur. Butenafine 1% cream is used for topical treatment of tinea corporis, tinea cruris, interdigital tinea pedis, and tinea versicolor. B. Griseofulvin Griseofulvin [gris-e-oh-FUL-vin] has been largely replaced by oral terbinafine for the treatment of dermatophytic infections of the nails, although it is still used for ringworm and dermatophytosis of the skin Pharm 5th 3-21-11.indb 438 3/21/11 2:28:46 PM III. Drugs For Cutaneous Mycotic Infections and hair. Griseofulvin requires treatment of 6 to 12 months in duration. It is only fungistatic. Griseofulvin accumulates in newly synthesized, keratin-containing tissue, where it causes disruption of the mitotic spindle and inhibition of fungal mitosis (Figure 35.16). Duration of therapy is dependent on the rate of replacement of healthy skin and nails. Ultrafine crystalline preparations are absorbed adequately from the gastrointestinal tract, and absorption is enhanced by high-fat meals. Griseofulvin induces hepatic CYP450 activity (Figure 35.17). It also increases the rate of metabolism of a number of drugs, including anticoagulants. It may exacerbate intermittent porphyria. C. Nystatin Nystatin [nye-STAT-in] is a polyene antibiotic, and its structure, chemistry, mechanism of action, and resistance profile resemble those of amphotericin B. Its use is restricted to topical treatment of Candida infections because of its systemic toxicity. The drug is negligibly absorbed from the gastrointestinal tract, and it is never used parenterally. It is administered as an oral agent ("swish and swallow" or "swish and spit") for the topical treatment of oral candidiasis. Excretion in the feces is nearly quantitative. Adverse effects are rare because of its lack of absorption orally, but nausea and vomiting occasionally occur. D. Imidazoles Imidazoles are azole derivatives, which currently include butoconazole [byoo-toe-KON-a-zole], clotrimazole [kloe-TRIM-a-zole], econazole [e-KONE-a-zole], ketoconazole, miconazole [my-KON-a-zole], oxiconazole [oks-i-KON-a-zole], sertaconazole [ser-ta-KOE-na-zole], sulconazole [sul-KON-a-zole], terconazole [ter-KON-a-zole], and tioconazole [tye-ohKONE-a-zole]. As a class of topical agents, they have a wide range of activity against Epidermophyton, Microsporum, Trichophyton, Candida albicans, and Malassezia furfur, depending on the agent. Topical use is associated with contact dermatitis, vulvar irritation, and edema. Miconazole is a potent inhibitor of warfarin metabolism and has produced bleeding in warfarin-treated patients even when applied locally to the vaginal area. No significant difference in clinical outcomes is associated with any azole or nystatin in the treatment of vulvar candidiasis. 439 Magnifier1-art Griseofulvin Figure 35.16 Inhibition of mitosis by griseofulvin. Griseofulvin P450 P450 P450 Metabolite Figure 35.17 Induction of hepatic cytochrome P450 activity by griseofulvin. E. Ciclopirox Ciclopirox [sye-kloe-PEER-oks] inhibits the transport of essential elements in the fungal cell, disrupting the synthesis of DNA, RNA, and protein. Ciclopirox is active against Trichophyton rubrum, Trichophyton mentagrophytes, Epidermophyton floccosum, Microsporum canis, Candida albicans, and Malassezia furfur. Ciclopirox 1% shampoo is used for treatment of seborrheic dermatitis. Ciclopirox 0.77% gel is used for treatment of interdigital tinea pedis, tinea corporis, and seborrheic dermatitis. Ciclopirox 8% solution is used for treatment of onychomycosis of nails without lanula involvement. Ciclopirox 0.77% cream and suspension is used for treatment of dermatomycosis, candidiasis, and tinea versicolor. F. Tolnaftate Tolnaftate [tole-NAF-tate] distorts the hyphae and stunts mycelial growth in susceptible fungi. Tolnaftate is active against Epidermophyton, Microsporum, and Malassezia furfur. [Note: Tolnaftate is not effective against Candida.] Tolnaftate is used to treat tinea pedis, tinea cruris, and tinea corporis. It is available as a 1% solution, cream, and powder. Pharm 5th 3-21-11.indb 439 3/21/11 2:28:47 PM 440 35. Antifungal Drugs Study questions Choose the ONE best answer. 35.1 A 60-year-old female referred to a dermatologist by her primary care physician because of a painless, inflamed, erupting ulcer that has been on her right hand for two months. This patient works in her vegetable and herb garden daily and states that the lesion began as a small red papule. Despite 10 days of treatment with cephalexin, the papule has continued to enlarge. The dermatologist cultured the ulcer and the results demonstrated the patient has sporotrichosis, an infection caused by Sporothrix schenckii. What is the most appropriate therapy that should be recommended to treat the infection? Correct answer = C. Itraconazole is the drug of choice for treatment of sporotrichosis. Itraconazole is well absorbed orally, but requires an acid environment for dissolution. Flucytosine is a synthetic pyrimidine antimetabolite that is often used in combination with Amphotericin B for the treatment of systemic mycoses. Micafungin is an echinocandin antifungal agent that has efficacy against Candida species, yet effectiveness against other fungal infections has not been established. A. Flucytosine. B. Amphotericin B. C. Itraconazole. D. Micafungin. 35.2 A 47-year-old female is admitted to the hospital for treatment of a Candida infection. Upon obtaining a medical history from the patient, the practitioner learns that the patient has had a liver transplant and is taking cyclosporine, to avoid organ rejection. What intravenous antifungal agent would avoid any potential drug interactions or potential toxicities of concomitant administration with cyclosporine, yet provide an efficacious treatment for the Candida infection? Correct answer = C. Micafungin is efficacious against Candida species and does not have any drug interaction with cyclosporine. Caspofungin should not be administered with cyclosporine, due to the possible increase of serum concentration of caspofungin caused by cyclosporine. Azole antifungal agents, such as Voriconazole and Posoconazole, may decrease the metabolism of cyclosporine, therefore, concomitant administration is not recommended. A. Caspofungin. B. Voriconazole. C. Micafungin. D. Posoconazole. 35.3 A 22-year-old male has been treating his "athlete's foot" with an over-the-counter drug without much success. Upon examination, it is found that the nail bed of both great toes is infected. Which one of the following antifungal agents would be most appropriate for this patient? A. Caspofungin. B. Fluconazole. C. Griseofulvin. D. Nystatin. E. Terbinafine. Pharm 5th 3-21-11.indb 440 Correct answer = E. Terbinafine is the drug of choice for the treatment of dermatophytic infections. Because it is fungicidal, it requires a shorter course of therapy than does griseofulvin. Drug interactions are also not a problem with terbinafine. Dermatophytes may respond to fluconazole, but this drug is reserved for more serious systemic infections. Nystatin and caspofungin are not useful in the treatment of dermatophytic infections. 3/21/11 2:28:47 PM 36 Antiprotozoal Drugs I. OVERVIEW Protozoal infections are common among people in underdeveloped tropical and subtropical countries, where sanitary conditions, hygienic practices, and control of the vectors of transmission are inadequate. However, with increased world travel, protozoal diseases, such as malaria, amebiasis, leishmaniasis, trypanosomiasis, trichomoniasis, and giardiasis, are no longer confined to specific geographic locales. Because they are eukaryotes, the unicellular protozoal cells have metabolic processes closer to those of the human host than to prokaryotic bacterial pathogens. Therefore, protozoal diseases are less easily treated than bacterial infections, and many of the antiprotozoal drugs cause serious toxic effects in the host, particularly on cells showing high metabolic activity, such as neuronal, renal tubular, intestinal, and bone marrow stem cells. Most antiprotozoal agents have not proved to be safe for pregnant patients. Drugs used to treat protozoal infections are summarized in Figure 36.1. II. CHEMOTHERAPY FOR AMEBIASIS Amebiasis (also called amebic dysentery) is an infection of the intestinal tract caused by Entamoeba histolytica. The disease can be acute or chronic, with patients showing varying degrees of illness, from no symptoms to mild diarrhea to fulminating dysentery. The diagnosis is established by isolating E. histolytica from fresh feces. Therapy is aimed not only at the acutely ill patient but also at those who are asymptomatic carriers, because dormant E. histolytica may cause future infections in the carrier and be a potential source of infection for others. A. Life cycle of Entamoeba histolytica Entamoeba histolytica exists in two forms: cysts that can survive outside the body and labile but invasive trophozoites that do not persist outside the body. Cysts, ingested through feces-contaminated food or water, pass into the lumen of the intestine, where the trophozoites are liberated. The trophozoites multiply, and they either invade and ulcerate the mucosa of the large intestine or simply feed on intestinal bacteria. [Note: One strategy for treating luminal amebiasis is to add antibiotics, such as tetracycline, to the treatment regimen, resulting in a reduction in intestinal flora, the ameba's major food source.] The trophozoites within the intestine are slowly carried toward the rectum, where they return to the cyst form and are excreted in feces. Pharm 5th 3-21-11.indb 441 AMEBIASIS Chloroquine ARALEN Dehydroemetine DEHYDROEMETINE Emetine IPECAC SYRUP Iodoquinol YODOXIN Metronidazole FLAGYL Paromomycin HUMATIN Tinidazole TINDAMAX MALARIA Artemisinin ARTEMISININ Chloroquine ARALEN Mefloquine LARIAM Primaquine PHOSPHATE TABLETS Pyrimethamine DARAPRIM Quinine/Quinidine QUALAQUIN, QUINIDINE GLUCONATE TRYPANOSOMIASIS Benznidazole RADANIL Melarsoprol MELARSOPROL Nifurtimox NIFURTIMOX Pentamidine NEBUPENT Suramin GERMANIN LEISHMANIASIS Sodium stibogluconate SODIUM STIBOGLUCONATE TOXOPLASMOSIS Pyrimethamine DARAPRIM GIARDIASIS Metronidazole FLAGYL Nitazoxanide ALINIA Tinidazole TINDAMAX Figure 36.1 Summary of antiprotozoal agents. 3/21/11 2:28:47 PM 442 36. Antiprotozoal Drugs STOMACH Systemic amebicides 1 Chloroquine Dehydroemetine Emetine Ingestion of cysts ILEUM 4 of 3 Penetration intestinal wall 2 LIVER COLON Formation of trophozoites Cyst formation Multiplication of trophozoites within colon wall COLON WALL 5 Systemic invasion Mixed amebicide (luminal and systemic activity) Metronidazole Tinidazole Luminal amebicides Paromomycin Iodoquinol 6 Expelled trophozoite (noninfective) Cysts discarded with feces RECTUM Expelled cyst (infective) Figure 36.2 Life cycle of Entamoeba histolytica, showing the sites of action of amebicidal drugs. Large numbers of trophozoites within the colon wall can also lead to systemic invasion. A summary of the life cycle of E. histolytica is presented in Figure 36.2. B. Classification of amebicidal drugs Therapeutic agents are classified as luminal, systemic, or mixed (luminal and systemic) amebicides according to the site where the drug is effective (see Figure 36.2). For example, luminal amebicides act on the parasite in the lumen of the bowel, whereas systemic amebicides are effective against amebas in the intestinal wall and liver. Mixed amebicides are effective against both the luminal and systemic forms of the disease, although luminal concentrations are too low for single-drug treatment. C. Mixed amebicides (metronidazole and tinidazole) 1. Metronidazole: Metronidazole [me-troe-NYE-da-zole], a nitroimidazole, is the mixed amebicide of choice for treating amebic infections and kills the E. histolytica trophozoites. [Note: Metronidazole also finds extensive use in the treatment of infections caused by Giardia lamblia, Trichomonas vaginalis, anaerobic cocci, and anaerobic gramnegative bacilli (for example, Bacteroides species). Metronidazole is the drug of choice for the treatment of pseudomembranous colitis Pharm 5th 3-21-11.indb 442 3/21/11 2:28:48 PM II. Chemotherapy For Amebiasis caused by the anaerobic, gram-positive bacillus Clostridium difficile and is also effective in the treatment of brain abscesses caused by these organisms.] 443 Drug crosses the blood-brain barrier a. Mechanism of action: Some anaerobic protozoal parasites (including amebas) possess ferrodoxin-like, low-redox-potential, electron-transport proteins that participate in metabolic electron removal reactions. The nitro group of metronidazole is able to serve as an electron acceptor, forming reduced cytotoxic compounds that bind to proteins and DNA, resulting in cell death. b. Pharmacokinetics: Metronidazole is completely and rapidly absorbed after oral administration (Figure 36.3). [Note: For the treatment of amebiasis, it is usually administered with a luminal amebicide, such as iodoquinol or paromomycin. This combination provides cure rates of greater than 90 percent.] Metronidazole distributes well throughout body tissues and fluids. Therapeutic levels can be found in vaginal and seminal fluids, saliva, breast milk, and cerebrospinal fluid (CSF). Metabolism of the drug depends on hepatic oxidation of the metronidazole side chain by mixed-function oxidase, followed by glucuronylation. Therefore, concomitant treatment with inducers of this enzymatic system, such as phenobarbital, enhances the rate of metabolism. Conversely, those drugs that inhibit this system, such as cimetidine, prolong the plasma half-life of metronidazole. The drug accumulates in patients with severe hepatic disease. The parent drug and its metabolites are excreted in the urine. The drug and glucuronylated metabolites appear in urine Metronidazole Figure 36.3 Administration and fate of metronidazole. c. Adverse effects: The most common adverse effects are those associated with the gastrointestinal tract, including nausea, vomiting, epigastric distress, and abdominal cramps (Figure 36.4). An unpleasant, metallic taste is commonly experienced. Other effects include oral moniliasis (yeast infection of the mouth) and, rarely, neurotoxicologic problems, such as dizziness, vertigo, and numbness or paresthesias in the peripheral nervous system. [Note: The latter are reasons for discontinuing the drug.] If taken with alcohol, a disulfiram-like effect occurs (see p. 120). Nausea d. Resistance: Resistance to metronidazole is not a therapeutic problem, although strains of trichomonads resistant to the drug have been reported. 2. Tinidazole: Tinidazole [tye-NI-da-zole] is a second-generation nitroimidazole that is similar to metronidazole in spectrum of activity, absorption, adverse effects, and drug interactions. It was approved by the U.S. Food and Drug Administration in 2004 for treatment of amebiasis, amebic liver abcess, giardiasis, and trichomoniasis but was used outside the United States for decades prior to approval. Tinidazole is as effective as metronidazole, with a shorter course of treatment, yet is more expensive than generic metronidazole. After treatment of invasive intestinal or extraintestinal amebic disease is complete, a luminal agent, such as iodoquinol, diloxanide furoate, or paromomycin, should be administered for treatment of the asymptomatic colonization state. Pharm 5th 3-21-11.indb 443 Metallic taste ON E D. Luminal amebicides GI disturbance Figure 36.4 Adverse effects of metronidazole. 3/21/11 2:28:50 PM 444 36. Antiprotozoal Drugs 1. Iodoquinol: Iodoquinol [eye-oh-doe-QUIN-ole], a halogenated 8-hydroxy quinolone, is amebicidal against E. histolytica and is effective against the luminal trophozoite and cyst forms. Side effects from iodoquinol include rash, diarrhea, and dose-related peripheral neuropathy, including a rare optic neuritis. Long-term use of this drug should be avoided. 2. Paromomycin: Paromomycin [par-oh-moe-MYE-sin], an aminogly- coside antibiotic, is only effective against the intestinal (luminal) forms of E. histolytica and tapeworm, because it is not significantly absorbed from the gastrointestinal tract. It is an alternative agent for cryptosporidiosis. Paromomycin is directly amebicidal and also exerts its antiamebic actions by reducing the population of intestinal flora. Its direct amebicidal action is probably due to the effects it has on cell membranes, causing leakage. Very little of the drug is absorbed on oral ingestion, but that which is absorbed is excreted in urine. Gastrointestinal distress and diarrhea are the principal adverse effects. E. Systemic amebicides These drugs are useful for treating liver abscesses and intestinal wall infections caused by amebas. 1. Chloroquine: Chloroquine [KLOR-oh-kwin] is used in combination CLINICAL SYNDROME Asymptomatic cyst carriers Diarrhea/dysentery Extraintestinal Amebic liver absess DRUG Iodoquinol or paromomycin Metronidazole plus iodoquinol or paromomycin Chloroquine plus metronidazole and/or diloxanide furoate Figure 36.5 Some commonly used therapeutic options for the treatment of amebiasis. with metronidazole and diloxanide furoate to treat and prevent amebic liver abscesses. It eliminates trophozoites in liver abscesses, but it is not useful in treating luminal amebiasis. Chloroquine is also effective in the treatment of malaria. 2. Emetine and dehydroemetine: Emetine [EM-e-teen] and dehydroemetine [de-hye-dro-EM-e-teen] are alternative agents for the treat- ment of amebiasis. They inhibit protein synthesis by blocking chain elongation.1 Intramuscular injection is the preferred route. Emetine is concentrated in the liver, where it persists for a month after a single dose. It is slowly metabolized and excreted, and it can accumulate. Its half-life in plasma is 5 days. The use of these ipecac alkaloids is limited by their toxicities (dehydroemetine is less toxic than emetine), and close clinical observation is necessary when these drugs are administered. They should not be taken for more than 5 days. Dehydroemetine is only available under a compassionate investigational new drug protocol through the Centers of Disease Control and Prevention. Among the untoward effects are pain at the site of injection, transient nausea, cardiotoxicity (for example, arrhythmias and congestive heart failure), neuromuscular weakness, dizziness, and rashes. A summary of the treatment of amebiasis is shown in Figure 36.5. INFO LINK Pharm 5th 3-21-11.indb 444 1 See Chapter 31 in Lippincott's Illustrated Reviews: Biochemistary for a more detailed discussion of protein synthesis. 3/21/11 2:28:51 PM III. Chemotherapy For Malaria 445 III. CHEMOTHERAPY FOR MALARIA Malaria is an acute infectious disease caused by four species of the protozoal genus Plasmodium. The parasite is transmitted to humans through the bite of a female Anopheles mosquito, which thrives in humid, swampy areas. Plasmodium falciparum is the most dangerous species, causing an acute, rapidly fulminating disease that is characterized by persistent high fever, orthostatic hypotension, and massive erythrocytosis (an abnormal elevation in the number of red blood cells accompanied by swollen, reddish limbs). P. falciparum infection can lead to capillary obstruction and death if treatment is not instituted promptly. Plasmodium vivax causes a milder form of the disease. Plasmodium malariae is common to many tropical regions, but Plasmodium ovale is rarely encountered. Resistance acquired by the mosquito to insecticides, and by the parasite to drugs, has led to new therapeutic challenges, particularly in the treatment of P. falciparum. A. Life cycle of the malarial parasite When an infected mosquito bites, it injects Plasmodium sporozoites into the bloodstream (Figure 36.6). The sporozoites migrate through the blood to the liver, where they form cyst-like structures containing thousands of merozoites. [Note: Diagnosis depends on laboratory identification of the parasites in red blood cells of peripheral blood smears.] 1 Drug effective against gametocytic form: An infected mosquito injects sporozoites. Primaquine Sporozoites 7 Drug effective against exoerythrocytic form: Primaquine Infected mosquito The female mosquito picks up gametocytes from an infected human. The sexual cycle occurs in the mosquito, where sporozoites are formed. Female mosquito LIVER Liver cell 2 Sporozoites migrate to the liver, where they form merozoites. 6 Some merozoites become gametocytes. Gametocytes Merozoites Infection can also result from use of a bloodcontaminated needle Drugs effective against erythrocytic form: Artemisinin Chloroquine Quinine Mefloquine Pyrimethamine 3 Merozoites are released and invade red blood cells. 4 Red blood cell In the red blood cell, the merozoite becomes a trophozoite. Trophozoite 5 In the red blood cell, the trophozoite multiplies, producing new merozoites. These are released when the red blood cell ruptures, and they can infect other red blood cells. Schizont Figure 36.6 Life cycle of the malarial parasite, Plasmodium falciparum, showing the sites of action of antimalarial drugs. Pharm 5th 3-21-11.indb 445 3/21/11 2:28:52 PM 446 36. Antiprotozoal Drugs Upon release, each merozoite invades a red blood cell, becoming a trophozoite and using hemoglobin as a nutrient. The trophozoites multiply and become merozoites. Eventually, the infected cell ruptures, releasing heme and merozoites that can enter other erythrocytes. [Note: Alternatively, released merozoites can become gametocytes, which are picked up by mosquitoes from the blood they ingest. The cycle thus begins again, with the gametocytes becoming sporozoites in the insect.] The effectiveness of drug treatment is related to the particular species of infecting plasmodium and the stage of its life cycle that is targeted. A summary of the life cycle of the parasite and the sites of therapeutic interventions are presented in Figure 36.6. B. Tissue schizonticide: Primaquine Metabolites appear in urine Primaquine Figure 36.7 Administration and fate of primaquine. Glucose 6-P-dehydrogenase deficiency results in a decrease in NADPH and GSH synthesis, making the cell more sensitive to oxidative agents, such as primaquine. This causes hemolysis. Glucose 6-P dehydrogenase Glucose 6-P NADP + 2 GSH Ribose 5-P NADPH + H+ GSSG Primaquine oxidizes GSH to GSSG. Therefore, less GSH is available to neutralize toxic compounds. Figure 36.8 Mechanism of primaquine-induced hemolytic anemia. GSH = reduced glutathione; GSSG = oxidized glutathione; NADP+ = nicotinamide adenine dinucleotide phosphate; NADPH = reduced nicotinamide adenine dinucleotide phosphate. Pharm 5th 3-21-11.indb 446 Primaquine [PRIM-a-kwin] is an 8-aminoquinoline that eradicates primary exoerythrocytic forms of P. falciparum and P. vivax and the secondary exoerythrocytic forms of recurring malarias (P. vivax and P. ovale). [Note: Primaquine is the only agent that can lead to radical cures of the P. vivax and P. ovale malarias, which may remain in the liver in the exoerythrocytic form after the erythrocytic form of the disease is eliminated.] The sexual (gametocytic) forms of all four plasmodia are destroyed in the plasma or are prevented from maturing later in the mosquito, thereby interrupting transmission of the disease. [Note: Primaquine is not effective against the erythrocytic stage of malaria and, therefore, is often used in conjunction with a blood schizonticide, such as chloroquine, quinine, mefloquine, or pyrimethamine.] 1. Mechanism of action: This is not completely understood. Metabolites of primaquine are believed to act as oxidants that are responsible for the schizonticidal action as well as for the hemolysis and methemoglobinemia encountered as toxicities. 2. Pharmacokinetics: Primaquine is well absorbed on oral administration and is not concentrated in tissues. It is rapidly oxidized to many compounds, primarily the deaminated drug. Which compound possesses the schizontocidal activity has not been established. Metabolites appear in urine (Figure 36.7). 3. Adverse effects: Primaquine has a low incidence of adverse effects, except for drug-induced hemolytic anemia in patients with genetically low levels of glucose-6-phosphate dehydrogenase2 (Figure 36.8). Other toxic manifestations observed after large doses of the drug include abdominal discomfort, especially when administered in combination with chloroquine (which may affect patient compliance), and occasional methemoglobinemia. Granulocytopenia and agranulocytosis are rarely seen, except in patients with lupus or arthritis, because both conditions are aggravated by the drug. Primaquine is contraindicated during pregnancy. All Plasmodium species may develop resistance to primaquine. C. Blood schizonticide: Chloroquine Chloroquine [KLOR-oh-kwin] is a synthetic 4-aminoquinoline that has been the mainstay of antimalarial therapy, and it is the drug of choice INFO LINK 2See Chapter 13 in Lippincott's Illustrated Reviews: Biochemistry for a discussion of glucose-6-phosphate dehydrogenase deficiency. 3/21/11 2:28:55 PM III. Chemotherapy For Malaria 1 The parasite digests the host cell's hemoglobin to obtain essential amino acids. 2 The process releases large amounts of heme, which is toxic to the parasite. 447 3 To protect itself, the parasite ordinarily polymerizes the heme to nontoxic hemozoin, which is sequestered in the parasite's food vacuole. PLASMODIUM IN RED BLOOD CELL 4 Chloroquine prevents the polymerization to hemozoin. The accumulation of heme results in lysis of both the parasite and the red blood cell. Chloroquine Heme Hemoglobin Amino acids Hemozoin Accumulated heme Figure 36.9 Action of chloroquine on the formation of hemozoin by Plasmodium species. in the treatment of erythrocytic P. falciparum malaria, except in resistant strains. Chloroquine is less effective against P. vivax malaria. It is highly specific for the asexual form of plasmodia. Chloroquine is also effective in the treatment of extraintestinal amebiasis. [Note: The antiinflammatory action of chloroquine explains its occasional use in rheumatoid arthritis and discoid lupus erythematosus.] 1. Mechanism of action: Although a detailed explanation of the mechanisms by which chloroquine kills plasmodial parasites is still incomplete, the following processes are essential for the drug's lethal action (Figure 36.9). After traversing the erythrocytic and plasmodial membranes, chloroquine (a diprotic weak base) is concentrated in the organism's acidic food vacuole, primarily by ion trapping. It is in the food vacuole that the parasite digests the host cell's hemoglobin to obtain essential amino acids. However, this process also releases large amounts of soluble heme (ferriprotoporphyrin IX), which is toxic to the parasite. To protect itself, the parasite ordinarily polymerizes the heme to hemozoin (a pigment), which is sequestered in the parasite's food vacuole. Chloroquine specifically binds to heme, preventing its polymerization to hemozoin. The increased pH and the accumulation of heme result in oxidative damage to the membranes, leading to lysis of both the parasite and the red blood cell. The binding to heme and prevention of its polymerization appear to be a crucial step in the drug's antiplasmodial activity, which may represent a unifying mechanism for such diverse compounds as chloroquine, quinidine, and mefloquine. Drug crosses the blood-brain barrier The drug and metabolites appear in urine Chloroquine Figure 36.10 Administration and fate of chloroquine. 2. Pharmacokinetics: Chloroquine is rapidly and completely absorbed following oral administration. Usually, 4 days of therapy suffice to cure the disease. The drug has a very large volume of distribution and concentrates in erythrocytes, liver, spleen, kidney, lung, melanin-containing tissues, and leukocytes. It persists in erythrocytes (see "Mechanism of action" above). The drug also penetrates the central nervous system (CNS) and traverses the placenta. Chloroquine is dealkylated by the hepatic mixed-function oxidase system, but some metabolic products retain antimalarial activity. Both parent Pharm 5th 3-21-11.indb 447 3/21/11 2:29:03 PM 448 36. Antiprotozoal Drugs drug and metabolites are excreted predominantly in urine (Figure 36.10). The excretion rate is enhanced with acidified urine. GI disturbance Skin rash Headache Blurred vision Figure 36. 11 Some adverse effects commonly associated with chloroquine. 3. Adverse effects: Side effects are minimal at the low doses used in the chemosuppression of malaria. At higher doses, many more toxic effects occur, such as gastrointestinal upset, pruritus, headaches, and blurred vision (Figure 36.11). [Note: An ophthalmologic examination should be routinely performed.] Discoloration of the nail beds and mucous membranes may be seen on chronic administration. Chloroquine should be used cautiously in patients with hepatic dysfunction or severe gastrointestinal problems and in patients with neurologic or blood disorders. Chloroquine can cause electrocardiographic (ECG) changes, because it has a quinidine-like effect. It may also exacerbate dermatitis produced by gold or phenylbutazone therapy. [Note: Patients with psoriasis or porphyria should not be treated with chloroquine, because an acute attack may be provoked.] 4. Resistance: Resistance of plasmodia to available drugs has become a serious medical problem throughout Africa, Asia, and most areas of Central and South America. Chloroquine-resistant P. falciparum exhibit multigenic alterations that confer a high level of resistance. [Note: When a chloroquine-resistant organism is encountered, therapy usually consists of an orally administered combination of quinine, pyrimethamine, and a sulfonamide such as sulfadoxine.] D. Blood schizonticide: Mefloquine Mefloquine [MEF-lo-kween] appears to be promising as an effective single agent for suppressing and curing infections caused by multidrugresistant forms of P. falciparum. Its exact mechanism of action remains to be determined, but, like quinine, it can apparently damage the parasite's membrane. Resistant strains have been identified. Mefloquine is absorbed well after oral administration and concentrates in the liver and lung. It has a long half-life (17 days) because of its concentration in various tissues and its continuous circulation through the enterohepatic and enterogastric systems. The drug undergoes extensive metabolism. Its major excretory route is through the feces. Adverse reactions at high doses range from nausea, vomiting, and dizziness to disorientation, hallucinations, and depression. ECG abnormalities and cardiac arrest are possible if mefloquine is taken concurrently with quinine or quinidine. E. Blood schizonticides: Quinine Quinine [KWYE-nine] interferes with heme polymerization, resulting in death of the erythrocytic form of the plasmodial parasite. It is reserved for severe infestations and for malarial strains that are resistant to other agents such as chloroquine. Taken orally, quinine is well distributed throughout the body and can reach the fetus in pregnant patients. Alkalinization of urine decreases its excretion. The major adverse effect of quinine is cinchonism, a syndrome causing nausea, vomiting, tinnitus, and vertigo. These effects are reversible and are not considered to be reasons for suspending therapy. However, quinine treatment should be suspended if a positive Coombs test for hemolytic anemia occurs. Drug interactions include potentiation of neuromuscular-blocking agents and elevation of digoxin levels if taken concurrently with quinine. Quinine absorption is retarded when the drug is taken with aluminum-containing antacids. Quinine is fetotoxic. Pharm 5th 3-21-11.indb 448 3/21/11 2:29:09 PM IV. Chemotherapy For Trypanosomiasis F. Blood schizonticide: Artemisinin Artemisinin [ar-te-MIS-in-in] is derived from the qinghaosu plant, which has been used in Chinese medicine for more than 2 millennia in the treatment of fevers and malaria. Artemisinin (or one of its derivatives) is available for the treatment of severe, multidrug-resistant P. falciparum malaria. Its antimalarial action involves the production of free radicals within the plasmodium food vacuole, following cleavage of the drug's endoperoxide bridge by heme iron in parasitized erythrocytes. It is also believed to covalently bind to and damage specific malarial proteins. Oral, rectal, and intravenous (IV) preparations are available, but the short half-lives preclude their use in chemoprophylaxis. They are metabolized in the liver and are excreted primarily in bile. Adverse effects include nausea, vomiting, and diarrhea, but, overall, artemisinin is remarkably safe. Extremely high doses may cause neurotoxicity and prolongation of the QT interval. 449 All Plasmodium species except chloroquine-resistant P. falciparum Chloroquine Chloroquine-resistant P. falciparum Quinine plus: Pyrimethamine-sulfadoxine or doxycycline or clindamycin Alternate: Mefloquine Prevention of relapses: P. vivax and P. ovale only Primaquine Prevention of malaria Chloroquine-sensitive geographic areas Chloroquine G. Blood schizonticide and sporontocide: Pyrimethamine The antifolate agent pyrimethamine [peer-i-METH-a-meen] is frequently employed to effect a radical cure as a blood schizonticide. It also acts as a strong sporonticide in the mosquito's gut when the mosquito ingests it with the blood of the human host. Pyrimethamine inhibits plasmodial dihydrofolate reductase3 at much lower concentrations than those needed to inhibit the mammalian enzyme. The inhibition deprives the protozoan of tetrahydrofolate, a cofactor required in the de novo biosynthesis of purines and pyrimidines and in the interconversions of certain amino acids. Pyrimethamine alone is effective against P. falciparum. In combination with a sulfonamide, it is also used against P. malariae and Toxoplasma gondii. If megaloblastic anemia occurs with pyrimethamine treatment, it may be reversed with leucovorin. Figure 36.12 shows some therapeutic options in the treatment of malaria. IV. CHEMOTHERAPY FOR TRYPANOSOMIASIS Trypanosomiasis refers to African sleeping sickness and American sleeping sickness, two chronic and, eventually, fatal diseases caused by species of Trypanosoma (Figure 36.13). In African sleeping sickness, the causative organisms, T. brucei gambiense and T. brucei rhodiense, initially live and grow in the blood. The parasite invades the CNS, causing an inflammation of the brain and spinal cord that produces the characteristic lethargy and, eventually, continuous sleep. Chagas disease (American sleeping sickness) is caused by T. cruzi and occurs in South America. A. Melarsoprol Melarsoprol [mel-AR-so-prol] is a derivative of mersalyl oxide, a trivalent arsenical. Its use is limited to the treatment of trypanosomal infections (usually in the late stage with CNS involvement), and it is lethal to these parasites. 1. Mechanism of action: The drug reacts with sulfhydryl groups of various substances, including enzymes in both the organism and host. The parasite's enzymes may be more sensitive than those of the INFO LINK Pharm 5th 3-21-11.indb 449 3See Chapter 28 in Lippincott's Illustrated Reviews: Biochemistry for a discussion of dihydrofolate reductase. Chloroquine-resistant geographic areas Mefloquine In pregnancy Chloroquine or mefloquine Figure 36.12 Treatment and prevention of malaria. TRYPANOSOMIASIS AMERICAN: Caused by Trypanosoma cruzi • Causes cardiomyopathy • Common in infants Transmitted by insect • feces contaminating the • eye or a break in the skin Treated with nifurtimox AFRICAN: Caused by Trypanosoma brucei by the bite of the • Transmitted tsetse fly • Causes "sleeping sickness" Trypanosoma brucei gambiense to enter the CNS • Slow Suramin pentamidine are • used onlyandin the early stages of disease Trypanosoma brucei rhodesiense • Early invasion of the CNS • Usually fatal if not treated Melarsoprol used when • there is CNS involvement Figure 36.13 Summary of trypanosomiasis. CNS = central nervous system. 3/21/11 2:29:12 PM 450 36. Antiprotozoal Drugs host. There is evidence that mammalian cells may be less permeable to the drug and are protected from its toxic effects. Trypanosomal resistance may also be due to decreased permeability of the drug. Drug crosses the blood-brain barrier Slow IV Metabolites appear in urine Melarsoprol 2. Pharmacokinetics: Melarsoprol usually is slowly

administered intravenously through a fine needle, even though it is absorbed from the gastrointestinal tract. Because it is very irritating, care should be taken not to infiltrate surrounding tissue. Adequate trypanocidal concentrations appear in the CSF, whereas pentamidine does not penetrate the CSF. Melarsoprol is, therefore, the agent of choice in the treatment of T. brucei rhodesiense, which rapidly invades the CNS, as well as for meningoencephalitis caused by T. brucei gambiense. The host readily oxidizes melarsoprol to a relatively nontoxic, pentavalent arsenic compound. The drug has a very short half-life and is rapidly excreted in urine (Figure 36.14). 3. Adverse effects: CNS toxicities are the most serious side effects of melarsoprol treatment. Encephalopathy may appear soon after the first course of treatment but usually subsides. In rare cases, however, it may be fatal. Hypersensitivity reactions may also occur, and fever may follow injection. Gastrointestinal disturbances, such as severe vomiting and abdominal pain, can be minimized if the patient is in the fasting state during drug administration and for several hours thereafter. Melarsoprol is contraindicated in patients with influenza. Hemolytic anemia has been seen in patients with glucose-6-phosphate dehydrogenase deficiency. Figure 36.14 Administration and fate of melarsoprol. B. Pentamidine isethionate Poor penetration into the CNS IM Drug appears slowly in urine Pentamidine Figure 36.15 Administration and fate of pentamidine. CNS = central nervous system; IM = intramuscular. Pentamidine [pen-TAM-i-deen] is active against a variety of protozoal infections, including many trypanosomes such as T. brucei gambiense, for which pentamidine is used to treat and prevent the organism's hematologic stage. However, some trypanosomes, including T. cruzi, are resistant. Pentamidine is also effective in the treatment of systemic blastomycosis (caused by the fungus Blastomyces dermatitidis) and in treating infections caused by Pneumocystis jiroveci (formerly called Pneumocystis carinii, the name now used to refer to the organism in animals). [Note: It is now considered to be a fungus, but it is not susceptible to antifungal drugs. Trimethoprim-sulfamethoxazole is preferred in the treatment of P. jiroveci infections. However, pentamidine is an alternative in treating patients with pneumonia caused by P. jiroveci who have failed to respond to trimethoprim-sulfamethoxazole. The drug is also used in treating P. jiroveci–infected individuals who are allergic to sulfonamides. Because of the increased incidence of pneumonia caused by this organism in immunocompromised patients, such as those infected with human immunodeficiency virus, pentamidine has assumed an important place in chemotherapy.] Pentamidine is also an alternative drug to stibogluconate in the treatment of leishmaniasis. 1. Mechanism of action: T. brucei concentrates pentamidine by an energy-dependent, high-affinity uptake system. [Note: Resistance is associated with inability to concentrate the drug.] Although its mechanism of action has not been defined, evidence exists that the drug binds to the parasite's DNA and interferes with its synthesis of RNA, DNA, phospholipid, and protein. 2. Pharmacokinetics: Fresh solutions of pentamidine are administered intramuscularly or as an aerosol (Figure 36.15). [Note: The IV route is Pharm 5th 3-21-11.indb 450 3/21/11 2:29:14 PM IV. Chemotherapy For Trypanosomiasis avoided because of severe adverse reactions, such as a sharp fall in blood pressure and tachycardia.] The drug is concentrated and stored in the liver and kidney for a long period of time. Because it does not enter the CSF, it is ineffective against the meningoencephalitic stage of trypanosomiasis. The drug is not metabolized, and it is excreted very slowly into the urine. Its half-life in the plasma is about 5 days. 451 Trypanosoma cruzi Human cell 3. Adverse effects: Serious renal dysfunction may occur, which reverses on discontinuation of the drug. Other adverse reactions are hypotension, dizziness, rash, and toxicity to β cells of the pancreas. C. Nifurtimox Nifurtimox [nye-FER-tim-oks] has found use only in the treatment of acute T. cruzi infections (Chagas disease), although treatment of the chronic stage of such infections has led to variable results. [Note: Nifurtimox is suppressive, not curative.] Being a nitroaromatic compound, nifurtimox undergoes reduction and eventually generates intracellular oxygen radicals, such as superoxide radicals and hydrogen peroxide4 (Figure 36.16). These highly reactive radicals are toxic to T. cruzi, which lacks catalase.5 [Note: Mammalian cells are partially protected from such substances by the presence of enzymes, such as catalase, glutathione peroxidase, and superoxide dismutase.] Nifurtimox is administered orally and is rapidly absorbed and metabolized to unidentified products that are excreted in the urine. Adverse effects are common following chronic administration, particularly among the elderly. Major toxicities include immediate hypersensitivity reactions such as anaphylaxis; delayed hypersensitivity reactions, such as dermatitis and icterus; and gastrointestinal problems that may be severe enough to cause weight loss. Peripheral neuropathy is relatively common, and disturbances in the CNS may also occur. In addition, cell-mediated immune reactions may be suppressed. In Trypanosoma cruzi Nifurtimox O_2^- H_2O_2 OHReactive oxygen intermediates Cell death In human cells Nifurtimox D. Suramin Suramin [SOO-ra-min] is used primarily in the early treatment and, especially, the prophylaxis of African trypanosomiasis. It is very reactive and inhibits many enzymes, among them those involved in energy metabolism (for example, glycerol phosphate dehydrogenase6), which appears to be the mechanism most closely correlated with trypanocidal activity. The drug must be injected intravenously. It binds to plasma proteins and remains in the plasma for a long time, accumulating in the liver and in the proximal tubular cells of the kidney. The severity of the adverse reactions demands that the patient be carefully followed, especially if he or she is debilitated. Although infrequent, adverse reactions include nausea and vomiting (which cause further debilitation of the patient); shock and loss of consciousness; acute urticaria; and neurologic problems, including paresthesia, photophobia, palpebral edema (edema of the eyelids), and hyperesthesia of the hands and feet. Albuminuria O_2^- H_2O_2 OH^- Reactive oxygen intermediates Superoxide dismutase Catalase Glutathione peroxidase H_2O Figure 36.16 Generation of toxic intermediates by nifurtimox. 4See Chapter 13 in Lippincott's Illustrated Reviews: Biochemistry for a discussion of reactive oxygen intermediates. INFO LINK 5See Chapter 13 in Lippincott's Illustrated Reviews: Biochemistry for a discussion of catalase. 6See Chapter 16 in Lippincott's Illustrated Reviews: Biochemistry for a discussion of glycerol phosphate dehydrogenase. Pharm 5th 3-21-11.indb 451 3/21/11 2:29:16 PM 452 36. Antiprotozoal Drugs tends to be common, but when cylindruria (the presence of renal casts in the urine) and hematuria occur, treatment should cease. E. Benznidazole Benznidazole [benz-NI-da-zole] is a nitroimidazole derivative that inhibits protein and RNA synthesis in T. cruzi cells. It is an alternative choice for treatment of acute and indeterminate phases of Chagas disease, but therapy with benznidazole does not offer any significant efficacy or toxicity advantages over that with nifurtimox. However, benznidazole is recommended as prophylaxis for preventing infections caused by T. cruzi among hematopoietic stem cell transplant recipients because treatment in potential donors is not always effective. V. CHEMOTHERAPY FOR LEISHMANIASIS IV There are three types of leishmaniasis: cutaneous, mucocutaneous, and visceral. [Note: In the visceral type (liver and spleen), the parasite is in the bloodstream and can cause very serious problems.] Leishmaniasis is transmitted from animals to humans (and between humans) by the bite of infected sandflies. The diagnosis is established by demonstrating the parasite in biopsy material and skin lesions. The treatments of leishmaniasis and trypanosomiasis are difficult, because the effective drugs are limited by their toxicities and failure rates. Pentavalent antimonials, such as sodium stibogluconate, are the conventional therapy used in the treatment of leishmaniasis, with pentamidine and amphotericin B as backup agents. Allopurinol has also been reported to be effective (it is converted to a toxic metabolite by the amastigote form7 of the organism). A. Life cycle of the causative organism: Leishmania species Drug is excreted in urine Stibogluconate Figure 36.17 Administration and fate of stibogluconate. The sandfly transfers the flagellated promastigote form of the protozoa, which is rapidly phagocytized by macrophages. In the macrophage, the promastigotes rapidly change to nonflagellated amastigotes and multiply, killing the cell. The newly released amastigotes are again phagocytized, and the cycle continues. B. Sodium stibogluconate Sodium stibogluconate [stib-o-GLOO-koe-nate] is not effective in vitro. Therefore, it has been proposed that reduction to the trivalent antimonial compound is essential for activity. The exact mechanism of action has not been determined. Evidence for inhibition of glycolysis in the parasite at the phosphofructokinase reaction8 has been found. Because it is not absorbed on oral administration, sodium stibogluconate must be administered parenterally, and it is distributed in the extravascular compartment. Metabolism is minimal, and the drug is excreted in urine (Figure 36.17). Adverse effects include pain at the injection site, gastro7See Chapter 21 in Lippincott's Illustrated Reviews: Microbiology for a INFO LINK discussion of leishmaniasis. 8See Chapter 8 in Lippincott's Illustrated Reviews: Biochemistry for a discussion of phosphofructokinase reaction. Pharm 5th 3-21-11.indb 452 3/21/11 2:29:17 PM VI. Chemotherapy For Toxoplasmosis intestinal upsets, and cardiac arrhythmias. Renal and hepatic function should be monitored periodically. VI. CHEMOTHERAPY FOR TOXOPLASMOSIS One of the most common infections in humans is caused by the protozoan Toxoplasma gondii, which is transmitted to humans when they consume raw or inadequately cooked infected meat.9 An infected pregnant woman can transmit the organism to her fetus. Cats are the only animals that shed oocysts, which can infect other animals as well as humans. The treatment of choice for this condition is a combination of sulfadiazine and pyrimethamine. Leucovorin is commonly administered to protect against folate deficiency. Other inhibitors of folate biosynthesis, such as trimethoprim and sulfamethoxazole, are without therapeutic efficacy in toxoplasmosis. [Note: At the first appearance of a rash, pyrimethamine should be discontinued, because hypersensitivity to this drug can be severe.] 453 Both cysts and trophozoites can be found in feces. Infection occurs by the ingestion of cysts in contaminated water or food, or by the fecal–oral route (via hands or fomites). VII. CHEMOTHERAPY FOR GIARDIASIS Giardia lamblia is the most commonly diagnosed intestinal parasite in the United States.10 It has only two life-cycle stages: the binucleate trophozoite with four flagellae and the drug-resistant, four-nucleate cyst (Figure 36.18). Ingestion, usually from contaminated drinking water, leads to infection. The trophozoites exist in the small intestine and divide by binary fission. Occasionally, cysts are formed that pass out in stools. Although some infections are asymptomatic, severe diarrhea can occur, which can be very serious in immune-suppressed patients. The treatment of choice is metronidazole for 5 days. One alternative agent is tinidazole, which is equally effective as metronidazole in the treatment of giardiasis but with a much shorter course of therapy (2 grams given once). Nitazoxanide [nye-ta-ZOXa-nide], a nitrothiazole derivative structurally similar to aspirin, was recently approved for the treatment of giardiasis. Nitazoxanide is also equally efficacious as metronidazole and, in comparison, has a two-day-shorter course of therapy. In the small intestine, excystation releases trophozoites. Trophozoites multiply in the lumen of the proximal small bowel, where they can be free or attached to the mucosa by a sucking disk. Encystation occurs as the parasites move toward the colon. Figure 36.18 Life cycle of Giardia lamblia. 9 INFO LINK Pharm 5th 3-21-11.indb 453 See Chapter 21 in Lippincott's Illustrated Reviews: Microbiology for a discussion of toxoplasmosis. See Chapter 21 in Lippincott's Illustrated Reviews: Microbiology for a discussion of giardiasis. 10 3/21/11 2:29:18 PM 454 36. Antiprotozoal Drugs Study Questions Choose the ONE best answer. 36.1 A 36-year-old male of Lebanese ancestry is being treated for Plasmodium vivax malaria. He experiences severe fatigue, back pain, and darkened urine. Which one of the following antimalarial drugs is most likely to have caused his symptoms? A. Pyrimethamine. B. Artemisinin. C. Chloroquine. D. Quinine. E. Primaquine. 36.2 Tinnitus, dizziness, blurred vision, and headache are indicative of toxicity to which one of the following antimalarial drugs? A. Primaquine. B. Quinine. C. Pyrimethamine. D. Chloroquine. E. Sulfadoxine. 36.3 Which of the following drugs is recommended for the treatment of severe, multidrug-resistant Plasmodium falciparum malaria? A. Artemisinin. B. Chloroquine. C. Quinine. D. Sodium stibogluconate. E. Primaquine. 36.4 A 22-year-old man, who frequently backpacks, complains of diarrhea and fatigue. Examination of stool specimens shows binucleate organisms with four flagellae. Which one of the following drugs would be effective in treating this patient's infestation? A. Metronidazole. B. Quinidine. C. Pentamidine. D. Sulfadoxine. E. Stibogluconate. 36 Antiprotozoal 5-16-11#.indd 454 Correct answer = E. The symptoms presented by the patient are consistent with hemolytic anemia. The patient is male and from the Mediterranean basin, both of which are factors associated with glucose 6-phosphate dehydrogenase deficiency. Primaquine is the most likely drug among those listed to cause hemolytic anemia in such individuals. Correct answer = B. The symptoms are characteristic of cinchonism, which is characteristic of quinine or quinidine. The other drugs do not cause this constellation of symptoms. Correct answer = A. Artemisinin is the antimalarial drug recommended for life-threatening, multi drug-resistant Plasmodium falciparum malaria. The parasite is resistant to chloroquine and quinine and would not be affected by primaquine or stibogluconate. Correct answer = A. The patient has giardiasis, and metronidazole is the drug of choice for this intestinal protozoal infection. He probably was infected by drinking contaminated water from a stream. The other drugs are not effective against giardia. 5/16/11 12:50:58 PM Anthelmintic Drugs 37 I. OVERVIEW CHEMOTHERAPY OF HELMINTIC INFECTIONS: FOR NEMATODES Three major groups of helminths (worms), nematodes, trematod, and cestodes, infect humans. As in all antibiotic regimens, the anthelmintic drugs (Figure 37.1) are aimed at metabolic targets that are present in the parasite but are either absent from or have different characteristics than those of the host. Figure 37.2 illustrates the high incidence of helmintic infections. Diethylcarbamazine BANOCIDE Ivermectin STROMECTOL Mebendazole VERMOX Pyrantel pamoate NEMEX Thiabendazole MINTEZOL II. DRUGS FOR THE TREATMENT OF NEMATODES Praziquantel BILTRICIDE Nematodes are elongated roundworms that possess a complete digestive system, including both a mouth and an anus. They cause infections of the intestine as well as the blood and tissues. CHEMOTHERAPY OF HELMINTIC INFECTIONS: FOR TREMATODES CHEMOTHERAPY OF HELMINTIC INFECTIONS: FOR CESTODES Albendazole ALBENZA Niclosamide NICLOCIDE A. Mebendazole Mebendazole [me-BEN-da-zole], a synthetic benzimidazole compound, is effective against a wide spectrum of nematodes. It is a drug of choice in the treatment of infections by whipworm (Trichuris trichiura), pinworm (Enterobius vermicularis), hookworms (Necator americanus and Ancylostoma duodenale), and roundworm (Ascaris lumbricoides). Mebendazole acts by binding to and interfering with the assembly of the parasites' microtubules and also by decreasing glucose uptake. Affected parasites are expelled with feces. Mebendazole is nearly insoluble in aqueous solution. Little of an oral dose (that is chewed) is absorbed, unless it is taken with a high-fat meal. It undergoes first-pass metabolism to inactive compounds. Mebendazole is relatively free of toxic effects, although patients may complain of abdominal pain and diarrhea. It is, however, contraindicated in pregnant women (Figure 37.3), because it has been shown to be embryotoxic and teratogenic in experimental animals. Figure 37.1 Summary of anthelmintic agents. B. Pyrantel pamoate Pyrantel pamoate [pi-RAN-tel PAM-oh-ate], along with mebendazole, is effective in the treatment of infections caused by roundworms, pinworms, and hookworms (Figure 37.4). Pyrantel pamoate is poorly absorbed orally and exerts its effects in the intestinal tract. It acts as a depolarizing, neuromuscular-blocking agent, causing persistent activation of the parasite's nicotinic receptors. The paralyzed worm is then expelled from the host's intestinal tract. Adverse effects are mild and include nausea, vomiting, and diarrhea. Pharm 5th 3-21-11.indb 455 3/21/11 2:29:19 PM 456 37. Anthelmintic Drugs Infections (percentage of world population) 0 10 0 5 20 30 Trichinella Strongyloides Tapeworms Schistosomes Enterobius Filarias Trichuris Hookworms Ascaris Nematode 10 Infections (100 millions) Trematode Cestode Figure 37.2 Relative incidence of helminth infections worldwide. Albendazole Ivermectin Mebendazole 15 C. Thiabendazole Thiabendazole [thye-a-BEN-da-zole], another synthetic benzimidazole, is effective against strongyloidiasis caused by Strongyloides stercoralis (threadworm), cutaneous larva migrans, and early stages of trichinosis (caused by Trichinella spiralis; see Figure 37.4). Thiabendazole, like the other benzimidazoles, affects microtubular aggregation. Although nearly insoluble in water, the drug is readily absorbed on oral administration. It is hydroxylated in the liver and excreted in urine. The adverse effects most often encountered are dizziness, anorexia, nausea, and vomiting. There have been reports of central nervous system (CNS) symptomatology. There have been a number of fatalities among the cases of erythema multiforme and Stevens-Johnson syndrome reportedly caused by thiabendazole. Its use is contraindicated during pregnancy. D. Ivermectin Ivermectin [eye-ver-MEK-tin] is the drug of choice for the treatment of onchocerciasis (river blindness) caused by Onchocerca volvulus and for cutaneous larva migrans and strongyloidiasis. Ivermectin targets the parasite's glutamate-gated chloride channel receptors. Chloride influx is enhanced, and hyperpolarization occurs, resulting in paralysis of the worm. The drug is given orally. It does not cross the blood-brain barrier and has no pharmacologic effects in the CNS. However, it is contraindicated in patients with meningitis, because their blood-brain barrier is more permeable, making CNS effects possible. Ivermectin is also contraindicated in pregnancy (see Figure 37.3). The killing of the microfilaria can result in a Mazotti-like reaction (fever, headache, dizziness, somnolence, and hypotension). E. Diethylcarbamazine Contraindicated in pregnancy Contraindicated in pregnancy Figure 37.3 Albendazole, ivermectin, and mebendazole are contraindicated in pregnancy. Diethylcarbamazine [dye-eth-il-kar-BAM-a-zeen] is used in the treatment of filariasis because of its ability to immobilize microfilariae and render them susceptible to host defense mechanisms. Combined with albendazole, diethylcarbamazine is effective in the treatment of Wuchereria bancrofti and Brugia malayi infections. It is rapidly absorbed following oral administration with meals and is excreted primarily in urine. Urinary alkalosis and renal impairment may require dosage reduction. Adverse effects are primarily caused by host reactions to the killed organisms. Symptoms include fever, malaise, rash, myalgias, arthralgias, and headache, and their severity is related to parasite load. Most patients have leukocytosis. Antihistamines or steroids may be given to ameliorate many of the symptoms. Figure 37.4 summarizes the major infections caused by nematodes and the common therapies for them. III. DRUGS FOR THE TREATMENT OF TREMATODES The trematodes (flukes) are leaf-shaped flatworms that are generally characterized by the tissues they infect. For example, they may be categorized as liver, lung, intestinal, or blood flukes (Figure 37.5). A. Praziquantel Trematode infections are generally treated with praziquantel [prayzi-KWON-tel]. This drug is an agent of choice for the treatment of all forms of schistosomiasis and other trematode infections and for cestode infections like cysticercosis. Permeability of the cell membrane to Pharm 5th 3-21-11.indb 456 3/21/11 2:29:20 PM III. Drugs For The Treatment Of Trematodes 457 ONCHOCERCIASIS (RIVER BLINDNESS) Causative agent: Onchocerca volvulus. Common in areas of Mexico, South America, and tropical Africa. Characterized by subcutaneous nodules, a pruritic skin rash, and ocular lesions often resulting in blindness. Therapy: Ivermectin. TRICHURIASIS (WHIPWORM DISEASE) Causative agent: Trichuris trichiura. Infection is usually asymptomatic; however, abdominal pain, diarrhea, and flatulence can occur. Therapy: Mebendazole. ENTEROBIASIS (PINWORM DISEASE) Causative agent: Enterobius vermicularis. Most commmon helminthic infection in the United States. Pruritus ani occurs, with white worms visible in stools or perianal region. Therapy: Mebendazole or pyrantel pamoate. HOOKWORM DISEASE Causative agents: Ancylostoma duodenale (Old World hookworm), Necator americanus (New World hookworm). Worm attaches to the intestinal mucosa, causing anorexia, ulcer-like symptoms, and chronic intestinal blood loss that leads to anemia. ASCARIASIS (ROUNDWORM DISEASE) Causative agent: Ascaris lumbricoides. Treatment is unnecessary in asymptomatic individuals who are not anemic. Therapy: Pyrantel pamoate or mebendazole. Second only to pinworms as the most prevalent multicellular parasite in the United States; approximately one third of the world's population is infected with this worm. STRONGYLOIDIASIS (THREADWORM DISEASE) Ingested larvae grow in the intestine, causing abdominal symptoms, including intestinal obstruction; roundworms may pass to blood and infect the lungs. Causative agent: Strongyloides stercoralis. Relatively uncommon compared with other intestinal nematodes; a relatively benign disease in normal individuals that can progress to a fatal outcome in immunocompromised patients. Therapy: Pyrantel pamoate or mebendazole. Therapy: Thiabendazole or ivermectin. FILARIASIS Causative agents: Wuchereria bancrofti, Brugia malayi. Worms cause blockage of lymph flow. Ultimately, local inflammation and fibrosis of the lymphatics occurs. After years of infestation, the arms, legs, and scrotum fill with fluid, causing elephantiasis. Therapy: A combination of diethylcarbamazine and albendazole. TRICHINOSIS Causative agent: Trichinella spiralis. Usually caused by consumption of insufficiently cooked meat, especially pork. Therapy: Thiabendazole (only in the early stages of disease). Figure 37.4 Characteristics of and therapy for commonly encountered nematode infections. Pharm 5th 3-21-11.indb 457 3/21/11 2:29:36 PM 458 37. Anthelmintic Drugs calcium is increased, causing contracture and paralysis of the parasite. Praziquantel is rapidly absorbed after oral administration and distributes into the cerebrospinal fluid. High levels occur in bile. The drug is extensively metabolized oxidatively, resulting in a short half-life. The metabolites are inactive and are excreted through urine and bile. Common adverse effects include drowsiness, dizziness, malaise, and anorexia as well as gastrointestinal upsets. The drug is not recommended for pregnant women or nursing mothers. Drug interactions due to increased metabolism have been reported with dexamethasone, phenytoin, and carbamazepine. Cimetidine, which inhibits cytochrome P450 isozymes, causes increased praziquantel levels. Praziquantel is contraindicated for the treatment of ocular cysticercosis, because destruction of the organism in the eye may damage the organ. IV. DRUGS FOR THE TREATMENT OF CESTODES The cestodes, or "true tapeworms," typically have a flat, segmented body and attach to the host's intestine (Figure 37.6). Like the trematodes, the tapeworms lack a mouth and a digestive tract throughout their life cycle. Schistosomiasis (New World) This disease is caused by Schistosoma • mansoni and Schistosoma japonicum. The Paragonimiasis This disease is caused by Paragonimus • westermani (lung fluke). The organisms primary site of infection is the gastrointestinal tract. Damage to the intestinal wall is caused by the host's inflammatory response to eggs deposited at that site. The eggs also secrete proteolytic enzymes that further damage the tissue. move from the gastrointestinal tract to the lung, which is the primary site of damage. Secondary bacterial infections can result in a cough that produces bloody sputum. Clinical presentation includes GI bleeding, • diarrhea, and liver damage. The disease is transmitted by direct skin • penetration. form of schistosomiasis is diagnosed • byThisidentification of characteristic eggs in The disease is transmitted by eating • raw crab meat. Paragonimiasis is diagnosed by • identifying eggs in the sputum and stool. • Therapy: Praziquantel. Clonorchiasis This disease is caused by Clonorchis • sinensis (Oriental liver fluke). The primary site of infection is the biliary tract, where the resulting inflammatory response can cause fibrosis and hyperplasia. The disease is transmitted by eating • raw freshwater fish. Clonorchiasis is diagnosed by • identifying eggs in the stool. • Therapy: Praziquantel. the stool. Schistosomiasis (Old World) This disease is caused by Schistosoma • haematobium. The primary sites of infection are veins of the urinary bladder, where the organism's eggs can induce fibrosis, granulomas, and hematuria. The disease is transmitted by direct skin • penetration. form of schistosomiasis is diagnosed • byThisidentifying characteristic eggs in the urine or bladder wall. • Therapy: Praziquantel. Figure 37.5 Characteristics of and therapy for commonly encountered trematode infections. Pharm 5th 3-21-11.indb 458 3/21/11 2:29:47 PM IV. Drugs For The Treatment Of Cestodes 459 A. Niclosamide Niclosamide [ni-KLOE-sa-mide] is the drug of choice for most cestode (tapeworm) infections. Its action has been ascribed to inhibition of the parasite's mitochondrial phosphorylation of adenosine diphosphate, which produces usable energy in the form of adenosine triphosphate. Anaerobic metabolism may also be inhibited. The drug is lethal for the cestode's scolex and segments of cestodes but not for the ova. A laxative is administered prior to oral administration of niclosamide. This is done to purge the bowel of all dead segments and so preclude digestion and liberation of the ova, which may lead to cysticercosis. Alcohol should be avoided within 1 day of niclosamide. B. Albendazole Albendazole [al-BEN-da-zole] is a benzimidazole that, like the others, inhibits microtubule synthesis and glucose uptake in nematodes. Its primary therapeutic application, however, is in the treatment of cestodal infestations, such as cysticercosis (caused by Taenia solium larvae) and hydatid disease (caused by Echinococcus granulosus). Cysticercosis • This disease is caused by Taenia solium • larvae. Infection produces cysticerci in Echinococcosis the brain (causing seizures, headache, and vomiting) and in the eyes. This disease (also called hydatid disease) is caused by Echinococcus granulosus (dog tapeworm). Infection produces large, hydatid cysts in the liver, lung, and brain. Anaphylactic reaction to worm antigens can occur if the cyst ruptures. The disease follows ingestion of eggs • from human feces. Cysticercosis is diagnosed by CT scan or • biopsy. Therapy: Praziquantel, albendazole, •and/or surgery. The disease follows ingestion of eggs in • dog feces. Sheep often serve as an intermediate host. is diagnosed by CT scan • orEchinococcosis biopsy of infected tissue and is • Taeniasis disease is caused by the larval form • ofThisTaenia saginata (beef tapeworm). The treated by surgical excision of cysts. Therapy: Albendazole. organism primarily infects the intestines and does not produce cysticerci. Most infected individuals are asymptomatic. The disease is transmitted by larvae in • undercooked or raw beef. Taeniasis is diagnosed by detection of • proglottids in stools. • Therapy: Niclosamide. Taeniasis This form of the disease is caused by • the adult Taenia solium (pork tapeworm). Intestines are the primary site of infection, where the organism can cause diarrhea. Most of these infections, however, are asymptomatic. Diphyllobothriasis The disease is transmitted by larvae in • undercooked pork or by ingestion of This disease is caused by Diphyllobothrium latum (fish •tapeworm). The adult worm in a host's intestine can be as long Taeniasis is diagnosed by detection of • proglottids in stools. • Therapy: Niclosamide. • The disease is transmitted by larvae in raw or undercooked fish. Diphyllobothriasis is diagnosed by detection of characteristic eggs in • stools. • Therapy: Niclosamide. tapeworm eggs. as 15 meters. Figure 37.6 Characteristics of and therapy for commonly encountered cestode infections. Pharm 5th 3-21-11.indb 459 3/21/11 2:30:02 PM 460 37. Anthelmintic Drugs Albendazole is erratically absorbed after oral administration, but absorption is enhanced by a high-fat meal. It undergoes extensive first-pass metabolism, including formation of the sulfoxide, which is also active. Albendazole and its metabolites are primarily excreted in urine. When used in short-course therapy (1–3 days) for nematodal infestations, adverse effects are mild and transient and include headache and nausea. Treatment of hydatid disease (3 months) has a risk of hepatotoxicity and, rarely, agranulocytosis or pancytopenia. Medical treatment of neurocysticercosis is associated with inflammatory responses to dying parasites in the CNS, including headache, vomiting, hyperthermia, convulsions, and mental changes. The drug should not be given during pregnancy (see Figure 37.3) or to children under 2 years of age. Study Questions Choose the ONE best answer. 37.1 A 48-year-old immigrant from Mexico presents with seizures and other neurologic symptoms. Eggs of Taenia solium are found upon examination of a stool specimen. A magnetic resonance image of the brain shows many cysts, some of which are calcified. Which one of the following drugs would be of benefit to this individual? Correct answer = C. The symptoms and other findings for this patient are consistent with neuro cysticercosis. Albendazole is the drug of choice for the treatment of this infestation. The other drugs are not effective against the larval forms of tapeworms. A. Ivermectin. B. Pyrantel pamoate. C. Albendazole. D. Diethylcarbamazine. E. Niclosamide. 37.2 A 56-year-old man from South America is found to be parasitized by both schistosomes and Taenia solium—the pork tapeworm. Which of the following anthelmintic drugs would be effective for both infestations? A. Albendazole. B. Ivermectin. C. Mebendazole. D. Niclosamide. E. Praziquantel. 37.3 . A 5-year-old is picked up early from preschool and taken to her pediatrician because of abdominal pain and perianal pruritis. The pediatrician used a cellophane tape swab over the perianal skin that demonstrated translucent eggs of Enterobius v ermicularis. For this infection, what is the most appropriate therapy? A. Fluconazole. B. Itraconazole. C. Ketoconazole. D. Mebendazole. 37 Anthelmintics 5-16-11#.indd 460 Correct answer = E. Praziquantel is a primary drug for the treatment of trematode and cestode infestations. Although albendazole is effective in cysticercosis, it is not active against flukes, and this patient has no evidence of cysticercosis. Niclosamide is also active against tapeworms but has no activity against blood flukes. Ivermectin and mebendazole treat nematode infestations. The answer = D. Mebendazole is a synthetic benzimidazole compound that is effective against Enterobius vermicularis. This organism causes pinworm disease, the most common helminthic infection in the United States. Fluconazole, itraconazole and ketoconazole are azole antifungal agents that do not have any activity against Enterobius vermicularis. 5/16/11 12:49:40 PM Antiviral Drugs I. OVERVIEW Viruses are obligate intracellular parasites. They lack both a cell wall and a cell membrane, and they do not carry out metabolic processes. Viral reproduction uses much of the host's metabolic machinery, and few drugs are selective enough to prevent viral replication without injury to the host. Therapy for viral diseases is further complicated by the fact that the clinical symptoms appear late in the course of the disease, at a time when most of the virus particles have replicated. [Note: This contrasts with bacterial diseases, in which the clinical symptoms are usually coincident with bacterial proliferation.] At this late, symptomatic stage of the viral infection, administration of drugs that block viral replication has limited effectiveness. However, some antiviral agents are useful as prophylactic agents. Only a few virus groups, including those that cause the viral infections discussed in this chapter, respond to available antiviral drugs. To assist in the review of these drugs, they are grouped according to the affected organisms (Figure 38.1). II. TREATMENT OF RESPIRATORY VIRUS INFECTIONS Viral respiratory tract infections for which treatments exist include those of influenza A and B and respiratory syncytial virus (RSV). [Note: Immunization against influenza A is the preferred approach. However, antiviral agents are used when patients are allergic to the vaccine, when the outbreak is due to an immunologic variant of the virus not covered by vaccines (for example, H1N1), or when outbreaks occur among unvaccinated individuals who are at risk and in closed settings (for example, in nursing homes).] A. Neuraminidase inhibitors Orthomyxoviruses that cause influenza contain the enzyme neura minidase, which is essential to the life cycle of the virus. Viral neura minidase can be selectively inhibited by the sialic acid analogs, oseltamivir [os-el-TAM-i-veer] and zanamivir [za-NA-mi-veer]. These drugs prevent the release of new virions and their spread from cell to cell. Unlike the adamantane analogs discussed below, oseltamivir and zanamivir are effective against both Type A and Type B influenza viruses. They do not interfere with the immune response to influenza A vaccine. Administered prior to exposure, neuraminidase inhibitors prevent infection, and, when administered within the first 24 to 48 hours after the onset of infection, they have a modest effect on the intensity and duration of symptoms. Pharm 5th 3-21-11.indb 461 38 FOR RESPIRATORY VIRUS INFECTIONS Amantadine SYMMETREL Oseltamivir TAMIFLU Ribavirin COPEGUS, REBETOL, RIBAPAK, RIBASPHERE, VIRAZOLE Rimantadine FLUMADINE Zanamivir RELENZA FOR HEPATIC VIRAL INFECTIONS Adefovir HEPSERA Entecavir BARACLUDE Interferon INTRON, AVONEX Lamivudine EPIVIR Telbivudine TYZEKA Tenofovir VIREAD FOR HERPESVIRUS AND CYTOMEGALOVIRUS INFECTIONS Acyclovir ZOVIRAX Cidofovir VISTIDE Famciclovir FAMVIR Fomivirsen VITRAVENE Foscarnet FOSCARNET Ganciclovir CYTOVENE Penciclovir DENAVIR Valacyclovir VALTREX Valganciclovir VALCYTE Vidarabine VIRA-A FOR HIV: NUCLEOSIDE AND NUCLEOTIDE REVERSE TRANSCRIPTASE INHIBITORS Abacavir ZIAGEN Didanosine VIDEX Emtricitabine EMTRIVA Lamivudine EPIVIR Stavudine ZERIT Tenofovir VIREAD Zalcitabine HIVID Zidovudine RETROVIR Figure 38.1 Summary of antiviral drugs. HIV = human immunodeficiency virus. (Continued on next page.) 3/21/11 2:30:03 PM 462 38. Antiviral Drugs FOR HIV: NONNUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITORS 1. Mode of action: Influenza viruses employ a specific neuraminidase that is inserted into the host cell membrane for the purpose of releasing newly formed virions. Oseltamivir and zanamivir are transition-state analogs of the sialic acid substrate and serve as inhibitors of the enzyme activity. PROTEASE INHIBITORS 2. Pharmacokinetics: Oseltamivir is an orally active prodrug that is rapidly hydrolyzed by the liver to its active form. Zanamivir, on the other hand, is not active orally and is either inhaled or administered intranasally. Both drugs are eliminated unchanged in the urine (Figure 38.2). Delavirdine RESCRIPTOR Efavirenz SUSTIVA Etravirine INTELENCE Nevirapine VIRAMUNE Amprenavir AGENERASE Atazanavir REYATAZ Darunavir PREZISTA Fosamprenavir LEXIVA Indinavir CRIXIVAN Lopinavir KALETRA Nelfinavir VIRACEPT Ritonavir NORVIR Saquinavir INVIRASE Tipranavir APTIVUS ENTRY INHIBITORS Enfuvirtide FUZEON Maraviroc SELZENTRY INTEGRASE INHIBITOR Raltegravir ISENTRESS FIXED DOSE COMBINATIONS Zidovudine + lamivudine COMBIVIR Zidovudine + lamivudine + abacavir TRIZIVIR Lamivudine + abacavir EPZICOM Emtricitabine + tenofovir TRUVADA Efavirenz + emtricitabine + tenofovir ATRIPLA Figure 38.1 Summary of antiviral drugs. HIV = human immunodeficiency virus. Oseltamivir is taken orally Zanamivir is either inhaled or administered intranasally Oseltamivir and zanamivir appear unchanged in urine the urine Oseltamivir Zanamivir Figure 38.2 Administration and metabolism of oseltamivir and zanamivir. Pharm 5th 3-21-11.indb 462 3. Adverse effects: The most common side effects of oseltamivir are gastrointestinal (GI) discomfort and nausea, which can be alleviated by taking the drug with food. Zanamivir is not associated with GI disturbance, because it is administered directly to the airways. Irritation of the respiratory tract does occur, however. Zanamivir should be avoided in individuals with severe reactive asthma or chronic obstructive respiratory disease, because bronchospasm may occur with the risk of fatality. Neither drug has been reported to have clinically significant drug interactions. 4. Resistance: Mutations of the neuraminidase enzyme have been identified in adults treated with either of the neuraminidase inhibitors. These mutants, however, are often less infective and virulent than the wild type. B. Inhibitors of viral uncoating The therapeutic spectrum of the adamantane derivatives, amantadine [a-MAN-ta-deen] and rimantadine [ri-MAN-ta-deen], is limited to influenza A infections, for which the drugs have been shown to be equally effective in both treatment and prevention. For example, these drugs are 70 to 90 percent effective in preventing infection if treatment is begun at the time of, or prior to, exposure to the virus. Also, both drugs reduce the duration and severity of systemic symptoms if started within the first 48 hours after exposure to the virus (Figure 38.3). Neither impairs the immune response to influenza A vaccine, and either can be administered as a supplement to vaccination, thus providing protection until antibody response occurs (usually 2 weeks in healthy adults). Treatment is particularly useful in high-risk patients who have not been vaccinated and during epidemics. [Note: Amantadine is also effective in the treatment of some cases of Parkinson disease.] 1. Mode of action: The primary antiviral mechanism of amantadine and rimantadine is to block the viral membrane matrix protein, M2, which functions as a channel for hydrogen ions. This channel is required for the fusion of the viral membrane with the cell membrane that ultimately forms the endosome (created when the virus is internalized by endocytosis). [Note: The acidic environment of the endosome is required for viral uncoating.] These drugs may also interfere with the release of new virions. 2. Pharmacokinetics: Both drugs are well absorbed orally. Amantadine distributes throughout the body and readily penetrates into the central nervous system (CNS), whereas rimantadine does not cross the blood-brain barrier to the same extent. Amantadine is not extensively metabolized. It is excreted into the urine and may accumulate to toxic levels in patients with renal failure. On the other 3/21/11 2:30:05 PM hand, rimantadine is extensively metabolized by the liver, and both the metabolites and the parent drug are eliminated by the kidney (Figure 38.4). 3. Adverse effects: The side effects of amantadine are mainly associated with the CNS. Minor neurologic symptoms include insomnia, dizziness, and ataxia. More serious side effects have been reported (for example, hallucinations and seizures). The drug should be employed cautiously in patients with psychiatric problems, cerebral atherosclerosis, renal impairment, or epilepsy. Rimantadine causes fewer CNS reactions, because it does not efficiently cross the blood-brain barrier. Both drugs cause GI intolerance. Amantadine and rimantadine should be used with caution in pregnant and nursing mothers, because they have been found to be embryotoxic and teratogenic in rats. 4. Resistance: Resistance can develop rapidly in up to 50 percent of treated individuals, and resistant strains can be readily transmitted to close contacts. Resistance has been shown to result from a change in one amino acid of the M2 matrix protein. Cross-resistance occurs between the two drugs. 463 Percent of patients showing improvement in symptoms II. Treatment Of Respiratory Virus Infections Placebo Amantadine 60 30 0 -10 24 48 72 Hours Hours Hours Time when treatment started Figure 38.3 Improvement in symptoms of individuals with naturally occurring influenza infections treated with amantadine. Amantadine crosses the blood-brain barrier Rimantadine does NOT extensively cross bloodbrain barrier Amantadine appears unchanged in urine Rimantadine and its metabolites appear in urine C. Ribavirin Ribavirin [rye-ba-VYE-rin] is a synthetic guanosine analog. It is effective against a broad spectrum of RNA and DNA viruses. For example, ribavirin is used in treating infants and young children with severe RSV infections. [Note: It is not indicated for use in adults with RSV.] Ribavirin is also effective in chronic hepatitis C infections when used in combination with interferon-α. Ribavirin may reduce the mortality and viremia of Lassa fever. 1. Mode of action: The mode of action of ribavirin has been studied only for the influenza viruses. The drug is first converted to the 5'-phosphate derivatives, the major product being the compound ribavirin-triphosphate, which exerts its antiviral action by inhibiting guanosine triphosphate formation, preventing viral messenger RNA (mRNA) capping, and blocking RNA-dependent RNA polymerase. [Note: Rhinoviruses and enteroviruses, which contain preformed mRNA and do not need to synthesize mRNA in the host cell to initiate an infection, are relatively resistant to the action of ribavirin.] 2. Pharmacokinetics: Ribavirin is effective orally and intravenously. Absorption is increased if the drug is taken with a fatty meal. An aerosol is used in certain respiratory viral conditions such as the treatment of RSV infection. Studies of drug distribution in primates have shown retention in all tissues, except brain. The drug and its metabolites are eliminated in urine (Figure 38.5). 3. Adverse effects: Side effects reported for oral or parenteral use of ribavirin have included dose-dependent transient anemia. Elevated bilirubin has been reported. The aerosol may be safer, although respiratory function in infants can deteriorate quickly after initiation of aerosol treatment. Therefore, monitoring is essential. Because of teratogenic effects in experimental animals, ribavirin is contraindicated in pregnancy (Figure 38.6). Pharm 5th 3-21-11.indb 463 Amantadine Rimantadine Figure 38.4 Administration and metabolism of amantadine and rimantadine. Poor penetration into CNS Aerosol IV Drug and metabolites appear in urine in urine Figure 38.5 Administration and metabolism of ribavirin. 3/21/11 2:30:09 PM 464 38. Antiviral Drugs III. TREATMENT OF HEPATIC VIRAL INFECTIONS Ribavirin Contraindicated in pregnancy Figure 38.6 Ribavirin causes teratogenic effects. Hepatitis B A. Interferon Hepatitis C 0 2 4 Millions of people Figure 38.7 The prevalence of chronic hepatitis B and C in the United States. Interferon-α Interferon-β Interferon-γ Chronic hepatitis B and C Relapsingremitting multiple sclerosis Chronic granulomatous disease Genital warts caused by papillomavirus Leukemia, hairy-cell Leukemia, chronic myelogenous Kaposi's sarcoma Figure 38.8 Some approved indications for interferon. Pharm 5th 3-21-11.indb 464 The hepatitis viruses thus far identified (A, B, C, D, and E) each have a pathogenesis specifically involving replication in and destruction of hepatocytes. Of this group, hepatitis B and hepatitis C are the most common causes of chronic hepatitis, cirrhosis, and hepatocellular carcinoma (Figure 38.7) and are the only hepatic viral infections for which therapy is currently available. [Note: Hepatitis A is a commonly encountered infection, but it is not a chronic disease.] Chronic hepatitis B may be treated with peginterferonα-2a, which is injected subcutaneously once weekly. [Note: Interferon-α2b injected intramuscularly or subcutaneously three times weekly is also useful in the treatment of hepatitis B, but peginteferon-α-2a has similar or slightly better efficacy.] Oral therapy includes lamivudine, adefovir, entecavir, tenofovir, or telbivudine. Combination therapy of an interferon plus lamivudine is no more effective than monotherapy with lamivudine. Patients with acquired immunodeficiency syndrome (AIDS) who are co-infected with hepatitis B are usually poor responders to interferon therapy. In the treatment of chronic hepatitis C, the preferred treatment is the combination of peginterferon-α-2a or peginterferon-α-2b plus ribavirin, which is more effective than the combination of standard interferons and ribavirin. Interferon [in-ter-FEER-on] is a family of naturally occurring, inducible glycoproteins that interfere with the ability of viruses to infect cells. Although interferon inhibits the growth of many viruses in vitro, its activity in vivo against viruses has been disappointing. The interferons are synthesized by recombinant DNA technology. At least three types of interferons exist, α, β, and γ (Figure 38.8). One of the 15 interferon-α glycoproteins, interferon-α-2b, has been approved for treatment of hepatitis B and C, condylomata acuminata, and cancers such as hairycell leukemia and Kaposi sarcoma. Interferon-β has some effectiveness in the treatment of multiple sclerosis. In so-called "pegylated" formulations, bis-monomethoxy polyethylene glycol has been covalently attached to either interferon-α-2a or -α-2b to increase the size of the molecule. The larger molecular size delays absorption from the injection site, lengthens the duration of action of the drug, and also decreases its clearance. 1. Mode of action: The antiviral mechanism is incompletely understood. It appears to involve the induction of host cell enzymes that inhibit viral RNA translation, ultimately leading to the degradation of viral mRNA and tRNA. 2. Pharmacokinetics: Interferon is not active orally, but it may be administered intralesionally, subcutaneously, or intravenously. Very little active compound is found in the plasma, and its presence is not correlated with clinical responses. Cellular uptake and metabolism by the liver and kidney account for the disappearance of interferon from the plasma. Negligible renal elimination occurs. 3. Adverse effects: Adverse effects include flu-like symptoms on injection, such as fever, chills, myalgias, arthralgias, and GI disturbances. Fatigue and mental depression are common. These symptoms subside with subsequent administrations. The principal dose-limiting toxicities are bone marrow suppression including granulocytopenia; neurotoxicity characterized by somnolence and behavioral disturbances; severe fatigue and weight loss; autoimmune disorders such 3/21/11 2:30:10 PM III. Treatment Of Hepatic Viral Infections 465 as thyroiditis; and, rarely, cardiovascular problems such as congestive heart failure. Acute hypersensitivity reactions and hepatic failure are rare. 4. Drug interactions: Interferon interferes with hepatic drug metabolism, and toxic accumulations of theophylline have been reported. Interferon may also potentiate the myelosuppression caused by other bone marrow–depressing agents such as zidovudine. B. Lamivudine This cytosine analog is an inhibitor of both hepatitis B virus (HBV) DNA polymerase and human immunodeficiency virus (HIV) reverse transcriptase. Lamivudine [la-MI-vyoo-deen] must be phosphorylated by host cellular enzymes to the triphosphate (active) form. This compound competitively inhibits HBV DNA polymerase at concentrations that have negligible effects on host DNA polymerase. As with many nucleotide analogs, the intracellular half-life of the triphosphate is many hours longer than its plasma half-life. Chronic treatment is associated with decreased plasma HBV DNA levels, improved biochemical markers, and reduced hepatic inflammation. Lamivudine is well absorbed orally and is widely distributed. Its plasma half-life is about 9 hours. Seventy percent is excreted unchanged in urine. Dose reductions are necessary when there is moderate renal insufficiency (creatinine clearance less than 50 mL/min). Lamivudine is well tolerated, with rare occurrences of headache and dizziness. C. Adefovir Adefovir dipivoxil [ah-DEH-for-veer die-pih-VOCKS-ill] is a nucleotide analog that is phosphorylated to adefovir diphosphate , which is then incorporated into viral DNA. This leads to termination of further DNA synthesis and prevents viral replication. Adefovir is administered once a day and is excreted in urine, with 45 percent as the active compound. Clearance is influenced by renal function. Both decreased viral load and improved liver function have occurred in patients treated with adefovir. As with other agents, discontinuation of adefovir results in severe exacerbation of hepatitis in about 25 percent of patients. Adefovir does not seem to have significant drug interactions. The drug should be used cautiously in patients with existing renal dysfunction. D. Entecavir Entecavir [en-TECK-ah-veer] is a guanosine analog approved for the treatment of HBV infections. Following intracellular phosphorylation to the triphosphate, it competes with the natural substrate, deoxyguanosine triphosphate, for viral reverse transcriptase. Entecavir has been shown to be effective against lamivudine-resistant strains of HBV. Liver inflammation and scarring are improved. Entecavir need only be given once a day. Entecavir undergoes both glomerular filtration and tubular secretion. Very little, if any, drug is metabolized. Renal function must be assessed periodically, and drugs that have renal toxicity should be avoided. Patients should be monitored closely for several months after discontinuation of therapy because of the possibility of severe hepatitis. E. Telbivudine Telbivudine [tel-BIV-yoo-dine] is a thymidine analog that can be used in the treatment of HBV. Unlike lamivudine and adefovir, telbivudine is not Pharm 5th 3-21-11.indb 465 3/21/11 2:30:10 PM 466 38. Antiviral Drugs active against HIV or other viruses. The drug is phosphorylated intracellularly to the triphosphate, which can either compete with endogenous thymidine triphosphate for incorporation into DNA or else be incorporated into viral DNA, where it serves to terminate further elongation of the DNA chain. The drug is administered orally, once a day, with or without food. Telbivudine is eliminated by glomerular filtration as the unchanged drug, and no metabolites have been detected. The dose must be adjusted in renal failure. The combination of telbivudine with lamivudine has been no more effective than telbivudine alone. G HO O Acyclovir Thymidine kinase, coded for by the viral genome, phosphorylates acyclovir more than 100-fold faster than does the host cell enzyme. G P O F. Tenofovir (See HIV section.) O Acycloguanosine monophosphate (Acyclo-GMP) Herpes viruses are associated with a broad spectrum of diseases, for example, cold sores, viral encephalitis, and genital infections (the latter being a hazard to the newborn during parturition). The drugs that are effective against these viruses exert their actions during the acute phase of viral infections and are without effect during the latent phase. Except for foscarnet and fomivirsen, all are purine or pyrimidine analogs that inhibit viral DNA synthesis. G G P P P O O P P P O IV. TREATMENT OF HERPESVIRUS INFECTIONS Subsequent phosphorylations are catalyzed by the enzymes of the host cell. Acycloguanosine triphosphate (Acyclo-GTP) 5' O 3' dGTP A. Acyclovir Template dGTP is not incorporated into the growing strand of viral DNA. 5' O 3' P C Growing strand O O P G C O P P O C G O P P O G C O P P O T A O P Incorporation of acyclo-GMP from acyclo-GTP into the growing strand of viral DNA causes chain termination, because acyclo-GMP lacks a 3'-hydroxyl group. Figure 38.9 Incorporation of acyclovir into replicating viral DNA, causing chain termination. dGTP = deoxyguanosine triphosphate Pharm 5th 3-21-11.indb 466 P Acyclovir [ay-SYE-kloe-ver] (acycloguanosine) is the prototypic antiherpetic therapeutic agent. It has a greater specificity than vidarabine against herpesviruses. Herpes simplex virus (HSV) Types 1 and 2, varicella-zoster virus (VZV), and some Epstein-Barr virus–mediated infections are sensitive to acyclovir. It is the treatment of choice in HSV encephalitis and is more efficacious than vidarabine at increasing the rate of survival. The most common use of acyclovir is in therapy for genital herpes infections. It is also given prophylactically to seropositive patients before bone marrow and after heart transplants to protect such individuals during posttransplant immunosuppressive treatments. 1. Mode of action: Acyclovir, a guanosine analog that lacks a true sugar moiety, is monophosphorylated in the cell by the herpes virus–encoded enzyme, thymidine kinase (Figure 38.9). Therefore, virus-infected cells are most susceptible. The monophosphate analog is converted to the di- and triphosphate forms by the host cells. Acyclovir triphosphate competes with deoxyguanosine triphosphate as a substrate for viral DNA polymerase and is itself incorporated into the viral DNA, causing premature DNA-chain termination (see Figure 38.9). Irreversible binding of the acyclovir-containing template primer to viral DNA polymerase inactivates the enzyme. The drug is less effective against the host enzyme. 2. Pharmacokinetics: Administration of acyclovir can be by an intravenous (IV), oral, or topical route. [Note: The efficacy of topical applications is doubtful.] The drug distributes well throughout the body, including the cerebrospinal fluid (CSF). Acyclovir is partially metabolized to an inactive product. Excretion into the urine occurs both by glomerular filtration and by tubular secretion (Figure 38.10). Acyclovir accumulates in patients with renal failure. The valyl ester, valacyclovir [val-a-SYE-kloe-veer], has greater oral bioavailability than acyclovir. This ester is rapidly hydrolyzed to acyclovir and achieves levels of the latter comparable to those from IV acyclovir administration. 3/21/11 2:30:14 PM IV. Treatment Of Herpesvirus Infections 3. Adverse effects: Side effects of acyclovir treatment depend on the route of administration. For example, local irritation may occur from topical application; headache, diarrhea, nausea, and vomiting may result after oral administration. Transient renal dysfunction may occur at high doses or in a dehydrated patient receiving the drug IV. High-dose valacyclovir can cause GI problems and thrombotic thrombocytopenic purpura in patients with AIDS. 4. Resistance: Altered or deficient thymidine kinase and DNA polymerases have been found in some resistant viral strains and are most commonly isolated from immunocompromised patients. Cross-resistance to the other agents in this family occurs. [Note: Cytomegalovirus (CMV) is resistant, because it lacks a specific viral thymidine kinase.] B. Cidofovir Cidofovir [si-DOE-foe-veer] is approved for treatment of CMV-induced retinitis in patients with AIDS. Cidofovir is a nucleotide analog of cytosine, the phosphorylation of which is not dependent on viral enzymes. It inhibits viral DNA synthesis. Slow elimination of the active intracellular metabolite permits prolonged dosage intervals and eliminates the permanent venous access used for ganciclovir therapy. Cidofovir is available for IV, intravitreal (injection into the eye's vitreous humor between the lens and the retina), and topical administration. Cidofovir produces significant toxicity to the kidney (Figure 38.11), and it is contraindicated in patients with preexisting renal impairment and in those who are taking concurrent nephrotoxic drugs, including nonsteroidal anti-inflammatory drugs. Neutropenia, metabolic acidosis, and ocular hypotony also occur. Probenecid must be co-administered with cidofovir to reduce the risk of nephrotoxicity, but probenecid itself causes rash, headache, fever, and nausea. Since the introduction of HAART (highly active antiretroviral therapy), the prevalence of CMV infections in immunocompromised hosts has markedly declined, and the importance of cidofovir in the treatment of these patients has also diminished. 467 Drug crosses the blood-brain barrier IV Topical Drug and metabolites appear in urine the urine Acyclovir Figure 38.10 Administration and metabolism of acyclovir. IV = intravenous. Intravitreal IV C. Fomivirsen Fomivirsen [foe-MI-veer-sen] is an antisense oligonucleotide directed against CMV mRNA. Its use is limited to those who cannot tolerate or have failed other therapies for CMV retinitis. A 2 to 4-week hiatus after discontinuing cidofovir is desirable to reduce toxicity. The drug is administered intravitreally. The common adverse effects include iritis, vitritis, and changes in vision. D. Foscarnet Unlike most of the antiviral agents, foscarnet [fos-KAR-net] is not a purine or pyrimidine analog. Instead, it is a phosphonoformate (a pyrophosphate derivative) and does not require activation by viral (or human) kinases. Foscarnet has broad in vitro antiviral activity. It is approved for CMV retinitis in immunocompromised hosts and for acyclovir-resistant HSV and herpes zoster infections. Foscarnet works by reversibly inhibiting viral DNA and RNA polymerases, thereby interfering with viral DNA and RNA synthesis. Mutation of the polymerase structure is responsible for resistant viruses. [Note: Cross-resistance between foscarnet and ganciclovir or acyclovir is uncommon.] Foscarnet is poorly absorbed orally and must be injected IV. It must also be given frequently to avoid relapse when plasma levels fall. It is dispersed throughout the body, Pharm 5th 3-21-11.indb 467 Topical Drug appears in urine Nephrotoxicity Foscarnet Figure 38.11 Administration, metabolism, and toxicity of cidofovir. IV = intravenous. 3/21/11 2:30:16 PM 468 38. Antiviral Drugs and greater than 10 percent enters the bone matrix, from which it slowly leaves. The parent drug is eliminated by glomerular filtration and tubular secretion into the urine (Figure 38.12). Adverse effects include nephrotoxicity, anemia, nausea, and fever. Due to chelation with divalent cations, hypocalcemia and hypomagnesemia are also seen. In addition, hypokalemia, hypo- and hyperphosphatemia, seizures, and arrhythmias have been reported. IV E. Ganciclovir Drug appears in urine the urine Ganciclovir [gan-SYE-kloe-veer] is an analog of acyclovir that has 8 to 20 times greater activity against CMV, which is the only viral infection for which it is approved. It is currently available for treatment of CMV retinitis in immunocompromised patients and for CMV prophylaxis in transplant patients. Foscarnet Figure 38.12 Administration and metabolism of foscarnet. Drug crosses the blood-brain barrier IV Drug appears in urine Ganciclovir Figure 38.13 Administration and metabolism of ganciclovir. 1. Mode of action: Like acyclovir, ganciclovir is activated through conversion to the nucleoside triphosphate by viral and cellular enzymes, with the actual pathway depending on the virus. CMV is deficient in thymidine kinase and, therefore, forms the triphosphate by another route. The nucleotide competitively inhibits viral DNA polymerase and can be incorporated into the DNA, thereby decreasing the rate of chain elongation. 2. Pharmacokinetics: Ganciclovir is administered IV and distributes throughout the body, including the CSF. Excretion into the urine occurs through glomerular filtration and tubular secretion (Figure 38.13). Like acyclovir, ganciclovir accumulates in patients with renal failure. Valganciclovir [val-gan-SYE-kloe-veer] is the valyl ester of ganciclovir. Like valacyclovir, valganciclovir has high oral bioavailability, because rapid hydrolysis in the intestine and liver after oral administration leads to high levels of ganciclovir. 3. Adverse effects: Adverse effects include severe, dose-dependent neutropenia. [Note: Combined treatment with zidovudine, azathioprine, or mycophenolate mofetil can result in additive neutropenia.] Ganciclovir is carcinogenic as well as embryotoxic and teratogenic in experimental animals. 4. Resistance: Resistant CMV strains have been detected that have lower levels of ganciclovir triphosphate . Topical Penciclovir appears unchanged urine in the urine Penciclovir F. Penciclovir and famciclovir Famciclovir appears unchanged in urine the urine Famciclovir Figure 38.14 Administration and metabolism of penciclovir and famciclovir. Pharm 5th 3-21-11.indb 468 Penciclovir [pen-SYE-kloe-veer] is an acyclic guanosine nucleoside derivative that is active against HSV-1, HSV-2, and VZV. Penciclovir is only administered topically (Figure 38.14). It is monophosphorylated by viral thymidine kinase, and cellular enzymes form the nucleoside triphosphate, which inhibits HSV DNA polymerase. Penciclovir triphosphate has an intracellular half-life 20 to 30-fold longer than does acyclovir triphosphate. Penciclovir is negligibly absorbed upon topical application and is well tolerated. Both pain and healing are shortened by approximately half a day in duration compared to placebo-treated subjects. Famciclovir [fam-SYE-kloe-veer], another acyclic analog of 2'-deoxyguanosine, is a prodrug that is metabolized to the active penciclovir. The antiviral spectrum is similar to that of ganciclovir, but it is presently approved only for treatment of acute herpes zoster. The drug is effective orally (see Figure 38.14). Adverse effects include headaches and nausea. Studies in experimental animals have shown an increased incidence of mammary adenocarcinomas and testicular toxicity. 3/21/11 2:30:20 PM IV. Treatment Of Herpesvirus Infections 469 G. Vidarabine (ara-A) Vidarabine [vye-DARE-a-been] (arabinofuranosyl adenine, ara-A, adenine arabinoside) is one of the most effective of the nucleoside analogs. However, it has been supplanted clinically by acyclovir, which is more efficacious and safe. Although vidarabine is active against HSV-1, HSV-2, and VZV, its use is limited to treatment of immunocompromised patients with herpetic and vaccinial keratitis and in HSV keratoconjunctivitis. [Note: Vidarabine is only available as an ophthalmic ointment.] Vidarabine, an adenosine analog, is converted in the cell to its 5'-triphosphate analog (ara-ATP), which is postulated to inhibit viral DNA synthesis. Some resistant HSV mutants have been detected that have altered polymerase. H. Trifluridine Trifluridine [trye-FLURE-i-deen] is a fluorinated pyrimidine nucleoside analog. It is structurally very similar to thymidine, the only difference Antiviral drug Mechanism of action Viruses or diseases affected Acyclovir Metabolized to acyclovir triphosphate, which inhibits viral DNA polymerase Herpes simplex, varicella-zoster, cytomegalovirus Amantadine Blockage of the M2 protein ion channel and its ability to modulate intracellular pH Influenza A Cidofovir Inhibition of viral DNA polymerase Cytomegalovirus; indicated only for virus-induced retinitis Famciclovir Same as penciclovir Herpes simplex, varicella-zoster Foscarnet Inhibition of viral DNA polymerase and reverse transcriptase at the pyrophosphate-binding site Cytomegalovirus, acyclovir-resistant herpes simplex, acyclovir-resistant varicellazoster Ganciclovir Inhibits viral DNA polmerase Cytomegalovirus Interferon-α Induction of cellular enzymes that interfere with viral protein synthesis Hepatitis B and C, human herpesvirus 8, papilloma virus, Kaposi sarcoma, hairy cell leukemia, chronic myelogenous leukemia Lamivudine Inhibition of viral DNA polymerase and reverse transcriptase Hepatitis B (chronic cases), human immunodeficiency virus type 1 Oseltamivir Inhibition of viral neuramidase Influenza A Penciclovir Metabolized to penciclovir triphosphate, which inhibits viral DNA polymerase Herpes simplex Ribavirin Interference with viral messenger RNA Lassa fever, hantavirus (hemorrhagic fever renal syndrome), hepatitis C (in chronic cases in combination with interferon-α) RSV in children and infants Rimantadine Blockage of the M2 protein ion channel and its ability to modulate intracellular pH Influenza A Valacyclovir Same as acyclovir Herpes simplex, varicella-zoster, cytomegalovirus Vidarabine Inhibits viral DNA synthesis HSV-1, HSV-2, and VZV; its use is limited to treatment of immunocompromised patients with HSV keratitis Zanamivir Inhibition of viral neuramidase Influenza A Figure 38.15 Summary of selected antiviral agents. RSV = respiratory syncytial virus; HSV = herpes simplex virus; VZV = varicella zoster virus. Pharm 5th 3-21-11.indb 469 3/21/11 2:30:22 PM 470 38. Antiviral Drugs Maraviroc blocks entry of HIV into the cell. Enfuvirtide blocks fusion of host and HIV membranes. After the viral RNA is released into the host cell, it is transcribed into a DNA copy by viral reverse transcriptase. NRTIs and NNRTIs inhibit this enzyme and, thus, prevent the synthesis of the essential DNA intermediate. Fusion inhibitor Viral penetration and uncoating Viral RNA Reverse transcriptase inhibitors Viral DNA Integrase inhibitors Host DNA Integrated viral DNA Precursor polyprotein Viral RNA Viral RNA Precursor polyprotein Protease inhibitors Viral proteins As the virion buds from the surface, the viral protease is activated and cleaves the polyproteins into their component proteins, which then assemble into the mature virion. Protease inhibitors prevent this essential step in virus maturation. Figure 38.16 Drugs used to prevent HIV from replicating. NRTI = nucleoside and nucleotide reverse transcriptase inhibitor; NNRTI = nonnucleoside reverse transcriptase inhibitor. Pharm 5th 3-21-11.indb 470 being the replacement of a methyl group on the pyrimidine ring of thymidine with a trifluoromethyl group. Once converted to the triphosphate, the agent is believed to competitively inhibit the incorporation of thymidine triphosphate into viral DNA and, to a lesser extent, to be incorporated into viral DNA, leading to the synthesis of a defective DNA that renders the virus unable to reproduce. Trifluridine monophosphate is an irreversible inhibitor of viral thymidine synthase. Trifluridine is active against HSV-1, HSV-2, and vaccinia virus. It is generally considered to be the drug of choice for treatment of HSV keratoconjunctivitis and recurrent epithelial keratitis. Because the triphosphate form of trifluridine can also incorporate to some degree into cellular DNA, the drug is considered to be too toxic for systemic use. Therefore, the use of trifluridine is restricted to topical application as a solution to the eye. A short half-life of approximately 12 minutes necessitates that the drug be applied frequently. Side effects include a transient irritation of the eye and palpebral (eyelid) edema. Figure 38.15 summarizes selected antiviral agents. V. OVERVIEW OF THE TREATMENT FOR HIV INFECTION Prior to approval of zidovudine in 1987, treatment of HIV infections focused on decreasing the occurrence of opportunistic infections that caused a high degree of morbidity and mortality in AIDS patients rather than on inhibiting HIV itself. Today, the viral life cycle is understood (Figure 38.16), and a highly active regimen is employed that uses combinations of drugs to suppress replication of HIV and restore the number of CD4+ cells and immunocompetence to the host. This multidrug regimen is commonly referred to as "highly active antiretroviral therapy," or HAART (Figure 38.17). There are five classes of antiretroviral drugs, each of which targets one of four viral processes. These classes of drugs are nucleoside and nucleotide reverse transcriptase inhibitors (NRTIs), nonnucleoside reverse transcriptase inhibitors (NNRTIs), protease inhibitors, entry inhibitors, and the integrase inhibitors. The current recommendation for primary therapy is to administer two NRTIs with either a protease inhibitor, an NNRTI, or an integrase inhibitor. Selection of the appropriate combination is based on 1) avoiding the use of two agents of the same nucleoside analog; 2) avoiding overlapping toxicities and genotypic and phenotypic characteristics of the virus; 3) patient factors, such as disease symptoms and concurrent illnesses; 4) impact of drug interactions; and 5) ease of adherence to a frequently complex administration regimen. The goals of therapy are to maximally and durably suppress viral load replication, to restore and preserve immunologic function, to reduce HIV-related morbidity and mortality, and to improve quality of life. VI. NRTIs USED TO TREAT HIV INFECTION A. Overview of NRTIs 1. Mechanism of action: NRTIs are analogs of native ribosides (nucleosides or nucleotides containing ribose), which all lack a 3'-hydroxyl group. Once they enter cells, they are phosphorylated by a variety of cellular enzymes to the corresponding triphosphate analog, which is preferentially incorporated into the viral DNA by virus reverse transcriptase. Because the 3'-hydroxyl group is not present, a 3'-5'-phosphodiester bond between an incoming nucleoside triphosphate and the growing DNA chain cannot be formed, and DNA chain elongation is terminated. Affinities of the drugs for many host cell DNA 3/21/11 2:31:43 PM VI. NRTIs Used To Treat HIV Infection polymerases are lower than they are for HIV reverse transcriptase, although mitochondrial DNA polymerase γ appears to be susceptible at therapeutic concentrations. 471 A Currently available drugs Nucleoside/-tide reverse transcriptase inhibitors: Abacavir • Stavudine Didanosine • Tenofovir Emtricitabine • Zalcitabine Lamivudine • Zidovudine 2. Pharmacokinetics: The NRTIs are primarily renally excreted, and all require dosage adjustment in renal insufficiency except abacavir, which is metabolized by alcohol dehydrogenase and glucuronyl transferase. Dosage adjustment is required when the creatinine clearance drops below 50 mL/min. • • • • 3. Adverse effects: Many of the toxicities of the NRTIs are believed to be due to inhibition of the mitochondrial DNA polymerase in certain tissues. As a general rule, the dideoxynucleosides, such as zalcitabine, didanosine, and stavudine, have a greater affinity for the mitochondrial DNA polymerase, leading to such toxicities as peripheral neuropathy, pancreatitis, and lipoatrophy. When more than one NRTI is given, care is taken not to have overlapping toxicities. All of the NRTIs have been associated with a potentially fatal liver toxicity characterized by lactic acidosis and hepatomegaly with steatosis. • Delavirdine • Efavirenz 4. Drug interactions: Due to the renal excretion of the NRTIs, there are not many drug interactions encountered with these agents except for zidovudine and tenofovir (see below). 5. Resistance: NRTI resistance is well characterized, and the most common mutation is the mutation at viral codon 184, which confers a high degree of resistance to lamivudine and emtricitabine but, more importantly, restores sensitivity to zidovudine and tenofovir. Because cross-resistance and antagonism occur between agents of the same analog class (thymidine, cytosine, guanosine, and adenosine), concomitant use of agents in the same class is contraindicated (for example, zidovudine plus stavudine). Nonnucleoside reverse transcriptase inhibitors: • Etravirine • Nevirapine Protease inhibitors: • Amprenavir • Atazanavir • Darunavir • Fosamprenavir • Indinavir • Lopinavir • Nelfinavir • Ritonavir • Saquinavir • Tipranavir Entry inhibitors: • Enfuvirtide • Maraviroc • Raltegravir Integrase inhibitor: B Combination therapy Two nucleoside/-tide reverse transcriptase inhibitors plus One protease inhibitor (+ ritonavir) or A nonnucleoside reverse transcriptase inhibitor or Integrase inhibitor B. Zidovudine (AZT, ZDV) Approved in 1987, the first agent available for treatment of HIV infection is the pyrimidine analog, 3'-azido-3'-deoxythymidine (AZT). AZT has the generic name of zidovudine [zye-DOE-vyoo-deen]. AZT is approved for use in children and adults and to prevent prenatal infection in pregnancy. It is also used for prophylaxis in individuals exposed to HIV infection. The drug is well absorbed after oral administration. If taken with food, peak levels may be lower, but the total amount of drug absorbed is not affected. Penetration across the blood-brain

barrier is excellent, and the drug has a half-life of 1 hour. The intracellular half-life, however, is approximately 3 hours. Most of the AZT is glucuronidated by the liver and then excreted in the urine (see Figure 38.18). In spite of its seeming specificity, AZT is toxic to bone marrow. Headaches are also common. The toxicity of AZT is potentiated if glucuronidation is decreased by co-administration of drugs like probenecid, acetaminophen, lorazepam, indomethacin, and cimetidine. They should be avoided or used with caution in patients receiving AZT. Both stavudine and ribavirin are activated by the same intracellular pathways and should not be given with AZT. C. Stavudine (d4T) Stavudine [STAV-yoo-deen] is an analog of thymidine, in which a double bond joins the 2’ and 3’ carbons of the sugar. Stavudine is a strong inhibitor of cellular enzymes such as the β and γ DNA polymerases, thus Pharm 5th 3-21-11.indb 471 Figure 38.17 Highly active antiretroviral therapy (HAART). Drug crosses the blood-brain barrier Leukopenia Metabolites appear in the urine Anemia AZT Figure 38.18 Administration, metabolism, and toxicity of zidovudine (AZT). 3/21/11 2:31:50 PM 472 38. Antiviral Drugs Drug crosses the blood-brain barrier Peripheral neuropathy Drug and metabolites appear in urine Pancreatitis Didanosine Figure 38.19 Administration, metabolism, and toxicity of didanosine. reducing mitochondrial DNA synthesis and resulting in toxicity. The drug is almost completely absorbed on oral ingestion and is not affected by food. Stavudine penetrates the blood-brain barrier. About half of the parent drug can be accounted for in the urine. Renal impairment interferes with clearance. The major and most common clinical toxicity is peripheral neuropathy along with lipoatrophy and hyperlipidemia. D. Didanosine (ddI) The second drug approved to treat HIV-1 infection was didanosine [dye-DAN-oh-seen] (dideoxyinosine, ddI), which is missing both the 2’and 3’-hydroxyl groups. Upon entry into the host cell, ddI is biotransformed into dideoxyadenosine triphosphate (ddATP) through a series of reactions that involve phosphorylation of the ddI, amination to dideoxyadenosine monophosphate, and further phosphorylation. Like AZT, the resulting ddATP is incorporated into the DNA chain, causing termination of chain elongation. Due to its acid lability, absorption is best if ddI is taken in the fasting state. The drug penetrates into the CSF but to a lesser extent than does AZT. About 55 percent of the parent drug appears in the urine (Figure 38.19). Pancreatitis, which may be fatal, is a major toxicity of ddI treatment and requires monitoring of serum amylase. The dose-limiting toxicity of ddI is peripheral neuropathy. Because of its similar adverse effect profile, concurrent use of stavudine is not recommended. E. Tenofovir (TDF) Drug crosses the blood-brain barrier GI disturbance Drug appears in urine Tenofovir Figure 38.20 Administration, metabolism, and toxicity of tenofovir. Tenofovir [te-NOE-fo-veer] is the first approved drug that is a nucleotide analog, namely, an acyclic nucleoside phosphonate analog of adenosine 5’-monophosphate. It is converted by cellular enzymes to the diphosphate, which is the inhibitor of HIV reverse transcriptase. Cross-resistance with other NRTIs may occur, but some AZT-resistant strains retain susceptibility to tenofovir. Tenofovir has a long half-life, allowing once-daily dosing. Most of the drug is recovered unchanged in the urine, and elimination is by filtration and active secretion. Serum creatinine must be monitored and doses adjusted in renal insufficiency. GI complaints are frequent and include nausea, diarrhea, and bloating (Figure 38.20). Tenofovir is the only NRTI with significant antiretroviral drug interactions. Tenofovir increases the concentrations of ddI to the point that ddI dosage reductions are required if the two are given together. However, these two agents are no longer recommended for combined use. Tenofovir decreases the concentrations of atazanavir such that atazanavir must be boosted with ritonavir (see p. 476) if given with tenofovir to maintain effective atazanavir concentrations. F. Lamivudine (3TC) Lamivudine [la-MI-vyoo-deen] (2’-deoxy-3’-thiacytidine, 3TC) is approved for treatment of HIV in combination with AZT, but it should not be used with other cytosine analogs due to antagonism. Lamivudine terminates the synthesis of the proviral DNA chain, and it inhibits the reverse transcriptase of both HIV and HBV. However, it does not affect mitochondrial DNA synthesis or bone marrow precursor cells. It has good bioavailability on oral administration, depends on the kidney for excretion, and is well tolerated. G. Emtricitabine (FTC) Emtricitabine [em-tri-SIGH-ta-been], a fluoro-derivative of lamivudine, inhibits both HIV and HBV reverse transcriptase. In a small clinical trial, Pharm 5th 3-21-11.indb 472 3/21/11 2:31:52 PM VII. NNRTIs Used To Treat HIV Infection 473 it was shown to be at least as effective as lamivudine in the treatment of HIV-infected individuals. Emtricitabine is orally active, with a mean bioavailability of 93 percent. Plasma half-life is about 10 hours, whereas it has a long intracellular half-life of 39 hours. Emtricitabine is eliminated essentially unchanged in urine. It does not affect cytochrome P450 (CYP450) isozymes and has no significant interactions with other drugs. Headache, diarrhea, nausea, and rash are its most common adverse effects. Emtricitabine causes hyperpigmentation of the soles and palms, and it has been associated with lactic acidosis, fatty liver, and hepatomegaly. Withdrawal of emtricitabine in HBV-infected patients may result in worsening of the hepatitis. H. Zalcitabine (ddC) Zacitabine [zal-SIGH-ta-been] was the first cytosine analog developed. However, due to severe toxicity, it was removed from the market. I. Abacavir (ABC) Abacavir [a-BA-ka-veer] is a guanosine analog. There may be some cross-resistance with strains resistant to AZT and lamivudine. Abacavir is well absorbed orally, and metabolites appear in the urine (Figure 38.21). Most of the drug is metabolized by non-CYP450–dependent reactions. A carboxylic acid derivative and a glucuronidated form have been identified. Common side effects include GI disturbances, headache, and dizziness. Approximately 5 percent of patients exhibit the “hypersensitivity reaction,” which is usually characterized by drug fever, plus one or more of the following symptoms of rash, GI symptoms, malaise, and respiratory distress (Figure. 38.22). Sensitized individuals should never be re-challenged because of rapidly appearing, severe reactions that lead to death. There is a newly approved HLA genetic test available to screen patients for the potential of this reaction. Figure 38.23 shows some adverse reactions commonly seen with nucleoside analogs. Metabolites appear in urine Abacavir Figure 38.21 Administration and fate of the abacavir. Fatigue GI disturbance 98.6 VII. NNRTIs USED TO TREAT HIV INFECTION Skin rash NNRTIs are highly selective, noncompetitive inhibitors of HIV-1 reverse transcriptase. They bind to HIV reverse transcriptase at a site adjacent to the active site, inducing a conformational change that results in enzyme inhibition. They do not require activation by cellular enzymes. Their major advantage is their lack of effect on the host blood-forming elements and their lack of cross-resistance with NRTIs. These drugs, however, do have common characteristics that include cross-resistance within the NNRTI class, drug interactions, and a high incidence of hypersensitivity reactions, including rash. Fever Figure 38.22 Hypersensitivity reactions to abacavir. Hepatosteatosis (fatty liver) A. First-generation NNRTI's 1. Nevirapine (NVP): Nevirapine [ne-VYE-ra-peen] is used in combination with other antiretroviral drugs for the treatment of HIV-1 infections in adults and children. Due to potential severe hepatotoxicity, nevirapine should not be initiated in women with CD4+ T-cell counts greater than 250 cells/mm3 or in men with CD4+ T cell counts greater than 400 cells/mm3. Nevirapine is well absorbed orally, and its absorption is not affected by food and antacids. The lipophilic nature of nevirapine accounts for its entrance into the fetus and mother’s milk and for its wide tissue distribution, including the CNS. Nevirapine is dependent upon metabolism for elimination, and most of the drug is excreted in urine as the glucuronide of hydroxylated Pharm 5th 3-21-11.indb 473 Lactic Acid Lactic acidosis Lipodystrophy Figure 38.23 Some adverse reactions of nucleoside analogs. 3/21/11 2:31:54 PM 474 38. Antiviral Drugs Drug crosses the blood-brain barrier Heptotoxicity Drug and metabolites appear in urine Nevirapine Figure 38.24 Administration, metabolism, and toxicity of nevirapine. Drug crosses the blood-brain barrier Metabolites appear in the bile Drug and metabolites appear in urine and feces Efavirenz Figure 38.25 Administration and metabolism of efavirenz. Not during pregnancy metabolites (Figure 38.24). Nevirapine is an inducer of the CYP3A4 family of CYP450 drug-metabolizing enzymes. Nevirapine increases the metabolism of protease inhibitors, but most combinations do not require dosage adjustment. Nevirapine increases the metabolism of a number of drugs, such as oral contraceptives, ketoconazole, methadone, metronidazole, quinidine, theophylline, and warfarin. The most frequently observed side effects are rash, fever, headache, and elevated serum transaminases and fatal hepatotoxicity. Severe dermatologic effects have been encountered, including StevensJohnson syndrome and toxic epidermal necrolysis. A 14-day titration period at half the dose is mandatory to reduce the risk of serious epidermal reactions and hepatotoxicity. 2. Delavirdine (DLV): Delavirdine [de-LA-vir-deen] has not undergone clinical trials as extensive as those of nevirapine and is not recommended as a preferred or alternate agent in the U.S. Department of Health and Human Services (DHHS) guidelines for initial therapy. Delavirdine is rapidly absorbed after oral administration and is unaffected by the presence of food. Delavirdine is extensively metabolized, and very little is excreted as the parent compound. Fecal and urinary excretion each account for approximately half the elimination. Delavirdine is an inhibitor of CYP450–mediated drug metabolism, including that of protease inhibitors. Fluoxetine and ketoconazole increase plasma levels of delavirdine, whereas phenytoin, phenobarbital, and carbamazepine result in substantial decreases in plasma levels of delavirdine. Rash is the most common side effect of delavirdine. 3. Efavirenz (EFV): Efavirenz [e-FA-veer-enz] treatment results in increases in CD4+ cell counts and a decrease in viral load comparable to that achieved by protease inhibitors when used in combination with NRTIs. Therefore, it is the preferred NNRTI on the DHHS guidelines. Following oral administration, efavirenz is well distributed, including to the CNS (Figure 38.25). It should be administered on an empty stomach to reduce adverse CNS effects. Most of the drug is bound to plasma albumin (99 percent) at therapeutic doses. A halflife of more than 40 hours accounts for its recommended once-aday dosing. Efavirenz is extensively metabolized to inactive products. Efavirenz is a potent inducer of CYP450 enzymes and, therefore, may reduce the concentrations of drugs that are substrates of the CYP450. Most adverse effects are tolerable and are associated with the CNS, including dizziness, headache, vivid dreams, and loss of concentration (Figure 38.26). Nearly half of the patients experience these complaints, which usually resolve within a few weeks. Rash is the other most common side effect, with an incidence of approximately 25 percent. Severe, life-threatening reactions are rare. Efavirenz should be avoided in pregnant women. B. Second-generation NNRTIs Dizziness Vivid dreams Figure 38.26 Adverse reactions of efavirenz. Pharm 5th 3-21-11.indb 474 1. Etravirine (ETR): Etravirine [et-ra-VYE-rine] is the first second-generation NNRTI. It is active against many of the strains of HIV that are resistant to the first-generation NNRTIs. HIV strains with the common K103N resistance mutation to the first generation of NNRTIs are fully susceptible to etravirine. Following oral administration, etravirine is well distributed, and bioavailability is enhanced when taken with a high-fat meal. Although it has a half-life of approximately 40 hours, it is indicated for twice-daily dosing. Etravirine is extensively metabolized 3/21/11 2:31:57 PM VIII. HIV Protease Inhibitors Used to Treat HIV Infection to inactive products. Because etravirine is a potent inducer of CYP450, the doses of CYP450 substrates may need to be increased when given with etravirine. Rash is the most common side effect. Etravirine is otherwise well tolerated, does not have the CNS side effects that are seen with efavirenz, and is pregnancy category B. Etravirine is indicated for HIV treatment–experienced, multidrug-resistant adult patients who have evidence of ongoing viral replication. VIII. HIV PROTEASE INHIBITORS USED TO TREAT HIV INFECTION Inhibitors of HIV protease have significantly altered the course of this devastating viral disease. Within a year of their introduction in 1995, the number of deaths in the United States due to AIDS declined, although the trend appears to be leveling off (Figure 38.27). A. Overview 475 Combination therapy available 80,000 AIDS 60,000 40,000 20,000 0 AIDS deaths '85 '87 '89 '91 '93 '95 '97 '99 '01 '03 '05 Figure 38.27 Estimated number of AIDS cases and deaths due to AIDS in the United States. Green background indicates years in which combination antiretroviral therapy came into common usage. These potent agents have several common features that characterize their pharmacology. 1. Mechanism of action: All of the drugs in this group are reversible inhibitors of the HIV aspartyl protease, which is the viral enzyme responsible for cleavage of the viral polyprotein into a number of essential enzymes (reverse transcriptase, protease, and integrase) and several structural proteins. The protease inhibitors exhibit at least a thousandfold greater affinity for HIV-1 and HIV-2 enzymes than they have for comparable human proteases, such as renin and cathepsin D/E. This accounts for their selective toxicity. The inhibition prevents maturation of the viral particles and results in the production of noninfectious virions. Treatment of antiretroviral naïve patients (those who have never had HIV therapy) with a protease inhibitor and two NRTIs results in a decrease in the plasma viral load to undetectable levels in 60 to 95 percent of patients. Treatment failures under these conditions are most likely due to a lack of patient adherence. Paresthesias Diarrhea Nausea and vomiting 2. Pharmacokinetics: Most protease inhibitors have poor oral bioavail- ability. High-fat meals substantially increase the bioavailability of some, such as nelfinavir and saquinavir, whereas the bioavailability of indinavir is decreased, and others are essentially unaffected. All are substrates for the CYP3A4 isozyme of CYP450, and individual protease inhibitors are also metabolized by other P450 isozymes. Metabolism is extensive, and very little of the protease inhibitors are excreted unchanged in urine. Dosage adjustments are unnecessary in renal impairment. Distribution into some tissues may be affected because protease inhibitors are substrates for the P-glycoprotein multidrug efflux pump. The presence of this pump in endothelial cells of capillaries in the brain may limit protease inhibitor access to the CNS. The HIV protease inhibitors are all substantially bound to plasma proteins, specifically α1-acid glycoprotein. This may be clinically important, because the concentration of α1-acid glycoprotein increases in response to trauma and surgery. 3. Adverse effects: Protease inhibitors commonly cause paresthe- sias, nausea, vomiting, and diarrhea (Figure 38.28). Disturbances in glucose and lipid metabolism also occur, including diabetes, hypertriglyceridemia, and hypercholesterolemia. Chronic admin- Pharm 5th 3-21-11.indb 475 Hypertriglyceridemia TRIGLYCERIDES Hyperglycemia GLUCOSE Hypercholesterolemia CHOLESTEROL Figure 38.28 Some adverse effects of the HIV protease inhibitors. 3/21/11 2:31:58 PM 476 38. Antiviral Drugs istration results in fat redistribution, including loss of fat from the extremities, fat accumulation in the abdomen and the base of the neck (“buffalo hump”; Figure 38.29), and breast enlargement. These physical changes may indicate to others that an individual is HIV infected. 4 Drug interactions: Drug interactions are a common problem for all Figure 38.29 Accumulation of fat at the base of the neck in a patient receiving a protease inhibitor. DRUG CLASS EXAMPLE ANTIARRHYTHMICS Quinidine ERGOT DERIVATIVES Ergotamine ANTIMYCOBACTERIAL DRUGS RIfampin BENZODIAZEPINES Triazolam INHALED STEROIDS Fluticasone HERBAL SUPPLEMENTS St. John’s wart HMG CoA REDUCTASE INHIBITORS Lovastatin Simvastatin NARCOTICS Fentanyl protease inhibitors, because they are not only substrates but also potent inhibitors of CYP isozymes. The inhibitory potency of the compounds lies between that of ritonavir, the most potent, and that of saquinavir, the least potent inhibitor of CYP isoenzymes. Drug interactions are, therefore, quite common. Drugs that rely on metabolism for their termination of action may accumulate to toxic levels. Examples of potentially dangerous interactions from drugs that are contraindicated with protease inhibitors include rhabdomyolysis from simvastatin or lovastatin, excessive sedation from midazolam or triazolam, and respiratory depression from fentanyl (Figure 38.30). Other drug interactions that require dosage modification and cautious use include warfarin, sildenafil, and phenytoin (Figure 38.31). In addition, inducers of CYP isozymes may result in the lowering of protease inhibitor plasma concentrations to suboptimal levels, contributing to treatment failures. Thus, drugs such as rifampin and St. John’s wort are also contraindicated with protease inhibitors. Meticulous attention must be paid to all of these detrimental interactions. 5. Resistance: Resistance occurs as an accumulation of stepwise mutations of the protease gene. Initial mutations result in decreased ability of the virus to replicate, but as the mutations accumulate, virions with high levels of resistance to the protease emerges. Suboptimal concentrations result in the more rapid appearance of resistant strains. B. Ritonavir (RTV) Contraindicated Ritonavir [ri-TOE-na-veer] is no longer used as a single protease inhibitor but, instead, is used as a pharmacokinetic enhancer or "booster" of other protease inhibitors. Ritonavir is a potent inhibitor of CYP3A, and concomitant ritonavir administration (at low doses) increases the bioavailability of the second protease inhibitor, often allowing for longer dosing intervals. The resulting higher Cmin levels of the “boosted" protease inhibitors also help to prevent the development of resistance. Therefore, “boosted" protease inhibitors are preferred agents in the DHHS treatment guidelines. Metabolism and biliary excretion are the primary methods of elimination. Ritonavir has a half-life of 3 to 5 hours. Because it is primarily an inhibitor of CYP450 isozymes, numerous drug interactions have been identified. Nausea, vomiting, diarrhea, headache, and circumoral paresthesias are among the more common adverse effects. C. Saquinavir (SQV) PROTEASE INHIBITORS Figure 38.30 Drugs that should not be coadministered with any protease inhibitor. Pharm 5th 3-21-11.indb 476 To maximize bioavailability, saquinavir [sa-KWIH-na-veer] is always given along with a low dose of ritonavir. High-fat meals also enhance absorption. Elimination of saquinavir is primarily by metabolism, followed by biliary excretion. Its half-life is 7 to 12 hours, requiring twice daily doses. Drugs that enhance the metabolism of saquinavir, such as rifampin, rifabutin, nevirapine, efavirenz, and other enzyme inducers, 3/21/11 2:32:00 PM VIII. HIV Protease Inhibitors Used to Treat HIV Infection should be avoided if possible. The most common adverse effects of saquinavir treatment include headache, fatigue, diarrhea, nausea, and other GI disturbances. Increased levels of hepatic aminotransferases have been noted, particularly in patients with concurrent viral hepatitis B or C infections. D. Indinavir (IDV) Indinavir [in-DIH-na-veer] is well absorbed orally and, of all the protease inhibitors, is the least protein bound, at 60 percent. Acidic gastric conditions are necessary for absorption. Absorption is decreased when administered with meals, although a light, low-fat snack is permissible. Ritonavir overcomes this problem and also permits twice-a-day dosing. Metabolism and hepatic clearance account for elimination of indinavir. The dosage should, therefore, be reduced in the presence of hepatic insufficiency. Indinavir has the shortest half-life of the protease inhibitors, at 1.8 hours. It is well tolerated, with the usual GI symptoms and headache predominating. Indinavir characteristically causes nephrolithiasis and hyperbilirubinemia. Adequate hydration is important to reduce the incidence of kidney stone formation, and patients should drink at least 1.5 L of water per day. Fat redistribution is particularly troublesome with this drug. 477 DRUG CLASS EXAMPLE ANTICOAGULANTS Warfarin ANTICONVULSANTS Phenytoin ANTIFUNGALS Voriconazole ANTIMYCOBACTERIALS Rifabutin ERECTILE DYSFUNCTION AGENTS Sildenafil Tadalafil Vardenafil LIPID-LOWERING AGENTS Atorvastatin NARCOTICS Methadone E. Nelfinavir (NFV) Nelfinavir [nel-FIN-a-veer] is a nonpeptide protease inhibitor. It is well absorbed and does not require strict food or fluid conditions, although it is usually given with food. Nelfinavir undergoes metabolism by several CYP isozymes. The major metabolite of nelfinavir produced by isoenzyme CYP2C19 has an antiviral activity equal to that of the parent compound, but it achieves plasma concentrations of only 40 percent of those of the parent compound. Nelfinavir is the only protease inhibitor that cannot be boosted by ritonavir, because it is not extensively metabolized by CYP3A. The half-life of nelfinavir is 5 hours. Diarrhea is the most common side effect and can be controlled by loperamide. Like other members of the class, nelfinavir can inhibit the metabolism of other drugs, resulting in required alterations of drug dosage or the prohibition of combined use. PROTEASE INHIBITORS Figure 38.31 Drugs that require dose modifications or cautious use with any protease inhibitor. F. Fosamprenavir (fAPV) Fosamprenavir [fos-am-PREN-a-veer] is a prodrug that is metabolized to amprenavir following oral absorption. Its long plasma half-life permits twice-a-day dosing. Co-administration of ritonavir increases the plasma levels of amprenavir and lowers the total daily dose. Fosamprenavir boosted with ritonavir is one of the alternative protease inhibitors according to the 2011 DHHS treatment guidelines. Nausea, vomiting, diarrhea, fatigue, paresthesias, and headache are common adverse effects. Like other members of the class, fosamprenavir can inhibit the metabolism of other drugs, resulting in required alterations of drug dosage or the prohibition of combined use. G. Lopinavir (LPV/r) Lopinavir [loe-PIN-a-veer] is a peptidomimetic alternative protease inhibitor, according to the 2011 DHHS treatment guidelines. Lopinavir has very poor intrinsic bioavailability, which is substantially enhanced by including a low dose of ritonavir in the formulation. GI adverse effects and hypertriglyceridemia are the most common side effects for lopinavir, in addition to the other protease inhibitor class side effects. Pharm 5th 3-21-11.indb 477 3/21/11 2:32:02 PM 478 38. Antiviral Drugs DRUGS MAJOR TOXICITIES AND CONCERNS Atazanavir Nausea, abdominal discomfort, headache, skin rash Darunavir Nausea, abdominal discomfort, headache, skin rash Fosamprenavir Nausea, diarrhea, vomiting, oral and perioral paresthesia, and rash Indinavir Benign hyperbilirubinemia, nephrolithiasis; take 1 hour before or 2 hours after food; may take with skim milk or a low-fat meal; drink >1.5 L of liquid daily Lopinavir Gastrointestinal, hyperlipidemia, insulin resistance Nelfinavir Diarrhea, nausea, flatulence, rash Ritonavir Diarrhea, nausea, taste perversion, vomiting, anemia, increased hepatic enzymes, increased triglycerides. Capsules require refrigeration, tablets do not. Take with meals; chocolate milk improves the taste Saquinavir Diarrhea, nausea, abdominal discomfort, elevated transaminase levels. Take with high-fat meal or within 2 hours of a full meal Tipranavir Nausea, vomiting, diarrhea, rash, severe hepatotoxicity, intracranial hemorrhage Like other members of the class, lopinavir can inhibit the metabolism of other drugs, resulting in required alterations of drug dosage or the prohibition of combined use. Enzyme inducers as well as St. John’s wort should be avoided, because they lower the plasma concentrations of lopinavir. Because the oral solution contains alcohol, disulfiram or metronidazole administration can cause unpleasant reactions. H. Atazanavir (ATV) Atazanavir [ah-ta-ZA-na-veer] is a preferred protease inhibitor. It inhibits HIV protease and is structurally unrelated to other HIV protease inhibitors. Atazanavir is well absorbed orally. It must be taken with food, because food increases absorption and bioavailability. The drug is highly protein bound (86 percent) and undergoes extensive CYP3A4-catalyzed biotransformation. It is excreted primarily in bile. Its half-life is about 7 hours, but it only needs to be administered once a day. Atazanavir is a competitive inhibitor of glucuronyl transferase, and benign hyperbilirubinemia and jaundice are known side effects. In the heart, atazanavir prolongs the PR interval and slows the heart rate. Atazanavir exhibits a decreased risk of hyperlipidemia, but it is not known if atazanavir is less likely to cause insulin resistance and lipodystrophy, as seen with other protease inhibitors. Like the other protease inhibitors, atazanavir is a potent inhibitor of CYP3A4 and has the potential for many drug interactions. Unboosted atazanavir is contraindicated with the use of proton-pump inhibitors, and administration must be spaced 10 hours apart from H_2-blockers and 1 hour after taking antacids. I. Tipranavir (TPV) Tipranavir [ti-PRA-na-veer] inhibits HIV protease in viruses that are resistant to the other protease inhibitors. Tipranavir is well absorbed when taken with food. The half-life is 6 hours, and it must be administered twice daily in combination with ritonavir. Tipranavir has unique actions both as a CYP450 inducer and a substrate that is different from the other protease inhibitors. Side effects are similar to those of the other protease inhibitors with the exception of two U.S. Food and Drug Administration black box warnings for severe and fatal hepatitis and rare cases of fatal and nonfatal intracranial hemorrhages. Most patients experiencing these severe side effects had underlying comorbidities. Tipranavir is useful in “salvage” regimens in patients with multidrug resistance. Figure 38.32 Summary of protease inhibitors. [Note: Lopinavir is co-formulated with ritonavir. Ritonavir inhibits the metabolism of lopinavir, J. Darunavir (DRV) thereby increasing its level in the plasma.] Darunavir [da-RU-na-veer] is the most recently approved protease inhibitor and is preferred by DHHS guidelines. Darunavir is approved for both initial therapy in naïve HIV-infected patients as well as the treatment of experienced patients with HIV that is resistant to other protease inhibitors. Darunavir must be taken with food to increase absorption. Its terminal elimination half-life is 15 hours when combined with ritonavir. Darunavir is extensively metabolized by the CYP3A enzymes and is also an inhibitor. The side effects are similar to those of the other protease inhibitors with the addition of possible rash. Early reports demonstrate a decreased risk of hyperlipidemia, but it is not known if darunavir is less likely to cause insulin resistance and lipodystrophy, as seen with other protease inhibitors. A summary of protease inhibitors is presented in Figure 38.32. Pharm 5th 3-21-11.indb 478 3/21/11 2:32:03 PM X. Integrase Inhibitor Used To Treat HIV Infection: Raltegravir 479 IX. ENTRY INHIBITORS USED TO TREAT HIV INFECTION A. Enfuvirtide Enfuvirtide [en-FU-veer-tide] was the first of a new class of antiretro viral drugs known as entry inhibitors. Enfuvirtide is a fusion inhibitor. For HIV to gain entry into the host cell, it must fuse its membrane with that of the host cell. This is accomplished by changes in the conformation of the viral transmembrane glycoprotein gp41, which occurs when HIV binds to the host cell surface. Enfuvirtide is a 36-amino-acid peptide that binds to gp41, preventing the conformational change. Enfuvirtide, in combination with other antiretroviral agents, is approved for therapy of treatment-experienced patients with evidence of viral replication despite ongoing antiretroviral drug therapy. As a peptide, it must be given subcutaneously. Most of the adverse effects are related to the injection, including pain, erythema, induration, and nodules, which occur in almost all patients. However, only 3 percent discontinue treatment because of them. Enfuvirtide must be reconstituted prior to administration. It is an expensive medication. B. Maraviroc Maraviroc [ma-RA-vi-roc] is the second entry inhibitor. Because it is well absorbed orally, it is formulated as an oral tablet. Maraviroc blocks the CCR5 co-receptor that works together with gp41 to facilitate HIV entry through the membrane into the cell. HIV may express preference for either the CCR5 co-receptor or the CXCR4 co-receptor or both. A test to determine viral tropism is required to distinguish the virus's use of the CCR5 from the CXCR4 co-receptor as well as mixed and dual tropic virus. Only the R5 virus that uses CCR5 to gain access to the cell can be treated with maraviroc. Maraviroc is metabolized by CYP450 liver enzymes, and the dose must be reduced when given with most protease inhibitors and increased in patients receiving the NNRTIs efavirenz, and etravirine. Maraviroc is generally well tolerated. X. INTEGRASE INHIBITOR USED TO TREAT HIV INFECTION: RALTEGRAVIR Raltegravir [ral-TEG-ra-veer] is the first of a new class of antiretroviral drugs known as integrase inhibitors. Raltegravir specifically inhibits the final step in integration of strand transfer of the viral DNA into our own host cell DNA. Raltegravir has a half-life of approximately 9 hours and is, therefore, dosed twice daily. The route of metabolism is UGT1A1-mediated glucuronidation and, therefore, drug interactions with CYP450 inducers, inhibitors, or substrates do not occur. Raltegravir is well tolerated, with nausea, headache, and diarrhea as the most common side effects. More serious side effects reported include elevated CK (creatine kinase) with muscle pain and rhabdomyolysis and possible depression with suicidal ideation. In combination with other antiretroviral agents, raltegravir is approved for both initial therapy of both treatment-naïve patients as well as treatment-experienced patients with evidence of viral replication despite ongoing antiretroviral drug therapy. Pharm 5th 3-21-11.indb 479 3/21/11 2:32:03 PM 480 38. Antiviral Drugs Study Questions Choose the ONE best answer. 38.1 A 30-year-old male patient with human immunodeficiency virus infection is being treated with a HAART (highly active antiretroviral therapy) regimen. Four weeks after initiating therapy, he comes to the emergency department complaining of fever, rash, and gastrointestinal upset. Which one of the following drugs is most likely the cause of his symptoms? Correct answer = C. The abacavir hypersensitivity reaction is characterized by fever, rash, and gastrointestinal uspet. The patient must stop therapy and not be rechallenged. A. Zidovudine. B. Nelfinavir. C. Abacavir. D. Efavirenz. E. Darunavir. 38.2 Chills, fever, and muscle aches are common reactions to which one of the following antiviral drugs? A. Acyclovir. B. Ganciclovir. C. Oseltamivir. D. Interferon. E. Ribavirin 38.3 An HIV infected woman is diagnosed with cytomegalovirus (CMV) retinitis. She has been on a HAART (highly active antiretroviral therapy) regimen containing zidovudine. Which of the following anti-CMV drugs is likely to cause additive myelosuppression with zidovudine? A. Acyclovir. B. Ganciclovir. C. Amantadine. D. Foscarnet. E. Ribavirin. 38.4 A 25-year-old man is diagnosed with HIV, and therapy is initiated. After the first week of therapy, the patient complains of headaches, irritability, and nightmares. Which one of the following antiretroviral drugs is most likely to be causing these symptoms? Correct answer = D. Interferon causes flu-like symptoms, including chills, fever, and myalgias, upon injection. Pretreatment with acetaminophen decreases the reaction. The other drugs do not cause this particular adverse effect. Correct answer = B. Ganciclovir is myelosuppressive in and of itself and will add to the myelosuppression caused by zidovudine. The combination has an increased risk of neutropenia and anemia. Foscarnet has anti-CMV activity, but it does not cause myelosuppression. The other drugs are not effective against CMV. Correct answer = A. CNS symptoms are characteristic of efavirenz, especially at the beginning of therapy, and occur in nearly 50 percent of patients. These adverse effects abate with continued administration of efavirenz. The other drugs are unlikely to cause CNS side effects. A. Efavirenz. B. Indinavir. C. Lamivudine. D. Nevirapine. E. Stavudine. Pharm 5th 3-21-11.indb 480 3/21/11 2:32:04 PM 39 Anticancer Drugs I. OVERVIEW It is estimated that 25 percent of the population of the United States will face a diagnosis of cancer during their lifetime, with 1.3 million new cancer patients diagnosed each year. Less than a quarter of these patients will be cured solely by surgery and/or local radiation. Most of the remainder will receive systemic chemotherapy at some time during their illness. In a small fraction (approximately 10 percent) of patients with cancer representing selected neoplasms, the chemotherapy will result in a cure or a prolonged remission. However, in most cases, the drug therapy will produce only a regression of the disease, and complications and/or relapse may eventually lead to death. Thus, the overall 5-year survival rate for cancer patients is about 65 percent, ranking cancer second only to cardiovascular disease as a cause of mortality. See Figure 39.1 for a list of the anticancer agents discussed in this chapter. II. PRINCIPLES OF CANCER CHEMOTHERAPY Cancer chemotherapy strives to cause a lethal cytotoxic event or apoptosis in the cancer cell that can arrest a tumor’s progression. The attack is generally directed toward DNA or against metabolic sites essential to cell replication, for example, the availability of purines and pyrimidines that are the building blocks for DNA or RNA synthesis (Figure 39.2). Ideally, these anticancer drugs should interfere only with cellular processes that are unique to malignant cells. Unfortunately, most currently available anticancer drugs do not specifically recognize neoplastic cells but, rather, affect all kinds of proliferating cells, both normal and abnormal. Therefore, almost all antitumor agents have a steep dose-response curve for both toxic and therapeutic effects. A. Treatment strategies 1. Goals of treatment: The ultimate goal of chemotherapy is a cure (that is, long-term, disease-free survival). A true cure requires the eradication of every neoplastic cell. If a cure is not attainable, then the goal becomes control of the disease (stop the cancer from enlarging and spreading) to extend survival and maintain the best quality of life. Thus, the individual maintains a “normal” existence, with the cancer being treated as a chronic disease. In either case, the neoplastic cell burden is initially reduced (debulked), either by surgery and/or by radiation, followed by chemotherapy, immunotherapy, or a combination of these treatment Pharm 5th 3-21-11.indb 481 ANTIMETABOLITES Capecitabine XELODA Cladribine LEUSTATIN Cytarabine CYTOSINE ARABINOSIDE Floxuridine FUDR Fludarabine FLUDARA 5-Fluorouracil EFUDEX Gemcitabine GEMZAR 6-Mercaptopurine PURINETHOL Methotrexate (MTX) TREXALL 6-Thioguanine THIOGUANINE TABLOID ANTIBIOTICS Bleomycin BLENOXANE Dactinomycin COSMEGEN Daunorubicin CERUBIDINE Doxorubicin ADRIAMYCIN Epirubicin ELLENCE Idarubicin IDAMYCIN ALKYLATING AGENTS Busulfan MYLERAN Carmustine BICNU Chlorambucil LEUKERAN Cyclophosphamide CYTOXAN Dacarbazine DTIC-DOME Ifosfamide IFEX Lomustine CEENU Mechlorethamine MUSTARGEN Melphalan ALKERAN Streptozocin ZANOSAR Temozolomide TEMODAR MICROTUBULE INHIBITORS Docetaxel TAXOTERE Paclitaxel ONXOL Vinblastine VELBAN Vincristine VINCASAR PFS, ONCOVIN Vinorelbine NAVELBINE Figure 39.1 Summary of chemotherapeutic agents. (Continued on next page.) 3/21/11 2:32:04 PM 482 39. Anticancer Drugs STEROID HORMONES AND THEIR ANTAGONISTS Aminoglutethimide CYTADREN Anastrozole ARIMIDEX Bicalutamide CASODEX Estrogens various Exemestane AROMASIN Flutamide EULEXIN Goserelin ZOLADEX Letrozole FEMARA Leuprolide LUPRON Megestrol acetate MEGACE Nilutamide NILANDRON Prednisone DELTASONE Tamoxifen NOVALDEX Toremifene FARESTON MONOCLONAL ANTIBODIES Bevacizumab AVASTIN Cetuximab ERBITUX Rituximab RITUXAN Trastuzumab HERCEPTIN OTHERS Asparaginase ELSPAR Carboplatin PARAPLATIN Cisplatin PLATINOL Etoposide TOPOSAR, VEPESID Gefitinib IRESSA Imatinib GLEEVEC Interferons PEG-INTRON Irinotecan CAMPTOSAR Oxaliplatin ELOXATIN Procarbazine MATULANE Topotecan HYCAMTIN Figure 39.1 (continued) Summary of chemotherapeutic agents. modalities (Figure 39.3). In advanced stages of cancer, the likelihood of controlling the cancer is far from reality and the goal is palliation (that is, alleviation of symptoms and avoidance of life-threatening toxicity). This means that chemotherapeutic drugs may be used to relieve symptoms caused by the cancer and improve the quality of life, even though the drugs may not lengthen life. 2. Indications for treatment: Chemotherapy is indicated when neoplasms are disseminated and are not amenable to surgery. Chemotherapy is also used as a supplemental treatment to attack micrometastases following surgery and radiation treatment, in which case it is called adjuvant chemotherapy. Chemotherapy given prior to the surgical procedure in an attempt to shrink the cancer is referred to as neoadjuvant chemotherapy, and chemotherapy given in lower doses to assist in prolonging a remission is known as maintenance chemotherapy. 3. Tumor susceptibility and the growth cycle: The fraction of tumor cells that are in the replicative cycle (“growth fraction”) influences their susceptibility to most cancer chemotherapeutic agents. Rapidly dividing cells are generally more sensitive to anticancer drugs, whereas slowly proliferating cells are less sensitive to chemotherapy. In general, nonproliferating cells (those in the G0 phase; Figure 39.4) usually survive the toxic effects of many of these agents. a. Cell-cycle specificity of drugs: Both normal cells and tumor cells go through growth cycles (see Figure 39.4). However, the number of cells that are in various stages of the cycle may differ in normal and neoplastic tissues. Chemotherapeutic agents that are effective only against replicating cells (that is, those cells that are cycling) are said to be cell-cycle specific (see Figure 39.4), whereas other agents are said to be cell-cycle nonspecific. The nonspecific drugs, although having generally more toxicity in cycling cells, are also useful against tumors that have a low percentage of replicating cells. METHOTREXATE 6-MERCAPTOPURINE THIOGUANINE Purine and pyrimidine synthesis Proteins Inhibit the de novo synthesis of purine ring. Inhibit nucleotide interconversions. Inhibition of dihydrofolate reductase leads to an inhibition of purine ring and dTMP biosynthesis. 5-FLUOROURACIL Inhibits dTMP synthesis. Ribonucleotides ALKYLATING AGENTS NITROSOUREAS CISPLATIN DACTINOMYCIN DOXORUBICIN DAUNORUBICIN Alter structure and function of DNA by cross-linking and/or fragmenting of DNA strands. Intercalate with DNA, disrupting DNA function. Deoxyribonucleotides BLEOMYCIN PEPTIDE ANTIBIOTICS DOXORUBICIN DAUNORUBICIN Scission of DNA by an oxidative process. CYTARABINE Terminates DNA chain elongation. Incorporated into DNA and RNA results in altered functioning of nucleic acids. RNA DNA Figure 39.2 Examples of chemotherapeutic agents affecting RNA and DNA. dTMP = deoxythymidine monophosphate. Pharm 5th 3-21-11.indb 482 3/21/11 2:32:05 PM II. Principles Of Cancer Chemotherapy 483 SIGNIFICANCE OF A 1-g TUMOR MASS A total of 109 cells is the smallest tumor burden that is physically detectable. These 1 billion cells represent a tumor weighing about 1 g or about the size of a small grape. Clinical symptoms usually first appear at this stage. 1-kg mass 10 12 1-g mass Tumor cell burden (log scale) Initial remissions are transient, with symptoms recurring between treatments. Survival is extended, but the patient eventually dies of the disease. Death Cancer cells become increasingly less responsive to treatment 10 10 10 Death PALLIATIVE CHEMOTHERAPY Patient symptomatic Patient asymptomatic 8 Surgery 10 6 Treatment with anticancer drug 1-mg mass 10 4 10 2 “Cure” Time CURATIVE CHEMOTHERAPY (solid tumors, such as testicular carcinoma) Tumor burden is initially reduced by surgery and/or radiation. Treatment of occult micrometastases is continued after clinical signs of cancer have disappeared. CURATIVE CHEMOTHERAPY (disseminated cancers, such as leukemia) Combination-drug chemotherapy reduces the chance of drug resistance. Each drug is chosen to have a different cellular site of action or different cell-cycle specificity. Each drug is chosen to have a different organ toxicity. Figure 39.3 Effects of various treatments on the cancer cell burden in a hypothetical patient. b. Tumor growth rate: The growth rate of most solid tumors in vivo is initially rapid, but growth rate usually decreases as the tumor size increases (see Figure 39.3). This is due to the unavailability of nutrients and oxygen caused by inadequate vascularization and lack of blood circulation. Reducing the tumor burden through surgery or radiation often promotes the recruitment of the remaining cells into active proliferation and increases their susceptibility to chemotherapeutic agents. B. Treatment regimens and scheduling Drugs are usually administered on the basis of body surface area, with an effort being made to tailor the medications to each patient. 1. Log kill: Destruction of cancer cells by chemotherapeutic agents follows first-order kinetics (that is, a given dose of drug destroys a constant fraction of cells). The term “log kill” is used to describe this phenomenon. For example, a diagnosis of leukemia is generally made when there are about 109 (total) leukemic cells. Consequently, if treatment leads to a 99.999-percent kill, then 0.001 percent of 109 cells (or 104 cells) would remain. This is defined as a five-log kill (reduction of 105 cells). At this point, the patient will become Pharm 5th 3-21-11.indb 483 3/21/11 2:32:06 PM 484 A 39. Anticancer Drugs The cell cycle Synthesis of cellular components required for mitosis Resting state (cell is not dividing) Mitotic phase (cell divides) Go M G2 G1 S DNA is replicated B Synthesis of enzymes needed for DNA synthesis Cell-cycle specific drugs Antimetabolites Bleomycin peptide antibiotics Vinca alkaloids Etoposide Effective for highgrowth-fraction malignancies, such as hematologic cancers C Cell-cycle nonspecific drugs Alkylating agents Antibiotics Cisplatin Nitrosoureas Effective for both lowgrowth-fraction malignancies, such as solid tumors, as well as high-growth-fraction malignancies Figure 39.4 Effects of chemotherapeutic agents on the growth cycle of mammalian cells. Pharm 5th 3-21-11.indb 484 asymptomatic, and the patient is in remission (see Figure 39.3). For most bacterial infections, a five-log (100,000-fold) reduction in the number of microorganisms results in a cure, because the immune system can destroy the remaining bacterial cells. However, tumor cells are not as readily eliminated, and additional treatment is required to totally eradicate the leukemic cell population. 2. Pharmacologic sanctuaries: Leukemic or other tumor cells find sanctuary in tissues such as the central nervous system (CNS), where transport constraints prevent certain chemotherapeutic agents from entering. Therefore, a patient may require irradiation of the craniospinal axis or intrathecal administration of drugs to eliminate the leukemic cells at that site. Similarly, drugs may be unable to penetrate certain areas of solid tumors. 3. Treatment protocols: Combination-drug chemotherapy is more successful than single-drug treatment in most of the cancers for which chemotherapy is effective. a. Combinations of drugs: Cytotoxic agents with qualitatively different toxicities, and with different molecular sites and mechanisms of action, are usually combined at full doses. This results in higher response rates, due to additive and/ or potentiated cytotoxic effects, and nonoverlapping host toxicities. In contrast, agents with similar dose-limiting toxicities, such as myelosuppression, nephrotoxicity, or cardiotoxicity, can be combined safely only by reducing the doses of each. b. Advantages of drug combinations: The advantages of such drug combinations are that they 1) provide maximal cell killing within the range of tolerated toxicity, 2) are effective against a broader range of cell lines in the heterogeneous tumor population, and 3) may delay or prevent the development of resistant cell lines. c. Treatment protocols: Many cancer treatment protocols have been developed, and each one is applicable to a particular neoplastic state. They are usually identified by an acronym. For example, a common regimen called POMP, used for the treatment of acute lymphocytic leukemia, consists of prednisone, oncovin (vincristine), methotrexate, and purinethol (mercaptopurine). Therapy is scheduled intermittently (approximately 21 days apart) to allow recovery of the patient’s immune system, which is also affected by the chemotherapeutic agent, thus reducing the risk of serious infection. C. Problems associated with chemotherapy Cancer drugs are toxins that present a lethal threat to the cells. It is, therefore, not surprising that cells have evolved elaborate defense mechanisms to protect themselves from chemical toxins, including chemotherapeutic agents. 1. Resistance: Some neoplastic cells (for example, melanoma) are inherently resistant to most anticancer drugs. Other tumor types may acquire resistance to the cytotoxic effects of a medication by mutating, particularly after prolonged administration of suboptimal drug doses. The development of drug resistance is minimized by short-term, intensive, intermittent therapy with combinations of 3/21/11 2:32:09 PM II. Principles Of Cancer Chemotherapy 485 drugs. Drug combinations are also effective against a broader range of resistant cells in the tumor population. A variety of mechanisms are responsible for drug resistance, each of which is considered separately in the discussion of a particular drug. 2. Multidrug resistance: Stepwise selection of an amplified gene that codes for a transmembrane protein (P-glycoprotein for “permeability” glycoprotein; Figure 39.5) is responsible for multidrug resistance. This resistance is due to adenosine triphosphate–dependent pumping of drugs out of the cell in the presence of P-glycoprotein. Crossresistance following the use of structurally unrelated agents also occurs. For example, cells that are resistant to the cytotoxic effects of the vinca alkaloids are also resistant to dactinomycin and to the anthracycline antibiotics as well as to colchicine, and vice versa. These drugs are all naturally occurring substances, each of which has a hydrophobic aromatic ring and a positive charge at neutral pH. [Note: P-glycoprotein is normally expressed at low levels in most cell types, but higher levels are found in the kidney, liver, pancreas, small intestine, colon, and adrenal gland. It has been suggested that the presence of P-glycoprotein may account for the intrinsic resistance to chemotherapy observed with adenocarcinomas.] Certain drugs at high concentrations (for example, verapamil) can inhibit the pump and, thus, interfere with the efflux of the anticancer agent. However, these drugs are undesirable because of adverse pharmacologic actions of their own. Pharmacologically inert pump blockers are being sought. 3. Toxicity: Therapy aimed at killing rapidly dividing cancer cells also affects normal cells undergoing rapid proliferation (for example, cells of the buccal mucosa, bone marrow, gastrointestinal [GI] mucosa, and hair follicles), contributing to the toxic manifestations of chemotherapy. a. Common adverse effects: Most chemotherapeutic agents have a narrow therapeutic index. Severe vomiting, stomatitis, bone marrow suppression, and alopecia occur to a lesser or greater extent during therapy with all antineoplastic agents. Vomiting is often controlled by administration of antiemetic drugs. Some toxicities, such as myelosuppression that predisposes to infection, are common to many chemotherapeutic agents (Figure 39.6), whereas other adverse reactions are confined to specific agents, such as, bladder toxicity with cyclophosphamide, cardiotoxicity with doxorubicin, and pulmonary fibrosis with bleomycin. The duration of the side effects varies widely. For example, alopecia is transient, but the cardiac, pulmonary, and bladder toxicities are irreversible. b. Minimizing adverse effects: Some toxic reactions may be ameliorated by interventions, such as the use of cytoprotectant drugs, perfusing the tumor locally (for example, a sarcoma of the arm), removing some of the patient’s marrow prior to intensive treatment and then reimplanting it, or promoting intensive diuresis to prevent bladder toxicities. The megaloblastic anemia that occurs with methotrexate can be effectively counteracted by administering folinic acid (leucovorin, 5-formyltetrahydrofolic acid; see below). With the availability of human granulocyte colony– Pharm 5th 3-21-11.indb 485 Vincristine, vinblastine doxorubicin, bleomycin etoposide, and others ADP + Pi ATP Vincristine, vinblastine, doxorubicin, bleomycin etoposide, and others Figure 39.5 The six membrane-spanning loops of the P-glycoprotein form a central channel for the ATP-dependent pumping of drugs from the cell. Vinblastine Nitrosoureas Cyclophosphamide Cytarabine Doxorubicin Carboplatin Procarbazine Etoposide Methotrexate 5-Fluorouracil Bleomycin Vincristine Methotrexate (with leucovorin) Mild Strong Relative myelosuppression Figure 39.6 Comparison of myelosuppressive potential of chemotherapeutic drugs. 3/21/11 2:32:13 PM 486 39. Anticancer Drugs stimulating factor (filgrastim), the neutropenia associated with treatment of cancer by many drugs can be partially reversed. Diet or intestinal flora Folate Methotrexate Folate Activetransport process TARGET CELL Dihydrofolate reductase dTMP Methotrexate FH2 FH4 Dihydrofolate reductase dUMP N5, N10-Methylene-FH4 Adenine Guanine Thymidine Methionine Serine Leucovorin rescue Administer N5-formyl-FH4 (leucovorin or folinic acid), which is converted to N5, N10-methylene-FH4 and, therefore, bypasses the inhibited reductase. Figure 39.7 Mechanism of action of methotrexate and the effect of administration of leucovorin. FH2 = dihydrofolate; FH4 = tetrahydrofolate; dTMP = deoxythymidine monophosphate; dUMP = deoxyuridine monophosphate. 4. Treatment-induced tumors: Because most antineoplastic agents are mutagens, neoplasms (for example, acute nonlymphocytic leukemia) may arise 10 or more years after the original cancer was cured. [Note: Treatment-induced neoplasms are especially a problem after therapy with alkylating agents.] III. ANTIMETABOLITES Antimetabolites are structurally related to normal compounds that exist within the cell. They generally interfere with the availability of normal purine or pyrimidine nucleotide precursors, either by inhibiting their synthesis or by competing with them in DNA or RNA synthesis. Their maximal cytotoxic effects are in S-phase (and are, therefore, cell-cycle specific). A. Methotrexate The vitamin folic acid plays a central role in a variety of metabolic reactions involving the transfer of one-carbon units1 and is essential for cell replication. Methotrexate [meth-oh-TREK-sate] (MTX) is structurally related to folic acid and acts as an antagonist of that vitamin by inhibiting dihydrofolate reductase2 (DHFR), which is the enzyme that converts folic acid to its active, coenzyme form, tetrahydrofolic acid (FH4). 1. Mechanism of action: Folic acid is obtained from dietary sources or from that produced by intestinal flora. It undergoes reduction to FH4 via a reaction catalyzed by intracellular nicotinamide-adenine dinucleotide phosphate–dependent DHFR (Figure 39.7). MTX enters the cell by active-transport processes that normally mediate the entry of N5-methyl-FH4. At high concentrations, the drug can also diffuse into the cell. MTX has an unusually strong affinity for DHFR and effectively inhibits the enzyme. Like tetrahydrofolate itself, MTX becomes polyglutamated within the cell, a process that favors intracellular retention of the compound due to increased negative charge. MTX polyglutamates also potently inhibit DHFR. This inhibition deprives the cell of folate coenzymes and leads to decreased production of compounds that depend on these coenzymes for their biosynthesis. Although these molecules include the nucleotides adenine, guanine, and thymidine and the amino acids methionine and serine, depletion of thymidine is the most prominent effect. This leads to depressed DNA, RNA, and protein synthesis and, ultimately, to cell death (see Figure 39.7). The inhibition of DHFR can only be reversed by a thousandfold excess of the natural substrate, dihydrofolate (FH2; see Figure 39.7), or by administration of leucovorin, which bypasses the blocked enzyme and replenishes the folate pool. [Note: Leucovorin, or folinic acid, is the N5-formyl group–carrying form of FH4.] MTX is specific for the S phase of the cell cycle. 2. Resistance: Nonproliferating cells are resistant to MTX, probably because of a relative lack of DHFR, thymidylate synthase, and/or INFO LINK Pharm 5th 3-21-11.indb 486 1 See Chapter 20 in Lippincott’s Illustrated Reviews: Biochemistry for a discussion of the one-carbon pool. 2 See Chapter 20 in Lippincott’s Illustrated Reviews: Biochemistry for a discussion of dihydrofolate reductase. 3/21/11 2:32:16 PM III. Antimetabolites the glutamylating enzyme. Decreased levels of the MTX polyglutamate have been reported in resistant cells and may be due to its decreased formation or increased breakdown. Resistance in neoplastic cells can be due to amplification (production of additional copies) of the gene that codes for DHFR, resulting in increased levels of this enzyme. The enzyme affinity for MTX may also be diminished. Resistance can also occur from a reduced influx of MTX, apparently caused by a change in the carrier-mediated transport responsible for pumping the drug into the cell. 3. Therapeutic uses: MTX, usually in combination with other drugs, is effective against acute lymphocytic leukemia, choriocarcinoma, Burkitt lymphoma in children, breast cancer, and head and neck carcinomas. In addition, low-dose MTX is effective as a single agent against certain inflammatory diseases, such as severe psoriasis and rheumatoid arthritis as well as Crohn disease. All patients receiving MTX require close monitoring for possible toxic effects. 4. Pharmacokinetics: a. Administration and distribution: MTX is variably absorbed at low doses from the GI tract, but it can also be administered by intramuscular, intravenous (IV), and intrathecal routes (Figure 39.8). [Note: Because MTX does not penetrate the blood-brain barrier, it is administered intrathecally to destroy neoplastic cells that are thriving in the sanctuary of the CNS.] High concentrations of the drug are found in the intestinal epithelium, liver, and kidney as well as in ascites and pleural effusions. MTX is also distributed to the skin. 487 Adequate hydration is important at high doses Poor penetration into CNS IV IM Intrathecal Unchanged drug appears in urine; at high doses, 7-OH metabolite is also excreted Methotrexate Figure 39.8 Administration and fate of methotrexate. CNS = central nervous system; IV = intravenous; IM = intramuscular. b. Fate: As previously mentioned, MTX is metabolized to polyglutamate derivatives. This property is important, because the polyglutamates, which also inhibit DHFR, remain within the cell even in the absence of extracellular drug. This is in contrast to MTX per se, which rapidly leaves the cell as the extracellular drug levels fall. High doses of MTX undergo hydroxylation at the 7 position and become 7-hyroxymethotrexate. This derivative is much less active as an antimetabolite. It is less water soluble than MTX and may lead to crystalluria. Therefore, it is important to keep the urine alkaline and the patient well hydrated to avoid renal toxicity. Excretion of the parent drug and the 7-OH metabolite occurs primarily via urine, although some of the drug and its metabolite appear in feces due to enterohepatic excretion. 5. Adverse effects: a. Commonly observed toxicities: In addition to nausea, vomiting, and diarrhea, the most frequent toxicities occur in tissues that are constantly renewing. Thus, MTX causes stomatitis, myelosuppression, erythema, rash, urticaria, and alopecia. Some of these adverse effects can be prevented or reversed by administering leucovorin (see Figure 39.7), which is taken up more readily by normal cells than by tumor cells. Doses of leucovorin must be kept minimal to avoid possible interference with the antitumor action of MTX. Pharm 5th 3-21-11.indb 487 3/21/11 2:32:18 PM 488 39. Anticancer Drugs b. Renal damage: Although uncommon during conventional therapy, renal damage is a complication of high-dose MTX and its 7-OH metabolite, which can precipitate in the tubules. Alkalinization of the urine and hydration help to prevent this problem. SH N N N N 6-Mercaptopurine Hypoxanthine-guanine phosphoribosyl transferase c. Hepatic function: Hepatic function should be monitored. Longterm use of MTX may lead to cirrhosis. SH N N O O P O O d. Pulmonary toxicity: This is a rare complication. Children who are being maintained on MTX may develop cough, dyspnea, fever, and cyanosis. Infiltrates are seen on radiographs. This toxicity is reversible with suspension of the drug. N N O HO e. Neurologic toxicities: These are associated with intrathecal administration of MTX and include subacute meningeal irritation, stiff neck, headache, and fever. Rarely, seizures, encephalopathy, or paraplegia occur. Long-lasting effects, such as learning disabilities, have been seen in children who received the drug by this route. HO 6-Thioinosinic acid (TIMP) Feedback inhibition of phosphoribosylamine synthesis AMP IMP TGMP f. Contraindications: Because MTX is teratogenic in experimental animals and is an abortifacient, it should be avoided in pregnancy. [Note: MTX is used with misoprostol to induce abortion.] XMP RNA Figure 39.9 Actions of 6-mercaptopurine. GMP = guanosine monophosphate; AMP = adenosine monophosphate; XMP = xanthosine monophosphate. B. 6-Mercaptopurine 6-Mercaptopurine [mer-kap-toe-PYOOR-een] (6-MP) is the thiol analog of hypoxanthine. 6-MP and 6-thioguanine were the first purine analogs to prove beneficial for treating neoplastic disease. [Note: Azathioprine, an immunosuppressant, exerts its cytotoxic effects after conversion to 6-MP.] 6-MP is used principally in the maintenance of remission in acute lymphoblastic leukemia. 6-MP and its analog, azathioprine, are also beneficial in the treatment of Crohn disease. 1. Mechanism of action: a. Nucleotide formation: To exert its antileukemic effect, 6-MP must penetrate target cells and be converted to the nucleotide analog, 6-MP-ribose phosphate (better known as 6-thioinosinic acid, or TIMP; Figure 39.9). The addition of the ribose phosphate is catalyzed by the salvage pathway enzyme, hypoxanthineguanine phosphoribosyl transferase (HGPRT).3 b. Inhibition of purine synthesis: A number of metabolic processes involving purine biosynthesis and interconversions are affected by the nucleotide analog, TIMP. Like adenosine monophosphate (AMP), guanosine monophosphate (GMP), and inosine mono phosphate (IMP), TIMP can inhibit the first step of de novo purine-ring biosynthesis (catalyzed by glutamine phosphoribosyl pyrophosphate amidotransferase). TIMP also blocks the formation of AMP and xanthinuric acid from inosinic acid.4 3See Chapter 22 in Lippincott’s Illustrated Reviews: Biochemistry for a discussion INFO LINK of hypoxanthine-guanine phosphoribosyl transferase. 4See Chapter 22 in Lippincott’s Illustrated Reviews: Biochemistry for a discussion of the conversion of IMP to other purine nucleotides. Pharm 5th 3-21-11.indb 488 3/21/11 2:32:19 PM III. Antimetabolites c. Incorporation into nucleic acids: TIMP is converted to thioguanine monophosphate (TGMP), which after phosphorylation to di- and triphosphates can be incorporated into RNA. The deoxyribonucleotide analogs that are also formed are incorporated into DNA. This results in nonfunctional RNA and DNA. 2. Resistance: Resistance is associated with 1) an inability to biotransform 6-MP to the corresponding nucleotide because of decreased levels of HGPRT (for example, in Lesch-Nyhan syndrome, in which patients lack this enzyme), 2) increased dephosphorylation, or 3) increased metabolism of the drug to thiouric acid or other metabolites. 3. Pharmacokinetics: Absorption by the oral route is erratic and incomplete. Once it enters the blood circulation, the drug is widely distributed throughout the body, except for the cerebrospinal fluid (CSF; Figure 39.10). The bioavailability of 6-MP can be reduced by the first-pass metabolism in the liver. While undergoing metabolism in the liver, 6-MP is converted to the 6-methylmercaptopurine derivative or to thiouric acid (an inactive metabolite). [Note: The latter reaction is catalyzed by xanthine oxidase.5] Because the xanthine oxidase inhibitor, allopurinol, is frequently used to reduce hyperuricemia in cancer patients receiving chemotherapy, it is important to decrease the dose of 6-MP by 75 percent in these individuals to avoid accumulation of the drug and exacerbation of toxicities (Figure 39.11). The parent drug and its metabolites are excreted by the kidney. 4. Adverse effects: Bone marrow depression is the principal toxicity. Side effects also include anorexia, nausea, vomiting, and diarrhea. Occurrence of hepatotoxicity in the form of jaundice has been reported in about one third of adult patients. C. 6-Thioguanine 6-Thioguanine [thye-oh-GWAH-neen] (6-TG), a purine analog, is primarily used in the treatment of acute nonlymphocytic leukemia in combination with daunorubicin and cytarabine. Like 6-MP, 6-TG is converted intracellularly to TGMP (also called 6-thioguanylic acid) by the enzyme HGPRT. TGMP is further converted to the di- and triphosphates, thioguanosine diphosphate and thioguanosine triphosphate, which then inhibit the biosynthesis of purines and also the phosphorylation of GMP to guanosine diphosphate. The nucleotide form of 6-TG is incorporated into DNA that leads to cell-cycle arrest. 489 Drug does not cross blood-brain barrier Drug and metabolites appear in urine the urine 6-Mercaptopurine Figure 39.10 Administration and fate of 6-mercaptopurine. 6-Mercaptopurine ? CAUTION Allopurinol Figure 39.11 Potential drug interaction between allopurinol and 6-mercaptopurine. 1. Pharmacokinetics: Similar to 6-MP, the absorption of oral 6-TG is also incomplete and erratic. The peak concentration in the plasma is reached in 2 to 4 hours after ingestion. When 6-TG is administered, it is converted to the S-methylation product, 2-amino-6-methylthiopurine by thiopurine methyltransferase (TPMT), which appears in the urine. Patients with low or intermediate TPMT activity accumulate higher concentrations of thioguanine cytotoxic metabolites compared to patients with normal TPMT activity. This results in INFO LINK Pharm 5th 3-21-11.indb 489 5See Chapter 22 in Lippincott’s Illustrated Reviews: Biochemistry for a discussion of xanthine oxidase. 3/21/11 2:32:21 PM 490 39. Anticancer Drugs unexpectedly high myelosuppression and has also been associated with the occurrence of secondary malignancies. Approximately 3 percent of whites and blacks express either a homozygous deletion or mutation of the TPMT gene. Because an estimated 10 percent of patients may be at increased risk for toxicity because of a heterozygous deletion or mutation of TPMT, TPMT genotyping is recommended before therapy. To a lesser extent, 6-thioxanthine and 6-thiouric acid are also formed by the action of guanase. Because the deamination product 6-thioanthine is an inactive metabolite, 6-TG may be administered along with allopurinol without any dose reduction. O F HN O N H 5-Fluorouracil (5-FU) TARGET CELL Carrier Uridine phosphorylase 5-FU 5-FUR 5-FUMP Phosphoribosyl transferase 2. Adverse effects: Bone marrow depression is the dose-related adverse effect. 6-TG is not recommended for maintenance therapy or continuous long-term treatments due to the risk of liver toxicity. Uridine kinase 5-FUTP D. Fludarabine 5-FUDP Ribonucleotide reductase RNA 5-FdUMP dTMP dUMP 5 10 Thymidylate synthetase N ,N - Methylene - FH4 FH 2 Needed for DNA synthesis and cell growth Figure 39.12 Mechanism of the cytotoxic action of 5-FU. 5-FU is converted to 5-flurodeoxyuridine monophosphate (5-FdUMP), which competes with deoxyuridine monophosphate (dUMP) for the enzyme thymidylate synthetase. 5-FU = 5-fluorouracil; 5-FUR = 5-fluorouridine; 5-FUMP = 5-fluorouridine monophosphate; 5-FUDP = 5-fluorouridine diphosphate; 5-FUTP = 5-fluorouridine triphosphate; dUMP = deoxyuridine monophosphate; dTMP = deoxythymidine monophosphate. Fludarabine [floo-DARE-a-been] is the 5’-phosphate of 2-fluoroadenine arabinoside, a purine nucleotide analog. It is useful in the treatment of chronic lymphocytic leukemia and may replace chlorambucil, the current drug of choice. Fludarabine is also effective against hairy cell leukemia and indolent non-Hodgkin lymphoma. Fludarabine is a prodrug, the phosphate being removed in the plasma to form 2-F-araA, which is taken up into cells and again phosphorylated (initially by deoxycytidine kinase). Although the exact cytotoxic mechanism is uncertain, the triphosphate is incorporated into both DNA and RNA. This decreases their synthesis in the S phase and affects their function. Resistance is associated with reduced uptake into cells, lack of deoxycytidine kinase, and decreased affinity for DNA polymerase as well as other mechanisms. Fludarabine is administered IV rather than orally, because intestinal bacteria split off the sugar to yield the very toxic metabolite, fluoroadenine. Urinary excretion accounts for partial elimination. In addition to nausea, vomiting, and diarrhea, myelosuppression is the dose-limiting toxicity. Fever, edema, and severe neurologic toxicity also occur. At high doses, progressive encephalopathy, blindness, and death have been reported. E. Cladribine Another purine analog, 2-chlorodeoxyadenosine, or cladribine [KLA-dribeen], undergoes reactions similar to those of fludarabine, and it must be converted to a nucleotide to be cytotoxic. It becomes incorporated at the 3’-terminus of DNA and, thus, hinders elongation. It also affects DNA repair and is a potent inhibitor of ribonucleotide reductase.6 Resistance may be due to mechanisms analogous to those that affect fludarabine, although cross-resistance is not a problem. Cladribine is effective against hairy cell leukemia, chronic lymphocytic leukemia, and non-Hodgkin lymphoma. It also has some activity against multiple sclerosis. The drug is given as a single, continuous infusion. Cladribine distributes throughout the body, including into the CSF. Severe bone marrow suppression is a common adverse effect, as is fever. Peripheral neuropathy has also been reported. The drug is teratogenic. INFO LINK Pharm 5th 3-21-11.indb 490 6 See Chapter 22 in Lippincott’s Illustrated Reviews: Biochemistry for a discussion of ribonucleotide reductase. 3/21/11 2:32:23 PM III. Antimetabolites F. 5-Fluorouracil 5-Fluorouracil [flure-oh-YOOR-ah-sil] (5-FU), a pyrimidine analog, has a stable fluorine atom in place of a hydrogen atom at position 5 of the uracil ring. The fluorine interferes with the conversion of deoxyuridylic acid to thymidylic acid, thus depriving the cell of thymidine, one of the essential precursors for DNA synthesis. 5-FU is employed primarily in the treatment of slowly growing solid tumors (for example, colorectal, breast, ovarian, pancreatic, and gastric carcinomas). When applied topically, 5-FU is also effective for the treatment of superficial basal cell carcinomas. 1. Mechanism of action: 5-FU per se is devoid of antineoplastic activity. It enters the cell through a carrier-mediated transport system and is converted to the corresponding deoxynucleotide (5-flurodeoxyuridine monophosphate [5-FdUMP]; Figure 39.12), which competes with deoxyuridine monophosphate for thymidylate synthase.7 5-FdUMP acts as a pseudosubstrate and is trapped with the enzyme and its coenzyme N5,N10-methylene tetrahydrofolic acid (leucovorin), in a ternary complex that cannot proceed to release products. DNA synthesis decreases due to lack of thymidine, leading to imbalanced cell growth and “thymidine-less death” of rapidly dividing cells. [Note: Leucovorin is administered with 5-FU, because the reduced folate coenzyme is required in the thymidylate synthase inhibition. Addition of the coenzyme increases the effectiveness of 5-FU to form a ternary complex and produce an antipyrimidine effect. For example, the standard regimen for advanced colorectal cancer today is irinotecan plus 5-FU/leucovorin.] 5-FU is also incorporated into RNA, and low levels have been detected in DNA. In the latter case, a glycosylase excises the 5-FU, damaging the DNA. 5-FU produces the anticancer effect in the S phase of the cell cycle. 491 Drug crosses blood-brain barrier IV Metabolites appear in urine the urine 5-Fluorouracil Figure 39.13 Administration and fate of 5-fluorouracil. IV = intravenous. 2. Resistance: Resistance is encountered when the cells have lost their ability to convert 5-FU into its active form (5-FdUMP) or when they have altered or increased thymidylate synthase levels. 3. Pharmacokinetics: Because of its severe toxicity to the GI tract, 5-FU is given IV or, in the case of skin cancer, topically (Figure 39.13). The drug penetrates well into all tissues, including the CNS. 5-FU is rapidly metabolized in the liver, lung, and kidney. It is eventually converted to fluoro-β-alanine, which is removed in the urine, and to CO_2, which is exhaled. The dose of 5-FU must be adjusted in the case of impaired hepatic function. Increased rate of 5-FU catabolism through elevated levels of dihydropyrimidine dehydrogenase (DPD) can decrease the bioavailability of 5-FU. The DPD level varies from individual to individual and may differ by as much as sixfold in the general population. Knowledge about an individual’s DPD activity should allow more appropriate dosing of 5-FU . 4. Adverse effects: In addition to nausea, vomiting, diarrhea, and alopecia, severe ulceration of the oral and GI mucosa, bone marrow depression (with bolus injection), and anorexia are frequently encountered. An allopurinol mouthwash has been shown to reduce INFO LINK Pharm 5th 3-21-11.indb 491 7 See Chapter 22 in Lippincott’s Illustrated Reviews: Biochemistry for a discussion of thymidylate synthase. 3/21/11 2:32:25 PM 492 39. Anticancer Drugs N H3C O O NH2 NH CO O F N HO Carboxylesterase H3C OH O O HO Thymidine phosphorylase OH G. Capecitabine N Capecitabine [cape-SITE-a-been] is a novel, oral fluoropyrimidine carbamate. It is approved for the treatment of metastatic breast cancer that is resistant to first-line drugs (for example, paclitaxel and anthracyclines) and is currently also used for treatment of colorectal cancer. OH 5'-dFCR F N O Cytidine deaminase O O H3C O HO Capecitabine HN F N F HN O oral toxicity. A dermopathy (erythematous desquamation of the palms and soles) called the “hand-foot syndrome” is seen after extended infusions. N H 5-FU 5'-dFUR Figure 39.14 Metabolic pathway of capecitabine to 5-fluorouracil (5-FU). 5'-dFCR = 5'-deoxy-5-fluorocytidine; 5'-dFUR = 5'-deoxy-5-fluorouridine. 1. Mechanism of action: After being absorbed, capecitabine, which is itself nontoxic, undergoes a series of enzymatic reactions, the last of which is hydrolysis to 5-FU. This step is catalyzed by thymidine phosphorylase, an enzyme that is concentrated primarily in tumors (Figure 39.14). Thus, the cytotoxic activity of capecitabine is the same as that of 5-FU and is tumor specific. The most important enzyme inhibited by 5-FU (and, thus, capecitabine) is thymidylate synthase. 2. Pharmacokinetics: Capecitabine has the advantage of being well absorbed following oral administration. It is extensively metabolized to 5-FU (as described above) and is eventually biotransformed into fluoro-β-alanine and CO_2. Metabolites are primarily eliminated in urine or, in the case of CO_2, exhaled. 3. Adverse effects:

These are similar to those with 5-FU, with the toxicity occurring primarily in the GI tract. Capecitabine should be used cautiously in patients with hepatic or renal impairment. The drug is contraindicated in individuals who are pregnant or lactating. Patients taking coumarin anticoagulants or phenytoin should be monitored for coagulation parameters and drug levels, respectively. H. Floxuridine Floxuridine [floks-YOOR-ih-deen] is an analog (floxuridine is 2′-deoxy5-fluorouridine) of 5-FU. When given by rapid intraarterial injection, floxuridine is rapidly catabolized in the liver to 5-FU and produces antimetabolite effects. The primary effect is to interfere with the synthesis of DNA and, to a lesser extent, inhibit the formation of RNA. The drug is excreted intact and as fluorouracil, urea, and α-fluoro-β-alanine in the urine. Floxuridine is effective in the palliative management of GI adeno carcinoma that has metastasized to the liver. The common adverse effects are nausea, vomiting, diarrhea, enteritis, stomatitis, and localized erythema. I. Cytarabine Cytarabine [sye-TARE-ah-been] (cytosine arabinoside, or ara-C) is an analog of 2′-deoxycytidine in which the natural ribose residue is replaced by D-arabinose. Ara-C acts as a pyrimidine antagonist. The major clinical use of ara-C is in acute nonlymphocytic (myelogenous) leukemia in combination with 6-TG and daunorubicin. 1. Mechanism of action: Ara-C enters the cell by a carrier-mediated process and, like the other purine and pyrimidine antagonists, must be sequentially phosphorylated by deoxycytidine kinase and other nucleotide kinases to the nucleotide form (cytosine arabinoside triphosphate, or ara-CTP) to be cytotoxic. Ara-CTP is an effective inhibitor of DNA polymerase. The nucleotide is also incorporated Pharm 5th 3-21-11.indb 492 3/21/11 2:32:26 PM III. Antimetabolites 493 into nuclear DNA and can retard chain elongation. It is, therefore, S-phase (and, hence, cell-cycle) specific. Poor penetration into CNS 2. Resistance: Resistance to ara-C may result from a defect in the trans- port process, a change in phosphorylating enzymes activity (especially deoxycytidine kinase), or an increased pool of the natural dCTP nucleotide. Increased deamination of the drug to uracil arabinoside (ara-U) can also cause resistance. IV Intrathecal 3. Pharmacokinetics: Ara-C is not effective when given orally, because of its deamination to the noncytotoxic ara-U by cytidine deaminase in the intestinal mucosa and liver. Given IV, it distributes throughout the body but does not penetrate the CNS in sufficient amounts to be effective against meningeal leukemia (Figure 39.15). However, it may be injected intrathecally. A new preparation that provides slow release into the CSF is also available. Ara-C undergoes extensive oxidative deamination in the body to ara-U, a pharmacologically inactive metabolite. Both ara-C and ara-U are excreted in urine. 4. Adverse effects: Nausea, vomiting, diarrhea, and severe myelosup- pression (primarily granulocytopenia) are the major toxicities associated with ara-C. Hepatic dysfunction is also occasionally encountered. At high doses or with intrathecal injection, ara-C may cause leukoencephalopathy or paralysis. Drug metabolites appear in urine the urine Cytarabine Figure 39.15 Administration and fate of cytarabine. J. Gemcitabine Gemcitabine [jem-SITE-ah-been] is an analog of the nucleoside deoxycytidine. It is used for the first-line treatment of locally advanced or metastatic adenocarcinoma of the pancreas. It also is effective against non–small cell lung cancer and several other tumors. NH2 N HO-H2C 1. Mechanism of action: Gemcitabine is a substrate for deoxycytidine kinase, which phosphorylates the drug to 2′,2′-difluorodeoxycytidine triphosphate (Figure 39.16). The latter compound inhibits DNA synthesis by being incorporated into sites in the growing strand that ordinarily would contain cytosine. Evidence suggests that DNA repair does not readily occur. Levels of the natural nucleotide, dCTP, are lowered, because gemcitabine competes with the normal nucleoside substrate for deoxycytidine kinase. Gemcitabine diphosphate inhibits ribonucleotide reductase, which is responsible for the generation of the deoxynucleoside triphosphates required for DNA synthesis. 2. Resistance: Resistance to the drug is probably due to its inability to be converted to a nucleotide, caused by an alteration in deoxycytidine kinase. In addition, the tumor cell can produce increased levels of endogenous deoxycytidine that compete for the kinase, thus overcoming the inhibition. 3. Pharmacokinetics: Gemcitabine is infused IV. It is deaminated to difluorodeoxyuridine, which is not cytotoxic, and is excreted in urine. 4. Adverse effects: Myelosuppression is the dose-limiting toxicity of gemcitabine. Other toxicities include nausea, vomiting, alopecia, rash, and a flu-like syndrome. Transient elevations of serum transaminases, proteinuria, and hematuria are common. Pharm 5th 3-21-11.indb 493 O N O F F HO Gemcitabine (2',2'-difluorodeoxycytidine) Deoxycytidine kinase NH2 N P P P O-H2C O HO O F N F 2',2'-difluorodeoxycytidine triphosphate Inhibits DNA synthesis Figure 39.16 Mechanism of action of gemcitabine. 3/21/11 2:32:28 PM 494 39. Anticancer Drugs IV. ANTIBIOTICS Poor penetration into the CNS IV Unchanged drug and metabolites appear in bile The antitumor antibiotics owe their cytotoxic action primarily to their interactions with DNA, leading to disruption of DNA function. In addition to intercalation, their abilities to inhibit topoisomerases (I and II) and produce free radicals also play a major role in their cytotoxic effect. They are cellcycle nonspecific. A. Dactinomycin Dactinomycin [dak-ti-noe-MYE-sin], known to biochemists as actinomycin D, was the first antibiotic to find therapeutic application in tumor chemotherapy. Dactinomycin is used in combination with surgery and vincristine for the treatment of Wilms tumor. In combination with MTX, dactinomycin is effective in the treatment of gestational choriocarcinoma. Some soft-tissue sarcomas also respond. Unchanged drug and metabolites appear in urine Dactinomycin Figure 39.17 Administration and fate of dactinomycin. CNS = central nervous system; IV = intravenous. 1. Mechanism of action: The drug intercalates into the minor groove of the double helix between guanine-cytosine base pairs of DNA,8 forming a stable dactinomycin-DNA complex. The complex interferes primarily with DNA-dependent RNA polymerase, although at high doses, dactinomycin also hinders DNA synthesis. The drug also causes single-strand breaks, possibly due to action on topoisomerase II or by generation of free radicals. 2. Resistance: Resistance is due to an increased efflux of the antibiotic from the cell via P-glycoprotein. DNA repair may also play a role. 3. Pharmacokinetics: The drug, administered IV, distributes to many tissues but does not enter the CSF (Figure 39.17). The drug is minimally metabolized in the liver. Most of the parent drug and its metabolites are excreted via bile, and the remainder is excreted via urine. Doxorubicin O2 Cytochrome P450 reductase Reduced metabolite Superoxide ion Hydrogen peroxide 4. Adverse effects: The major dose-limiting toxicity is bone marrow depression. The drug is immunosuppressive. Other adverse reactions include nausea, vomiting, diarrhea, stomatitis, and alopecia. Extravasation during injection produces serious problems. Dactinomycin sensitizes to radiation, and inflammation at sites of prior radiation therapy may occur. B. Doxorubicin and daunorubicin Strand breaks in DNA Figure 39.18 Doxorubicin interacts with molecular oxygen, producing superoxide ions and hydrogen peroxide, which cause single-strand breaks in DNA. Doxorubicin [dox-oh-ROO-bi-sin] and daunorubicin [daw-noe-ROObi-sin] are classified as anthracycline antibiotics. Doxorubicin is the hydroxylated analog of daunorubicin. Idarubicin [eye-da-RUE-bi-sin], the 4-demethoxy analog of daunorubicin, and epirubicin [eh-pee-ROO-bihsin] are also available. Applications for these agents differ despite their structural similarity and their apparently similar mechanisms of action. Doxorubicin is one of the most important and widely used anticancer drugs. It is used in combination with other agents for treatment of sarcomas and a variety of carcinomas, including breast and lung, as well as for treatment of acute lymphocytic leukemia and lymphomas. Daunorubicin and idarubicin are used in the treatment of acute leukemias. INFO LINK Pharm 5th 3-21-11.indb 494 8 See Chapter 29 in Lippincott's Illustrated Reviews: Biochemistry for a discussion of DNA structure. 3/21/11 2:32:31 PM IV. Antibiotics 1. Mechanism of action: Doxorubicin and other anthracyclines induce cytotoxicity through several different mechanisms. For example, doxorubicin-derived free radicals can induce membrane lipid peroxidation, DNA strand scission, and direct oxidation of purine or pyrimidine bases, thiols, and amines (Figure 39.18). 2. Pharmacokinetics: All these drugs must be administered IV, because they are inactivated in the GI tract. Extravasation is a serious problem that can lead to tissue necrosis. The anthracycline antibiotics bind to plasma proteins as well as to other tissue components, where they are widely distributed. They do not penetrate the blood-brain barrier or the testes. All these drugs undergo extensive hepatic metabolism. Via bile is the major route of excretion, and the drug dose must be modified in patients with impaired hepatic function (Figure 39.19). Some renal excretion also occurs, but the dose generally need not be adjusted in patients with renal failure. Because of the dark red color of the anthracycline drugs, the veins may become visible surrounding the site of infusion, and the drugs also impart a red color to the urine. 3. Adverse effects: Irreversible, dose-dependent cardiotoxicity, apparently a result of the generation of free radicals and lipid peroxidation, is the most serious adverse reaction and is more common with daunorubicin and doxorubicin than with idarubicin and epirubicin. Irradiation of the thorax increases the risk of cardiotoxicity. Addition of trastuzumab to protocols with doxorubicin or epirubicin increases congestive heart failure. There has been some success with the iron chelator dexrazone in protecting against the cardiotoxicity of doxorubicin. [Note: A new liposomal-encapsulated doxorubicin has been reported to be less cardiotoxic than the usual formulation.] As with dactinomycin, both doxorubicin and daunorubicin also cause transient bone marrow suppression, stomatitis, and GI tract disturbances. Increased skin pigmentation is also seen. Alopecia is usually severe. Occurrence of multidrug resistance is common, but it is less frequent than with plant alkaloids. C. Bleomycin Bleomycin [blee-oh-MYE-sin] is a mixture of different copper-chelating glycopeptides that, like the anthracycline antibiotics, cause scission of DNA by an oxidative process. Bleomycin is cell-cycle specific and causes cells to accumulate in the G2 phase. It is primarily used in the treatment of testicular cancers in combination with vinblastine or etoposide. Response rates are close to 100 percent if cisplatin is added to the regimen. Bleomycin is also effective, although not curative, for squamous cell carcinomas and lymphomas. 1. Mechanism of action: A DNA-bleomycin-Fe2+ complex appears to undergo oxidation to bleomycin-Fe3+. The liberated electrons react with oxygen to form superoxide or hydroxyl radicals, which, in turn, attack the phosphodiester bonds of DNA, resulting in strand breakage and chromosomal aberrations (Figure 39.20). INFO LINK Pharm 5th 3-21-11.indb 495 495 Poor penetration into the CNS IV Unchanged drug and metabolites appear in bile Unchanged drug and metabolites appear in urine Doxorubicin Daunorubicin Figure 39.19 Administration and fate of doxorubicin and daunorubicin. CNS = central nervous system; IV = intravenous. DNA-bleomycin-Fe2+ DNA-bleomycin-Fe3+ Superoxide and hydroxyl radicals Strand breaks in DNA Figure 39.20 Bleomycin causes breaks in DNA by an oxidative process. 9 See Chapter 17 in Lippincott's Illustrated Reviews: Biochemistry for a discussion of phosphatidylinositol activation. 3/21/11 2:32:34 PM 496 39. Anticancer Drugs 2. Resistance: Although the mechanisms of resistance have not been elucidated, experimental systems have implicated increased levels of bleomycin hydrolase (or deamidase), glutathione-S-transferase, and possibly, increased efflux of the drug. DNA repair also may contribute. 3. Pharmacokinetics: Bleomycin is administered by a number of routes, including subcutaneous, intramuscular, IV, and intracavitary. The bleomycin-inactivating enzyme (a hydrolase) is high in a number of tissues (for example, liver and spleen) but is low in lung and is absent in skin (accounting for the drug's toxicity in those tissues). Most of the parent drug is excreted unchanged into the urine by glomerular filtration, necessitating dose adjustment in patients with renal failure. 4. Adverse effects: Pulmonary toxicity is the most serious adverse effect, progressing from rales, cough, and infiltrate to potentially fatal fibrosis. The pulmonary fibrosis that is caused by bleomycin is often referred as "bleomycin lung." Mucocutaneous reactions and alopecia are common. Hypertrophic skin changes and hyper pigmentation of the hands are prevalent. There is a high incidence of fever and chills and a low incidence of serious anaphylactoid reactions. Bleomycin is unusual in that myelosuppression is rare. V. ALKYLATING AGENTS O O N H2N N N N N N DNA N N NH 2 DNA Guanine bases in adjacent strands of DNA A. Mechlorethamine CH 2 CH 2 Cl CH 3 N Mechlorethamine [mek-lor-ETH-ah-meen] was developed as a vesicant (nitrogen mustard) during World War I. Its ability to cause lympho cytopenia led to its use in lymphatic cancers. Because it can covalently attach to two separate nucleotides, such as guanine on the DNA molecules, it is called a "bifunctional agent." Mechlorethamine was used primarily in the treatment of Hodgkin disease and may find use in the treatment of some solid tumors. CH 2 CH 2 Cl Mechlorethamine - 2 Cl CH 3 N O N H2N N CH 2 CH 2 CH 2 CH 2 N N N N DNA O N N DNA Cross-linked strands of DNA Figure 39.21 Alkylation of guanine bases in DNA is responsible for the cytotoxic effect of mechlorethamine. Pharm 5th 3-21-11.indb 496 Alkylating agents exert their cytotoxic effects by covalently binding to nucleophilic groups on various cell constituents. Alkylation of DNA is probably the crucial cytotoxic reaction that is lethal to the tumor cells. Alkylating agents do not discriminate between cycling and resting cells, but they are most toxic for rapidly dividing cells. They are used in combination with other agents to treat a wide variety of lymphatic and solid cancers. In addition to being cytotoxic, all are mutagenic and carcinogenic and can lead to secondary malignancies such as acute leukemia. NH 2 1. Mechanism of action: Mechlorethamine is transported into the cell, where the drug forms a reactive intermediate that alkylates the N7 nitrogen of a guanine residue in one or both strands of a DNA molecule (Figure 39.21). This alkylation leads to cross-linkages between guanine residues in the DNA chains and/or depurination, thus facilitating DNA strand breakage. Alkylation can also cause miscoding mutations. Although alkylation can occur in both cycling and resting cells (and, therefore, is cell-cycle nonspecific), proliferating cells are more sensitive to the drug, especially those in the G1 and S phases. 2. Resistance: Resistance has been ascribed to decreased permeability of the drug, increased conjugation with thiols such as glutathione, and, possibly, increased DNA repair. 3/21/11 2:32:35 PM V. Alkylating Agents 3. Pharmacokinetics: Mechlorethamine is very unstable, and solutions must be made up just prior to administration. Mechlorethamine is also a powerful vesicant (blistering agent) and is only administered IV. Because of its reactivity, scarcely any drug is excreted. 4. Adverse effects: The adverse effects caused by mechlorethamine include severe nausea and vomiting (centrally mediated). [Note: These effects can be diminished by pretreatment with ondansetron, granisetron, or palonosetron with dexamethasone.] Severe bone marrow depression limits extensive use. Latent viral infections (for example, herpes zoster) may appear because of immunosuppression. Extravasation is a serious problem. If it occurs, the area should be infiltrated with isotonic sodium thiosulfite to inactivate the drug. B. Cyclophosphamide and ifosfamide These drugs are very closely related mustard agents that share most of the same primary mechanisms and toxicities. They are unique in that they can be taken orally and are cytotoxic only after generation of their alkylating species, which are produced through hydroxylation by cytochrome P450 (CYP450). These agents have a broad clinical spectrum, being used either singly or as part of a regimen in the treatment of a wide variety of neoplastic diseases, such as Burkitt lymphoma and breast cancer. Nonneoplastic disease entities, such as nephrotic syndrome and intractable rheumatoid arthritis, are also effectively treated with low doses of cyclophosphamide. 497 Cyclophosphamide Ifosfamide P450 Active phosphoramide mustard DNA Alkylated DNA Figure 39.22 Activation of cyclophosphamide and ifosfamide by hepatic cytochrome P450. 1. Mechanism of action: Cyclophosphamide [sye-kloe-FOSS-fah-mide] is the most commonly used alkylating agent. Both cyclophosphamide and ifosfamide [eye-FOSS-fah-mide] are first biotransformed to hydroxylated intermediates primarily in the liver by the CYP450 system (Figure 39.22). The hydroxylated intermediates then undergo breakdown to form the active compounds, phosphoramide mustard and acrolein. Reaction of the phosphoramide mustard with DNA is considered to be the cytotoxic step. 2. Resistance: Resistance results from increased DNA repair, decreased drug permeability, and reaction of the drug with thiols (for example, glutathione). Cross-resistance does not always occur. 3. Pharmacokinetics: Unlike most of the alkylating agents, cyclophosphamide and ifosfamide can be administered by the oral route (Figure 39.23). After oral administration, minimal amounts of the parent drug are excreted into the feces (after biliary transport) or into the urine by glomerular filtration. 4. Adverse effects: The most prominent toxicities of both drugs (after alopecia, nausea, vomiting, and diarrhea) are bone marrow depression, especially leukocytosis, and hemorrhagic cystitis, which can lead to fibrosis of the bladder. The latter toxicity has been attributed to acrolein in the urine in the case of cyclophosphamide and to toxic metabolites of ifosfamide. [Note: Adequate hydration as well as IV injection of MESNA (sodium 2-mercaptoethane sulfonate), which neutralizes the toxic metabolites, minimizes this problem.] Other toxicities include effects on the germ cells, resulting in amenorrhea, testicular atrophy, aspermia, and sterility. Veno-occlusive disease of the liver is seen in about 25 percent of the patients. A fairly high incidence of neurotoxicity has been reported in patients on high-dose Pharm 5th 3-21-11.indb 497 Drug crosses the blood-brain barrier Oral route preferred IV Metabolites appear in urine the urine Cyclophosphamide Figure 39.23 Administration and fate of cyclophosphamide. IV = intravenous. 3/21/11 2:32:37 PM 498 39. Anticancer Drugs Drug crosses the blood-brain barrier Carmustine Carmustine Lomustine IV Metabolites appear in urine the urine Carmustine/Lomustine Figure 39.24 Administration and fate of carmustine/lomustine. IV = intravenous. ifosfamide, probably due to the metabolite, chloroacetaldehyde. Secondary malignancies may appear years after therapy. C. Nitrosoureas Carmustine [KAR-mus-teen] and lomustine [LOE-mus-teen] are closely related nitrosoureas. Because of their ability to penetrate the CNS, the nitrosoureas are primarily employed in the treatment of brain tumors. They find limited use in the treatment of other cancers. [Note: Streptozocin (STREP-toe-zoe-sin) is another nitrosourea that is specifically toxic to the β cells of the islets of Langerhans, hence its use in the treatment of insulinomas.] 1. Mechanism of action: The nitrosoureas exert cytotoxic effects by an alkylation that inhibits replication and, eventually, RNA and protein synthesis. Although they alkylate DNA in resting cells, cytotoxicity is expressed primarily on cells that are actively dividing. Therefore, nondividing cells can escape death if DNA repair occurs. Nitrosoureas also inhibit several key enzymatic processes by carbamoylation of amino acids in proteins in the targeted cells. 2. Resistance: Although the true nature of resistance to nitrosoureas is unknown, it probably results from DNA repair and reaction of the drugs with thiols. 3. Pharmacokinetics: In spite of the similarities in their structures, carmustine is administered IV, whereas lomustine is given orally. Because of their lipophilicity, they distribute widely in the body to many tissues, but their most striking property is their ability to readily penetrate the CNS. The drugs undergo extensive metabolism. Lomustine is metabolized to active products. The kidney is the major excretory route for the nitrosoureas (Figure 39.24). 4. Adverse effects: These include delayed hematopoietic depression, which may be due to metabolic products. An aplastic marrow may develop on prolonged use. Renal toxicity and pulmonary fibrosis related to duration of therapy is also encountered. [Note: Streptozotocin is also diabetogenic.] D. Dacarbazine Dacarbazine [dah-KAR-bah-zeen], an agent that has found use in the treatment of melanoma, is an alkylating agent that must undergo biotransformation to an active metabolite, methyltriazenoimidazole carboxamide (MTIC). This metabolite is responsible for the drug's activity as an alkylating agent by forming methylcarbonium ions that can attack the nucleophilic groups in the DNA molecule. Thus, similar to other alkylating agents, the cytotoxic action of dacarbazine has been attributed to the ability of its metabolite to methylate DNA on the O6 position of guanine. Dacarbazine is administered IV. Its major adverse effects are nausea and vomiting. Myelosuppression (thrombocytopenia and neutropenia) occur later in the treatment cycle. Hepatotoxicity with hepatic vascular occlusion may also occur in long-term treatments. E. Temozolomide The treatment of tumors in the brain is particularly difficult. Recently, temozolomide [te-moe-ZOE-loe-mide], a triazene agent, has been approved for use against treatment-resistant gliomas and anaplastic Pharm 5th 3-21-11.indb 498 3/21/11 2:32:39 PM VI. Microtubule Inhibitors astrocytomas. Temozolomide is related to dacarbazine, because both must undergo biotransformation to an active metabolite, MTIC, which probably is responsible for the methylation of DNA on the 6 position of guanine. Unlike dacarbazine, temozolomide does not require the CYP450 system for metabolic transformation, and it undergoes chemical transformation under normal physiological pH. Temozolomide also has the property of inhibiting the repair enzyme, O6-guanineDNA-alkyltransferase. A property that distinguishes temozolomide from dacarbazine is the former's ability to cross the blood-brain barrier. Temozolomide is taken orally and has excellent oral bioavailability. The parent drug and metabolites are excreted in urine (Figure 39.25). Temozolomide is taken for 5 consecutive days and repeated every 28 days. Similar to dacarbazine, its major initial toxicities are nausea and vomiting. Myelosuppression (thrombocytopenia and neutropenia) occur later in the treatment cycle. F. Other alkylating agents Melphalan [MEL-fah-lan], a phenylalanine derivative of nitrogen mustard, is used in the treatment of multiple myeloma. This is a bifunctional alkylating agent that can be given orally. Although melphalan can be given orally, the plasma concentration differs from patient to patient due to variation in intestinal absorption and metabolism. The dose of melphalan is carefully adjusted by monitoring the platelet and white blood cell counts. Chlorambucil [clor-AM-byoo-sil] is another bifunctional alkylating agent that is used in the treatment of chronic lymphocytic leukemia. Both melphalan and chlorambucil have moderate hematologic toxicities and upset the GI tract. Busulfan [byoo-SUL-fan] is another oral agent that is effective against chronic granulocytic leukemia. Busulfan is also a bifunctional alkylating agent that can cause myelosuppression. In aged patients, busulfan can cause pulmonary fibrosis. Like other alkylating agents, all of these agents are leukemogenic. 499 Temozolomide crosses the blood-brain barrier Dacarbazine Temozolomide IV Metabolites appear in urine the urine Temozolomide/Dacarbazine Figure 39.25 Administration and fate of temozolomide and dacarbazine. IV = intravenous. VI. MICROTUBULE INHIBITORS The mitotic spindle is part of a larger, intracellular skeleton (cytoskeleton) that is essential for the movements of structures occurring in the cytoplasm of all eukaryotic cells. The mitotic spindle consists of chromatin plus a system of microtubules composed of the protein tubulin. The mitotic spindle is essential for the equal partitioning of DNA into the two daughter cells that are formed when a eukaryotic cell divides. Several plant-derived substances used as anticancer drugs disrupt this process by affecting the equilibrium between the polymerized and depolymerized forms of the microtubules, thereby causing cytotoxicity. A. Vincristine and vinblastine Vincristine [vin-KRIS-teen] (VX) and vinblastine [vin-BLAS-teen] (VBL) are structurally related compounds derived from the periwinkle plant, Vinca rosea. They are, therefore, referred to as the vinca alkaloids. A new (and less toxic) agent is vinorelbine [vye-NOR-el-been] (VRB). Although the vinca alkaloids are structurally very similar to each other, their therapeutic indications are different. They are generally administered in combination with other drugs. VX is used in the treatment of acute lymphoblastic leukemia in children, Wilms tumor, Ewing soft-tissue sarcoma, and Hodgkin and non-Hodgkin lymphomas as well as some other rapidly proliferating neoplasms. [Note: VX (trade name, ONCOVIN) is the "O" in the POMP regimen for leukemia and the MOPP regimen for Pharm 5th 3-21-11.indb 499 3/21/11 2:32:40 PM 500 39. Anticancer Drugs A Normal mitosis Metaphase Chromosome Spindle Tubulin molecules stacked to form miotic spindle Anaphase B Mitosis blocked by vinca alkaloids Metaphase Tubulin molecules fail to polymerize in the presence of vinca alkaloids Anaphase Hodgkin lymphoma. Due to relatively milder bone-suppressing ability, VX is used in a number of other protocols.] VBL is administered with bleomycin and cisplatin for the treatment of metastatic testicular carcinoma. It is also used in the treatment of systemic Hodgkin and nonHodgkin lymphomas. VRB is beneficial in the treatment of advanced non–small cell lung cancer, either as a single agent or with cisplatin. 1. Mechanism of action: VX and VBL are both cell-cycle specific and phase specific, because they block mitosis in metaphase (M phase). Their binding to the microtubular protein, tubulin, is GTP dependent and blocks the ability of tubulin to polymerize to form microtubules. Instead, paracrystalline aggregates consisting of tubulin dimers and the alkaloid drug are formed. The resulting dysfunctional spindle apparatus, frozen in metaphase, prevents chromosomal segregation and cell proliferation (Figure 39.26). 2. Resistance: Resistant cells have been shown to have an enhanced efflux of VX, VBL, and VRB via P-glycoprotein in the cell membrane. Alterations in tubulin structure may also affect binding of the vinca alkaloids. 3. Pharmacokinetics: IV injection of these agents leads to rapid cytotoxic effects and cell destruction. This, in turn, can cause hyper uricemia due to the oxidation of purines that are released from fragmenting DNA molecules, producing uric acid. The hyperuricemia is ameliorated by administration of the xanthine oxidase–inhibitor allopurinol. The vinca alkaloids are concentrated and metabolized in the liver by the CYP450 pathway. They are excreted in bile and feces. Doses must be modified in patients with impaired hepatic function or biliary obstruction. 4. Adverse effects: Both VX and VBL have certain toxicities in common. These include phlebitis or cellulitis, if the drugs extravasate during injection, as well as nausea, vomiting, diarrhea, and alopecia. However, the adverse effects of VX and VBL are not identical. VBL is a more potent myelosuppressant than VX, whereas peripheral neuropathy (paresthesias, loss of reflexes, foot drop, and ataxia) is associated with VX. Constipation is more frequently encountered with VX, which can also cause inappropriate antidiuretic hormone secretion. The anticonvulsants phenytoin, phenobarbital, and carbamazepine can accelerate the metabolism of VX, whereas the azole antifungal drugs can slow its metabolism. Granulocytopenia is dose limiting for VRB. B. Paclitaxel and docetaxel Dissolution of the mitotic spindle leads to cell death Figure 39.26 Mechanism of action of the microtubule inhibitors. Pharm 5th 3-21-11.indb 500 Better known as Taxol, paclitaxel [PAK-li-tax-el] is the first member of the taxane family to be used in cancer chemotherapy. A semisynthetic paclitaxel is now available through chemical modification of a precursor found in the needles of Pacific yew species. Substitution of a side chain has resulted in docetaxel [doe-see-TAX-el], which is the more potent of the two drugs. Paclitaxel has shown good activity against advanced ovarian cancer and metastatic breast cancer. Favorable results have been obtained in non–small cell lung cancer when administered with cisplatin. Docetaxel is showing impressive benefits, with fewer side effects, in these conditions. 3/21/11 2:32:43 PM VII. Steroid Hormones And Their Antagonists 1. Mechanism of action: Both drugs are active in the G2/M phase of the cell cycle. They bind reversibly to the β-tubulin subunit, but unlike the vinca alkaloids, they promote polymerization and stabilization of the polymer rather than disassembly (Figure 39.27). Thus, they shift the depolymerization-polymerization process to accumulation of microtubules. The overly stable microtubules formed are nonfunctional, and chromosome desegregation does not occur. This results in death of the cell. 2. Resistance: Like the vinca alkaloids, resistance has been associated with the presence of amplified P-glycoprotein or a mutation in the tubulin structure. 3. Pharmacokinetics: These agents are infused and have similar pharmacokinetics. Both have a large volume of distribution, but neither enters the CNS. Hepatic metabolism by the CYP450 system and biliary excretion are responsible for their elimination in stool. Thus, dose modification is not required in patients with renal impairment, but doses should be reduced in patients with hepatic dysfunction. 4. Adverse effects: The dose-limiting toxicity of paclitaxel and docetaxel is neutropenia. [Note: Patients with fewer than 1500 neutrophils/mm3 should not be given these agents.] Treatment with granulocyte colony–stimulating factor (filgrastim) can help to reverse neutropenia and prevent the problems associated with this condition. Peripheral neuropathy can develop with either of these drugs. A transient, asymptomatic bradycardia is sometimes observed with paclitaxel, and fluid retention is seen with docetaxel. The latter drug is contraindicated in patients with cardiac disease. Alopecia occurs, but vomiting and diarrhea are uncommon. [Note: Because of serious hypersensitivity reactions (including dyspnea, urticaria, and hypotension), a patient who is to be treated with paclitaxel is premedicated with dexamethasone and diphenhydramine as well as with an H2 blocker.] VII. STEROID HORMONES AND THEIR ANTAGONISTS 501 A Normal mitosis Metaphase Anaphase Chromosome Spindle Tubulin molecules are stacked to form the mitoic spindle Spindle dissolves after anaphase, allowing the cell to divide B Mitosis blocked by paclitaxel Metaphase Anaphase Chromosome Spindle Unusually stable tubulin molecules stack and fail to depolymerize Cell remains frozen in metaphase Figure 39.27 Paclitaxel stabilizes microtubules, rendering them nonfunctional. Tumors that are steroid hormone–sensitive may be either 1) hormone responsive, in which the tumor regresses following treatment with a specific hormone; 2) hormone dependent, in which removal of a hormonal stimulus causes tumor regression; or 3) both. Hormone treatment of responsive tumors usually is only palliative, except in the case of the cytotoxic effect of glucocorticoids at higher doses (for example, prednisone) on lymphomas. Removal of hormonal stimuli from hormone-dependent tumors can be accomplished by surgery (for example, in the case of orchiectomy—surgical removal of one or both testes— for patients with advanced prostate cancer) or by drugs (for example, in breast cancer, for which treatment with the antiestrogen tamoxifen is used to prevent estrogen stimulation of breast cancer cells). For a steroid hormone to influence a cell, that cell must have intracellular (cytosolic) receptors that are specific for that hormone (Figure 39.28A). A. Prednisone Prednisone [PRED-ni-sone] is a potent, synthetic, anti-inflammatory corticosteroid with less mineralocorticoid activity than cortisol. The use Pharm 5th 3-21-11.indb 501 3/21/11 2:32:46 PM 502 39. Anticancer Drugs Mechanism of steroid hormone action A Steroid TARGET CELL CYTOPLASM 1. Mechanism of action: Prednisone itself is inactive and must first be reduced to prednisolone by 11-β-hydroxysteroid dehydrogenase. This steroid then binds to a receptor that triggers the production of specific proteins (see Figure 39.28A). Inactive receptor Steroid hormone binds to intracellular receptor. Activated receptor complex NUCLEUS Gene Steroid-receptor complex binds to chromatin, activating the transcription of specific genes. Effects such as cellular growth and proliferation B mRNA mRNA Specific proteins Actions of antiestrogen drugs Tamoxifen Steroid Tamoxifen Steroid TARGET CELL Antiestrogen drug competes with natural hormone for intracellular receptor. Inactive receptor complex Figure 39.28 Action of steroid hormones and antiestrogen agents. mRNA = messenger RNA. Pharm 5th 3-21-11.indb 502 of this compound in the treatment of lymphomas arose when it was observed that patients with Cushing syndrome, which is associated with hypersecretion of cortisol, have lymphocytopenia and decreased lymphoid mass. [Note: At high doses, cortisol is also lymphocytolytic and leads to hyperuricemia due to the breakdown of lymphocytes.] Prednisone is primarily employed to induce remission in patients with acute lymphocytic leukemia and in the treatment of both Hodgkin and non-Hodgkin lymphomas. 2. Resistance: Resistance is associated with an absence of the receptor protein or a mutation that lowers receptor affinity for the hormone. However, in some resistant cells, a receptor-hormone complex is formed, although a stage of gene expression is apparently affected. 3. Pharmacokinetics: Prednisone is readily absorbed orally. Like other glucocorticoids, it is bound to plasma albumin and transcortin. It undergoes 11-β-hydroxylation to prednisolone in the liver. Prednisolone is the active drug. The latter is glucuronidated and excreted in urine along with the parent compound. 4. Adverse effects: Prednisone has many of the adverse effects associated with glucocorticoids. It can predispose to infection (due to its immunosuppressant action) and to ulcers and pancreatitis. Other effects include hyperglycemia, cataract formation, glaucoma, osteoporosis, and change in mood (euphoria or psychosis). B. Tamoxifen Tamoxifen [tah-MOX-ih-fen] is an estrogen antagonist. It is structurally related to the synthetic estrogen diethylstilbestrol and is used for firstline therapy in the treatment of estrogen receptor–positive breast cancer. Tamoxifen has weak estrogenic activity, and it is classified as a selective estrogen-receptor modulator (SERM). Another SERM that has been approved for advanced breast cancer in postmenopausal women is toremifene [tore-EM-ih-feen]. It also finds use prophylactically in reducing breast cancer occurrence in women who are at high risk. However, because of possible effects stimulating premalignant lesions due to its estrogenic properties, tamoxifen is currently approved only for 5 years of use. 1. Mechanism of action: Tamoxifen binds to the estrogen receptor, but the complex is transcriptionally not productive. That is, the complex fails to induce estrogen-responsive genes, and RNA synthesis does not ensue (Figure 39.28B). The result is a depletion (down-regulation) of estrogen receptors, and the growth-promoting effects of the natural hormone and other growth factors are suppressed. [Note: Estrogen competes with tamoxifen. Therefore, in premenopausal women, the drug is used with a gonadotropin-releasing hormone (GnRH) analog such as leuprolide, which lowers estrogen levels.] The action of tamoxifen is not related to any specific phase of the cell cycle. 3/21/11 2:32:49 PM VII. Steroid Hormones And Their Antagonists 503 2. Resistance: Resistance is associated with a decreased affinity for the receptor or the presence of a dysfunctional receptor. 3. Pharmacokinetics: Tamoxifen is effective on oral administration. It is partially metabolized by the liver. Some metabolites possess antagonist activity, whereas others have agonist activity. Unchanged drug and its metabolites are excreted predominantly through the bile into the feces (Figure 39.29). 4. Adverse effects: Side effects caused by tamoxifen are similar to the effects of natural estrogen, including hot flashes, nausea, vomiting, skin rash, vaginal bleeding, and discharge (due to some slight estrogenic activity of the drug and some of its metabolites). Hypercalcemia requiring cessation of the drug may occur. Tamoxifen can also lead to increased pain if the tumor has metastasized to bone. Tamoxifen has the potential to cause endometrial cancer. Other toxicities include thromboembolism and effects on vision. [Note: Because of a more favorable adverse effect profile, aromatase inhibitors are making an impact in the treatment of breast cancer.] Unchanged drug and metabolites are excreted via bile into feces Tamoxifen Figure 39.29 Administration and fate of tamoxifen. C. Aromatase inhibitors The aromatase reaction is responsible for the extra-adrenal synthesis of estrogen from androstenedione, which takes place in liver, fat, muscle, skin, and breast tissue, including breast malignancies. Peripheral aromatization is an important source of estrogen in postmenopausal women. Aromatase inhibitors decrease the production of estrogen in these women. 1. Aminoglutethimide: Aminoglutethimide [ah-mee-noe-glue-TETHih-mide] was the first aromatase inhibitor to be identified for the treatment of metastatic breast cancer in postmenopausal women. Aminoglutethimide was shown to inhibit both the adrenal synthesis of pregnenolone (a precursor of estrogen) from cholesterol as well as the extra-adrenal synthesis. Because the drug also inhibits hydrocortisone synthesis, which evokes a compensatory rise in adrenocorticotropic hormone secretion sufficient to overwhelm the blockade of the adrenal gland, the drug is usually taken with hydrocortisone. Due to its nonselective properties and unfavorable side effects, as well as the need to concomitantly administer hydrocortisone (cortisol), newer aromatase inhibitors (described below) have been developed. 2. Anastrozole and letrozole: The imidazole aromatase inhibitors, such as anastrozole [an-AS-troe-zole] and letrozole [LE-troe-zole], are nonsteroidal. They have gained favor in the treatment of breast cancer because 1) they are more potent (they inhibit aromatization by greater than 96 percent, compared to less than 90 percent with aminoglutethimide), 2) they are more selective than aminoglutethimide, 3) they do not need to be supplemented with hydrocortisone, 4) they do not predispose to endometrial cancer, and 5) they are devoid of the androgenic side effects that occur with the steroidal aromatase inhibitors. Although anastrozole and letrozole are considered to be second-line therapy after tamoxifen for hormonedependent breast cancer in the United States, they have become first-line drugs in other countries for the treatment of breast cancer Pharm 5th 3-21-11.indb 503 3/21/11 2:32:50 PM 504 39. Anticancer Drugs A in postmenopausal women. They are orally active and cause almost a total suppression of estrogen synthesis. They are cleared primarily by liver metabolism. HYPOTHALAMUS GnRH (LHRH) Leuprolide Goserelin ANTERIOR PITUITARY 3. Exemestane: A steroidal, irreversible inhibitor of aromatase, exemestane [ex-uh-MES-tane], is orally well absorbed and widely distributed. Hepatic metabolism is by the CYP3A4 isozyme, but, to date, no interactions have been reported. Because the metabolites are excreted in urine, doses of the drug must be adjusted in patients with renal failure. Its major toxicities are nausea, fatigue, and hot flashes. Acne and hair chang

THYMOGLOBULIN Basiliximab SIMULECT Daclizumab ZENAPAX Muromonab-CD3 ORTHOCLONE OKT3 ADRENOCORTICOIDS Methylprednisolone MEDROL Prednisolone ORAPRED, PRELONE Prednisone DELTASONE Figure 40.1 Immunosuppressant drugs. 3/21/11 2:32:58 PM 514 Cytokine 40. Immunosuppressants Actions IL-1 Enhances
activity of NK cells Attracts neutrophils and macrophages IL-2 Induces proliferation of antigen-primed T cells Enhances activity of NK cells IFN-γ Enhances activity of macrophages and NK cells Increases expression of MHC molecules Enhances production of IgG2a TNF-α Cytotoxic effect on tumor cells Induces cytokine secretion in the inflammatory
response Figure 40.2 Summary of selected cytokines. IL = interleukin; IFN = interferon; TNF = tumor necrosis factor; NK = natural killer; MHC = major histocompatibility complex; IgG = immunoglobulin G. II. SELECTIVE INHIBITORS OF CYTOKINE PRODUCTION AND FUNCTION Cytokines are soluble, antigen-nonspecific, signaling proteins that
bind to cell surface receptors on a variety of cells. The term cytokine includes the molecules known as interleukins (ILs), interferons (IFNs), tumor necrosis factors (TNFs), transforming growth factors, and colony-stimulating factors. Of particular interest when discussing immunosuppressive drugs is IL-2, a growth factor that stimulates the
proliferation of antigen-primed (helper) T cells, which subsequently produce more IL-2, IFN-γ, and TNF-a (Figure 40.2). These cytokines collectively activate natural killer cells, macrophages, and cytotoxic T lymphocytes. Clearly, drugs that interfere with the production or activity of IL-2, such as cyclosporine, will significantly dampen the immune
response and, thereby, decrease graft rejection. A. Cyclosporine Cyclosporine [sye-kloe-SPOR-een] is a lipophilic cyclic polypeptide composed of 11 amino acids (several of the amino acids are methylated on the peptidyl nitrogen). The drug is extracted from the soil fungus Beauveria nivea. Cyclosporine is used to prevent rejection of kidney, liver, and
cardiac allogeneic transplants. Cyclosporine is most effective in preventing acute rejection of transplanted organs when combined in a double-drug or triple-drug regimen with corticosteroids and an antimetabolite such as mycophenolate mofetil. Cyclosporine is an alternative to methotrexate for the treatment of severe, active rheumatoid arthritis. It
can also be used for patients with recalcitrant psoriasis that does not respond to other therapies, and it is also used for xerophthalmia. 1. Mechanism of action: Cyclosporine preferentially suppresses cellmediated immune reactions, whereas humoral immunity is affected to a far lesser extent. After diffusing into the T cell, cyclosporine binds to a
cyclophilin (more generally called an immunophilin) to form a complex that binds to calcineurin (Figure 40.3). The latter is responsible for dephosphorylating NFATc (cytosolic Nuclear Factor of Activated T cells). Because the cyclosporine-calcineurin complex cannot perform this reaction, NFATc cannot enter the nucleus to promote the reactions that
are required for the synthesis of a number of cytokines, including IL-2. The end result is a decrease in IL-2, which is the primary chemical stimulus for increasing the number of T lymphocytes. 2. Pharmacokinetics: Cyclosporine may be given either orally or by intravenous (IV) infusion. Oral absorption is variable. Interpatient variability may be due to
metabolism by a cytochrome P450 (CYP3A4) in the gastrointestinal (GI) tract, where the drug is metabolized. Cyclosporine is also a substrate for P-glycoprotein (P-gp), a drug efflux pump, which limits cyclosporine absorption by transporting the drug back into the gut lumen. About 50 percent of the drug is associated with the blood fraction. Half of
this is in the erythrocytes, and less than one tenth is bound to the lymphocytes. Cyclosporine is extensively metabolized, primarily by hepatic CYP3A4. [Note: When other drug substrates for this enzyme are given concomitantly, many drug interactions have been reported.] It is not clear whether any of the 25 or more metabolites have any activity.
Excretion of the metabolites is through the biliary route, with only a small fraction of the parent drug appearing in the urine. Pharm 5th 3-21-11.indb 514 3/21/11 2:32:59 PM II. Selective Inhibitors Of Cytokine Production And Function Activation of the T-cell receptor results in increased intracellular Ca^{2+} 1 Tacrolimus 2 515 Antigenpresenting cell
Activation of calcineurin, a Ca^{2+}-dependent phosphatase 6 Cell-mediated immune response IL-2 receptor CD80; 86 Signal 1 Release of IL-2 5 Signal 2 IL-2 Cyclosporine 3 T CELL Inactive NFATc P + Cyclophilin Calcineurin FK-binding proteins (FKBP) CD28 T-Cell receptor Ca^{2+} IL-2 As a result of dephosphorylation by calcineurin, NFATc moves from
the cytoplasm to the nucleus Signal 3 P mTOR Active NFATc Sirolimus IL-2 CYTOPLASM 4 NFATc associates with other nuclear components, leading to activation of genes encoding cytokines Active NFATc Go 3' IL-2 gene M G2 G1 NUCLEUS IL-2 mRNA IL-2 mRNA S Cell cycle Figure 40.3 Mechanism of action of cyclosporine and tacrolimus. Il-2 =
interleukin-2; mTOR = mammalian target of rapamycin; NFATc = cytosolic nuclear factor of activated T cells; mRNA = messenger RNA. 3. Adverse effects: Many of the adverse effects caused by cyclosporine are dose dependent. Therefore, it is important to monitor blood levels of the drug. Nephrotoxicity is the most common and important adverse
effect of cyclosporine, and it is critical to monitor kidney function. Reduction of the cyclosporine dosage can result in reversal of nephrotoxicity in most cases, although nephrotoxicity may be irreversible in 15 percent of patients. [Note: Coadministration of drugs that also can cause kidney dysfunction (for example, the aminoglycoside antibiotics) and
anti-inflammatories, such as diclofenac, naproxen, or sulindac, can potentiate the nephrotoxicity of cyclosporine. Because hepatotoxicity can also occur, liver function should be periodically assessed.] Infections in patients taking cyclosporine are common and may be life-threatening. Viral infections due to the herpes group and cytomegalovirus (CMV)
are prevalent. Lymphoma may occur in all transplanted patients due to the net level of immunosuppression and has not been linked to any one particular agent. Anaphylactic reactions can occur on parenteral administration. Other toxicities include hypertension, hyperlipidemia, hyperkalemia (it is important not to use K^+-sparing diuretics in these
patients), tremor, hirsutism, glucose intolerance, and gum hyperplasia. Pharm 5th 3-21-11.indb 515 3/21/11 2:33:02 PM 516 40. Immunosuppressants B. Tacrolimus 100 Tacrolimus [ta-CRAW-lih-mus] (originally called FK506) is a macrolide that is isolated from the soil fungus Streptomyces tsukubaensis. Tacrolimus is approved for the prevention of
rejection of liver and kidney transplants and is given with a corticosteroid and/or an antimetabolite. This drug has found favor over cyclosporine, not only because of its potency and decreased episodes of rejection (Figure 40.4), but also because lower doses of corticosteroids can be used, thus reducing the likelihood of steroid-associated adverse
effects. An ointment preparation has been approved for moderate to severe atopic dermatitis that does not respond to conventional therapies. Graft survival, percent Tacrolimus Cyclosporine 50 0 0 1 2 3 4 Years after transplant 5 Figure 40.4 Five-year renal allograft survival in patients treated with cyclosporine or tacrolimus. IL-2 IL-2 receptor
Sirolimus FK-binding proteins (FKBP) + mTOR + The sirolimus-FKBP complex inhibits mTOR, thereby inhibiting translation and causing T cells to arrest in the G1 phase. mTOR increases translation of selected mRNAs that promote transition from G1 to S phase of the cell cycle. Figure 40.5 Mechanism of action of sirolimus. mTOR = molecular target
of rapamycin (sirolimus). IL = interleukin; mRNA = messenger RNA Pharm 5th 3-21-11.indb 516 1. Mechanism of action: Tacrolimus exerts its immunosuppressive effect in the same manner as cyclosporine, except that it binds to a different immunophilin, FKBP-12 (FK-binding protein; see Figure 40.3). 2. Pharmacokinetics: Tacrolimus may be
administered orally or IV. The oral route is preferable, but, as with cyclosporine, oral absorption of tacrolimus is incomplete and variable, requiring tailoring of doses. Tacrolimus is subject to gut metabolism by CYP3A4/5 isoenzymes and is a substrate for P-gp. Together, both of these mechanisms limit the oral bioavailability of tacrolimus. Absorption
is decreased if the drug is taken with high-fat or high-carbohydrate meals. Tacrolimus is from 10- to 100-fold more potent than cyclosporine. It is highly bound to serum proteins and is also concentrated in erythrocytes. Like cyclosporine, tacrolimus undergoes hepatic metabolism by the CYP3A4/5 isozyme, and the same drug interactions occur. At
least one metabolite of tacrolimus has been shown to have immunosuppressive activity. Renal excretion is very low, and most of the drug and its metabolites are found in the feces. 3. Adverse effects: Nephrotoxicity and neurotoxicity (tremor, seizures, and hallucinations) tend to be more severe in patients who are treated with tacrolimus than in
patients treated with cyclosporine, but careful dose adjustment can minimize this problem. Development of posttransplant, insulin-dependent diabetes mellitus is a problem, especially in black and Hispanic patients. Other toxicities are the same as those for cyclosporine, except that tacrolimus does not cause hirsutism or gingival hyperplasia.
Compared with cyclosporine, tacrolimus has also been found to have a lower incidence of cardiovascular toxicities, such as hypertension and hyperlipidemia, both of which are common disease states found in kidney transplant recipients. Anaphylactoid reactions to the injection vehicle have been reported. The drug interactions are the same as those
described for cyclosporine. C. Sirolimus Sirolimus [sih-ROW-lih-mus] is a macrolide obtained from fermentations of the soil mold Streptomyces hygroscopicus. The earlier name, and one that is sometimes still used, is rapamycin. Sirolimus is approved for use in renal transplantation, to be used together with cyclosporine and corticosteroids, allowing
lower doses of those medications to be used, thereby lowering their toxic potential. The combination of sirolimus and cyclosporine is apparently synergistic because sirolimus works later in the immune activation cascade. To limit the long-term side effects of 3/21/11 2:33:04 PM II. Selective Inhibitors Of Cytokine Production And Function 517 the
calcineurin inhibitor, sirolimus is often used in calcineurin inhibitor withdrawal protocols in patients who remain rejection free during the first 3 months posttransplant. The antiproliferative action of sirolimus has found use in cardiology. Sirolimus-coated stents inserted into the cardiac vasculature inhibit restenosis of the blood vessels by reducing
proliferation of the endothelial cells. In addition to its immunosuppressive effects, sirolimus also inhibits proliferation of cells in the graft intimal areas and, thus, is effective in halting graft vascular disease. 1. Mechanism of action: Sirolimus and tacrolimus bind to the same cytoplasmic FK-binding protein, but instead of forming a complex with
calcineurin, sirolimus binds to mTOR, interfering with Signal 3. The latter is a serine-threonine kinase. [Note: TOR proteins are essential for many cellular functions, such as cell-cycle progression, DNA repair, and as regulators involved in protein translation.] Binding of sirolimus to mTOR blocks the progression of activated T cells from the G1 to the
S phase of the cell cycle and, consequently, the proliferation of these cells (see Figure 40.5). Unlike cyclosporine and tacrolimus, sirolimus does not owe its effect to lowering IL-2 production but, rather, to inhibiting the cellular responses to IL-2. 2. Pharmacokinetics: The drug is available only as oral preparations. Although it is readily absorbed, high-
fat meals can decrease the drug's absorption. Sirolimus has a long half-life (57 to 62 hours) compared to those of cyclosporine and tacrolimus, and a loading dose is recommended at the time of initiation of therapy, but only requires once daily dosing. Like both cyclosporine and tacrolimus, sirolimus is metabolized by the CYP3A4 isozyme and interacts
with the same drugs as do cyclosporine and tacrolimus. Sirolimus also increases the drug concentrations of cyclosporine, and careful blood level monitoring of both agents must be done to avoid harmful drug toxicities. The parent drug and its metabolites are predominantly eliminated in feces. 3. Adverse effects: A common side effect of sirolimus is
hyperlipidemia (elevated cholesterol and triglycerides), which can require treatment. The combination of cyclosporine and sirolimus is more nephrotoxic than cyclosporine alone due to the drug interaction between the two, necessitating lower doses. Although the administration of sirolimus and tacrolimus appears to be less nephrotoxic, sirolimus can
still potentiate the nephrotoxicity of tacrolimus, and drug levels of both must be monitored closely. Other untoward problems are headache, nausea and diarrhea, leukopenia, and thrombocytopenia. Impaired wound healing has been noted with sirolimus in obese patients and those with diabetes, which can be especially problematic immediately
following the transplant surgery and in patients receiving corticosteroids. D. Everolimus Everolimus [e-ve-RO-li-mus] (another mTOR inhibitor) was recently approved by the U.S. Food and Drug Administration for use in renal transplantation in combination with low-dose cyclosporine and corticosteroids. It was originally approved in 2009 for second-
line treatment in patients with advanced renal cell carcinoma. Pharm 5th 3-21-11.indb 517 3/21/11 2:33:04 PM 518 40. Immunosuppressants 1. Mechanism of action: Everolimus has the same mechanism of action as sirolimus. It inhibits activation of T cells by forming a complex with FKBP-12 and subsequently blocking mTOR. 2. Pharmacokinetics:
Everolimus differs from sirolimus in its pharmacokinetic profile. Everolimus is rapidly absorbed, attaining maximal concentrations in 1 to 2 hours post dose, but absorption is decreased with high-fat meals. Everolimus is a substrate of CYP3A4 and P-gp and, thus, is subject to the same drug interactions as previously mentioned immunosuppressants.
Everolimus avidly binds erythrocytes, and monitoring of whole blood trough concentrations is recommended. It has a much shorter half-life than does sirolimus at 30 ± 11 hours and requires twice-daily dosing. Everolimus increases drug concentrations of cyclosporine, thereby enhancing the nephrotoxic effects of cyclosporine, and is, therefore,
recommended to be used with reduced doses of cyclosporine. 3. Adverse effects: Everolimus has similar side effects to sirolimus, including hyperlipidemia, impaired or delayed wound healing following transplantation, and enhanced nephrotoxicity in combination with higher doses of cyclosporine. An additional adverse effect noted with everolimus is
angioedema, which may increase with concomitant use of angiotensin-converting enzyme inhibitors. There is also an increased risk of kidney arterial and venous thrombosis, resulting in graft loss, usually in the first 30 days posttransplantation. III. IMMUNOSUPPRESSIVE ANTIMETABOLITES Immunosuppressive antimetabolite agents are generally
used in combination with corticosteroids and the calcineurin inhibitors, cyclosporine and tacrolimus. A. Azathioprine Azathioprine [ay-za-THYE-oh-preen] was the first agent to achieve widespread use in organ transplantation. It is a prodrug that is converted first to 6-mercaptopurine (6-MP) and then to the corresponding nucleotide, thioinosinic acid.
The immunosuppressive effects of azathioprine are due to this nucleotide analog. Because of their rapid proliferation in the immune response and their dependence on the de novo synthesis of purines required for cell division, lymphocytes are predominantly affected by the cytotoxic effects of azathioprine. [Note: The drug has little effect on
suppressing a chronic immune response.] Its major nonimmune toxicity is bone marrow suppression. Concomitant use with angiotensin-converting enzyme inhibitors or cotrimoxazole in renal transplant patients can lead to an exaggerated leukopenic response. Allopurinol, an agent used to treat gout, significantly inhibits the metabolism of
azathioprine. Therefore, the dose of azathioprine must be reduced by 60 to 75 percent. Nausea and vomiting are also encountered. (See p. 488 for a discussion of the mechanism of action, resistance, and pharmacokinetics of 6-MP.) B. Mycophenolate mofetil Mycophenolate mofetil [mye-koe-FEN-oh-late MAW-feh-til] has, for the most part, replaced
azathioprine because of its safety and efficacy in prolonging graft survival. It has been successfully used in heart, kid- Pharm 5th 3-21-11.indb 518 3/21/11 2:33:04 PM IV. Antibodies 519 O HN N N 2-O POH C 3 2 O N Mycophenolate O 2-O 3POH2C O N HN N N H O GMP IMP dehydrogenase OH OH Inosine monophosphate OH Blocking the formation
of GMP deprives rapidly proliferating T and B cells of a key precursor required for nucleic acid synthesis. OH Xanthosine monophosphate Figure 40.6 Mechanism of action of mycophenolate. GMP = guanosine monophosphate. ney, and liver transplants. As an ester, it is rapidly hydrolyzed in the GI tract to mycophenolic acid. This is a potent,
reversible, uncompetitive inhibitor of inosine monophosphate dehydrogenase, which blocks the de novo formation of guanosine phosphate. Thus, like 6-MP, it deprives the rapidly proliferating T and B cells of a key component of nucleic acids (Figure 40.6). [Note: Lymphocytes lack the salvage pathway for purine synthesis and, therefore, are
dependent on de novo purine production.] Mycophenolic acid is quickly and almost completely absorbed after oral administration. Both mycophenolic acid and its glucuronidated metabolite are highly bound (greater than 90 percent) to plasma albumin, but no displacement-type interactions have been reported. The glucuronide metabolite is excreted
predominantly in urine. The most common adverse effects include diarrhea, nausea, vomiting, abdominal pain, leukopenia, and anemia. Higher doses of mycophenolate mofetil (3 g/day) were associated with a higher risk of CMV infection. [Note: mycophenolic acid is less mutagenic or carcinogenic than azathioprine.] Concomitant administration with
antacids containing magnesium or aluminum, or with cholestyramine, can decrease absorption of the drug. C. Enteric-coated mycophenolate sodium In an effort to minimize the GI effects associated with mycophenolate mofetil, enteric-coated mycophenolate sodium was developed. The active drug (mycophenolic acid) is contained within a delayed-
release formulation designed to release in the neutral pH of the small intestine. Enteric-coated mycophenolate sodium at 720 mg and mycophenolate mofetil at 1000 mg contain equivalent amounts of mycophenolic acid. In Phase III studies, the new formulation was found to be equivalent to mycophenolate mofetil in the prevention of acute rejection
episodes in kidney transplant recipients. However, the rate of GI adverse events was similar to that with mycophenolate mofetil. IV. ANTIBODIES The use of antibodies plays a central role in prolonging allograft survival. They are prepared either by immunization of rabbits or horses with human lymphoid cells (producing a mixture of polyclonal
antibodies directed against a number of lymphocyte antigens), or by hybridoma technology Pharm 5th 3-21-11.indb 519 3/21/11 2:33:06 PM 520 40. Immunosuppressants Murine antibodies contain "muro" in their name. Muromonab Humanized antibodies contain "zu" in their name. Daclizumab Chimeric antibodies contain "xi" in their name.
(producing antigen-specific, monoclonal antibodies). [Note: Hybridomas are produced by fusing mouse antibody-producing cells with immortal, malignant plasma cells (Figure 40.7). Hybrid cells are selected and cloned, and the antibody specificity of the clones is determined. Clones of interest can be cultured in large quantities to produce clinically
useful amounts of the desired antibody. Recombinant DNA technology can also be used to replace part of the mouse gene sequence with human genetic material, thus "humanizing" the antibodies produced, making them less antigenic.] The names of monoclonal antibodies conventionally contain "muro" if they are from a murine (mouse) source and
"xi" or "zu" if they are chimerized or humanized, respectively (see Figure 40.7). The suffix "mab" (monoclonal antibody) identifies the category of drug. The polyclonal antibodies, although relatively inexpensive to produce, are variable and less specific, which is in contrast to monoclonal antibodies, which are homogeneous and specific. A.
Antithymocyte globulins Basiliximab Figure 40.7 Conventions for naming monoclonal antibodies. [Note: Muromonab was named before the convention was adopted to make the last three letters in their names mab.] Thymocytes are cells that develop in the thymus and serve as T-cell precursors. The antibodies developed against them are prepared by
immunization of large rabbits or horses with human lymphoid cells and, thus, are polyclonal. They are primarily used, together with other immunosuppressive agents, at the time of transplantation to prevent early allograft rejection, or they may be used to treat severe rejection episodes or corticosteroid-resistant acute rejection. Rabbit formulations of
polyclonal antithymocyte globulin are more commonly used over the horse preparation due to greater potency. The antibodies bind to the surface of circulating T lymphocytes, which then undergo various reactions, such as complement-mediated destruction, antibody-dependent cytotoxicity, apoptosis, and opsonization. The antibody-bound cells are
phagocytosed in the liver and spleen, resulting in lymphopenia and impaired T-cell responses. The antibodies are slowly infused intravenously, and their half-life extends from 3 to 9 days. Because the humoral antibody mechanism remains active, antibodies can be formed against these foreign proteins. [Note: This is less of a problem with the
humanized antibodies.] Other adverse effects include chills and fever, leukopenia and thrombocytopenia, infections due to CMV or other viruses, and skin rashes. B. Muromonab-CD3 (OKT3) Muromonab-CD3 [myoo-roe-MOE-nab] is a murine monoclonal antibody that is synthesized by hybridoma technology and directed against the glycoprotein CD3
antigen of human T cells. MuromonabCD3 is used for treatment of acute rejection of renal allografts as well as for corticosteroid-resistant acute allograft rejection in cardiac and hepatic transplant patients. It is also used to deplete T cells from donor bone marrow prior to transplantation. 1. Mechanism of action: Binding to the CD3 protein results in a
disruption of T-lymphocyte function, because access of antigen to the recognition site is blocked. Circulating T cells are depleted, thereby decreasing their participation in the immune response. Because muromonab-CD3 recognizes only one antigenic site, the immunosuppression is less broad than that seen with the polyclonal antibodies. T cells
usually return to normal within 48 hours of discontinuation of therapy. 2. Pharmacokinetics: The antibody is administered IV. Initial binding of muromonab-CD3 to the antigen transiently activates the T cell Pharm 5th 3-21-11.indb 520 3/21/11 2:33:07 PM IV. Antibodies 521 and results in cytokine release (cytokine storm). It is, therefore, customary to
premedicate the patient with methylprednisolone, diphenhydramine, and acetaminophen to alleviate the cytokine-release syndrome. 3. Adverse effects: Anaphylactoid reactions may occur. Cytokinerelease syndrome may follow the first dose. The symptoms can range from a mild, flu-like illness to a life-threatening, shock-like reaction. High fever is
common. Central nervous system effects, such as seizures, encephalopathy, cerebral edema, aseptic meningitis, and headache, may occur. Infections can increase, including some due to CMV. Muromonab-CD3 is contraindicated in patients with a history of seizures, in those with uncompensated heart failure, in pregnant women, and in those who are
breast-feeding. Because of these adverse effects and the improved tolerability of rabbit antithymocyte globulin and the IL-2 receptor antagonists, muromonab-CD3 is rarely used today. C. IL-2-receptor antagonists The antigenicity and short serum half-life of the murine monoclonal antibody have been averted by replacing most of the murine amino
acid sequences with human ones by genetic engineering. Basiliximab [bah-si-LIK-si-mab] is said to be "chimerized" because it consists of 25 percent murine and 75 percent human protein. Daclizumab [dah-KLIZyoo-mab] is 90 percent human protein, and is designated "humanized." Both agents have been approved for prophylaxis of acute rejection in
renal transplantation in combination with cyclosporine and corticosteroids. They are not used for the treatment of ongoing rejection. In late 2009, daclizumab was withdrawn from the U.S. market by the manufacturer due to a diminished demand for the product. 1. Mechanism of action: Both compounds are anti-CD25 antibodies and bind to the α
chain of the IL-2 receptor on activated T cells. They thus interfere with the proliferation of these cells. Basiliximab is about 10-fold more potent than daclizumab as a blocker of IL-2 stimulated T-cell replication. Blockade of this receptor foils the ability of any antigenic stimulus to activate the T-cell response system. 2. Pharmacokinetics: Both
antibodies are given IV. The serum half-life of daclizumab is about 20 days, and the blockade of the receptor is 120 days. Five doses of daclizumab are usually administered, the first at 24 hours before transplantation, and the next four doses at 14-day intervals. The serum half-life of basiliximab is about 7 days. Usually, two doses of this drug are
administered, the first at 2 hours prior to transplantation, and the second at 4 days after the surgery. 3. Adverse effects: Both daclizumab and basiliximab are well tolerated. Their major toxicity is GI. No clinically relevant antibodies to the drugs have been detected, and malignancy does not appear to be a problem. D. Alemtuzumab Alemtuzumab [al-
em-TOOZ-oo-mab], a humanized monoclonal antibody directed against CD52, exerts its effects by causing profound depletion of T cells from the peripheral circulation. This effect may last for up to 1 year. Alemtuzumab is currently approved for the treatment of refractory B-cell chronic lymphocytic leukemia. Although it is not Pharm 5th 3-21-11.indb
521 3/21/11 2:33:07 PM 522 40. Immunosuppressants DRUG Antigen ACTION ADVERSE EFFECTS Alemtuzumab Depletion of T lymphocytes Cytokine-release syndrome; neutropenic, pancytopenia Antithymocyte globulins Destruction of T lymphocytes Profound immunosuppression Muromonab-CD3 Destruction of T lymphocytes Cyclosporine Blocks
calcineurin and inhibits IL-2 synthesis Cytokine-release syndrome T-cell receptor Nephrotoxicity, neurotoxicity, hepatotoxicity Tacrolimus (FK506) Blocks calcineurin and inhibits IL-2 synthesis Nephrotoxicity, neurotoxicity, diabetes Basiliximab Blocks the IL-2 receptor Gastrointestinal disorders Daclizumab Blocks the IL-2 receptor Gastrointestinal
disorders Sirolimus Blocks cytokine-stimulated cell proliferation Blocks cytokine-stimulated cell proliferation Hyperlipidemia, thrombocytopenia, leukopenia, headache, nausea Hyperlipidemia, constipation, delayed wound healing, anemia Azathioprine Inhibits purine synthesis Bone marrow suppression, hepatotoxicity, thrombocytopenia, anemia,
neoplasia Mycophenolate mofetil Inhibits purine synthesis Activated calcineurin Dephosphorylation of NFATc IL-2 gene promotion IL-2 IL-2 receptors Everolimus Progression into cell cycle GI upset, nausea, diarrhea, leukopenia, tumors, increased susceptibility to infection Cell proliferation Figure 40.8 Sites of action of immunosuppressants. Il-2 =
interleukin-2; NFATc = cytosolic nuclear factor of activated T cells; GI = gastrointestinal. currently approved for use in organ transplantation, it is being used in combination with sirolimus and low-dose calcineurin inhibitors in corticosteroid-avoidance protocols at many transplant centers. Preliminary results are promising, with low rates of rejection
with a prednisone-free regimen. Side effects include first-dose cytokine-release syndrome, requiring premedication with acetaminophen, diphenhydramine, and corticosteroids. Adverse effects include neutropenia, anemia, and, rarely, pancytopenia. Intermediate term results have shown an increase in B-cell mediated rejection and development of
autoimmune disorders in a small number of patients and, thus, this agent should be used with caution. A summary of the major immunosuppressive drugs is presented in Figure 40.8. Pharm 5th 3-21-11.indb 522 3/21/11 2:33:08 PM V. Corticosteroids 523 V. CORTICOSTEROIDS The corticosteroids were the first pharmacologic agents to be used as
immunosuppressives both in transplantation and in various autoimmune disorders. They are still one of the mainstays for attenuating rejection episodes. For transplantation, the most common agents are prednisone or methylprednisolone, whereas prednisone or prednisolone are used for autoimmune conditions. [Note: In transplantation, they are
used in combination with agents described previously in this chapter.] The steroids are used to suppress acute rejection of solid organ allografts and in chronic graft-versus-host disease. In addition, they are effective against a wide variety of autoimmune conditions, including refractory rheumatoid arthritis, systemic lupus erythematosus, temporal
arthritis, and asthma. The exact mechanism responsible for the immunosuppressive action of the corticosteroids is unclear. The T lymphocytes are affected most. The steroids are able to rapidly reduce lymphocyte populations by lysis or redistribution. On entering cells, they bind to the glucocorticoid receptor. The complex passes into the nucleus and
regulates the translation of DNA. Among the genes affected are those involved in inflammatory responses. The use of these agents is associated with numerous adverse effects. For example, they are diabetogenic and can cause hypercholesterolemia, cataracts, osteoporosis, and hypertension with prolonged use. Consequently, efforts are being
directed toward reducing or eliminating the use of steroids in the maintenance of allografts. Pharm 5th 3-21-11.indb 523 3/21/11 2:33:09 PM 524 40. Immunosuppressants Study Questions Choose the ONE best answer. 40.1 A 45-year-old male who received a renal transplant 3 months previously and is being maintained on prednisone, cyclosporine,
and mycophenolate mofetil is found to have increased creatinine levels, and a kidney biopsy indicating severe rejetion. Which of the following courses of therapy would be appropriate? A. Increased dose of prednisone. B. Hemodialysis. C. Treatment with rabbit antithymocyte globulin. D. Treatment with sirolimus. E. Treatment with azathioprine. 40.2
A 23-year-old female suffering from grand mal epilepsy is being controlled with phenytoin. She is a candidate for a renal transplant. Which agent might exacerbate the seizures in this patient? A. Mycophenolate mofetil. B. Sirolimus. C. Cyclosporine. D. Tacrolimus. E Prednisone 40.3 Which of the following drugs used to prevent allograft rejection can
cause hyperlipidemia? A. Azathioprine. B. Basiliximab. C. Tacrolimus. D. Mycophenolate mofetil. E. Sirolimus. 40.4 Which of the following drugs specifically inhibit calcineurin in the activated T lymphocytes? A. Daclizumab. B. Tacrolimus. C. Prednisone. D. Sirolimus. E. Mycophenolate mofetil. Pharm 5th 3-21-11.indb 524 Correct answer = C. This
patient is apparently undergoing an acute rejection of the kidney. The most effective treatment would be administration of an antibody. Increasing the dose of prednisone may have some effect, but would not be enough to treat the rejection. Sirolimus is used prophylactically with cyclosporine to prevent renal rejection but is less effective when an
episode is occurring. Furthermore, the combination of cyclosporine and sirolimus is more nephrotoxic than cyclosporine alone. Azathioprine has no benefit over mycophenolate. Correct answer = D. Central nervous system problems, such as headache and tremor, as well as seizures are among the adverse effects commonly associated with tacrolimus.
Cyclosporine, sirolimus, and tacrolimus are metabolized by the CYP3A4 isozyme of the cytochrome P450 oxidases. Phenytoin can induce this enzyme; thus, the doses of these agents must be carefully adjusted and their blood levels carefully monitored in this patient. Mycophenolate mofetil has predominantly gastrointestinal side effects. Correct
answer = E. Patients who are receiving sirolimus can develop elevated cholesterol and triacylglycerol levels, which can be controlled by statin therapy. None of the other agents has this adverse effect. Correct answer = B. Tacrolimus binds to FKBP-12, which, in turn, inhibits calcineurin and interferes in the cascade of reactions that synthesize
interleukin-2 (IL-2) and lead to T-lymphocyte proliferation. Although daclizumab also interferes with T-lymphocyte proliferation, it does so by binding to the CD25 site on the IL-2 receptor. Prednisone can affect not only T-cell proliferation but also that of B cells and is, therefore, nonspecific. Sirolimus, while also binding to FKBP-12, does not inhibit
calcineurin. Mycophenolate mofetil exerts its immunosuppressive action by inhibiting inosine monophosphate dehydrogenase, thus depriving the cells of guanosine, a key component of nucleic acids. 3/21/11 2:33:09 PM UNIT VIII Anti-inflammatory Drugs and Autacoids 41 Anti-inflammatory Drugs I. OVERVIEW Inflammation is a normal, protective
response to tissue injury caused by physical trauma, noxious chemicals, or microbiologic agents. Inflammation is the body's effort to inactivate or destroy invading organisms, remove irritants, and set the stage for tissue repair. When healing is complete, the inflammatory process usually subsides. However, inappropriate activation of our immune
system can result in inflammation, leading to immunemediated diseases such as rheumatoid arthritis (RA). Normally, our immune system can differentiate between self and nonself. In RA, white blood cells (WBCs) view the synovium (tissue that nourishes cartilage and bone) as nonself and initiate an inflammatory attack. WBC activation leads to
stimulation of T lymphocytes (the cell-mediated part of our immune system), which will recruit and activate monocytes and macrophages. These cells secrete pro-inflammatory cytokines, including tumor necrosis factor (TNF)-α and interleukin (IL)-1, into the synovial cavity. The release of cytokines will then cause 1) increased cellular infiltration into
the endothelium due to release of histamines, kinins, and vasodilatory prostaglandins; 2) increased production of C-reactive protein by hepatocytes (a marker for inflammation); 3) increased production and release of proteolytic enzymes (collagenases and metalloproteinases) by chondrocytes (cells that maintain cartilage), leading to degradation of
cartilage and joint space narrowing; 4) increased osteoclast activity (osteoclasts regulate bone breakdown), resulting in focal bone erosions and bone demineralization around joints; and 5) systemic manifestations in which organs such as the heart, lungs, and liver are adversely affected. In addition to T-lymphocyte activation, B lymphocytes are also
involved and will produce rheumatoid factor (inflammatory marker) and other autoantibodies with the purpose of maintaining inflammation. These defensive reactions will cause progressive tissue injury, resulting in joint damage and erosions, functional disability, significant pain, and reduction in quality of life. Pharmacotherapy in the management of
RA includes anti-inflammatory and/or immunosuppressive agents that will modulate/reduce the inflammatory process with the goals of reducing inflammation and pain, halting (or at least slowing) the progression of the disease. The agents to be discussed include nonsteroidal anti-inflammatory drugs (NSAIDs) and celecoxib (cyclooxygenase-2
inhibitor), acetaminophen, and disease-modifying antirheumatic drugs (DMARDs). Additionally, agents used for the treatment of gout will be reviewed (Figure 41.1). Pharm 5th 3-21-11.indb 525 NSAIDs Aspirin BAYER, BUFFERIN, ECOTRIN Celecoxib CELEBREX Diclofenac CATAFLAM, FLECTOR, PENNSAID, VOLTAREN Diflunisal DOLOBID
Etodolac LODINE Fenamates: Meclofenamate MECLOMEN Fenoprofen NALFON Flurbiprofen ANSAID Ibuprofen ADVIL, MOTRIN Indomethacin INDOCIN Ketorolac Acular, Acuvail, TORADOL Ketoprofen ORUDIS Meloxicam MOBIC Methyl salicylate WINTERGREEN OIL Nabumetone RELAFEN Naproxen ALEVE, ANAPROX, NAPROSYN Oxaprozin
DAYPRO Piroxicam FELDENE Sulindac CLINORIL Tolmetin TOLMETIN SODIUM OTHER ANALGESICS Acetaminophen (Paracetamol) TYLENOL Figure 41.1 Summary of anti-inflammatory drugs. NSAIDs = nonsteroidal anti-inflammatory drugs; COX = cyclooxygenase. (Continued on next page.) 3/21/11 2:33:09 PM 526 41. Anti-inflammatory Drugs
DRUGS FOR ARTHRITIS Abatacept ORENCIA Adalimumab HUMIRA Anakinra KINERET Certolizumab CIMZIA Chloroquine ARALEN Etanercept ENBREL Gold salts MYOCHRYSINE Golimumab SIMPONI Infliximab REMICADE Leflunomide ARAVA Methotrexate RHEUMATREX, TREXALL D-Penicillamine CUPRIMINE, DEPEN Rituximab RITUXAN
DRUGS FOR GOUT Allopurinol ZYLOPRIM Febuxostat ULORIC Colchicine COLCRYS Probenecid BENEMID Sulfinpyrazone ANTURANE Figure 41.1 (continued) Summary of anti-inflammatory drugs. COX-1 Substrate binding site COX-2 Substrate binding site COX-2 has a larger and more flexible substrate channel than COX-1, and COX-2 has a larger
space at the site where inhibitors bind. Figure 41.2 Structural differences in active sites of cyclooxygenase (COX)-1 and COX-2. Pharm 5th 3-21-11.indb 526 II. PROSTAGLANDINS All of the NSAIDs act by inhibiting the synthesis of prostaglandins. Thus, an understanding of NSAIDs requires comprehension of the actions and biosynthesis of
prostaglandins—unsaturated fatty acid derivatives containing 20 carbons that include a cyclic ring structure. [Note: These compounds are sometimes referred to as eicosanoids; "eicosa" refers to the 20 carbon atoms.] A. Role of prostaglandins as local mediators Prostaglandins and related compounds are produced in minute quantities by virtually all
tissues. They generally act locally on the tissues in which they are synthesized, and they are rapidly metabolized to inactive products at their sites of action. Therefore, the prostaglandins do not circulate in the blood in significant concentrations. Thromboxanes, leukotrienes, and the hydroperoxyeicosatetraenoic and hydroxyeicosatetraenoic acids
(HPETEs and HETEs, respectively) are related lipids that are synthesized from the same precursors as the prostaglandins and use interrelated pathways. B. Synthesis of prostaglandins Arachidonic acid, a 20-carbon fatty acid, is the primary precursor of the prostaglandins and related compounds. Arachidonic acid is present as a component of the
phospholipids of cell membranes, primarily phosphatidylinositol and other complex lipids. Free arachidonic acid is released from tissue phospholipids by the action of phospholipase A2 and other acyl hydrolases via a process controlled by hormones and other stimuli. There are two major pathways in the synthesis of the eicosanoids from arachidonic
acid. 1. Cyclooxygenase pathway: All eicosanoids with ring structures (that is, the prostaglandins, thromboxanes, and prostacyclins) are synthesized via the cyclooxygenase pathway. Two related isoforms of the cyclooxygenase enzymes have been described. Cyclooxygenase-1 (COX-1) is responsible for the physiologic production of prostanoids,
whereas cyclooxygenase-2 (COX-2) causes the elevated production of prostanoids that occurs in sites of chronic disease and inflammation. COX-1 is a constitutive enzyme that regulates normal cellular processes, such as gastric cytoprotection, vascular homeostasis, platelet aggregation, and reproductive and kidney functions. COX-2 is constitutively
expressed in tissues such as the brain, kidney, and bone. Its expression at other sites is increased during states of chronic inflammation. The two enzymes share 60 percent homology in amino acid sequence. However, the conformation for the substrate-binding sites and catalytic regions is slightly different. For example, COX-2 has a larger and more
flexible substrate channel than COX-1, and COX-2 has a large space at the site where inhibitors bind (Figure 41.2). [Note: The structural differences between COX-1 and COX-2 permitted the development of COX-2 selective inhibitors.] Another distinguishing characteristic of COX-2 is that its expression is induced by inflammatory mediators like TNF-α
and IL-1, but can also be pharmacologically inhibited by glucocorticoids (Figure 41.3), which may contribute to the significant anti-inflammatory effects of these drugs. 2. Lipoxygenase pathway: Alternatively, several lipoxygenases can act on arachidonic acid to form 5-HPETE, 12-HPETE, and 15-HPETE, 3/21/11 2:33:28 PM II. Prostaglandins C
Cyclooxygenase pathway C which are unstable peroxidized derivatives that are converted to the corresponding hydroxylated derivatives (the HETEs) or to leukotrienes or lipoxins, depending on the tissue (see Figure 41.3). Antileukotriene drugs, such as zileuton, zafirlukast, and montelukast, are useful for the treatment of moderate to severe asthma
(see p. 344). 527 COX-1 gene transcription COX-2 gene transcription C. Actions of prostaglandins D. Prostaglandins: Therapeutic uses Prostaglandins have a major role in modulating pain, inflammation, and fever. They also control many physiological functions, such as acid secretion and mucus production in the gastrointestinal (GI) tract, uterine
contractions, and renal blood flow. Prostaglandins are also among the chemical mediators that are released in allergic and inflammatory processes. 1. Misoprostol: Misoprostol, a PGE1 analog, is used to protect the mucosal lining of the stomach during chronic NSAID treatment. The drug decreases the incidence of gastric and duodenal ulcers caused
by NSAIDs. [Note: There is a combination product containing diclofenac and misoprostol.] Misoprostol is also used off-label in obstetric settings for labor induction. (See Chapter 28.) a. Mechanism of action: Misoprostol interacts with prostaglandin receptors on parietal cells within the stomach, reducing gastric acid secretion. Furthermore,
misoprostol has a GI cytoprotective effect by stimulating mucus and bicarbonate production. This combination of acid reduction and cytoprotective effects gives misoprostol a unique therapeutic advantage to counteract NSAID-induced stomach ulceration. Misoprostol increases uterine contractions by interacting with prostaglandin receptors in the
uterus. b. Adverse effects: Misoprostol has a black box warning due to the potential risk to induce abortion (U.S. Food and Drug Administration [FDA] pregnancy category X). Therefore, the drug is contraindicated during pregnancy. Other common side effects are: diarrhea, abdominal pain, spotting (in women), and Pharm 5th 3-21-11.indb 527
Induced by: • Oxidative stress • Injury • Ischemia • Seizures • Neuro- + Many of the actions of prostaglandins are mediated by their binding to a wide variety of distinct cell membrane receptors that operate via G proteins, which subsequently activate or inhibit adenylyl cyclase or stimulate phospholipase C. This causes an enhanced formation of
diacylglycerol and inositol 1,4,5-trisphosphate. Prostaglandin F2α (PGF2α), the leukotrienes, and thromboxane A2 (TXA2) mediate certain actions by activating phosphatidyl inositol metabolism, leading to an increase in intracellular Ca^{2+}. Prostaglandins and their metabolites, produced endogenously in tissues, act as local signals that fine-tune the
response of a specific cell type. Their functions vary widely, depending on the tissue and the specific enzymes within the pathway that are available at that particular site. For example, the release of TXA2 from platelets during tissue injury triggers the recruitment of new platelets for aggregation (the first step in clot formation) as well as local
vasoconstriction. However, PGI2, produced by endothelial cells, has opposite effects, inhibiting platelet aggregation and producing vasodilation. The net effect on platelets and blood vessels depends on the balance of these two prostaglandins. degenerative diseases Glucocorticoids mRNA mRNA Membrane phospholipids Arachidonic acid COX-2 COX-
1 Nonsteroidal anti-inflammatory drugs (NSAIDS) Selective COX-2 inhibitors Prostaglandins Prostaglandins Lipoxygenase pathway Membrane phospholipids Arachidonic acid 5-Lipoxygenase Leukotrienes Figure 41.3 Synthesis of prostaglandins and leukotrienes. COX = cyclooxygenase. 3/21/11 2:33:31 PM 528 41. Anti-inflammatory Drugs headache.
When used off-label for labor induction, for termination of pregnancy, or for cervical ripening, misoprostol can cause maternal or fetal complications such as death, infection, uterine damage, and fetal bradycardia. Iloprost nebulizer 7–9 times per day Metabolites of iloprost are excreted in urine (68%) and feces (12%) Iloprost Figure 41.4
Administration and fate of iloprost. 2. Iloprost: Iloprost, a synthetic analog of prostacyclin, or PGI2, is a very potent pulmonary vasodilator that is used for the treatment of pulmonary arterial hypertension. It mimics the effects of the naturally produced prostaglandin in endothelial cells. When inhaled, iloprost produces a significant reduction in
pulmonary hypertension. The fact that this drug is given via pulmonary inhalation represents an advantage due to a more localized effect with less systemic blood pressure reduction. However, the short half-life of the drug requires frequent dosing (Figure 41.4). a. Mechanism of action: Iloprost produces a significant reduction in pulmonary arterial
resistance with a subsequent increase in cardiac index and oxygen delivery. These actions are mediated through activation of the IP receptors (prostacyclin receptors), increasing the production of intracellular cyclic adenosine monophosphate (cAMP). TXA2 production is also inhibited by iloprost. b. Side effects: Dizziness, headache, flushing and
fainting are usually the most common side effects (Figure 41.5). Bronchospasm and cough can also occur after iloprost inhalation. Dizziness Headache Flushing 3. Latanoprost, travoprost, and bimatoprost: Latanoprost is a PGF2α analog that is indicated for the treatment of open angle glaucoma and elevated intraocular pressure. Travoprost is a pro-
drug that is metabolized to the active free acid. They are administered as ophthalmic solutions once a day and are as effective as timolol or better in reducing intraocular pressure. Bimatoprost mimics endogenous prostamides (prostaglandin-ethanolamides), resulting in the same effective reduction of intraocular pressure. Also, bimatoprost increases
eyelash prominence, length, and darkness and has also been approved for the treatment of eyelash hypotrichosis. a. Mechanism of action: By binding to the prostaglandin FP receptors, latanoprost and travoprost increase uveoscleral outflow, reducing intraocular pressure. Bimatoprost's effects appear to be similar. b. Side effects: Ocular reactions
include blurred vision, iris color change (increased brown pigmentation), increased number and pigment of eyelashes, ocular irritation, and foreign body sensation. Fainting Figure 41.5 Some adverse reactions to iloprost. Pharm 5th 3-21-11.indb 528 4. Alprostadil: Alprostadil is a PGE1 that is naturally produced in tissues, such as seminal vesicles and
cavernous tissues, in the placenta, and in the ductus arteriosus of the fetus. Therapeutically, alprostadil can be used to treat erectile dysfunction or to keep the ductus arteriosus open in neonates with congenital heart conditions until surgery is possible. PGE1 maintains the patency of the ductus arteriosus during pregnancy. The ductus closes soon
after delivery to allow normal blood circulation between the lungs and the heart. Infusion of the drug maintains the ductus open as it naturally occurs during pregnancy, allowing time until surgical correction is possible. 3/21/11 2:33:33 PM III. Nonsteroidal Anti-inflammatory Drugs 529 a. Mechanism of action: Local administration of alprostadil in the
urethra (suppository) or into the corpus cavernosa (injection) can produce an erection suitable for intercourse. These effects are mediated by an increase in intracellular cAMP leading to activation of protein kinase and smooth muscle relaxation. Blood becomes entrapped by relaxation of the trabecular smooth muscles and by dilation of cavernosal
arteries. b. Side effects: When used for the treatment of erectile dysfunction, alprostadil can produce symptomatic hypotension, dizziness, and syncope. Local adverse reactions include penile, urethral, and testicular pain; prolonged erections; and priapism. When administered intravenously (IV) in neonates, apnea, fever, sepsis, and seizures have been
reported. 5. Lubiprostone: Lubiprostone is a PGE1 derivative used for the treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation. a. Mechanism of action: Lubiprostone stimulates chloride channels (ClC-2) in the luminal cells of the intestinal epithelium, thereby increasing intestinal fluid secretion. The increased
chloride concentration within the intestinal lumen softens the stool and increases intestinal motility. b. Side effects: Nausea is the most common side effect of lubiprostone (Figure 41.6), which can be decreased if taken with food. Dosedependent diarrhea is the second most reported adverse reaction, followed by headache and abdominal pain. III.
NONSTEROIDAL ANTI-INFLAMMATORY DRUGS The NSAIDs are a group of chemically dissimilar agents that differ in their antipyretic, analgesic, and anti-inflammatory activities. They act primarily by inhibiting the cyclooxygenase enzymes that catalyze the first step in prostanoid biosynthesis. This leads to decreased prostaglandin synthesis with
both beneficial and unwanted effects. Detection of serious cardiovascular events associated with COX-2 inhibitors has led to withdrawal of rofecoxib and valdecoxib from the market (celecoxib is still available for the treatment of osteoarthritis, RA, pain, and adjuvant treatment of familial adenomatous polyposis). Additionally, the FDA has required that
the labeling of the traditional NSAIDs and celecoxib be updated to include the following: 1) a warning of the potential risks of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal, as well as a warning that these risk may increase with duration of use and that patients with cardiovascular disease or risk
factors may be at greater risk; 2) a warning that use is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft surgery; and 3) a notice that there is increased risk of serious GI adverse events, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can
occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious GI events. Aspirin, however, has proven to be beneficial in patients for the primary and secondary prevention of cardiovascular events and is most commonly used for this purpose rather than for pain control. Pharm 5th 3-21-11.indb 529
Nausea Diarrhea Figure 41.6 Some adverse reactions to lubiprostone. 3/21/11 2:33:34 PM 530 41. Anti-inflammatory Drugs A. Aspirin and other salicylic acid derivatives Acetyl group that is transferred to cyclooxygenase C OOH O C CH3 O Aspirin (Acetylsalicylic acid) H_2O Cyclooxygenase (active) Normal deacetylation by esterase Acetylated
cyclooxygenase (inactive) Acetate C CH3 O C OOH Aspirin [AS-pir-in] is the prototype of traditional NSAIDs and was officially approved by the FDA in 1939. It is the most commonly used salicylic acid derivative and is the drug to which all other anti-inflammatory agents are compared. 1. Mechanism of action: Aspirin is a weak organic acid that is
unique among the NSAIDs in that it irreversibly acetylates (and, thus, inactivates) cyclooxygenase (Figure 41.7). The other NSAIDs, including salicylate , are all reversible inhibitors of cyclooxygenase. Aspirin is rapidly deacetylated by esterases in the body, thereby producing salicylate, which has anti-inflammatory, antipyretic, and analgesic effects.
The antipyretic and anti-inflammatory effects of salicylate are due primarily to the blockade of prostaglandin synthesis at the thermoregulatory centers in the hypothalamus and at peripheral target sites. Furthermore, by decreasing prostaglandin synthesis, salicylate also prevents the sensitization of pain receptors to both mechanical and chemical
stimuli. Aspirin may also depress pain stimuli at subcortical sites (that is, the thalamus and hypothalamus). 2. Actions: The NSAIDs, including aspirin, have three major therapeutic actions: they reduce inflammation (anti-inflammation), pain (analgesia), and fever (antipyrexia; Figure 41.8). However, as described later in this section, not all NSAIDs are
equally effective in each of these actions. OH Salicylic acid (Salicylate) Figure 41.7 Metabolism of aspirin and acetylation of cyclooxygenase by aspirin. a. Anti-inflammatory actions: Because aspirin inhibits cyclooxygen ase activity, it diminishes the formation of prostaglandins and, thus, modulates those aspects of inflammation in which prostaglandins
act as mediators. Aspirin inhibits inflammation in arthritis, but it neither arrests the progress of the disease nor induces remission. NSAIDs Strong Antiinflammatory effect Weak Analgesic effect Antipyretic effect Strong Acetaminophen Figure 41.8 Actions of nonsteroidal antiinflammatory drugs (NSAIDs) and acetaminophen. Pharm 5th 3-21-11.indb
530 b. Analgesic action: PGE2 is thought to sensitize nerve endings to the action of bradykinin, histamine, and other chemical mediators released locally by the inflammatory process. Thus, by decreasing PGE2 synthesis, aspirin and other NSAIDs repress the sensation of pain. The salicylates are used mainly for the management of pain of low to
moderate intensity arising from musculoskeletal disorders rather than that arising from the viscera. Combinations of opioids and NSAIDs are effective in treating pain caused by malignancy. c. Antipyretic action: Fever occurs when the set-point of the anterior hypothalamic thermoregulatory center is elevated. This can be caused by PGE2 synthesis,
which is stimulated when endogenous fever-producing agents (pyrogens), such as cytokines, are released from WBCs that are activated by infection, hypersensitivity, malignancy, or inflammation. The salicylates lower body temperature in patients with fever by impeding PGE2 synthesis and release. Aspirin and other NSAIDs reset the "thermostat"
toward normal. This rapidly lowers the body temperature of febrile patients by increasing heat dissipation as a result of peripheral vasodilation and sweating. Aspirin has no effect on normal body temperature. 3/21/11 2:33:36 PM III. Nonsteroidal Anti-inflammatory Drugs 531 d. Respiratory actions: At therapeutic doses, aspirin increases alveolar
ventilation. [Note: Salicylates uncouple oxidative phosphorylation, which leads to elevated CO_2 and increased respiration.] Higher doses work directly on the respiratory center in the medulla, resulting in hyperventilation and respiratory alkalosis that usually is adequately compensated for by the kidney. At toxic levels, central respiratory paralysis
occurs, and respiratory acidosis ensues due to continued production of CO_2. e. Gastrointestinal effects: Normally, prostacyclin (PGI2) inhibits gastric acid secretion, whereas PGE2 and PGF2α stimulate synthesis of protective mucus in both the stomach and small intestine. In the presence of aspirin, these prostanoids are not formed, resulting in
increased gastric acid secretion and diminished mucus protection. This may cause epigastric distress, ulceration, hemorrhage, and iron-deficiency anemia. Aspirin doses of 1 to 4.5 g/day can produce loss of 2 to 8 mL of blood in the feces per day. Buffered and enteric-coated preparations are only marginally helpful in dealing with this problem. Agents
used for the prevention of gastric and/ or duodenal ulcers include the PGE1-derivative misoprostol and the proton-pump inhibitors (PPIs) esomeprazole, lansoprazole, dexlansoprazole, omeprazole, pantoprazole, and rabeprazole). PPIs can also be used for the treatment of an NSAID-induced ulcer and are especially appropriate if the patient will need
to continue NSAID treatment. H2-antihistamines (cimetidine, famotidine, nizatidine, and ranitidine) relieve dyspepsia due to NSAIDS, but they may mask serious GI complaints and may not be as effective as PPIs for healing and preventing ulcer formation. f. Effect on platelets: TXA2 enhances platelet aggregation, whereas PGI2 decreases it. Low
doses (81 to 325 mg daily) of aspirin can irreversibly inhibit thromboxane production in platelets via acetylation of cyclooxygenase (Figure 41.9). Because platelets lack nuclei, they cannot synthesize new enzyme, and the lack of thromboxane persists for the lifetime of the platelet (3–7 days). As a result of the decrease in TXA2 production, platelet
aggregation (the first step in thrombus formation) is reduced, producing an antiplatelet effect with a prolonged bleeding time. Finally, aspirin also inhibits cyclooxygenase in endothelial cells, resulting in reduced PGI2 formation. However, endothelial cells possess nuclei and are able to re-synthesize new cyclooxygenase. Thromboxane A2
Prostaglandin H2 Cyclooxygenase-1 (COX-1) Aspirin Arachidonic acid Membrane phospholipids Figure 41.9 Aspirin irreversibly inhibits platelet cyclooxygenase-1. g. Actions on the kidney: Cyclooxygenase inhibitors prevent the synthesis of PGE2 and PGI2, prostaglandins that are responsible for maintaining renal blood flow, particularly in the
presence of circulating vasoconstrictors (Figure 41.10). Decreased synthesis of prostaglandins can result in retention of sodium and water and may cause edema and hyperkalemia in some patients. Interstitial nephritis can also occur with all NSAIDs. 3. Therapeutic uses: a. Anti-inflammatory, antipyretic, and analgesic uses: The salicylic acid
derivatives are used in the treatment of gout, rheumatic fever, osteoarthritis, and RA. These agents are also used to treat common conditions (headache, arthralgia, and myalgia) requiring analgesia. Pharm 5th 3-21-11.indb 531 3/21/11 2:33:36 PM 532 41. Anti-inflammatory Drugs Response of renal blood flood Disease states leading to increased
vasoconstrictors Decreased renal blood flow Renal disease Cardiovascular disease No treatment Increased vasoconstrictors: Angiotensin II Catecholamines Vasopressin Cirrhosis Nephrosis Heart failure Diuretics Decreased blood volume Patient treated with NSAIDs Prostaglandin synthesis normally antagonizes intrarenal effects of vasoconstrictors.
NSAIDs inhibit prostaglandin synthesis, leaving actions of vasoconstrictors unopposed. Vasoconstriction Figure 41.10 Renal effect of NSAIDs inhibition of prostaglandin synthesis. NSAIDs = nonsteroidal anti-inflammatory drugs. Vasomotor collapse Coma Dehydration Lethal 150 Plasma concentration of salicylate (mg/dL) Severe Intoxication 100 Mild
50 Tinnitus Central hyperventilation Anti-inflammatory 10 0 Analgesic Antipyretic Antiplatelet Gastric bleeding Impaired blood clotting Hypersensitivity reactions Figure 41.11 Dose-dependent effects of salicylate. Pharm 5th 3-21-11.indb 532 b. External applications: Salicylic acid is used topically to treat acne, corns, calluses, and warts. Methyl
salicylate ("oil of wintergreen") is used externally as a cutaneous counterirritant in liniments. c. Cardiovascular applications: Aspirin is used to inhibit platelet aggregation. Low doses are used prophylactically to 1) reduce the risk of recurring transient ischemic attacks (TIAs) and stroke or death in those who have had single or multiple episodes of TIA
or stroke, 2) reduce the risk of death in those having an acute myocardial infarction, 3) reduce the risk of recurrent nonfatal myocardial infarction and/or death in patients with previous myocardial infarction or unstable angina pectoris, 4) reduce the risk of myocardial infarction and sudden death in patients with chronic stable angina pectoris, and 5)
reduce the cardiovascular risk in patients undergoing certain revascularization procedures. 4. Pharmacokinetics: a. Administration and distribution: After oral administration, the un-ionized salicylates are passively absorbed partly from the stomach and mostly from the upper small intestine (dissolution of the tablets is favored at the higher pH of the
gut). Rectal absorption of the salicylates is slow and unreliable. Salicylates must be avoided in children and teenagers (less than 20 years old) with viral infections, such as varicella (chickenpox) or influenza, to prevent Reye syndrome. Salicylates (except for diflunisal) cross both the blood-brain barrier and the placenta and are absorbed through intact
skin (especially methyl salicylate). b. Dosage: The salicylates exhibit analgesic activity at low doses. Only at higher doses do these drugs show anti-inflammatory activity (Figure 41.11). For example, two 325-mg aspirin tablets administered four times daily produce analgesia, whereas 12 to 20 tablets per day produce both analgesic and anti-
inflammatory activity. For long-term myocardial infarction prophylaxis, the dose is 81 to 162 mg/day; for those with RA or osteoarthritis, the initial dose is 3 grams/day; for stroke prophylaxis, the dose is 50 to 325 3/21/11 2:33:39 PM III. Nonsteroidal Anti-inflammatory Drugs 533 mg/day; and in a patient having an acute myocardial infarction, the
dose is 162 to 325 mg of nonenteric-coated aspirin chewed and swallowed immediately. c. Fate: At dosages of 650 mg/day, aspirin is hydrolyzed to salicylate and acetic acid by esterases in tissues and blood (see Figure 41.7). Salicylate is converted by the liver to water-soluble conjugates that are rapidly cleared by the kidney, resulting in elimination
with first-order kinetics and a serum half-life of 3.5 hours. At anti-inflammatory dosages (more than 4 g/day), the hepatic metabolic pathway becomes saturated, and zero-order kinetics are observed, with the drug having a half-life of 15 hours or more (Figure 41.12). Saturation of the hepatic enzymes requires treatment for several days to 1 week.
Being an organic acid, salicylate is secreted into the urine and can affect uric acid excretion. Namely, at low doses of aspirin, uric acid secretion is decreased, whereas at high doses, uric acid secretion is increased. Therefore, aspirin should be avoided in patients with gout. Both hepatic and renal function should be monitored periodically in those
receiving long-term, high-dose aspirin therapy, and aspirin should be avoided in patients with chronic kidney disease. Aspirin (high dose) Aspirin (low dose) 11 12 11 12 10 11 1 2 10 3 9 4 8 7 6 5 $t_{1/2}$ = 3 hours 12 1 2 1 10 9 2 9 34 45 8 8 7 7 6 6 5 3 $t_{1/2}$ = 15 hours Figure 41.12 Effect of dose on the half-life of aspirin. 5. Adverse effects: a.
Gastrointestinal: The most common GI effects of the salicylates are epigastric distress, nausea, and vomiting. Microscopic GI bleeding is almost universal in patients treated with salicylates. [Note: Aspirin is an acid. Because aspirin is uncharged at stomach pH, it readily crosses into mucosal cells, where it ionizes (becomes negatively charged) and
becomes trapped, thus potentially causing direct damage to the cells. Aspirin should be taken with food and large volumes of fluids to diminish dyspepsia. Additionally, misoprostol or a PPI may be taken concurrently. b. Blood: The irreversible acetylation of platelet cyclooxygenase reduces the level of platelet TXA2, resulting in inhibition of platelet
aggregation and a prolonged bleeding time. For this reason, aspirin should not be taken for at least 1 week prior to surgery. When salicylates are administered, anticoagulants may have to be given in reduced dosage, and careful monitoring and counseling of patients are necessary. c. Respiration: In toxic doses, salicylates cause respiratory
depression and a combination of uncompensated respiratory and metabolic acidosis. d. Metabolic processes: Large doses of salicylates uncouple oxidative phosphorylation. The energy normally used for the production of adenosine triphosphate is dissipated as heat, which explains the hyperthermia caused by salicylates when taken in toxic quantities.
e. Hypersensitivity: Approximately 15 percent of patients taking aspirin experience hypersensitivity reactions. Symptoms of true allergy include urticaria, bronchoconstriction, and angioedema. Fatal anaphylactic shock is rare. Pharm 5th 3-21-11.indb 533 3/21/11 2:33:40 PM 534 41. Anti-inflammatory Drugs Decreased urate excretion (contraindicated
in patients with gout) Probenecid Sulfinpyrazone Hemorrhage Heparin or oral anticoagulants Drug-drug interactions with salicylates leading to altered effects of drugs or metabolites are shown in red Bilirubin Phenytoin Valproic acid Sulfinpyrazone Thiopental Thyroxine Triiodothyronine Increased plasma concentration, leading to prolonged half-
lives, therapeutic effects, and toxicity Figure 41.13 Drugs interacting with salicylates. f. Reye syndrome: Aspirin and other salicylates given during viral infections have been associated with an increased incidence of Reye syndrome, which is an often fatal, fulminating hepatitis with cerebral edema. This is especially encountered in children, who,
therefore, should be given acetaminophen instead of aspirin when such medication is required to reduce fever. Ibuprofen is also appropriate. g. Drug interactions: Concomitant administration of salicylates with many classes of drugs may produce undesirable side effects. Because aspirin is found in many over-the-counter agents, patients should be
counseled to read labels to verify aspirin content to avoid overdose. Salicylate is roughly 80 to 90 percent plasma protein bound (albumin) and can be displaced from its protein-binding sites, resulting in increased concentration of free salicylate . Alternatively, aspirin could displace other highly protein-bound drugs, such as warfarin, phenytoin, or
valproic acid, resulting in higher free concentrations of the other agent (Figure 41.13). Chronic aspirin use should be avoided in patients receiving probenecid or sulfinpyrazone, because these agents cause increased renal excretion of uric acid, whereas aspirin (less than 2 g/day) causes reduced clearance of uric acid. Concomitant use of ketorolac
and aspirin is contraindicated because of increased risk of GI bleeding and platelet aggregation inhibition. h. In pregnancy: Aspirin is classified as FDA pregnancy category C risk during the first and second trimesters and category D during the third trimester. Because salicylates are excreted in breast milk, aspirin should be avoided during pregnancy
and while breastfeeding. 6. Toxicity: Salicylate intoxication may be mild or severe. The mild form is called salicylism and is characterized by nausea, vomiting, marked hyperventilation, headache, mental confusion, dizziness, and tinnitus (ringing or roaring in the ears). When large doses of salicylate are administered, severe salicylate intoxication may
result (see Figure 41.11). The symptoms listed above are followed by restlessness, delirium, hallucinations, convulsions, coma, respiratory and metabolic acidosis, and death from respiratory failure. Children are particularly prone to salicylate intoxication. Ingestion of as little as 10 g of aspirin (or 5 mL of methyl salicylate, with the latter being used as
a counterirritant in liniments) can cause death in children. Treatment of salicylism should include measurement of serum salicylate concentrations and of pH to determine the best form of therapy. In mild cases, symptomatic treatment is usually sufficient. Increasing the urinary pH enhances the elimination of salicylate. In serious cases, mandatory
measures include the IV administration of fluid, dialysis (hemodialysis or peritoneal dialysis), and the frequent assessment and correction of acid-base and electrolyte balances. B. Propionic acid derivatives Ibuprofen [eye-byoo-PROE-fen] was the first in this class of agents to become available in the United States. It has been joined by naproxen [nah-
PROX-en], fenoprofen [fen-oh-PROE-fen], ketoprofen [key-toePROE-fen], flurbiprofen [flur-bye-PROE-fen], and oxaprozin [ox-ah-PROEzin]. All of these drugs possess anti-inflammatory, analgesic, and anti- Pharm 5th 3-21-11.indb 534 3/21/11 2:33:41 PM III. Nonsteroidal Anti-inflammatory Drugs 535 pyretic activity. Additionally, they can alter platelet
function and prolong bleeding time. They have gained wide acceptance in the chronic treatment of RA and osteoarthritis, because their GI effects are generally less intense than those of aspirin. These drugs are reversible inhibitors of the cyclooxygenases and, like aspirin, inhibit the synthesis of prostaglandins but not of leukotrienes. All are well
absorbed on oral administration and are almost totally bound to serum albumin. [Note: Oxaprozin has the longest half-life and is administered once daily.] They undergo hepatic metabolism and are excreted by the kidney. The most common adverse effects are GI, ranging from dyspepsia to bleeding. Side effects involving the central nervous system
(CNS), such as headache, tinnitus, and dizziness, have also been reported. Ibuprofen is used IV to close a patent ductus arteriosus (PDA). It appears to have fewer adverse effects than IV indomethacin. C. Acetic acid derivatives This group of drugs includes indomethacin [in-doe-METH-a-sin], sulindac [sul-IN-dak], and etodolac [eh-TOE-doh-lak]. All
have anti-inflammatory, analgesic, and antipyretic activity. They act by reversibly inhibiting cyclooxygenase. They are generally not used to lower fever. Despite its potency as an anti-inflammatory agent, the toxicity of indomethacin limits its use to the treatment of acute gouty arthritis, to close a PDA in neonates, in ankylosing spondylitis, and in
osteoarthritis of the hip. Sulindac is an inactive prodrug that is closely related to indomethacin. Although the drug is less potent than indomethacin, it is useful in the treatment of RA, ankylosing spondylitis, osteoarthritis, and acute gout. The adverse reactions caused by sulindac are similar to, but less severe than, those of the other NSAIDs, including
indomethacin. Etodolac has effects similar to those of the other NSAIDs. GI problems are less common. D. Oxicam derivatives Piroxicam [peer-OX-i-kam] and meloxicam [mel-OX-i-kam] are used to treat RA, ankylosing spondylitis, and osteoarthritis. They have long halflives, which permits once-daily administration, and the parent drug as well as its
metabolites are renally excreted in the urine. GI disturbances are encountered in approximately 20 percent of patients treated with piroxicam. Meloxicam inhibits both COX-1 and COX-2, with preferential binding for COX-2, and at low to moderate doses shows less GI irritation than piroxicam. However, at high doses, meloxicam is a nonselective
NSAID, inhibiting both COX-1 and COX-2. Meloxicam excretion is predominantly in the form of metabolites and occurs equally in urine and feces. E. Fenamates Mefenamic [meh-FEN-a-mick] acid and meclofenamate [meh-KLO-fena-mate] have no advantages over other NSAIDs as anti-inflammatory agents. Their side effects, such as diarrhea, can be
severe, and they are associated with inflammation of the bowel. Cases of hemolytic anemia have been reported. F. Heteroaryl acetic acids Diclofenac [dye-KLO-feh-nak] and tolmetin [tole-MET-in] are approved for long-term use in the treatment of RA, osteoarthritis, and ankylosing spondylitis. Diclofenac is more potent than indomethacin or naproxen.
An ophthalmic preparation is also available. Diclofenac accumulates in synovial fluid, and the primary route of excretion for the drug and its Pharm 5th 3-21-11.indb 535 3/21/11 2:33:41 PM 536 41. Anti-inflammatory Drugs metabolites is the kidney. Tolmetin is an effective anti-inflammatory, antipyretic, and analgesic agent with a half-life of 5 hours.
It is 99 percent bound to plasma proteins, and metabolites can be found in the urine. Toxicities of these two agents are similar to those of the other NSAIDs. Ketorolac [key-toe-ROLE-ak] is a potent analgesic but has moderate antiinflammatory effects. It is available for oral administration, for intramuscular use in the treatment of postoperative pain,
and for topical use for allergic conjunctivitis. Ketorolac undergoes hepatic metabolism, and the drug and its metabolites are eliminated via urine. Ketorolac is indicated for short-term relief of moderate to severe pain for up to 5 days after the first dose is administered via IV or intramuscular dosing at the doctor's office or in a hospital. This agent is to
be avoided in pediatric patients. In patients with mild pain, and those with chronic conditions, the dose should not exceed 40 mg/day. Ketorolac can cause fatal peptic ulcers as well as GI bleeding and/or perforation of the stomach or intestines. G. Nabumetone Nabumetone [na-BYOO-meh-tone] is indicated for the treatment of RA and osteoarthritis
and is associated with a low incidence of adverse effects. Nabumetone is metabolized by the liver to an active metabolite, which displays anti-inflammatory, antipyretic, and analgesic activities. The active metabolite is then hepatically metabolized to inactive metabolites with subsequent renal elimination. Therefore, cautious use of this agent in

patients with hepatic impairment is warranted. Additionally, the dose should be adjusted in those with creatinine clearance of less than 50 mL/min. Drug equally active against COX-1 and COX-2 Meloxicam Celecoxib Ibuprofen H. Celecoxib Naproxen Aspirin –4 –3 –2 –1 0 1 2 log IC80 COX-2 IC80 COX-1 Increasing COX-2 selectivity Increasing COX-1 selectivity Figure 41.14 Relative selectivity of some commonly used NSAIDs. Data shown as the logarithm of their ratio of IC80 (drug concentration to achieve 80 percent inhibition of cyclooxygenase). Celecoxib [sel-eh-COCKS-ib] is significantly more selective for inhibition of COX-2 than of COX-1 (Figure 41.14). This selectivity against COX2 provides a therapeutic advantage over nonselective COX inhibitors, allowing the proper management of chronic inflammatory conditions. In fact, at concentrations achieved in vivo , celecoxib does not block COX1. Unlike the inhibition of COX-1 by aspirin (which is rapid and irreversible), the inhibition of COX-2 is time dependent and reversible. Celecoxib is approved for treatment of RA, osteoarthritis, acute to moderate pain, and for adjuvant treatment of patients with familial adenomatous polyposis to reduce the number of adenomatous colorectal polyps. Unlike aspirin, celecoxib does not inhibit platelet aggregation and does not increase bleeding time. Celecoxib has both similar efficacy to NSAIDs in the treatment of pain and in the risk for cardiovascular events. Celecoxib, when used without concomitant aspirin therapy, has been shown to be associated with less GI bleeding and dyspepsia. However, this benefit is lost when aspirin is added to celecoxib therapy. In patients at high risk for ulcers (that is, history of peptic ulcer disease), use of PPIs with celecoxib and aspirin may be necessary to avoid gastric ulcers. 1. Pharmacokinetics: Celecoxib is readily absorbed, reaching a peak concentration in about 3 hours. It is extensively metabolized in the liver by cytochrome P450 (CYP2C9) and is excreted in feces and urine. Its half-life is about 11 hours, and the drug is usually taken once a day but can be administered as divided doses twice daily. The daily recommended dose should be reduced by 50 percent in those with moderate hepatic impairment, and celecoxib should be avoided in patients with severe hepatic and renal diseases. Pharm 5th 3-21-11.indb 536 3/21/11 2:33:42 PM IV. Acetaminophen 537 Therapeutic disadvantages of selected NSAIDs* Upper GI disturbances are common No antipyretic effect Very potent; should be used only after less toxic agents have proven ineffective CNS disturbances are common Therapeutic advantages of selected NSAIDs Salicylates: Aspirin Salicylate salts Diflunisal Acetic acids: Indomethacin Sulindac Tolmetin Propionic acids: Ibuprofen Fenoprofen Flurbiprofen Ketoprofen Naproxen Oxaprozin Low cost; long history of safety Less GI irritation than aspirin Long half-life permits daily or twice daily dosing Lower toxicity and better acceptance in some patients. Naproxen is considered by some experts as one of the safest NSAIDs Oxicams: Piroxicam Meloxicam Fenamates: Potential for increasing myocardial infarctions and strokes Mefenamic acid Meclofenamic acid COX-2 inhibitors Less GI irritation than aspirin Celecoxib Figure 41.15 Summary of nonsteroidal anti-inflammatory agents (NSAIDs). GI = gastrointestinal; CNS = central nervous system; COX-2 = cyclooxygenase-2. *As a group, with the exception of aspirin, these drugs may have the potential to increase myocardial infarctions and strokes. 2. Adverse effects: Headache, dyspepsia, diarrhea, and abdominal pain are the most common adverse effects. Celecoxib is contraindicated in patients who are allergic to sulfonamides. [Note: If there is a history of sulfonamide drug allergy, the use of a nonselective NSAID along with a PPI is recommended.] As with other NSAIDs, kidney toxicity may occur. Celecoxib should be avoided in patients with chronic renal insufficiency, severe heart disease, volume depletion, and/or hepatic failure. Patients who have had anaphylactoid reactions to aspirin or nonselective NSAIDs may be at risk for similar effects when challenged with celecoxib. Inhibitors of CYP2C9, such as fluconazole, fluvastatin, and zafirlukast, may increase serum levels of celecoxib. Celecoxib has the ability to inhibit CYP2D6 and, thus, could lead to elevated levels of some β-blockers (propranolol), antidepressants (amitriptyline), and antipsychotic drugs (risperidone). Figure 41.15 summarizes some of the therapeutic advantages and disadvantages of members of the NSAID family. IV. ACETAMINOPHEN Acetaminophen [a-SEAT-a-MIN-oh-fen], (N-acetyl-p-aminophenol, or APAP) inhibits prostaglandin synthesis in the CNS. This explains its antipyretic and analgesic properties. Acetaminophen has less effect on cyclooxygenase in peripheral tissues, which accounts for its weak anti-inflammatory activity. Acetaminophen does not affect platelet function or increase blood-clotting time. Acetaminophen is not considered to be an NSAID. Pharm 5th 3-21-11.indb 537 3/21/11 2:33:44 PM 538 41. Anti-inflammatory Drugs A. Therapeutic uses HNCOCH3 HNCOCH3 HNCOCH3 OH Sulfate Glucuronide Acetaminophen Cytochrome P-450 mixedfunction oxidase Nucleophilic hepatic cell proteins NCOCH 3 Glutathione Therapeutic doses Toxic doses O Toxic intermediate HNCOCH 3 Glutathione OH HNCOCH 3 Mercapturic acid (nontoxic) OH Cell macromolecules Cell death Figure 41.16 Metabolism of acetaminophen. Acetaminophen is a suitable substitute for the analgesic and antipyretic effects of aspirin for those patients with gastric complaints, those in whom prolongation of bleeding time would be a disadvantage, and those who do not require the anti-inflammatory action of aspirin. Acetaminophen is the analgesic/antipyretic of choice for children with viral infections or chickenpox (recall that aspirin increases the risk of Reye syndrome). Acetaminophen does not antagonize the uricosuric agents probenecid or sulfinpyrazone and, therefore, may be used in patients with gout who are taking these drugs. B. Pharmacokinetics Acetaminophen is rapidly absorbed from the GI tract. A significant firstpass metabolism occurs in the luminal cells of the intestine and in the hepatocytes. Under normal circumstances, acetaminophen is conjugated in the liver to form inactive glucuronidated or sulfated metabolites. A portion of acetaminophen is hydroxylated to form N-acetyl benzoiminoquinone, (N-acetyl-p-benzoquinoneimine, or NAPQI), a highly reactive and potentially dangerous metabolite that reacts with sulfhydryl groups and causes liver damage. At normal doses of acetaminophen, the N-acetylbenzoiminoquinone reacts with the sulfhydryl group of glutathione, forming a nontoxic substance (Figure 41.16). Acetaminophen and its metabolites are excreted in urine. C. Adverse effects With normal therapeutic doses, acetaminophen is virtually free of any significant adverse effects. Skin rash and minor allergic reactions occur infrequently. There may be minor alterations in the leukocyte count, but these are generally transient. Renal tubular necrosis is a rare complication of prolonged, large-dose therapy. With large doses of acetaminophen, the available glutathione in the liver becomes depleted, and N-acetylbenzoiminoquinone reacts with the sulfhydryl groups of hepatic proteins, forming covalent bonds (see Figure 41.16). Hepatic necrosis, a very serious and potentially life-threatening condition, can result. Patients with hepatic disease, viral hepatitis, or history of alcoholism are at higher risk of acetaminophen-induced hepatotoxicity. Renal tubular necrosis may also occur. [Note: Administration of N-acetylcysteine, which contains sulfhydryl groups to which the toxic metabolite can bind, can be lifesaving if administered within 10 hours of the overdose.] This agent should be avoided in patients with severe hepatic impairment. Periodic monitoring of liver enzymes tests is recommended for those on high-dose acetaminophen. V. DISEASE-MODIFYING ANTIRHEUMATIC AGENTS DMARDs are used in the treatment of RA and have been shown to slow the course of the disease, induce remission, and prevent further destruction of the joints and involved tissues. When a patient is diagnosed with RA, the American College of Rheumatology recommends initiation of therapy with DMARDs within 3 months of diagnosis (in addition to NSAIDs, low-dose corticosteroids, physical therapy, and occupational therapy). Therapy with DMARDs is initiated rapidly to help stop the progression of the disease at the earlier stages. Pharm 5th 3-21-11.indb 538 3/21/11 2:33:45 PM V. Disease-Modifying Antirheumatic Agents 539 A. Choice of drug No one DMARD is efficacious and safe in every patient, and trials of several different drugs may be necessary. Most experts begin DMARD therapy with one of the traditional drugs, such as methotrexate or hydroxychloroquine. These agents are efficacious and are generally well tolerated, with well-known side-effect profiles. Inadequate response to the traditional agents may be followed by use of newer DMARDs, such as leflunomide, anakinra, and TNF inhibitors (adalimumab, etanercept, golimumab, certolizumab, and infliximab). Combination therapies are both safe and efficacious. In most cases, methotrexate is combined with one of the other DMARDs. In patients who do not respond to combination therapy with methotrexate plus TNF inhibitors, or other combinations, treatment with rituximab or abatacept may be tried. Most of these agents are contraindicated for use in pregnant women. B. Methotrexate Methotrexate [meth-oh-TREX-ate], used alone or in combination therapy, has become the mainstay of treatment in patients with rheumatoid or psoriatic arthritis. Methotrexate slows the appearance of new erosions within involved joints on radiographs. Response to methotrexate occurs within 3 to 6 weeks of starting treatment. It is an immunosuppressant, and this may account for its effectiveness in autoimmune diseases. The other DMARDs can be added to methotrexate therapy if there is partial or no response to maximum doses of methotrexate. Doses of methotrexate required for this treatment are much lower than those needed in cancer chemotherapy and are given once a week, thereby minimizing adverse effects. The most common side effects observed after methotrexate treatment of RA are mucosal ulceration and nausea. Cytopenias (particularly depression of the WBC count), cirrhosis of the liver, and an acute pneumonia-like syndrome may occur with chronic administration. [Note: Taking leucovorin once daily after methotrexate reduces the severity of the adverse effects.] Contrary to early concerns, there have been minimal unexpected side effects after more than 20 years of surveillance, but periodic monitoring for signs of infections, complete blood counts, and liver enzymes tests are recommended. C. Leflunomide Leflunomide (le-FLOO-no-mide) is an immunomodulatory agent that preferentially causes cell arrest of the autoimmune lymphocytes through its action on dihydroorotate dehydrogenase (DHODH). Activated proliferating lymphocytes require constant DNA synthesis to proliferate. Pyrimidines and purines are the building blocks of DNA, and DHODH is necessary for pyrimidine synthesis. After biotransformation, leflunomide becomes a reversible inhibitor of DHODH (Figure 41.17). Leflunomide has been approved for the treatment of RA. It not only reduces pain and inflammation associated with the disease but also appears to slow the progression of structural damage by inhibiting osteoclast production. Leflunomide can be used as monotherapy or as an addition to methotrexate in combination therapy. 1. Pharmacokinetics: Leflunomide is well absorbed after oral administration. It is extensively bound to albumin (more than 90 percent) and has a half-life of 14 to 18 days. [Note: Because of its long halflife, loading doses are necessary, and, in cases of toxicity, drug elimination protocols are required.] Leflunomide is rapidly converted to an active metabolite. The metabolites are excreted in the urine and feces. The active metabolite undergoes biliary recycling. Pharm 5th 3-21-11.indb 539 2 ATP + CO2 + Glutamine 2 ADP + Pi + Glutamate Carbamoyl phosphate Dihydroorotate NAD+ Dihydroorotate dehydrogenase Leflunomide NADH + H+ Orotate Orotidine 5'-monophosphate (OMP) Uridine 5'-monophosphate (UMP) Figure 41.17 Site of action of leflunomide. 3/21/11 2:33:46 PM 540 41. Anti-inflammatory Drugs 2. Adverse effects: The most common of these are headache, diarrhea, and nausea. Other untoward effects are weight loss; allergic reactions, including a flu-like syndrome; skin rash; alopecia; and hypokalemia. Leflunomide is teratogenic in experimental animals and, therefore, is contraindicated in pregnancy and in women of child-bearing potential. It should be used with caution in patients who have liver disease, because it is cleared by both biliary and renal excretion. Monitoring parameters include signs of infections, complete blood counts, and liver enzymes tests. D. Hydroxychloroquine This agent is also used in the treatment of malaria. It is used for early, mild RA, often combined with methotrexate. When used alone, it does not slow joint damage. Its mechanism of action may include inhibition of phospholipase A2 and platelet aggregation, membrane stabilization, effects on the immune system, and antioxidant activity. Hydroxychloroquine may cause ocular toxicity, including irreversible retinal damage as well as corneal deposits. It may also cause CNS disturbances, GI upset, and skin discoloration and eruptions. E. Sulfasalazine Sulfasalazine [sul-fa-SAH-la-zeen] is also used for early, mild RA in combination with hydroxycholoroquine and methotrexate. Onset of activity is 1 to 3 months, and it is associated with leukopenia. Its mechanism of action in treating RA is unclear. F. D-Penicillamine D-Penicillamine [pen-ih-SILL-a-meen], an analog of the amino acid cysteine, slows the progression of bone destruction and RA. This agent is used as add-on therapy to existing NSAID/glucocorticoid therapy, but use in patients on DMARD therapy is avoided due to serious adverse events (for example, blood dyscrasias and renal impairment). Prolonged treatment with penicillamine has serious side effects, ranging from dermatologic problems to nephritis and aplastic anemia. [Note: D-Penicillamine is used as a chelating agent in the treatment of poisoning by heavy metals. It is also of benefit in treating cystinuria.] G. Gold salts Gold compounds, like the other drugs in this group, cannot repair existing damage. They can only prevent further injury. The currently available gold preparation is auranofin for oral administration. This agent is taken up by macrophages and will suppress phagocytosis and lysosomal enzyme activity. This mechanism retards the progression of bone and articular destruction, and beneficial effects may be seen in 3 to 6 months. The gold compounds are being used infrequently by rheumatologists because of the need for meticulous monitoring for serious toxicity (for example, myelosuppression) and the costs of monitoring. H. Azathioprine As an immunosuppressive agent, azathioprine is orally or parenterally used in kidney transplant rejection prophylaxis, and it is also useful in the treatment of autoimmune conditions, such as RA, lupus nephritis, and psoriatic arthritis. It is a chemical analog of the endogenous purines adenine, guanine, and hypoxanthine. The drug is metabolized to 6-mercaptopurine by the liver. Azathioprine can be combined with aspirin, NSAIDs, and/or low dose glucocorticoids in the treatment of RA. Pharm 5th 3-21-11.indb 540 3/21/11 2:33:46 PM VI. Biologic Therapies In Rheumatoid Arthritis 541 Combination with other DMARDs has not been studied. In patients who have low or absent thiopurine S-methyltransferase activity, dose adjustments are recommended. Continuous cell blood count and liver function should be monitored in patients receiving treatment with azathioprine. Patients with RA previously treated with alkylating agents, such as cyclophosphamide, chlorambucil, and melphalan, may have a prohibitive risk of neoplasia if treated with azathioprine. Due to the mutagenic potential of this drug, female patients with RA should avoid azathioprine during pregnancy or breast-feeding. I. Cyclophosphamide Cyclophosphamide is a bifunctional alkylating agent related to mechlorethamine (nitrogen mustard), and it is sometimes used for the treatment of RA (off-label use). Cyclophosphamide produces cytotoxic effects on both B and T cells and selectively suppresses B-lymphocyte activity. Decreased immunoglobulin secretion has been described in patients treated with low-dose cyclophosphamide for autoimmune diseases. As with other immunosuppressants, the use of cyclophosphamide in RA modulates the immune response, thus improving the disease conditions. The drug is cytotoxic to many tissues, including the kidneys and the heart. Also, the myelosuppressive effects of cyclophosphamide can increase the risk of infection or bleeding. This drug is teratogenic and should be avoided during pregnancy and breast-feeding. Common side effects also include GI disturbances, alopecia, and infertility. J. Glucocorticoids Glucocorticoids (see Chapter 26) are potent anti-inflammatory drugs that are commonly used in patients with RA to bridge the time until DMARDs are effective. Doses up to 10 mg of prednisone are usually used. Timely dose reductions and cessation are necessary to avoid adverse effects associated with long-term use. VI. BIOLOGIC THERAPIES IN RHEUMATOID ARTHRITIS Interleukin-1 and TNF-α are pro-inflammatory cytokines involved in the pathogenesis of RA. When secreted by synovial macrophages, IL-1 and TNF-α stimulate synovial cells to proliferate and synthesize collagenase, thereby degrading cartilage, stimulating bone resorption, and inhibiting proteoglycan synthesis. The TNF inhibitors (etanercept, adalimumab, infliximab, golimumab, and certolizumab) have been shown to decrease signs and symptoms of RA, reduce progression of structural damage, and improve physical function. Clinical response can be seen within 2 weeks of therapy. If a patient has failed therapy with one TNF inhibitor, a trial with a different TNF inhibitor is appropriate. Many experts propose that a TNF inhibitor plus methotrexate be considered as standard therapy for patients with rheumatoid and psoriatic arthritis. Indeed, TNF inhibitors can be administered with any of the other DMARDs, except for anakinra, an IL-1 receptor antagonist. Patients receiving TNF inhibitors are at increased risk for infections (tuberculosis and sepsis), fungal opportunistic infections, and pancytopenia. Live vaccinations should not be administered while on TNF-inhibitor therapy. Rarely, demyelinating disorders and bone marrow suppression may occur. Thoroughly searching for latent tuberculosis using chest radiography and/or purified protein derivative testing is recommended before therapy is started. These agents should be used very cautiously in those with heart failure, because they can cause and worsen preexisting heart failure. An Pharm 5th 3-21-11.indb 541 3/21/11 2:33:46 PM 542 41. Anti-inflammatory Drugs The incidence of remission in patients receiving entanercept plus methotrexate was greater than that found in patients taking entanercept or methotrexate alone. increased risk of lymphoma and other cancers has been observed with the use of TNF-α inhibitors. However, the risk of malignancies associated with these therapies has been hard to establish because the incidence is very low, and they are usually administered together with other treatments. Failure to respond to one TNF blocker does not preclude response to another. As with DMARDs, the decision to continue or stop a biological agent can often be made within 3 months after initiation of therapy. Patients in remission (%) A. Etanercept 40 Etanercept plus methotrexate 40% 30 20 Etanercept 16% Methotrexate 13% 10 0 Figure 41.18 Incidence of remission from the symptoms of rheumatoid arthritis after 1 year of therapy. Etanercept [ee-TAN-er-cept] is a genetically engineered, soluble, recombinant, fully human receptor fusion protein that binds to TNF-α, thereby blocking its interaction with cell surface TNF receptors. This agent is approved for use in patients with moderate to severe RA, either alone or in combination with methotrexate. It is also approved for use in patients with polyarticular-course juvenile RA, psoriatic arthritis, ankylosing spondylitis, and psoriasis. The combination of etanercept and methotrexate is more effective than methotrexate or etanercept alone in retarding the disease process, improving function, and achieving remission (Figure 41.18). Upon discontinuation of etanercept, the symptoms of arthritis generally return within a month. 1. Pharmacokinetics: Etanercept is given subcutaneously twice a week. The time to maximum serum concentration after a single injection is about 72 hours. Its median half-life is 115 hours. 2. Adverse effects: Etanercept is well tolerated. No toxicities or antibodies have been reported. However, it can produce local inflammation at the site of injection. B. Infliximab Infliximab (in-FLIX-i-mab) is a chimeric immunoglobulin Gκ monoclonal antibody composed of human and murine regions. The antibody binds specifically to human TNF-α, and inhibits binding with its receptors. Infliximab is approved for use in combination with methotrexate in patients with RA who have had inadequate response to methotrexate monotherapy. This agent is not indicated for use alone, because monotherapy allows the body to develop anti-infliximab antibodies, with a reduction in efficacy. Additional indications include plaque psoriasis, psoriatic arthritis, ulcerative colitis, ankylosing spondylitis, and Crohn disease, for both fistulizing and nonfistulizing disease. [Note: Increased levels of TNF-α are found in fecal samples of patients with Crohn disease]. 1. Pharmacokinetics: Infliximab is infused IV over at least 2 hours. It distributes in the vascular compartment and has a half-life of 9.5 days. Its metabolism and elimination have not been described. 2. Adverse effects: Infusion site reactions, such as fever, chills, pruritus, and urticaria, have occurred. Infections leading to pneumonia, cellulitis, and other conditions (such as activation of latent tuberculosis) have also been reported. Leukopenia, neutropenia, thrombocytopenia, and pancytopenia have occurred. Whether treatment with infliximab predisposes to lymphoma, a condition that occurs with immunosuppressive or immune-altering drugs, remains to be established. [Note: Infliximab treatment does predispose to infections, which may be life threatening.] Pharm 5th 3-21-11.indb 542 3/21/11 2:33:47 PM VI. Biologic Therapies In Rheumatoid Arthritis 543 C. Adalimumab Adalimumab [a-dal-AYE-mu-mab] is a recombinant monoclonal antibody that binds to TNF-α, thereby interfering with endogenous TNF-α activity by blocking its binding to the surface receptors. Use of adalimumab results in reductions in the concentrations of MMP-1 (collagenase), MMP-3 (stromelysin-1), C reactive protein, and markers of cartilage and synovium turnover that parallel improvement in disease activity. This agent is indicated for treatment of moderate to severe RA, either as monotherapy or in combination with methotrexate. It is also indicated for psoriatic arthritis, ankylosing spondylitis, and Crohn disease. 1. Pharmacokinetics: Adalimumab is administered subcutaneously weekly or every other week. The average absolute bioavailability is 64% and concentrations in the synovial fluid may reach 31 to 96 percent of serum concentrations. 2. Adverse effects: It may cause headache, nausea, agranulocytosis, rash, reaction at the injection site, or increased risk of infection (i.e., urinary tract infections, upper respiratory tract infections, and sinusitis). D. Golimumab Golimumab [goe-LIM-ue-mab] neutralizes the biological activity of TNF-α by binding to it and blocking its interaction with cell surface receptors. Golimumab binds to both the soluble and the transmembrane bioactive forms of human TNF-α, and, therefore, a significant reduction in pro-inflammatory and autoimmune responses is observed. 1. Pharmacokinetics: This compound is administered subcutaneously once a month in combination with methotrexate or other nonbiologic DMARD. 2. Adverse effects: Golimumab may increase hepatic enzymes. Similarly to other TNF inhibitors, this drug may increase the risk of malignancies and serious infections, including tuberculosis and opportunistic infections. Common injection site reactions include erythema, itching, and burning. E. Certolizumab pegol This is a unique TNF-α blocker that contains a Fab fragment of a humanized antibody and is a potent neutralizer of TNF-α biological actions. Certolizumab pegol does not contain a fragment crystallizable (Fc) region and, thus, does not fix complement or cause antibody-dependent cell-mediated cytotoxicity. Certolizumab is combined with polyethylene glycol, and it is usually administered every 2 weeks in combination with methotrexate. Adverse effects are similar to other TNF inhibitors. F. Anakinra Il-1 is induced by inflammatory stimuli and mediates a variety of immunologic responses, including degradation of cartilage and stimulation of bone resorption. Anakinra [an-a-KIN-ra] is an IL-1 receptor antagonist because it binds to the IL-1 receptor, thus preventing actions of IL-1. Anakinra treatment leads to a modest reduction in the signs and symptoms of moderately to severely active RA in adult patients who have failed one or more DMARDs. The drug may be used alone or in com- Pharm 5th 3-21-11.indb 543 3/21/11 2:33:48 PM 544 41. Anti-inflammatory Drugs bination with DMARDs (other than TNF inhibitors). Patients should be monitored for signs of infection (tuberculosis and opportunistic infections have not been reported with this agent) and undergo absolute neutrophil counts, because this agent is associated with neutropenia. This agent is administered subcutaneously once a day if renal function is normal, and every other day in those with moderate to severe renal impairment. G. Abatacept T lymphocytes need two interactions to become activated: 1) the antigen-presenting cell (that is, macrophages or B cells) must interact with the receptor on the T cell, and 2) the CD80/CD86 protein on the antigen-presenting cell must interact with the CD28 protein on the T cell. The result is activated T lymphocytes responsible for the release of pro-inflammatory cytokines and maintenance of inflammation in RA. However, T lymphocytes contain another protein, CTLA4, which can bind to the CD80/86 protein found on the antigen-presenting cell. In fact, CTLA4 has higher binding affinity for CD80/86 than does CD28. Binding of CTLA4 to CD80/86 results in deactivation of the T lymphocyte. Abatacept [a-BAT-ah-cept] (CTLA-4Ig) is a soluble recombinant fusion protein made up of the extracellular domain of human CTLA4, and it competes with CD28 for binding on CD80/CD86 protein, thereby preventing full T-cell activation. This agent is indicated for reducing signs and symptoms, inducing major clinical response, slowing the progression of structural damage, and improving physical function in adult patients with moderate to severe RA who have had an inadequate response to DMARDs, such as methotrexate or TNF inhibitors. Abatacept can be used alone or with DMARDs other than TNF inhibitors or anakinra. 1. Pharmacokinetics: The recommended dose is based upon weight and is administered as an IV infusion over 30 minutes at weeks 2 and 4 after the first infusion and every 4 weeks thereafter with monitoring for infusion reactions. The terminal half-life in RA patients administered multiple doses of 10 mg/kg is 13 days (range, 8–25 days). 2. Adverse effects: The most commonly reported adverse effects include headache, upper respiratory infections, nasopharyngitis, and nausea. Concurrent use with TNF inhibitors and anakinra is not recommended due to increased risk of serious infections. H. Rituximab B lymphocytes are derived from the bone marrow and are necessary for efficient immune response. In RA, however, B cells can perpetuate the inflammatory process in the synovium by 1) activating T lymphocytes; 2) producing autoantibodies, such as anti-CCP (anti–cyclic citrullinated peptide antibody) and rheumatoid factor; and 3) producing pro-inflammatory cytokines, such as TNF-α and IL-1. Rituximab [ri-TUK-si-mab] is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes, resulting in B-cell depletion. This agent is indicated for use in combination with methotrexate to reduce signs and symptoms of moderate to severe RA in adult patients who have had an inadequate response to one or more TNF-inhibitors. Rituximab has been shown to reduce joint erosion and joint space narrowing in these patients. Pharm 5th 3-21-11.indb 544 3/21/11 2:33:48 PM VII. Drugs Employed In The Treatment Of Gout 545 1. Pharmacokinetics: Rituximab is administered as two 1000-mg IV infusions separated by 2 weeks. To reduce the severity of infusion reactions, methylprednisolone at 100 mg IV or its equivalent is administered 30 minutes prior to each infusion. The mean terminal elimination half-life after the second dose is 19 days. 2. Adverse effects: Infusion reactions (that is, urticaria, hypotension, and angioedema) are the most common complaints with this agent and typically occur during the first infusion. The infusion may be interrupted and the patient treated with vasopressors, antihistamines, and fluids if these symptoms occur. If the infusion is to be continued, then the rate of infusion should be reduced by 50 percent after symptoms have completely resolved. VII. DRUGS EMPLOYED IN THE TREATMENT OF GOUT Gout is a metabolic disorder characterized by high levels of uric acid in the blood. Hyperuricemia can lead to deposition of sodium urate crystals in tissues, especially the joints and kidney. Hyperuricemia does not always lead to gout, but gout is always preceded by hyperuricemia. In humans, sodium urate is the end product of purine metabolism. The deposition of urate crystals initiates an inflammatory process involving the infiltration of granulocytes that phagocytize the urate crystals (41.19). This process generates oxygen metabolites, which damage tissues, resulting in the release of lysosomal enzymes that evoke an inflammatory response. In addition, there is increased production of lactate in the synovial tissues. The resulting local decrease in pH fosters further deposition of urate crystals. The cause of hyperuricemia is an overproduction of uric acid relative to the patient's ability to excrete it. Most therapeutic strategies for gout involve lowering the uric acid level below the saturation point (below 6 mg/dL), thus preventing the deposition of urate crystals. This can be accomplished by 1) interfering with uric acid synthesis with allopurinol, 2) increasing uric acid excretion with probenecid or sulfinpyrazone, 3) inhibiting leukocyte entry into the affected joint with colchicine, or 4) administration of NSAIDs. A. Treating acute gout Acute gouty attacks can result from a number of conditions, including excessive alcohol consumption, a diet rich in purines, and kidney disease. Acute attacks are treated with indomethacin to decrease movement of granulocytes into the affected area. NSAIDs other than indomethacin are also effective at decreasing pain and inflammation. [Note: Aspirin is contraindicated, because it competes with uric acid for the organic acid secretion mechanism in the proximal tubule of the kidney.] The initial NSAID dose should be doubled within the first 24 to 48 hours (maintain recommended dosing interval per specific NSAID) and then reduced over the next few days. Intraarticular administration of glucocorticoids (when only one or two joints are affected) is also appropriate in the acute setting. Patients are candidates for prophylactic therapy if they have had more than two attacks per year, the first attack is severe or complicated with kidney stones, serum urate is greater than 10 mg/ dL, or urinary urate excretion exceeds 1000 mg per 24 hours. B. Treating chronic gout Chronic gout can be caused by 1) a genetic defect, such as one resulting in an increase in the rate of purine synthesis; 2) renal deficiency; 3) LeschNyhan syndrome; or 4) excessive production of uric acid associated with Pharm 5th 3-21-11.indb 545 Purines DNA, RNA Hypoxanthine Xanthine oxidase Allopurinol Xanthine Xanthine oxidase Allopurinol Uric acid Uric acid crystals Hydrolytic enzymes Lysosomes NEUTROPHIL Phagocytosis of uric acid crystals by neutrophils Leukotrienes Colchicine Release of leukotrienes and other mediators of inflammation Rupture of lysosome, followed by death of phagocyte and release of hydrolytic enzymes Acute inflammation Figure 41.19 Role of uric acid in the inflammation of gout. 3/21/11 2:33:50 PM 546 41. Anti-inflammatory Drugs cancer chemotherapy. Treatment strategies for chronic gout include the use of uricosuric drugs that increase the excretion of uric acid, thereby reducing its concentration in plasma, and the use of allopurinol, which is a selective inhibitor of the terminal steps in the biosynthesis of uric acid. Uricosuric agents are first-line agents for patients with gout associated with reduced urinary excretion of uric acid. Allopurinol is preferred in patients with excessive uric acid synthesis, with previous histories of uric acid stones, or with renal insufficiency. C. Colchicine Colchicine [KOL-chi-seen], a plant alkaloid, has been used for the treatment of acute gouty attacks as well as chronic gout. It is neither a uricosuric nor an analgesic agent, although it relieves pain in acute attacks of gout. Colchicine does not prevent the progression of gout to acute gouty arthritis, but it does have a suppressive, prophylactic effect that reduces the frequency of acute attacks and relieves pain. 1. Mechanism of action: Colchicine binds to tubulin, a microtubular protein, causing its depolymerization. This disrupts cellular functions, such as the mobility of granulocytes, thus decreasing their migration into the affected area. Furthermore, colchicine blocks cell division by binding to mitotic spindles. Colchicine also inhibits the synthesis and release of the leukotrienes (see Figure 41.19). 2. Therapeutic uses: The anti-inflammatory activity of colchicine is specific for gout, usually alleviating the pain of acute gout within 12 hours. (Note: Colchicine must be administered within 24 to 48 hours of onset of attack to be effective). NSAIDs have largely replaced colchicine in the treatment of acute gouty attacks. Colchicine is currently used for prophylaxis of recurrent attacks and will prevent attacks in more than 80 percent of patients. 3. Pharmacokinetics: Colchicine is administered orally, followed by rapid absorption from the GI tract. It is also available combined with probenecid (see below). Colchicine is recycled in the bile and is excreted unchanged in feces or urine. Use should be avoided in patients with a creatinine clearance of less than 10 mL/min. 4. Adverse effects: Colchicine treatment may cause nausea, vomiting, abdominal pain, and diarrhea (Figure 41.20). Chronic administration may lead to myopathy, neutropenia, aplastic anemia, and alopecia. The drug should not be used in pregnancy, and it should be used with caution in patients with hepatic, renal, or cardiovascular disease. Dosage adjustments are required in patients taking CYP3A4 inhibitors like clarithromycin, itraconazole, ketoconazole, nefazodone, telithromycin, and protease inhibitors. The fatal dose has been reported as low as 7 to 10 mg (the maximum dose for gout flare prophylaxis is 1.2 mg in 24 hours and 1.8 mg for treatment). For patients with severe renal impairment, the dose should be reduced. D. Allopurinol Allopurinol [al-oh-PURE-i-nole] is a purine analog. It reduces the production of uric acid by competitively inhibiting the last two steps in uric acid biosynthesis that are catalyzed by xanthine oxidase (see Figure 41.19). [Note: Uric acid is less water soluble than its precursors. When xanthine oxidase is inhibited, the circulating purine derivatives (xan- Pharm 5th 3-21-11.indb 546 3/21/11 2:33:50 PM VII. Drugs Employed In The Treatment Of Gout 547 thine and hypoxanthine) are more soluble and, therefore, are less likely to precipitate.] 1. Therapeutic uses: Allopurinol is effective in the treatment of primary hyperuricemia of gout and hyperuricemia secondary to other conditions, such as that associated with certain malignancies (those in which large amounts of purines are produced, particularly after treatment with chemotherapeutic agents) or in renal disease. This agent can be used if the patient's creatinine clearance is less than 50 mL/min, in which case, the dosage should be reduced. 2. Pharmacokinetics: Allopurinol is completely absorbed after oral administration. The primary metabolite is alloxanthine (oxypurinol), which is also a xanthine oxidase inhibitor with a half-life of 15 to 18 hours. The half-life of allopurinol is 2 hours. Thus, effective inhibition of xanthine oxidase can be maintained with once-daily dosage. The drug and its active metabolite are excreted in the feces and urine. 3. Adverse effects: Allopurinol is well tolerated by most patients. Hypersensitivity reactions, especially skin rashes, are the most common adverse reactions, occurring in approximately 3 percent of patients. The reactions may occur even after months or years of chronic administration, and allopurinol therapy should be discontinued. Because acute attacks of gout may occur more frequently during the first several weeks of therapy, colchicine or NSAIDs should be administered concurrently. GI side effects, such as nausea and diarrhea, are common. Allopurinol interferes with the metabolism of 6-mercaptopurine, the immunosuppressant azathioprine, and theophylline, requiring a reduction in dosage of these drugs. Nausea GI disturbance Diarrhea Agranulocytosis Aplastic anemia E. Febuxostat Febuxostat [feb-UX-o-stat] is a new xanthine oxidase inhibitor. Although it is structurally unrelated to allopurinol, it has the same indications as those of allopurinol. The same drug interactions with 6-mercaptopurine, azathioprine, and theophylline apply. Its adverse effect profile is similar to that of allopurinol. F. Uricosuric agents: Probenecid and sulfinpyrazone Alopecia Figure 41.20 Some adverse effects of colchicine. GI = gastrointestinal. The uricosuric drugs are weak organic acids that promote renal clearance of uric acid by inhibiting the urate-anion exchanger in the proximal tubule that mediates urate reabsorption. Probenecid [proe-BEN-esid], a general inhibitor of the tubular secretion of organic acids, and sulfinpyrazone [sul-fin-PEER-a-zone], a derivative of phenylbutazone, are the two most commonly used uricosuric agents. At therapeutic doses, they block proximal tubular resorption of uric acid. [Note: At low dosage, these agents block proximal tubular secretion of uric acid.] These drugs have few adverse effects, although gastric distress may force discontinuance of sulfinpyrazone. Probenecid blocks the tubular secretion of penicillin and is sometimes used to increase levels of some antibiotics. It also inhibits excretion of naproxen, ketoprofen, and indomethacin. Probenecid should be avoided if the patient's creatinine clearance is less than 50 ml/min. Sulfinpyrazone is contraindicated in patients with bone marrow suppression and periodic complete blood count monitoring is commended during treatment with sulfinpyrazone. In the United States, sulfinpyrazone is rarely used today. Pharm 5th 3-21-11.indb 547 3/21/11 2:33:52 PM 548 41. Anti-inflammatory Drugs Study Questions Choose the ONE best answer. 41.1 In which one of the following conditions would aspirin be contraindicated? A. Myalgia. B. Fever. C. Peptic ulcer. D. Rheumatoid arthritis. E. Unstable angina. 41.2 Which one of the following statements concerning COX-2 inhibitors is correct? A. The COX-2 inhibitors show greater analgesic activity than traditional NSAIDs. B. The COX-2 inhibitors decrease platelet function. C. The COX-2 inhibitors do not affect the kidney. D. The COX-2 inhibitors show anti-inflammatory activity similar to that of the traditional NSAIDs. E. The COX-2 inhibitors are cardioprotective. 41.3 An 8-year-old girl has a fever and muscle aches from a presumptive viral infection. Which one of the following drugs would be most appropriate to treat her symptoms? A. Acetaminophen. B. Aspirin. C. Celecoxib. D. Codeine. E. Indomethacin. 41.4 A 70-year-old man has a history of ulcer disease. He has recently experienced swelling and pain in the joints of his hands. His physician wants to begin therapy with an NSAID. Which one of the following drugs might also be prescribed along with the NSAID to reduce the risk of activating this patient's ulcer disease? A. Allopurinol. B. Colchicine. C. Misoprostol. D. Probenecid. E. Sulindac. Pharm 5th 3-21-11.indb 548 Correct answer = C. Among the nonsteroidal antiinflammatory drugs, aspirin is one of the worst for causing gastric irritation. Aspirin is an effective analgesic and is used to reduce muscle pain. It also has antipyretic actions, so it can be used to treat fever. Because of its anti-inflammatory properties, aspirin is used to treat pain related to the inflammatory process (for example, in the treatment of rheumatoid arthritis). Low doses of aspirin also decrease the incidence of transient ischemic attacks. Correct answer = D. The COX-2 inhibitors show similar analgesic and anti-inflammatory activity compared to traditional NSAIDs. They do not affect platelets. Like NSAIDs, COX-2 inhibitors may cause the development of acute renal failure due to renal vasoconstriction. COX-2 inhibitors have the potential for increasing the risk of myocardial infarction. Correct answer = A. Aspirin should be avoided in children because of an association with Reye's syndrome. Indomethacin has antipyretic activity but is too toxic for use in these circumstances. Celecoxib is indicated for alleviation of pain, and codeine has no antipyretic effects. Correct answer = C. Misoprostol is a prostaglandin analog that can reduce gastric acid and pepsin secretion and promote the formation of mucus in the stomach. It is indicated for the purpose of decreasing the risk of ulcer activation in patients taking NSAIDs. The other choices are not appropriate for alleviating the gastric irritation caused by NSAIDs. 3/21/11 2:33:52 PM Autacoids and Autacoid Antagonists 42 I. OVERVIEW Prostaglandins, histamine, and serotonin belong to a group of endogenous compounds called autacoids. These heterogeneous substances have widely differing structures and pharmacologic activities. They all have the common feature of being formed by the tissues on which they act and, therefore, function as local hormones. [Note: The word "autacoid" comes from the Greek: autos (self) and akos (medicinal agent, or remedy).] The autacoids also differ from circulating hormones in that they are produced by many tissues rather than in specific endocrine glands. The drugs described in this chapter (Figure 42.1) are either autacoids or autacoid antagonists (compounds that inhibit the synthesis of certain autacoids or that interfere with their interactions with receptors). II. PROSTAGLANDINS Prostaglandins are unsaturated fatty acid derivatives that act on the tissues in which they are synthesized and are rapidly metabolized to inactive products at the site of action.1 A. Therapeutic uses of prostaglandins Systemic administration of prostaglandins evokes a bewildering array of effects, a fact that limits the therapeutic usefulness of these agents. 1. Pregnancy termination: Several of the prostaglandins find use as abortifacients (agents causing abortions). The most effective option available involves oral administration of mifepristone [miFEP-ri-stone] (RU-486, a synthetic steroid with antiprogestational effects), followed 48 hours later by the synthetic prostaglandin E1 analog misoprostol [mye-so-PROST-ole] administered orally or vaginally (Figure 42.2). This regimen results in complete abortion rates exceeding 95 percent. The overall case-fatality rate for abortion is less than one death per 100,000 procedures. Infection, hemorrhage, and retained tissue are among the more common complications. INFO LINK Pharm 5th 3-21-11.indb 549 PROSTAGLANDINS Mifepristone MIFEPREX Misoprostol CYTOTEC H1 ANTIHISTAMINES Acrivastine (with pseudoephedrine) SEMPREX-D Cetirizine ZYRTEC Chlorpheniramine CHLOR-TRIMETON Cyclizine MAREZINE Desloratadine CLARINEX Diphenhydramine BENADRYL Dimenhydrinate DRAMAMINE Doxepin SINEQUAN Doxylamine UNISOM SLEEPTABS Fexofenadine ALLEGRA Hydroxyzine VISTARIL, ATARAX Levocetirizine XYZAL Loratadine CLARITIN Meclizine BONINE, ANTIVERT Promethazine PHENERGAN DRUGS USED TO TREAT MIGRAINE HEADACHE Almotriptan AXERT Dihydroergotamine D.H.E. 45, MIGRANAL Eletriptan RELPAX Frovatriptan FROVA Naratriptan AMERGE Rizatriptan MAXALT Sumatriptan IMITREX Zolmitriptan ZOMIG Figure 42.1 Summary of drugs affecting the autacoids. 1See Chapter 17 in Lippincott's Illustrated Reviews: Biochemistry for a discussion of prostaglandin synthesis and actions. 3/21/11 2:33:52 PM 550 42. Autacoids and Autacoid Antagonists 2. Peptic ulcers: Misoprostol is sometimes used to inhibit the secretion of gastric acid and to enhance mucosal resistance to injury in patients with gastric ulcer, who are chronically taking nonsteroidal anti-inflammatory agents. Proton-pump inhibitors, such as omeprazole, and H2 antihistamines also reduce the risk of gastric ulcer and are better tolerated than misoprostol, which induces intestinal disorders. Misoprostol Mifepristone, followed at least 24 hours later by misoprostol admistered vaginally, is effective in terminating pregnancy in the first trimester. III. HISTAMINE Histamine is a chemical messenger mostly generated in mast cells that mediates a wide range of cellular responses, including allergic and inflammatory reactions, gastric acid secretion, and neurotransmission in parts of the brain. Histamine has no clinical applications, but agents that interfere with the action of histamine (antihistamines) have important therapeutic applications. Abortifacient A. Location, synthesis, and release 1. Location: Histamine occurs in practically all tissues, but it is unevenly distributed, with high amounts found in lung, skin, and the gastrointestinal tract (sites where the "inside" of the body meets the "outside"). It is found at high concentration in mast cells or basophils. Histamine also occurs as a component of venoms and in secretions from insect stings. Gastric ulcer Misoprostol Inhibits secretion of HCl and pepsin, and enhances mucosal resistance. 2. Synthesis: Histamine is an amine formed by the decarboxylation of the amino acid histidine by histidine decarboxylase,2 an enzyme that is expressed in cells throughout the body, including central nervous system (CNS) neurons, gastric mucosa parietal cells, mast cells, and basophils (Figure 42.3). In mast cells, histamine is stored in granules as an inactive complex composed of histamine and the polysulfated anion, heparin, along with an anionic protein. If histamine is not stored, it is rapidly inactivated by amine oxidase enzymes. Useful in patients with gastric ulcer who chronically take aspirin. Figure 42.2 Therapeutic applications of misoprostol. 3. Release of histamine: The release of histamine may be the primary response to some stimuli, but, most often, histamine is just one of several chemical mediators released. The release of histamine from tissues is caused by the destruction of cells as a result of cold, bacterial toxins, bee sting venoms, or trauma. Allergies and anaphylaxis can also trigger release of histamine. N N Decarboxylase N CH2 CH2 H2N C H N H2 N CH2 C OOH Histidine CO2 Figure 42.3 Biosynthesis of histamine. Histamine B. Mechanism of action Histamine released in response to various stimuli exerts its effects by binding to one or more of four types of histamine receptors, H1, H2, H3, and H4 receptors. H1 and H2 receptors are widely expressed and are the targets of clinically useful drugs. H3 and H4 receptors are expressed in only a few cell types, and their roles in drug action are unclear. All types of histamine receptors have seven transmembrane helical domains and transduce extracellular signals by way of G protein–mediated secondmessenger systems. Some of histamine's wide range of pharmacologic effects are mediated by both H1 and H2 receptors. For example, the H1 INFO LINK Pharm 5th 3-21-11.indb 550 2 See Chapter 21 in Lippincott's Illustrated Reviews: Biochemistry for a discussion of histamine. 3/21/11 2:33:55 PM IV. H1 Antihistamines receptors are important in producing smooth muscle contraction and increasing capillary permeability (Figure 42.4). Histamine promotes vasodilation of small blood vessels by causing vascular endothelium to release nitric oxide.3 Also, histamine can enhance the secretion of pro-inflammatory cytokines in several cell types and in local tissues. Histamine binds to G-coupled H1 receptors and stimulates the inositol phospholipid signaling pathways, resulting in the formation of inositol-1,4,5-trisphosphate (IP3) and diacylglycerol and an increase in intracellular calcium4. Histamine H1 receptors mediate many pathological processes, including allergic rhinitis, atopic dermatitis, conjunctivitis, urticaria, bronchoconstriction, asthma, and anaphylaxis. On the other hand, histamine stimulates the parietal cells in the stomach, causing an increase in acid secretion via activation of H2 receptors. Stimulation of these receptors enhances the production of cyclic adenosine monophosphate (cAMP) by adenylyl cyclase. 551 H1 Receptors EXOCRINE EXCRETION Increased production of nasal and bronchial mucus, resulting in respiratory symptoms. BRONCHIAL SMOOTH MUSCLE Constriction of bronchioles results in symptoms of asthma and decreased lung capacity. INTESTINAL SMOOTH MUSCLE Constriction results in intestinal cramps and diarrhea. SENSORY NERVE ENDINGS Causes itching and pain. C. Role in allergy and anaphylaxis The symptoms resulting from intravenous injection of histamine are similar to those associated with anaphylactic shock and allergic reactions. These include contraction of airway smooth muscle, stimulation of secretions, dilation and increased permeability of the capillaries, and stimulation of sensory nerve endings. 1. Role of mediators: Symptoms associated with allergy and anaphylactic shock result from the release of certain mediators from their storage sites. Such mediators include histamine, serotonin, leukotrienes, and the eosinophil chemotactic factor of anaphylaxis. In some cases, these cause a localized allergic reaction, producing, for example, actions on the skin or respiratory tract. Under other conditions, these mediators may cause a full-blown anaphylactic response. It is thought that the difference between these two situations results from differences in the sites from which mediators are released and in their rates of release. For example, if the release of histamine is slow enough to permit its inactivation before it enters the bloodstream, a local allergic reaction results. However, if histamine release is too fast for inactivation to be efficient, a full-blown anaphylactic reaction occurs. IV. H1 ANTIHISTAMINES The term antihistamine, without a modifying adjective, refers to the classic H1-receptor blockers. These compounds do not influence the formation or release of histamine. Rather, they block the receptor-mediated response of a target tissue. [Note: This contrasts with the action of cromolyn, which inhibits the release of histamine from mast cells and is useful in the treatment of asthma.] The H1-receptor blockers can be divided into first- and second-generation drugs (Figure 42.5). The older first-generation drugs are still widely used because they are effective and inexpensive. However, most of these drugs penetrate the CNS and cause sedation. Furthermore, they tend to interact with other receptors, producing a variety of unwanted adverse effects. By contrast, the second-generation agents are specific for Skin H1 and H2 Receptors CARDIOVASCULAR SYSTEM Lowers systemic blood pressure by reducing peripheral resistance. Causes positive chronotropism (mediated by H2 receptors) and a positive inotropism (mediated by both H1 and H2 receptors). SKIN Dilation and increased permeability of the capillaries results in leakage of proteins and fluid into the tissues. In the skin, this results in the classic "triple response": wheal formation, reddening due to local vasodilation, and flare ("halo"). H2 Receptors Stomach Stimulation of gastric hydrochloric acid secretion. Figure 42.4 Actions of histamine. 3See Chapter 13 in Lippincott's Illustrated Reviews: Biochemistry for a INFO LINK discussion of nitric oxide. 4See Chapter 17 in Lippincott's Illustrated Reviews: Biochemistry for a discussion of the polyphosphatidylinositol pathway. Pharm 5th 3-21-11.indb 551 3/21/11 2:33:57 PM 552 42. Autacoids and Autacoid Antagonists Marked potential for producing sedation Used to treat motion sickness First generation Chlorpheniramine Cyclizine Diphenhydramine Dimenhydrinate Doxepin Doxylamine Hydroxyzine Meclizine Promethazine Second generation Acrivastine Cetirizine Desloratadine Fexofenadine Loratadine Weak potential for producing sedation 8 pt bold text Nonsedating Figure 42.5 Summary of therapeutic advantages and disadvantages of some H1 histamine–receptor blocking agents. H1 receptors, and, because they carry polar groups, they do not penetrate the blood-brain barrier, causing less CNS depression than the first-generation drugs. Among these agents, desloratadine [des-lor-AH-tah-deen], fexofenadine [fex-oh-FEN-a-deen], and loratadine [lor-AT-a-deen] show the least sedation (Figure 42.6). [Note: The histamine receptors are distinct from those that bind serotonin, acetylcholine, and the catecholamines.] A. Actions The action of all the H1-receptor blockers is qualitatively similar. They are much more effective in preventing symptoms than reversing them once they have occurred. However, most of these blockers have additional effects unrelated to their blocking of H1 receptors, which probably reflect binding of the H1 antagonists to cholinergic, adrenergic, or serotonin receptors (Figure 42.7). B. Therapeutic uses 1. Allergic and inflammatory conditions: H1-receptor blockers are useful in treating allergies caused by antigens acting on immunoglobulin E antibody–sensitized mast cells. For example, antihistamines are the drugs of choice in controlling the symptoms of allergic rhinitis and urticaria because histamine is the principal mediator. However, the H1-receptor blockers are not used in treating bronchial asthma because histamine is only one of several mediators of that condition. [Note: Epinephrine has actions on smooth muscle that are opposite to those of histamine, and it acts at different receptors. Therefore, epinephrine is the drug of choice in treating systemic anaphylaxis and other conditions that involve massive release of histamine.] Glucocorticoids show greater anti-inflammatory effects than the H1 antihistamines. 2. Motion sickness and nausea: Along with the antimuscarinic agent scopolamine, certain H1-receptor blockers, such as diphenhydramine [dye-fen-HYE-dra-meen], dimenhydrinate [dye-men-HYE-dri-nate] (a chemical combination of diphenhydramine and a theophylline derivative), cyclizine [SYE-kli-zeen], meclizine [MEK-li-zeen], and hydroxyzine [hye-DROX-ee-zeen] (see Figure 42.5), are the most effective agents for prevention of the symptoms of motion sickness. The antihistamines prevent or diminish vomiting and nausea mediated by both the chemoreceptor and vestibular pathways. The antiemetic action of these medications seems to be due to their blockade of central H1 and muscarinic receptors. 3. Somnifacients: Although they are not the medications of choice, many first-generation antihistamines, such as diphenhydramine and doxylamine [dox-IL-a-meen], have strong sedative properties and are used in the treatment of insomnia (see Figure 42.5). They are both available over the counter (OTC), or without a prescription. The use of first-generation H1 antihistamines is contraindicated in the treatment of individuals working in jobs in which wakefulness is critical. C. Pharmacokinetics H1-receptor blockers are well absorbed after oral administration, with maximum serum levels occurring at 1 to 2 hours. The average plasma half-life is 4 to 6 hours, except for that of meclizine, which is 12 to 24 hours. H1-receptor blockers have high bioavailability and are distributed Pharm 5th 3-21-11.indb 552 3/21/11 2:33:58 PM IV. H1 Antihistamines 553 D. Adverse effects First-generation H1-receptor blockers have a low specificity, interacting not only with histamine receptors but also with muscarinic cholinergic receptors, α-adrenergic receptors, and serotonin receptors (see Figure 42.7). The extent of interaction with these receptors and, as a result, the nature of the side effects, varies with the structure of the drug. Some side effects may be undesirable, and others may have therapeutic value. Furthermore, the incidence and severity of adverse reactions for a given drug varies between individual subjects. 1. Sedation: First-generation H1 antihistamines, such as chlorpheniramine [klor-fen-IR-a-meen], diphenhydramine, hydroxyzine, and promethazine [proe-METH-a-zeen], bind to H1 receptors and block the neurotransmitter effect of histamine in the CNS. The most frequently observed adverse reaction is sedation (Figure 42.8). Other central actions include tinnitus, fatigue, dizziness, lassitude (a sense of weariness), uncoordination, blurred vision, and tremors. Sedation is less common with the second-generation drugs, which do not readily enter the CNS. Second-generation H1 antihistamines are specific for peripheral H1 receptors and penetrate the CNS poorly. Because of their lower potential to induce drowsiness, loratadine and fexofenadine may be recommended for individuals working in jobs where wakefulness is critical. Relative drowsiness in all tissues, including the CNS. All first-generation H1 antihistamines and some second-generation H1 antihistamines, such as desloratadine and loratadine, are metabolized by the hepatic cytochrome P450 system. Cetirizine [seh-TEER-ih-zeen] is excreted largely unchanged in urine, and fexofenadine is excreted largely unchanged in feces. After a single oral dose, the onset of action occurs within 1 to 3 hours. The duration of action for many oral H1 antihistamines is at least 24 hours, allowing once-daily dosing. The active enantiomer of cetirizine is available as levocetirizine. It is recommended for once-daily dosing at bedtime. Acrivastine Cetirizine Fexofenadine Loratadine Figure 42.6 Relative potential for causing drowsiness in patients receiving second-generation H1 antihistamines. H1 Antihistamines Particularly diphenhydramine and promethazine Receptors Cholinergic Dry mouth Urinary retention Sinus tachycardia All H1 antihistamines Particularly promethazine α–Adrenergic Hypotension Dizziness Reflex tachycardia Dopamine Serotonin Appetite Histamine H1 Histamine H2 Allergic inflammation, itching, sneezing, and rhinorrhea Neurotransmission in the CNS Sedation Cognitive and psychomotor performance Appetite Figure 42.7 Effects of H1 antihistamines at histamine, adrenergic, cholinergic, and serotonin-binding receptors. Many secondgeneration antihistamines do not enter the brain and, therefore, show minimal CNS effects. Pharm 5th 3-21-11.indb 553 3/21/11 2:34:00 PM 554 42. Autacoids and Autacoid Antagonists 2. Dry mouth: Oral antihistamines also exert weak anticholinergic effects, leading not only to dryness in the nasal passage, but also to a tendency to dry out the oral cavity. Drowsiness 3. Drug interactions: Interaction of H1-receptor blockers with other drugs can cause serious consequences, such as potentiation of the effects of all other CNS depressants, including alcohol. Persons taking monoamine oxidase inhibitors (MAOIs) should not take antihistamines because the MAOIs can exacerbate the anticholinergic effects of the antihistamines. In addition, the first-generation antihistamines (diphenhydramine and others) have considerable anti cholinergic (antimuscarinic) actions. These actions would decrease the effectiveness of cholinesterase inhibitors (donepezil, rivastigmine, and galantamine) in the treatment of Alzheimer disease. Urinary retention Tachycardia BP Hypotension Vertigo Dry mouth Increased appetite Figure 42.8 Some adverse effects observed with first-generation H1 antihistamines. BP = blood pressure. Pharm 5th 3-21-11.indb 554 4. Overdoses: Although the margin of safety of H1-receptor blockers is relatively high, and chronic toxicity is rare, acute poisoning is relatively common, especially in young children. The most common and dangerous effects of acute poisoning are those on the CNS, including hallucinations, excitement, ataxia, and convulsions. If untreated, the patient may experience a deepening coma and collapse of the cardiorespiratory system. V. HISTAMINE H2-RECEPTOR BLOCKERS Histamine H2-receptor blockers have little, if any, affinity for H1 receptors. Although antagonists of the histamine H2 receptor (H2 antagonists) block the actions of histamine at all H2 receptors, their chief clinical use is as inhibitors of gastric acid secretion in the treatment of ulcers and heartburn. By competitively blocking the binding of histamine to H2 receptors in the gastric parietal cells, these agents reduce intracellular concentrations of cAMP and, thereby, secretion of gastric acid. The four drugs used in the United States, cimetidine, ranitidine, famotidine, and nizatidine, are discussed in Chapter 28. VI. DRUGS USED TO TREAT MIGRAINE HEADACHE It has been estimated that tens of millions of men and women in the United States suffer from severe migraine headaches. Migraine can usually be distinguished clinically from the two other common types of headaches (that is, cluster headache and tension-type headache) by its characteristics (Figure 42.9). Migraines, for example, present as a pulsatile, throbbing pain, whereas cluster headaches present as excruciating, sharp, steady pain, and tension-type headaches as dull pain, with a persistent, tightening feeling in the head. Patients with severe migraine headaches report one to five attacks per month of moderate to severe pain, usually unilateral. The headaches affect patients for a major part of their lives and result in considerable health costs. A. Types of migraine There are two main types of migraine headaches. The first, migraine without aura (previously called common migraine), is a severe, unilateral, pulsating headache that typically lasts from 2 to 72 hours. These headaches are often aggravated by physical activity and are accompanied by nausea, vomiting, photophobia (hypersensitivity to light), and phonophobia (hypersensitivity to sound). Approximately 85 per- 3/21/11 2:34:02 PM VI. Drugs Used To Treat Migraine Headache 555 MIGRAINE CLUSTER TENSION TYPE Family history Yes No Yes Sex Females more often than males Males more often than females Females more often than males Onset Variable During sleep Under stress Location Usually unilateral Behind or around one eye Bilateral in band around head Character and severity Pulsating, throbbing Excruciating, sharp, steady Dull, persistent, tightening Duration 2–72 hours per episode 15–90 minutes per episode 30 minutes to 7 days per episode Associated symptoms Visual auras, sensitivity to light and sound, pale facial appearance, nausea and vomiting Unilateral or bilateral sweating, facial flushing, nasal congestion, lacrimation, pupillary changes Mild intolerance to light and noise, anorexia Figure 42.9 Characteristics of migraine, cluster, and tension-type headaches. cent of patients with migraine do not have aura. In the second type, migraine with aura (previously called classic migraine), the headache is preceded by neurologic symptoms called auras, which can be visual, sensory, and/or cause speech or motor disturbances. Most commonly, these prodromal symptoms are visual, occurring approximately 20 to 40 minutes before headache pain begins. In the 15 percent of migraine patients whose headache is preceded by an aura, the aura itself allows diagnosis. The headache itself in migraines with or without auras is similar. For both types of migraines, women are threefold more likely than men to experience either type of migraine. B. Biologic basis of migraine headaches The first manifestation of migraine with aura is a spreading depression of neuronal activity accompanied by reduced blood flow in the most posterior part of the cerebral hemisphere. This hypoperfusion gradually spreads forward over the surface of the cortex to other contiguous areas of the brain. The vascular alteration is accompanied by functional changes. For example, the hypoperfused regions show an abnormal response to changes in arterial partial pressure of CO2. The hypo perfusion persists throughout the aura and well into the headache phase, after which hyperperfusion occurs. Patients who have migraine without aura do not show hypoperfusion. However, the pain of both types of migraine may be due to extracranial and intracranial arterial dilation. This stretching leads to release of neuroactive molecules, such as substance P. C. Symptomatic treatment of acute migraine Acute treatments can be classified as nonspecific (symptomatic) or migraine specific. Nonspecific treatment includes analgesics, such as nonsteroidal anti-inflammatory drugs, and antiemetics, such as prochlorperazine, to control vomiting. Opioids are reserved as rescue medication when other treatments of a severe migraine attack are not successful. Specific migraine therapy includes triptans and dihydroergotamine, both of which are 5-HT1D receptor agonists. It has been proposed that Pharm 5th 3-21-11.indb 555 3/21/11 2:34:03 PM 556 42. Autacoids and Autacoid Antagonists activation of 5-HT1D receptors by these agents leads either to vasoconstriction or to inhibition of the release of pro-inflammatory neuropeptides on the trigeminal nerve innervating cranial blood vessels. 1. Triptans: This class of drugs includes sumatriptan [SOO-ma-triptan], naratriptan [NAR-a-trip-tan], rizatriptan [rye-za-TRIP-tan], eletriptan [EH-leh-trip-tan], almotriptan [AL-moh-trip-tan], frovatriptan (frova-TRIP-tan), and zolmitriptan [zole-ma-TRIP-tan]. These agents rapidly and effectively abort or markedly reduce the severity of migraine headaches in about 70 percent of patients. The triptans are serotonin agonists, acting at a subgroup of serotonin receptors found on small peripheral nerves that innervate the intracranial vasculature. The nausea that occurs with dihydroergotamine and the vasoconstriction caused by ergotamine (see below) are much less pronounced with the triptans, particularly rizatriptan and zolmitriptan. Sumatriptan is given subcutaneously, intranasally, or orally. Zolmitriptan is available orally and by nasal spray. [Note: All other agents are taken orally.] The onset of the parenteral drug (which is indicated for treatment of cluster headaches) is about 20 minutes, compared with 1 to 2 hours when the drug is administered orally. The drug has a short duration of action, with an elimination half-life of 2 hours. Headache commonly recurs within 24 to 48 hours after a single dose of drug, but in most patients, a second dose is effective in aborting the headache. Rizatriptan and eletriptan are modestly more effective than sumatriptan, the prototype drug, whereas, naratriptan and almotriptan are better tolerated. Frovatriptan is the longest-acting triptan, with a half-life of more than 24 hours. Individual responses to triptans vary, and more than one drug trial may be necessary before treatment is successful. Significant elevation of blood pressure and cardiac events have been reported with triptan use. Therefore, triptans should not be administered to patients with risk factors for coronary artery disease without performing a cardiac evaluation prior to administration. Other adverse events with the use of triptans include pain and pressure sensations in the chest, neck, throat, and jaw. 2. Dihydroergotamine: Dihydroergotamine [dye-hye-droe-er-GOTa-meen], a derivative of ergotamine, is administered intravenously and has an efficacy similar to that of sumatriptan, but nausea is a common adverse effect. D. Prophylaxis Therapy to prevent migraine is indicated if the attacks occur two or more times a month and if the headaches are severe or complicated by serious neurologic signs. Propranolol is the drug of choice, but other β-blockers, particularly nadolol, have been shown to be effective. Other drugs that are effective for prevention of recurrent, refractory, severe migraine are shown in Figure 42.10. Pharm 5th 3-21-11.indb 556 3/21/11 2:34:03 PM VI. Drugs Used To Treat Migraine Headache 557 Agents used to treat an acute attack TRIPTANS Triptans rapidly and effectively abort or markedly reduce the severity of migraine headaches in about 80 percent of patients. Triptans are serotonin agonists, acting at 5-HT1D receptors. Agents used in prophylaxis DIHYDROERGOTAMINE Dihydroergotamine is a vasoconstrictor. Several classes of drugs are effective in reducing the frequency and severity of migraine attacks: β-Blockers: Propranolol and nadolol. Tricyclic antidepressant: Amitriptyline Anticonvulsant: Divalproex Calcium-channel blocker: Verapamil Most effective when given during the prodromal phase. Contraindicated in pregnancy, and in patients with peripheral vascular disease or coronary artery disease. ANALGESICS Anti-inflammatory drugs, such as aspirin, naproxen, and ibuprofen, are useful in relieving migraine attacks. Severe pain may require administration of opioids, such as codeine sulfate or meperidine. Time Start of attack Asymptomatic phase Between attacks, no symptoms or pathologic features are evident. Prodromal phase Visual disturbances that precede the actual headache. Associated with arterial vasoconstriction, and release of serotonin. Headache phase Pain, nausea and vomiting. Associated with cerebral vasodilation and lowerthan-normal levels of serotonin. Figure 42.10 Drugs useful in the treatment and prophylaxis of migraine headaches. Pharm 5th 3-21-11.indb 557 3/21/11 2:34:10 PM 558 42. Autacoids and Autacoid Antagonists Study Questions Choose the ONE best answer. 42.1 Dihydroergotamine: A. Causes vasodilation. B. Exerts its actions by binding to specific ergot amine receptors. C. Is useful in treating acute migraine headaches. D. Is useful for maintaining uterine muscle tone during pregnancy. E. Has actions similar to those of nitroprusside. 42.2 A 43-year-old ship's captain complains of seasonal allergies. Which one of the following would be indicated? A. Cyclizine. B. Doxepin. C. Doxylamine. D. Hydroxyzine. E. Fexofenadine. 42.3 Which one of the following statements concerning H1 antihistamines is correct? A. Second-generation H1 antihistamines are relatively free of adverse effects. B. Because of the established long-term safety of first-generation H1 antihistamines, they are the first choice for initial therapy. C. The motor coordination involved in driving an automobile is not affected by the use of firstgeneration H1 antihistamines. D. H1 antihistamines can be used in the treatment of acute anaphylaxis. E. Both first- and second-generation H1 antihistamines readily penetrate the blood-brain barrier. 42.4 Which one of the following drugs could significantly impair the ability to drive an automobile? A. Diphenhydramine. B. Ergotamine. C. Fexofenadine. D. Ranitidine. E. Sumatriptan. Pharm 5th 3-21-11.indb 558 Correct answer = C. Ergotamines act to counteract cerebral vasodilation which plays a role in migraine headaches. Vasoconstriction leading to tissue ischemia is one of the toxic complications associated with an overdose of these drugs. The ergot alkaloids interact with adrenergic, dopaminergic, and serotonin receptors. They are contraindicated in pregnancy because of their ability to cause uterine contraction and abortion. Nitroprusside is a powerful vasodilator used to treat the vasoconstriction that is characteristic of an overdose with ergot alkaloids. Correct answer = E. The use of first-generation H1 antihistamines is contraindicated in the treatment of pilots and others who must remain alert. Because of its lower potential to induce drowsiness, fexofenadine may be recommended for individuals working in jobs in which wakefulness is critical. Correct answer = A. Second-generation H1 antihistamines are preferred over first-generation agents because they are relatively free of adverse effects. Driving performance is adversely affected by firstgeneration H1 antihistamines. Epinephrine, not antihistamine, is an acceptable treatment for acute anaphylaxis. Second-generation H1 antihistamines penetrate the blood-brain barrier to a lesser degree than the first-generation drugs. Correct answer = A. Diphenhydramine can impair operation of an automobile by causing drowsiness and by impairing accommodation. The other agents do not have this restriction. 3/21/11 2:34:10 PM 43 Toxicology I. OVERVIEW Toxicology seeks to characterize the potentially adverse effects of foreign chemicals and their dose–response relationships to protect public health. Toxicology is defined as the study of the adverse effects of chemicals on living organisms. The term "toxicity" is defined as the inherent capacity of a chemical to cause injury (which is related to dose and duration of exposure). Thus, all chemicals, including drugs, have some

degree of toxicity. This was first documented by the physician Paracelsus (1493–1541), who stated, "All substances are poisons: There is none which is not a poison. The right dose differentiates a poison from a remedy." The adverse effects of therapeutic drugs have been discussed in previous chapters as the drugs have been presented and, therefore, will not be considered here. Instead, examples of nondrug chemicals and illicit drugs that are of public health concern, along with some basic concepts in toxicology, are presented. Exposure 1 (input) Inhalation Self-injection Oral II. TOXIC ACTIONS OF CHEMICALS Toxic chemicals from the environment may contact the skin and/or be absorbed after ingestion or inhalation. These exogenous chemicals are distributed to various organs, where they may be metabolized to products that may be more or less toxic than the original/parent chemical (Figure 43.1). The parent compound or its metabolites interact with target macromolecules, resulting in a toxic effect. A. Common target tissues Any tissue or organ within the body can potentially be affected by a chemical toxin, and, indeed, most chemicals adversely affect more than one tissue. However, the lungs ("portal of entry" for gases, vapors, and particles that can be inhaled); liver ("portal of entry" for ingested chemicals); and tissues with a high blood flow, such as brain and kidney, are particularly vulnerable to the toxic actions of chemicals. In addition, the heart is sensitive to any toxin-induced disruption in ionic gradients. B. Nonselective actions Exposure to certain chemicals, such as corrosive compounds, leads to local irritation and/or caustic effects that are nonselective in nature and occur at the site of application or exposure. Examples include exposure to strongly alkaline or acidic substances, which cause injury by denaturation of macromolecules, such as proteins, which are vital for cellular function. Conversion of a xenobiotic into electrophilic species causes chronic toxicity, whereas a nucleophilic species causes acute toxicity. Pharm 5th 3-21-11.indb 559 2 Absorption 3 Topical Distribution 4 Metabolism 5 Interaction with target 6 Elimination (output) Toxin may modify proteins, DNA, receptors or other essential molecules. Figure 43.1 Exposure, absorption, distribution, and mode of action of toxins. 3/21/11 2:34:18 PM 560 43. Toxicology C. Selective actions Many chemicals produce their toxic effects by interfering with the functions of specific biochemical pathways and/or affect the function of macromolecules within a tissue. For example, the rodenticide warfarin inhibits the vitamin K–dependent posttranslational modification of certain clotting factors by the liver (see p. 240). Selective toxic actions of chemicals are usually apparent only after the chemical has been absorbed and distributed within the body, in contrast to nonselective actions, which generally occur at the site of exposure. D. Immediate and delayed actions Irritation of the eyes Many compounds have toxic actions that will quickly lead to symptoms following exposure. For example, inhibition of acetylcholinesterase by an organophosphate insecticide, such as malathion, will rapidly lead to symptoms of excess acetylcholine at synapses and neuroeffector junctions (see p. 52). However, many chemicals exert effects that have latency periods of as long as several decades (for example, the carcinogen asbestos can lead to mesothiolema and pathology of the lung even 15 to 30 years after exposure). III. OCCUPATIONAL AND ENVIRONMENTAL TOXINS Irritation of respiratory system Nausea Dizziness Headache Death Figure 43.2 Adverse effects of halogenated hydrocarbons. Pharm 5th 3-21-11.indb 560 A. Halogenated hydrocarbons Halogenated hydrocarbons are usually volatile, and exposure can be through inhalation or ingestion. They are lipid soluble and can pass through the blood-brain barrier. Most will depress the central nervous system (CNS) when acute exposures are high. 1. Carbon tetrachloride: Individuals can be exposed to carbon tetra chloride through consumption of contaminated drinking water. Although transient, low-level inhalation of carbon tetrachloride can produce irritation of the eyes and respiratory system. Higher levels, whether inhaled or ingested, can produce nausea, vomiting, stupor, convulsions, coma, and death from CNS depression (Figure 43.2). Carbon tetrachloride undergoes a cytochrome P450–mediated metabolic activation to produce free radicals that cause lipid peroxidation and membrane breakdown. A nonlethal acute exposure can occur within a period of several hours to several days and produce centrilobular hepatonecrosis and kidney damage. 2. Chloroform: The adverse effects associated with chloroform exposure are similar to those with carbon tetrachloride. Exposures can occur through ingestion or inhalation, and toxic dose will result in nausea, vomiting, dizziness, headaches, and stupor. Chloroform can also sensitize the heart to catecholamine-induced arrhythmias. Chloroform is hepatotoxic and nephrotoxic due to its metabolic activation. B. Aromatic hydrocarbons As with the halogenated hydrocarbons, aromatic hydrocarbons tend to be volatile, and exposure can occur through inhalation and ingestion. Large acute exposures can cause CNS depression, and lead to cardiac arrhythmias through sensitization of heart cells to catecholamines. However, other aspects of their toxicological profile can differ significantly from that of the halogenated hydrocarbons. 3/21/11 2:34:19 PM III. Occupational And Environmental Toxins 1. Benzene: Approximately half of the national exposure to benzene occurs through tobacco smoke. Chronic benzene exposure in humans produces hematopoietic toxicities, of which the most serious are agranulocytosis and leukemia, particularly acute myelo genous leukemia. Nonoccupational exposures to benzene can occur as a result of combustion of fossil fuels, including automobile gasoline, and by consumption of contaminated water. 2. Toluene: Automobile emissions are the principal source of exposure in ambient air, whereas indoors exposure occurs from the use of household products containing toluene-like degreasers, certain paints and primers, and furniture polish. Acute and chronic exposure to toluene can produce CNS depression, with symptoms including drowsiness; ataxia; tremors; and impaired speech, hearing, and vision. Chronic exposure may also produce damage to the liver and kidneys. Deaths have occurred at high levels of exposure. 561 Methanol NAD+ Alcohol dehydrogenase Fomepizole NADH Formaldehyde NAD+ Aldehyde dehydrogenase NADH Formic acid C. Alcohols 1. Methanol (wood alcohol) and ethylene glycol: These primary alcohols are themselves relatively nontoxic and cause mainly CNS sedation. However, methanol and ethylene glycol are oxidized to toxic products: formic acid in the case of methanol, and glycolic, glyoxylic, and oxalic acids in the case of ethylene glycol. Fomepizole inhibits this oxidative pathway, preventing the formation of toxic metabolites, and allows the parent alcohols to be excreted by the kidney (Figure 43.3). Coma, seizures, hyperpnea, and hypotension all suggest that a substantial portion of the parent alcohols has been metabolized to toxic acids. 2. Isopropanol: This secondary alcohol is metabolized to acetone via alcohol dehydrogenase. Acetone cannot be further oxidized to carboxylic acids and, therefore, shows only limited acidemia and toxicity. Retinal injury Permanent blindnes Ethylene glycol NAD+ Fomepizole NADH Glycolaldehyde NAD+ Aldehyde dehydrogenase D. Pesticides Pesticides are a large class of chemicals designed to kill pests or organisms that society considers to be unhealthy, harmful, a nuisance, or destructive. Although their use is often controversial, they have had a significant impact on public health through the reduction of insectborne diseases, such as yellow fever and malaria, and they have increased crop yields in agriculture. A large variety of different classes of pesticides are currently used throughout the world. Some of the more commonly used compounds are considered here. 1. Organophosphosphate and carbamate insecticides: Carbamate insecticides are used in the United States whereas both carbamates and organophosphates insecticides are used worldwide They exert their toxicity through inhibition of acetylcholinesterase, with subsequent accumulation of excess acetylcholine. Alcohol dehydrogenase NADH Glycolate Calcium oxalate crystals Renal failure Figure 43.3 Metabolism of methanol and ethylene glycol. 2. Pyrethroids: The pyrethroids exert their mammalian and insect toxicity by extending the open time of sodium channels throughout the central and peripheral nervous systems. Symptoms of toxicity include loss of coordination, tremors, convulsions, and burning and itching sensations. Pyrethroids can also act as dermal and respiratory allergens, and exposure can lead to contact dermatitis Pharm 5th 3-21-11.indb 561 3/21/11 2:34:20 PM 562 43. Toxicology Blocking electron transfer by any one of these inhibitors stops electron flow from substrate to oxygen and inhibits energy production by oxidative phosphorylation. Substrate (reduced) e– NAD+ e– FMN Amytal Rotenone e– CoQ e– Cyto bc1 Antimycin A e– Cyto c e– Cyto a+a3 – CN CO Sodium azide e– O2 Figure 43.4 Site-specific inhibitors of electron transport. or asthma-like symptoms. Death, when it occurs in humans, is usually due to respiratory failure. Fortunately, the pyrethroids are much more toxic to insects, because insects have limited ability to eliminate these compounds. 3. Rotenone: Rotenone is used primarily as an insecticide and is applied to a wide variety of crops. It acts by inhibiting the oxidation of the reduced form of nicotinamide-adenine dinucleotide (Figure 43.4). Symptoms of poisoning include nausea and vomiting, with convulsions and death at very high dose. E. Rodenticides In contrast to insecticides, which are often applied by spraying, the rodenticides are usually used in the form of solid baits ingested by rodents. Consequently, the public health threat posed by its use is usually through accidental or suicidal ingestion. The most commonly used rodenticides are the anticoagulants such as warfarin. F. Heavy metals The heavy metals that are currently of most concern from a public health perspective are lead, mercury, and cadmium. They all exert their toxic effects by binding to certain functional groups on critical macromolecules within the body, thereby inactivating the function of those macromolecules. These functional groups include hydroxyl groups, carboxylic acid groups, sulfhydryl groups, and amino groups. Heavy metal intoxication can be treated by drugs termed chelators (see p. 536), which form complexes with the metals and prevent their binding to the endogenous macromolecules. Acute exposures to high levels of heavy metals are rare in the United States and are usually confined to occupational exposures. Such high exposures often result in nonselective corrosive effects. Of much greater public health concern are the more widespread chronic exposures to low levels of these toxic elements. 1. Lead: Lead is ubiquitous in the environment, with sources of exposure including old paint, drinking water, industrial pollution, food, and contaminated dust. However, with the elimination of tetraethyl lead in gasoline during the mid-1980s in the United States, environmental exposure to organic lead has been reduced, and most chronic exposure to lead occurs with inorganic lead salts, such as those in paint used in housing constructed prior to 1978. Age-dependent differences in the absorption of ingested lead are known to occur. Adults absorb about 10 percent of an ingested dose, whereas children absorb about 40 percent. Inorganic forms of lead are initially distributed to the soft tissues and more slowly redistribute to bone, teeth, and hair. Most lead will eventually make its way to bone, where it can be detected by x-ray examination. Lead has an apparent blood half-life of about 1 to 2 months, whereas its half-life from bone is 20 to 30 years. Chronic exposure to lead can have serious effects on several tissues. a. Central nervous system: The CNS effects of lead have often been termed lead encephalopathy. Symptoms include headaches, confusion, clumsiness, insomnia, fatigue, and impaired concentration. As the disease progresses, clonic convulsions and coma can occur. Death is rare given the ability to treat lead intoxication with chelation therapy. Children are more susceptible than adults to the CNS effects of lead. Furthermore, blood levels Pharm 5th 3-21-11.indb 562 3/21/11 2:34:21 PM III. Occupational And Environmental Toxins 563 of 5 to 20 μg/dL in children have been shown to lower IQ in the absence of other symptoms. It has been estimated that as many as 9 percent of the children in the United States may have blood lead levels greater than 10 μg/dL. b. Gastrointestinal system: The actions of lead on the gastrointestinal tract are varied and often lead subjects to seek medical help. Early symptoms can include discomfort and constipation (and, occasionally, diarrhea), whereas higher exposures can produce painful intestinal spasms (Figure 43.5). Calcium gluconate infusion is effective for relief of pain. c. Blood: Lead has complex effects on the constituents of blood, leading to hypochromic, microcytic anemia as a result of a shortened erythrocyte life span and through disruption of heme synthesis. Lead inhibits several enzymes involved in the synthesis of heme, thereby leading to increased blood levels of protoporphyrin IX and aminolevulinic acid as well as increased urinary excretion of δ-aminolevulinic acid and coproporphyrinogen (Figure 43.6). Elevated blood and urinary levels of these intermediates can be used diagnostically for determining lead intoxication, provided that blood lead levels are greater than about 25 μg/dL. Below that, elevated levels of heme intermediates cannot be observed, even though IQ effects can be observed in children. 2. Mercury: Potential exposure to mercury constitutes a significant health concern, because various forms of mercury are released into the human environment by industry, by natural release from the oceans and the earth's crust, and through the burning of fossil fuels. Human exposure to three different forms of mercury can occur. a. Elemental mercury: Toxic exposures to elemental mercury are usually occupational, in which the vapors are inhaled. Symptoms of elemental mercury toxicity include tremors, depression, memory loss, decreased verbal skills, and inflammation of the kidneys. High concentrations of elemental mercury are corrosive and cause nonselective toxicity within the pulmonary system. b. Inorganic mercury salts: Exposures to inorganic salts of mercury, such as mercuric chloride, that lead to adverse health effects are usually occupational in nature. Inorganic salts are often corrosive and can destroy the mucosa of the mouth if ingested. Renal damage can also be observed several hours after exposure. Hazardous exposures of the public to inorganic forms of mercury are uncommon. c. Organic mercury: Any form of mercury that contains at least one covalent bond to a carbon atom is considered to be organic mercury. Organic forms of mercury tend to be more lipid soluble than the inorganic salts as well as much less corrosive. Therefore, significant absorption results after ingestion, which occurs primarily from consumption of foods, particularly fish, contaminated with methylmercury. Symptoms of high levels of organic mercury can appear several days to several weeks after ingestion and are primarily neurologic in nature. These symptoms include visual disturbances, paresthesias, ataxia, hearing loss, Pharm 5th 3-21-11.indb 563 Insomnia GI disturbance Fatigue Headache Figure 43.5 Adverse effects of lead poisoning. GI = gastrointestinal. LEAD POISONING • Ferrochelatase and ALA dehydratase are inhibited by lead. • Protoporphyrin and ALA secreted in the urine in lead poisoning. Glycine + Succinyl CoA δ-Aminolevulinic acid Lead Porphobilinogen Hydroxymethylbilane Uroporphyrinogen III Coproporphyrinogen III Protoporphyrinogen IX Protoporphyrin IX Lead Heme Figure 43.6 Adverse effect of lead poisoning on heme biosynthesis. 3/21/11 2:34:24 PM 564 43. Toxicology mental deterioration, muscle tremors, movement disorders, and, with severe exposure, paralysis and death. Organic mercury poisoning in elderly individuals is sometimes misdiagnosed as Parkinson disease or Alzheimer disease. Although all forms of mercury are toxic to the fetus, organic mercury is the most dangerous, because its lipid solubility allows passage through the placenta. 3. Cadmium: The most frequent human exposures to cadmium occur through ingestion or inhalation. Widespread exposure to the public can occur through ingestion of food that is contaminated as a result of cadmium uptake by plants from fertilizers and manure, and through atmospheric deposition. Large inhalational exposures are usually occupational in nature, although low-level exposure occurs from the burning of fossil fuels, which releases cadmium into the environment. Cigarette smoke is also a source of cadmium. Cadmium is used heavily by a variety of industries, and environmental contamination from these sources is a major concern. Cadmium absorption upon ingestion is poor, with about 5 percent bioavailability. Upon inhalation, about 10 to 40 percent of the dose is absorbed. Most of the cadmium in the body will eventually distribute to the liver and kidneys, largely as a result of its binding to metallothionein. The halflife of cadmium is 10 to 30 years. Although cadmium can affect many tissues, its major toxicities are seen in the kidneys and lungs. G. Gases and inhaled particles Chemicals can be inhaled as gases, solids, and aerosols. Some chemicals that make their way to the alveoli can be rapidly absorbed and distributed to other tissues. Other particulates can become lodged in the alveoli and exert serious local toxicity without being absorbed into the bloodstream. O2 Content (mL/100 mL blood) CO-Hb binds oxygen with high affinity, which decreases delivery of oxygen to tissues. Zero percent CO-Hb 20 Fifty percent CO-Hb 10 0 0 40 80 120 Partial pressure of oxygen (pO2) (mm Hg) Figure 43.7 Effect of carbon monoxide on the oxygen affinity of hemoglobin. CO-Hb = carbon monoxyhemoglobin. Pharm 5th 3-21-11.indb 564 1. Carbon monoxide: Carbon monoxide is a gas that is colorless, odorless, and tasteless, making it impossible for individuals to detect without a carbon monoxide detector. It is a natural byproduct of the combustion of carbonaceous materials, and common sources of this gas include automobiles, poorly vented furnaces, fireplaces, wood-burning stoves, kerosene space heaters, and charcoal grills. Following inhalation, carbon monoxide rapidly binds to hemoglobin to produce carboxyhemoglobin. The binding affinity of carbon monoxide to hemoglobin is 230 to 270 times greater than that of oxygen. Consequently, even low concentrations of carbon monoxide in the air can produce significant levels of carboxyhemoglobin. In addition, bound carbon monoxide increases hemoglobin affinity for oxygen at the other oxygen-binding sites. This high-affinity binding of oxygen prevents the unloading of oxygen at the tissues, further reducing oxygen delivery (Figure 43.7). The symptoms of carbon monoxide intoxication are consistent with hypoxia, with the brain and heart showing the greatest sensitivity. Symptoms include headache, dyspnea, lethargy, confusion, and drowsiness, whereas higher exposure levels can lead to seizures, coma, and death. The management of a carbon monoxide–poisoned patient includes prompt removal from the source of carbon monoxide and institution of 100-percent oxygen by nonrebreathing face-mask or endotracheal tube. In patients with severe intoxication, oxygenation in a hyperbaric chamber is recommended/followed. 3/21/11 2:34:25 PM IV. Antidotes 2. Cyanide: Once absorbed into the body, cyanide quickly binds to many metalloenzymes, thereby rendering them inactive. Its principal toxicity occurs as a result of the inactivation of the enzyme cytochrome oxidase (cytochrome a3), leading to the inhibition of cellular respiration. Therefore, even in the presence of oxygen, those tissues, such as the brain and heart, which require a high oxygen demand, are adversely affected. Death can occur quickly due to respiratory arrest of oxidative phosphorylation and production of adenosine triphosphate. Cyanide poisoning can be treated with specific antidotes (see p. 227). 3. Silica: Workers in mines, foundries, construction sites, and stone cutters are at particular risk for silicosis, perhaps the oldest known occupational disease. Silicosis is a progressive lung disease that results in fibrosis and, often, emphysema. Silicosis is currently incurable, and the prognosis is often poor. However, with lower exposures, silicosis does not always end in death or debilitation. 4. Asbestos: The greatest public health threat from asbestos is pulmonary in nature as a result of inhalation of the fibers, some of which stay permanently in the lung alveoli. The three diseases most commonly associated with asbestos exposure are asbestosis, mesothelioma, and lung cancer. Symptoms of these diseases may not be apparent for up to 15 to 30 years following exposure to asbestos. Asbestosis is a chronic pulmonary disease that is characterized by interstitial fibrosis in the lungs and pleural fibrosis or calcification. Initial symptoms include shortness of breath that can eventually develop into severe cough and chest pains. Asbestosis is a progressive disease with no specific treatment, and it can be fatal. Mesothelioma is a rare cancer, usually in the chest wall (or peritoneum), which seems to be caused only by asbestos. The first noticeable symptom is usually pain in the vicinity of the lesion, with dyspnea and cough developing with pleural mesothelioma. Patients usually survive no longer than 2 years after diagnosis. With all forms of asbestos-induced treatment, disease is largely symptomatic and supportive. IV. ANTIDOTES Specific chemical antidotes for poisoning have been developed for a number of chemicals or classes of toxicants (Figure 43.8). The following are examples of strategies that form the basis for the use of specific chemical antidotes, with an example of how each can be applied. 565 POISON OR SYNDROME ANTIDOTE(S) Acetaminophen N-Acetylcysteine Anticholinergic agents Physostigmine Benzodiazepine Flumazenil Carbon monoxide Oxygen (+/– hyperbaric chamber) Cyanide Amyl nitrite pearls Sodium nitrite Sodium thiosulfate Digitalis Digoxin-immune Fab Methanol Ethylene glycol Fomepizole Heparin Protamine sulfate Lead Dimercaptosuccinic acid Mercury Arsenic Gold Dimercaprol Methemoglobinemia Methylene blue Opiates Naloxone, nalmefene, or naltrexone Organophosphates Carbamates Nerve gases Atropine Pralidoxime Figure 43.8 Common antidotes. A. Pharmacologic antagonization of toxic action Atropine is a muscarinic-receptor antagonist that is used as an antidote for intoxication by the anticholinesterases (see p. 55). It works by blocking access of excess acetylcholine to muscarinic receptors. B. Removal of toxicant-mediated oxidative stress Acetaminophen at very high doses will produce liver necrosis as a result of its metabolic activation by cytochrome P450. Administration of N-acetylcysteine serves as a substitute for glutathione by removing reactive metabolites produced from acetaminophen. To be effective, N-acetylcysteine must be given as early as possible (within 8–10 hours of ingestion of acetaminophen). Pharm 5th 3-21-11.indb 565 3/21/11 2:34:27 PM 566 43. Toxicology C. Alternative target provided Cyanide poisoning is treated with a two-step process. Sodium nitrite is administered to induce the oxidation of hemoglobin to methemoglobin, which has a high binding affinity for cyanide to produce cyanmethemoglobin. Amyl nitrite can also be used for this purpose. The second step in the antidotal treatment of cyanide intoxication is to accelerate its detoxification. Administration of sodium thiosulfate will accelerate the production of thiocyanate, which is much less toxic than cyanide and is also quickly excreted in urine. In patients with smoke inhalation and cyanide toxicity, the induction of methemoglobin should be avoided unless the carboxyhemoglobin concentration is less than 10 percent. Otherwise, the oxygen-carrying capacity of blood becomes too low. D. Reduced metabolic activation The toxicity of methanol is thought to be mediated by formic acid, which is produced by the metabolism of methanol by alcohol dehydrogenase. Fomepizole is an antidote to methanol, because it inhibits alcohol dehydrogenase (see Figure 43.3). Slowing the rate of methanol metabolism decreases the production of formic acid, thereby reducing the toxicity. E. Restored altered target Acetylcholinesterase that has been inhibited as a result of phosphorylation by organophosphorus compounds often can be reactivated by the antidote oximes (see p. 52). F. Chelation Chelators are drugs that will form covalent bonds with cationic metals. The chelator-metal complex is then excreted in urine, thereby greatly facilitating the excretion of the heavy metal. Unfortunately, chelators are not specific to heavy metals, and essential metals, such as zinc, often can also be chelated. Additionally, some chelators have potentially serious adverse effects themselves, and their use in treatment of heavy metal intoxication is undertaken only when the benefits of chelation therapy outweigh the associated risks. 1. Dimercaprol: Dimercaprol, also known as British anti-Lewisite , was the first chelator utilized, having been developed during World War II as a chelator for the arsenical war gas Lewisite. Dimercaprol is used by itself to chelate mercury and arsenic and in combination with edetate calcium disodium to treat lead intoxication. It is not effective after oral administration and is usually given intramuscularly. Use of dimercaprol is often limited by its capacity to increase blood pressure and heart rate. 2. Succimer: Succimer (dimercaptosuccinic acid) is a derivative of dimercaprol that is effective upon oral administration. A second advantage of succimer over dimercaprol is the lack of increased blood pressure and heart rate during treatment. Some elevation of serum levels of hepatic enzymes can be observed with succimer treatment. Succimer is currently approved for treatment of lead intoxication, but may be effective in chelation of other metals as well. 3. Edetate calcium disodium: Edetate calcium disodium is used primarily for treatment of lead intoxication, but it can also be used for poisoning by other metals. It is not effective after oral administra- Pharm 5th 3-21-11.indb 566 3/21/11 2:34:27 PM V. Designer And Street Drugs tion and is usually given intravenously or intramuscularly. The calcium disodium salt of ethylenediaminetetraacetic acid (EDTA) must be the form used to prevent chelation of calcium and its depletion from the body. Edetate calcium disodium can cause renal damage that is reversible upon cessation of the drug. V. DESIGNER AND STREET DRUGS "Designer drugs" are synthetic derivatives of federally controlled substances, created by slightly altering the molecular structure of existing drugs and produced illegally in clandestine laboratories for illicit use. Most of these drugs have some psychoactive properties and cause visual disturbances, but they are not true hallucinogens like lysergic acid diethylamide. 567 A Presynaptic inhibitory receptors SYNAPTIC CLEFT A. Methylenedioxymethamphetamine Many of the most popular designer drugs on the street today are amphetamine analogs. Methylenedioxymethamphetamine (MDMA) is one of the most commonly used designer drugs. Commonly known as Ecstasy , MDMA possesses central stimulant and psychedelic effects. Its use is popular among those attending late-night "rave" parties, dance clubs, and rock concerts. 1. Mechanism of action: The main effect of MDMA is on neurons that synthesize and release the neurotransmitter serotonin (5-HT). MDMA causes 5-HT release into the synaptic cleft, inhibits its synthesis, and blocks its reuptake (Figure 43.9). The effect is an increased 5-HT concentration in the synaptic cleft and a depletion of intracellular 5-HT stores. 5-HT regulates mood, appetite, and body temperature. Users of MDMA will, therefore, manifest more of a serotonergic effect compared with the dopaminergic effects (amphetamine toxicity associated with amphetamines; see p. 121). MDMA's effects begin within the first hour after ingestion of an oral dose and usually last 3 to 6 hours. 2. Clinical manifestations: a. Cardiopulmonary: Cardiopulmonary manifestations of Ecstasy use include tachycardia, tachypnea, hypertension, vasospasm, pulmonary hypertension, dysrhythmias, valvular disease, and myocardial infarction. b. Neurologic: Symptoms include mydriasis, nystagmus, head jerking, hyperthermia, sexual dysfunction, seizures, cerebral infarction, dopamine and 5-HT depletion in the synapse leading to potential for irreversible neuron destruction, and 5-HT syndrome, especially in combination with other serotonergic drugs. No drug PRESYNAPTIC NEURON Serotonin POSTSYNAPTIC NEURON B Acute effect of MDMA MDMA Postsynaptic response MDMA causes serotonin release into the synaptic cleft, inhibits its synthesis, and blocks its reuptake. The effect is an increased sertonin concentration in the synaptic cleft and a depletion of intracellular serotonin stores. Figure 43.9 Proposed mechanism of action of methylenedioxymethamphetamine (MDMA). c. Psychologic: Most users of Ecstasy describe a sense of well-being and social interactivity as well as feelings of empathy, euphoria, agitation, visual and tactile hallucinations, and, occasionally, anxiety. Chronic abuse leads to symptoms of psychosis (from dopaminergic affects) and obsessive-compulsive behavior. d. Musculoskeletal: Common signs and symptoms include teeth grinding (bruxism), jaw clenching (trismus), increased muscular activity resulting in cramping, and rhabdomyolysis. Pharm 5th 3-21-11.indb 567 3/21/11 2:34:28 PM 568 43. Toxicology e. Other manifestations: Dehydration and hyperglycemia are common, as is metabolic acidosis in chronic use and overdose. Hyponatremia is of concern, because dilution from increased water intake, in addition to increased diuresis secondary to inhibition of antidiuretic hormone, may reduce sodium, thereby predisposing the patient to seizures and cerebral edema. 3. Treatment: Treatment of isolated MDMA ingestion is supportive. Asymptomatic MDMA-induced hyponatremia is treated with fluid restriction. Refractory hypertension may be treated with nitroprusside or phentolamine. Hyperthermia is treated by aggressive external cooling with ice water, mist, and fans. Anxiety, agitation, and convulsions are treated with diazepam. B. γ-Hydroxybutyric acid In the dance and "rave" clubs, γ-hydroxybutyric acid (GHB) has become widely abused due to its ability to rapidly produce a euphoric state. The fast and effective intoxication and the amnestic effect produced by GHB have made the drug attractive to sexual assault perpetrators. GHB is usually administered in an oral form and is rapidly and effectively absorbed by the gastrointestinal tract. The onset of action is quite rapid, with an effect usually being felt within 15 minutes and peaking anywhere between 40 and 120 minutes. 1. Mechanism of action: The actions of exogenous GHB are mediated primarily by the GABAB receptor. Low doses of the drug stimulate dopamine synthesis but inhibit its release, causing dopamine to concentrate in the nerve terminal. With higher doses of GHB, dopamine release is triggered. GHB also has effects through the endogenous opioid system, which may explain its euphoria-producing properties. 2. Clinical manifestations: a. Cardiopulmonary: Chronic use of GHB can cause severe cardiopulmonary complications, such as hypoxia, bradycardia, hypotension, bradypnea, and dysrhythmia. b. Central nervous system: CNS effects are common and include euphoria in small doses, deep sleep in moderate doses, and a comatose state in large doses. Amnestic effects and loss of sexual inhibition make GHB a common drug in the commission of sexual battery. Hallucinations, agitation (especially upon arousal), seizures, myoclonus, and slurred speech are also common. c. Psychologic: Most users describe a sense of well-being and euphoria as well as being socially interactive and empathetic. d. Other: Other physiologic manifestations include salivation, vomiting, and hypothermia. 3. Treatment: Treatment of isolated GHB ingestion is supportive. In patients with significant CNS depression due to GHB overdose, intubation for airway protection is essential because of the high incidence of emesis. Bradycardia unresponsive to stimulation should be treated with atropine. Pentobarbital has been used successfully in the treatment of severe GHB withdrawal. Pharm 5th 3-21-11.indb 568 3/21/11 2:34:28 PM V. Designer And Street Drugs 569 Study Questions Choose the ONE best answer. 43.1 A 3-year-old boy is brought to the Emergency Department by his mother, who reports that he has been crying continuously and "doesn't want to play or eat" for the last few days. She also states that he has not had regular bowel movements, with mostly constipation and occasional diarrhea, and frequently complains of abdominal pain. The child now has an altered level of consciousness, is difficult to arouse, and begins to seize. The clinician rules out infection and other medical causes. Upon questioning, the mother states that the house is in an older neighborhood, that her house has not been re-modeled or repainted since the 1940s, and that the paint is chipping around the windows and doors. The child is other-wise breathing on his own and urinating normally. Which toxin would you expect to be causing such severe effects in this child? A. Mercury. B. Lead. C. Cadmium. D. Asbestos. E. Cyanide. 43.2 A 41-year-old male pocketwatch maker reports to the Emergency Department after he was found unconscious on the floor of the shop by a coworker. The coworker states that the patient complained of being cold this morning around 8 a.m. (the central heat was broken, and the outdoor temperature was 34°F) and that since noon, he had been complaining of headache, drowsiness, confusion, and nausea. The clinician notices that he has cherry red lips and nail beds. What is the most likely toxin causing his signs and symptoms? A. Asbestos. B. Cyanide. C. Chloroform. D. Carbon monoxide. E. Ecstasy. Pharm 5th 3-21-11.indb 569 Correct answer = B. Lead poisoning is common among children in older homes painted before lead was removed from paint. Paint chips with lead are easily ingested by toddlers, and excessively high lead levels can lead to the signs and symptoms described plus clumsiness, confusion, headaches, coma, constipation, intestinal spasms, and anemia. Death is rare when chelation therapy is used. Succimer is typically a good chelating agent for lead. Mercury is not typically a concern in this age group. When ingested, elemental mercury is relatively harmless, and children of this age are not typically exposed to occupational mercury salts (mercury chloride) or organic mercury, such as that found in thimerosal. Mercury also has signs and symptoms such as movement disorders and tremors. Cadmium poisoning is typically a result of ingestion through contaminated food and causes kidney and lung damage, which this child does not exhibit. The shortness of breath that can eventually develop into severe cough seen with asbestos poisoning is also not seen with this child. If he had cyanide poisoning, death would have occurred quickly following respiratory arrest of oxidative phosphorylation and production of adenosine triphosphate, but this child has been exhibiting symptoms over several days. Correct answer = D. Although watch makers and other professionals who use electroplating may be at higher risk for cyanide exposure because many plating baths use cyanide-containing ingredients (for example, potassium cyanide), this patient shows classic signs of carbon monoxide poisoning, such as cherry red lips and nail beds, headache, confusion, nausea, and drowsiness leading to unconsciousness. The history also leads us to believe that this person may have been using a Sterno stove or space heater to stay warm, which would be consistent with the description. Asbestos poisoning commonly first presents as lung cancer or mesothelioma. Cyanide in low doses from such an occupational exposure can present with loss of consciousness, headache, and confusion. However, cyanide toxicity also typically includes giddiness in the early stages, perceived difficulty breathing, and pink skin (not just lips and nails), and then later rapidly progresses to deep coma and death. Chloroform can cause dizziness, fatigue, and unconsciousness, but these patients do not present with cherry red lips and nails. These symptoms are not consistent with Ecstasy overdose, in which hyperthermia, not "feeling cold" is typically seen. 3/21/11 2:34:28 PM 570 43. Toxicology Study Questions (continued) Choose the ONE best answer. 43.3 A 50-year-old migrant worker comes to the Emergency Department from the field he was working in and complains of diarrhea, tearing, nausea and vomiting, and sweating. The clinician notices that he looks generally anxious and has fine fasciculations in the muscles of the upper chest as well as pinpoint pupils. Which antidote should he receive first? A. N-Acetylcysteine. B. Sodium nitrite. C. Ethylenediaminetetraacetic acid (EDTA). D. Atropine. E. Fomepizole. 43.4 A 20-year-old woman presents to the Emergency Department after being dumped in the ambulance bay with a note that said only that "she was doing Ecstasy at a party when she became unconscious."This patient currently remains unconscious, with a heart rate of 140 bpm, temperature of 103.5°F, pinpoint pupils, absent bowel sounds, blood pressure of 85/40 mm Hg, profuse sweating, and oxygen saturation of 86 percent on room air. Which of the following would not be a clinical manifestation of an Ecstasy patient? A. Tachycardia. B. Hyperthermia. C. Pinpoint pupils. D. Diaphoresis. E. Respiratory depression. 43.5 A 23-year-old man presents to the Emergency Department unconscious with his girlfriend, who tells the clinician that they were at a "rave," and a couple who they met gave them what looked like water in a bottle. Her boyfriend drank about one fourth of the bottle and suddenly collapsed. He currently is hypoxic, bradycardic, hypotensive, bradypnic, and has electrocardiographic changes. She states that they do not do drugs, and they just went to the party for the music. The urine drug screen is negative for opioids, marijuana, methadone, benzodiazepines, barbiturates, phencyclidine, amphetamines, and cocaine. The clinician suspects γ-hydroxybutyric acid (GHB) intoxication. GHB ingestions commonly produce which of the following? Correct answer = D. Atropine is appropriate for this patient, who has symptoms consistent with organophosphate (insecticide) poisoning. The mnemonic SLUDGE (salivation, lacrimation, urination, diaphoresis, gastrointestinal motility diarrhea, and emesis) can be used to remember the signs and symptoms of cholinergic toxicity. An anticholinergic antidote, atropine will control these muscarinic symptoms. The antidote pralidoxime can be used to treat the nicotinic symptoms like fasciculations (involuntary muscle quivering or twitching). N-Acetylcysteine is the antidote for acetaminophen overdose and acts as a sulfhydryl donor. Sodium nitrite is one of the antidotes included in the cyanide antidote kit (amyl nitrite, sodium nitrite, and sodium thiosulfate.) Ethylenediaminetetraacetic acid is the chelating agent for heavy metals like lead. Fomepizole is the antidote for methanol and ethylene glycol. Correct answer = C. Tachycardia, hyperthermia, diaphoresis, and unconsciousness are typical signs and symptoms of ecstasy overdose. Pinpoint pupils as well as absent bowel sounds, low oxygen saturation (respiratory depression), and hypotension are good indicators of opioid overdose. This is likely a multidrug overdose. Correct answer = D. Respiratory depression is associated with γ-hydroxybutyric acid (GHB) ingestion. This patient has symptoms associated with GHB toxicity. The other choices are all associated with an Ecstasy overdose. A. Tachycardia. B. Hyperthermia. C. Hypertension. D. Respiratory depression. E. Diaphoresis. Pharm 5th 3-21-11.indb 570 3/21/11 2:34:28 PM

Information contained in this Index Note: Page numbers followed by f indicate figures. Trade names of drugs are shown in capital letters and generic names are shown in italics. Page numbers in bold indicate main discussions. A Abacavir (ABC), 461f, 471, 473, 473f Abatacept, 526f, 539, 544 ABC. See Abacavir (ABC) Abciximab, 243f, 249, 249f ABELCET, 430. See also Amphotericin B ABILIFY. See Aripiprazole Abortifacients, 549, 550f Absence seizures, 182f, 183, 184f Absorption of drugs, 1, 1f, 6–10 administration route and, 5f blood flow and, 8 P-glycoprotein and, 8, 8f pH and, 7–8 Acamprosate, 112f, 121 Acarbose, 301f, 308f, 311, 314f ACCOLATE. See Zafirlukast ACCUNEB. See Albuterol ACCUPRIL. See Quinapril ACCURETIC. 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