2

General Principles of Pharmacology

KEY TERMS

Affinity: The force of attraction of a molecule to a receptor site
Agonist: A drug that has a direct stimulatory effect on a receptor
Antagonist: A drug that interferes with the action of an agonist
Ceiling dose: The dose above which no further beneficial drug effect will occur
Enteral: The administration of a drug through the gastrointestinal (GI) tract, by mouth
Efficacy: The magnitude of response obtained from optimal receptor site occupancy by a drug
Half-life: The time it takes for half the drug to be removed from the body
Intrinsic activity: The ability to cause an effect or action
Parenteral: The administration of a drug bypassing the GI tract, usually through injection into the body in various ways but also including inhalation and topical administration
Partial agonist: A drug with affinity for the receptor site, but unable to produce a strong effect or action
Pharmacodynamics: The mechanisms of drug action involving biochemical and physiologic effects of drugs
Pharmacokinetics: The absorption, distribution, metabolism, and excretion of a drug
Pharmacotherapeutics: The use of pharmacologic agents to diagnose, treat, or prevent disease
Potency: The concentration at which the drug elicits 50% of its maximal response, related to the drug's affinity for the receptor
Receptor site: A specialized area on a cell or within a cell where a drug acts to initiate a series of biochemical and physiologic effects
Strong agonist: Drug that produces a significant physiologic response when only a relatively small number of receptors are occupied
Toxicity: Overdose, undesirable effects, or poisoning

KEY ACRONYMS

IM: Intramuscular
IV: Intravenous
ROA: Route of administration
SC: Subcutaneous

The science of pharmacology is the study of drugs. The science developed when early individuals observed the effects of herbs and plant extracts on themselves or others. Historically, the clinician was responsible for information about the sources, physical and chemical properties, and compounding and dispensing of drugs. These activities are now delegated to pharmacologists and pharmacists. Today, the practitioner's responsibility relates to the clinical application of this knowledge. Oral health professionals must understand basic principles of pharmacology as they apply to drugs used in oral health care as well as other drugs taken by the dental patient. This understanding provides for more efficient communication when explaining drug effects to the patient or when medical consultation is necessary. Important principles include:

- knowing how a drug works, called *the mechanism of action*;
- the potential adverse (or side) effects (ADEs) that are possible;

- oral health education information related to drug effects;
- the risks of taking a drug.

These principles apply to all therapeutic agents (including vitamins, herbs, and nutritional supplements) and pertain to a drug's mechanism of action (pharmacodynamics), the movement of the drug through the body (pharmacokinetics), and potential adverse effects when the drug is taken (pharmacotherapeutic variables).

Self-Study Review

1. List four principles of pharmacology that the oral health professional must understand in order to provide information on drug effects.
2. Define *pharmacodynamics* and *pharmacokinetics* as they apply to drugs.

PHARMACODYNAMICS

Pharmacodynamics is the science of molecular interactions between drugs and body constituents. It relates to the biochemical and physiologic actions of drugs. When a drug is delivered to the tissue cells, it goes through several steps. The first step in initiating a drug-induced effect is the formation of a complex, or bond, between the drug molecule and a cell component called the drug **receptor**. The receptor site where a drug acts to initiate a series of biochemical and physiologic effects is that drug's site of action. The molecular event that follows this drug-receptor interaction is called the drug's **mechanism of action**. An example of this process is the action of epinephrine in local anesthetic agents. Following the injection of a local anesthetic solution (delivery), epinephrine binds to its receptor on vascular smooth muscle (complex formation) and causes the muscle cell to constrict (drug-receptor interaction), resulting in vasoconstriction (mechanism of action). Most drugs go through a similar process; however, it should be understood that not all drugs produce their effects by interacting with specific receptors. This concept will become apparent as one considers drug action in future chapters. A number of drugs form chemical bonds with small molecules, chelating agents, or metallic cations. A practical example of this type of drug-receptor interaction is the therapeutic neutralization of gastric acid by antacids. Many other drugs act by mechanisms that are not yet understood.

Receptors

Drug receptors are large, highly specialized molecules, which are components of the plasma membrane or are located intracellularly. A single cell may have hundreds of different receptor sites, and a drug may interact with a variety of different receptor types or subtypes, producing different pharmacologic effects. Drug molecules and their receptors must have similar structures (structural specificity), described as "lock and key" complementary fits. Figure 2-1 illustrates the complementary fit and the interaction with different receptors. Only one molecule can bind to a receptor at a time; i.e., two drugs cannot occupy the same receptor at the same time. Receptors have a variety of other features that determine their function, location in the body, relationship to cellular membranes, and binding capacity (Box 2-1), including:

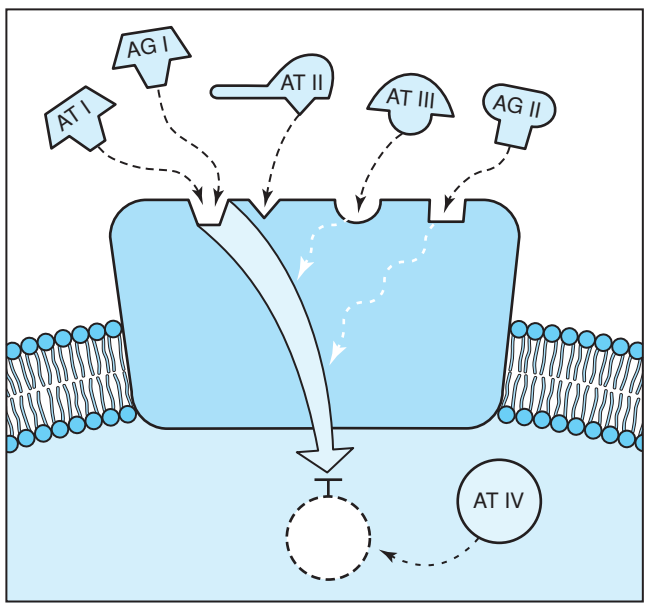

Figure 2-1 Complementary Receptor-Molecule Fit. Major features of classical receptors. Drug molecules (AG, agonist; AT, antagonist) and their receptors must have a similar structure (structural specificity), described as a "lock and key" complementary fit. AT I and AG I compete for the same receptor site, AG I to enhance and AT I to block signal; AG II and AT III enhance or block signal, respectively, by binding to alternative sites that influence signal transmission; AT II binds to an alternative site and blocks AG I activation site. AT IV blocks signal at intracellular signal reception site.

- electrochemical force (either electropositive or electronegative) that functions to attract the drug molecule to the receptor
- the trait of being hydrophilic or hydrophobic to attract or repel a molecule
- are cellular macromolecules

BOX 2-1. Characteristics of Drug Receptors

- Cellular macromolecules
- Location on the cell surface or within the cell
- Hundreds of different receptors on a single cell
- Complementary fit between drug and receptor
- Electrochemical charge
- Hydrophilic or hydrophobic
- Only one drug molecule can occupy a receptor at one time

The drug molecule binds to the complementary receptor and stimulates the receptor to produce a definable pharmacologic response.

Chemical Bonds

Drugs attach to or interact with these receptor sites through various types of chemical bonds. These include ionic, hydrogen, and covalent bonds, and van der Waals forces. Hydrogen bonding and ionic bonding are the most common types between drugs and receptors. The bonds are similar in that both involve an electrochemical attraction. These interactions require little energy and are made and broken easily.

Ionic Bonds

Ionic interactions occur between atoms with opposite charges. An atom with an excess of electrons imparts a negative charge, which causes an attraction to an atom with a deficiency of electrons. A simple example of this type of interaction is reflected in the attraction between sodium and chloride ions (sodium chloride [Na^+/Cl^-]). Applying the concept to the attraction between drug molecules and receptor sites, a positively charged drug molecule is attracted to a negatively charged receptor site. These bonds are weak and are easily reversed.

Hydrogen Bonds

When bound to nitrogen or oxygen, hydrogen atoms become positively polarized and bind to negatively polarized atoms such as oxygen, nitrogen, or sulfur. These bonds are generally weaker than ionic bonds.

Covalent Bonds

Covalent bonds are the strongest type of bond between a drug and its receptor, resulting from the sharing of electrons by two atoms. The energy required to overcome such interactions can be so great that the bond is often irreversible. Fortunately, such drug–receptor interactions are not common. A good example of a covalent bond is the complex formed between tetracycline and dentin to produce a permanent intrinsic discoloration.

van der Waals Forces

These nondescript forces contribute to the mutual attraction between organic molecules through a shifting of electron density in or around a molecule that results in the generation of transient positive or negative charges. This provides for a weak attractive force between some drugs and their receptors.

Attractive Forces Between Drugs and Receptors

Drug molecules move in constant random motion in the cellular area, binding to receptors and breaking away from receptors. The following forces govern the potential for a complex to form.

Affinity

When a drug molecule moves so close to its receptor that the attractive force between them becomes great enough to overcome the random motion of the drug molecule, the drug binds to the receptor. This phenomenon is called **affinity**. The affinity of a drug for a particular receptor and the type of binding that occurs is intimately related to the drug's chemical structure. Because two drug molecules cannot occupy the same receptor site at the same time, the drug with the greater affinity will bind more readily to the receptor. Affinity is expressed by its dissociation constant (K_D), which is the concentration of a drug required in solution to achieve 50% occupancy of its receptors. When two drugs of equal concentrations are competing for the same receptor population, the drug with the greater affinity will bind with more receptors (and stimulate the receptor to cause an action) at any given instant (Fig. 2-2). Thus, a lower concentration of that drug will produce the same level of pharmacologic effect. This means that drugs with good affinity have greater **potency**; i.e., they require a smaller dose to cause a specific effect. Consequently, potency is related to the affinity of a drug.

Figure 2.2 illustrates that when equal concentrations of two drugs are in equilibrium with the same receptor population (square indentations), the drug with the greater affinity (Drug A) will make a greater number of effective bindings at any given instant. The result is that Drug A is more potent, and a lower concentration of Drug A is required to produce the same level of pharmacologic effect as that produced by Drug B.

Agonists

Drugs that have direct stimulatory effects on receptors are called **agonists**. A strong agonist produces a significant physiologic response when only a relatively small number of receptors are occupied. The ability of an agonist to interact with a receptor and initiate a response is the function of its **intrinsic activity**. Using these terms in an example, when a small dose of a drug (agonist) produces a desired effect, the drug has good *affinity* and good *intrinsic activity*. A weak agonist must be bound to many more receptors to produce the same effect, so a much larger dose of a weak agonist will be required to produce the desired effect—i.e., the drug has lower affinity and/or lower intrinsic activity. A partial agonist has affinity for the receptor, but very low intrinsic activity. Therefore, it will never produce the same effect as a strong agonist or a weak agonist, even when all receptors are occupied. This can be illustrated with the log dose–response of three different drugs with affinity to the same receptors, as shown in Figure 2-3, where a low dose of Drug A (strong agonist) produces a full effect, Drug B (weak agonist) must have a higher dose to reach that effect, and Drug C (partial agonist) never reaches the effect produced by Drugs A or B. An example of the above concept would be the use of 5 mg of morphine to relieve strong pain, compared with 50 mg of meperidine (Demerol) to relieve the same degree of pain,

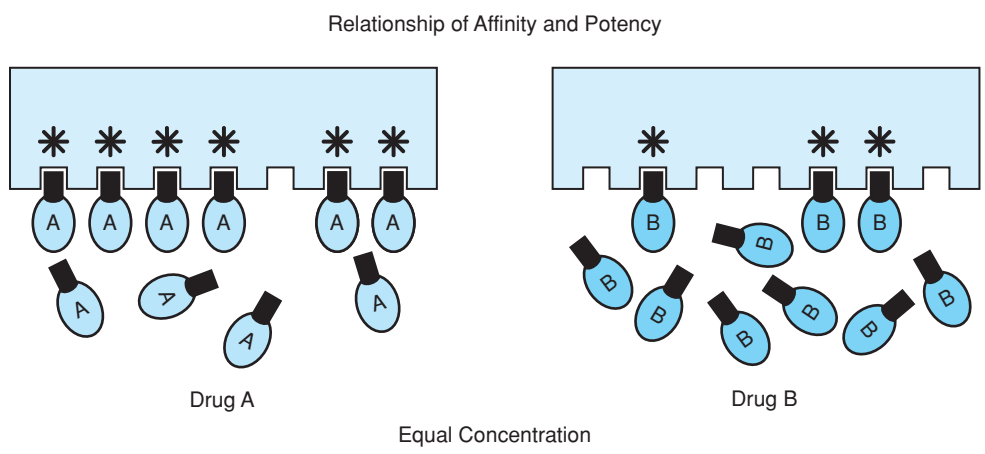

Figure 2-2 Relationship between Drug Affinity to Receptor and Potency. When equal concentrations of two drugs are in equilibrium with the same receptor population (square indentations), the drug with the greater affinity (Drug A) will make a greater number of effective bindings at any given instant. Thus, a lower concentration of Drug A will be required to produce the same level of pharmacologic effect as that produced by Drug B.

and further compared with 65 mg of propoxyphene (Darvon), which will not relieve strong pain, no matter how high the dose given. Thus the affinity and the intrinsic activity of an agonist determine efficacy of a drug.

Efficacy

Efficacy is the maximum response produced by a drug. It is a state of optimal receptor occupancy by the drug molecules; additional doses would produce no further beneficial effect. This concept is often referred to as the **ceiling dose**. As seen with the affinity of a drug for a particular receptor, the efficacy of a drug is also related to its chemical structure. This concept is referred to as the *intrinsic activity relationship*. The quantification of a specific response elicited by a drug given in a range of doses (5 mg, 10 mg, 50 mg, etc.) is called the graded dose–response relationship. This relationship is expressed visually and mathematically with a dose–response curve. The curve is established by placing the logarithmic value for the dose (or log dose) on the x-axis and the quantified response on the y-axis (Fig. 2-4). The upper plateau of the dose–response curve represents the efficacy or the maximal effect of a drug associated with a specific dose. A good example of this concept is acetaminophen, which has a ceiling dose of about 1,000 mg for pain relief. Taking 2,000 mg in a single dose will not produce greater pain relief and may lead to toxicity (overdose). The lowest dose of a drug that will produce a measurable response is called the *threshold dose*. The dose range of acetaminophen for pain relief is 325 mg to 1,000 mg. Therefore, 325 mg would be the threshold dose of acetaminophen.

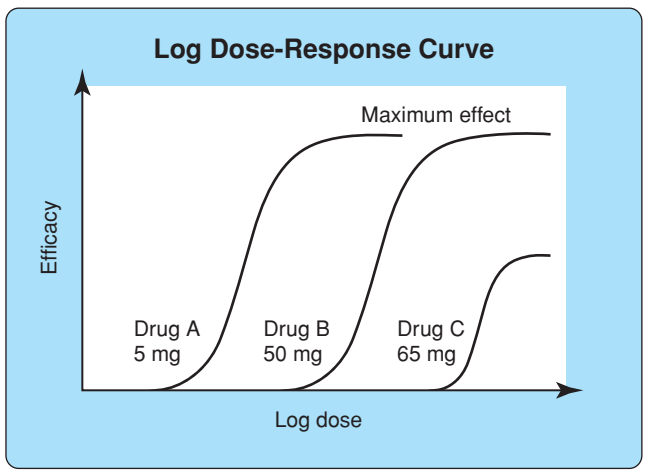

Figure 2-3 Log Dose-Response Curve Illustrating Three Different Drugs (a Strong Agonist, a Weak Agonist, and a Partial Agonist) with Affinity for the Same Receptors. Drugs A and B have the same efficacy, but it takes more of Drug B to produce the effect. Drug C does not have the same efficacy of Drugs A and B, even at a higher dose.

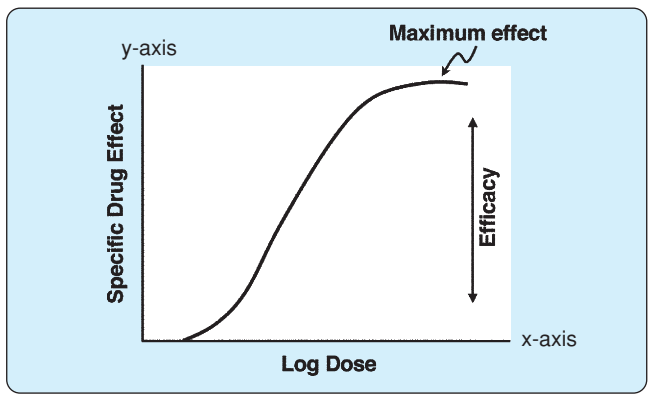

Figure 2-4 Log Dose Curve for Efficacy. A drug's efficacy, or maximum effect, is represented by the upper plateau of the dose–response curve.

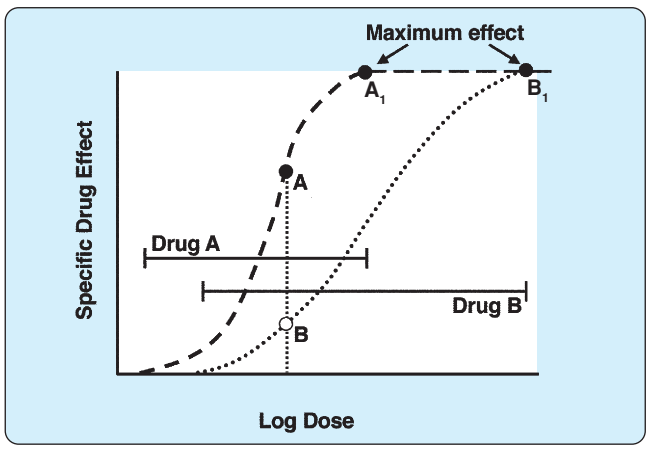

Figure 2-5 Log Dose of Potency and Efficacy. This shows two drugs with same efficacy (A, B), but different potency (A, B). Potency relates to two or more drugs by comparing the doses required to produce a given effect.

Potency

Potency is defined as the relative pharmacologic activity of a dose of a compound compared with a dose of a different agent producing the same effect. The concept provides a mechanism by which to compare the ability of two or more drugs, with affinity for the same receptor, to produce a given effect as a function of dose. Potency *is related to the affinity of a drug to its receptor, whereas* efficacy *is related to the intrinsic activity of that drug once a drug–receptor complex is formed.* It is determined by the relative position of the dose-response curve along the dose axis as illustrated in Figure 2-5. Note that for the maximum effect, the dose of Drug A is smaller than that required for Drug B, illustrating that Drug A is more potent than Drug B, yet they have the same efficacy. An example is the ability of two nonsteroidal agents (ketorolac and ibuprofen) to relieve dental pain. Ketorolac at 20 mg relieves dental pain to the same degree as 400 mg of ibuprofen. Therefore, ketorolac has greater potency and equal efficacy.

Antagonists

An **antagonist** is a drug that interferes with the action of an agonist, but has no effect in the absence of an agonist. Antagonists can be classified as receptor or nonreceptor antagonists.

Receptor Antagonists

Receptor antagonists can bind at the active site (called agonist binding domain) and prevent the binding of the agonist, or they may bind to an adjacent site (overlapping with the agonist binding domain) and prevent the conformational change required for receptor activation by an agonist. Receptor antagonism can be either reversible (competitive) or irreversible (noncompetitive):

- A competitive antagonist binds reversibly to the active site of the agonist and maintains the receptor in its inactive conformation. In other words, it has affinity for a receptor but no efficacy (i.e., it cannot cause an effect). It competes with the agonist for the receptor, and the outcome depends on the degree of affinity of the competitive antagonist compared with the agonist. A competitive antagonist forms a reversible drug-receptor complex, which can be overcome by increasing the dose of the agonist. Consequently, the inhibition is surmountable. In effect, the presence of a competitive antagonist reduces the potency of the agonist. A practical example of this type of antagonism with relevance to dentistry is the reversal of respiratory depression caused by excessive doses of an opioid analgesic (agonist) with naloxone, an opioid antagonist.
- A noncompetitive antagonist binds either to the active site or to an allosteric (adjacent) site of the receptor. It binds to the active site either covalently or with very high affinity, both of which are effectively irreversible. An allosteric noncompetitive antagonist prevents the receptor from being activated, even when the agonist is bound to the active site. In effect, the presence of a noncompetitive antagonist reduces the efficacy of the agonist. Aspirin is a practical example of a noncompetitive antagonist. It irreversibly affects cyclooxygenase, the enzyme responsible for the process that causes platelets to clump together and produce a clot. This reduces clotting and increases the bleeding time. Normal platelet function can be reestablished only by the generation of new platelets in the bone marrow.

Nonreceptor Antagonists

A nonreceptor antagonist may be either a chemical or physiologic antagonist.

Chemical Antagonist

A chemical antagonist may either bind a molecule at some point in the activation pathway or directly inhibit the agonist. A practical example of this type of antagonism with relevance to dentistry is the one produced by local anesthetic agents. They block sodium channels in the activation pathway of chemicals that promote depolarization of nerve fibers. By blocking depolarization, information about tissue damage (in the form of electrical impulses) is not transmitted to the cortex, and the patient will not experience pain.

Physiologic Antagonist

A physiologic antagonist activates pathways that oppose the action of the agonist. An example of this type of antagonism is reflected in the action of epinephrine on blood vessels (vasoconstriction) following an allergic reaction (anaphylaxis) and histamine release. The effect of epinephrine overcomes the effect of histamine (vasodilation) on the same blood vessel, and the vessel becomes constricted.

Mixed Agonist–Antagonists

Mixed agonist–antagonists are drugs that have both agonistic and antagonistic properties. When used alone, such a drug behaves as an agonist. However, when another drug that competes for the same receptor site is administered concurrently,

the agonist–antagonist will also act as an antagonist. A practical example of an agonist–antagonist is pentazocine, an opioid analgesic; when used alone, it interacts with its opioid receptor to produce analgesia, but it antagonizes the action of other opioid agonists.

Receptor Classification

Receptors are classified according to the type of drug they interact with or according to the specific physiologic response produced by the drug–receptor complex. Receptor sites may also be subclassified by evaluating the effects of different agonists in the presence of a given antagonist. The previous example of using epinephrine to counteract the effects of histamine illustrates this concept. Earlier in this chapter, it was noted that drugs can interact with different receptors. Epinephrine can bind to receptors in the bronchioles of the lungs to cause bronchodilation, and it can bind to different receptors on blood vessels to cause vasoconstriction; hence, one drug interacts with two different receptors and causes two different actions.

Similarly, receptors and receptor subtypes exist for many other agents. The number of any given receptor types or subtypes on a cell also may vary. Certain disease states or drugs taken long term and/or in large doses may increase (up-regulate) or decrease (down-regulate) the number of receptors and provide a degree of adaptability in the face of changing physiologic events. Developing tolerance to a drug so the former dose no longer causes an adequate effect and a higher dose is needed to cause the effect illustrates this concept.

Toxicity

Any drug at a high-enough concentration can produce a toxic effect (overdose). In the context of this discussion, **toxicity** refers to undesirable effects associated with the administration of *therapeutic* dosages of drugs. These adverse effects may be:

- An exaggeration of direct effects seen at higher doses. For example, barbiturates may produce sedation, drowsiness, and reduced rate of respiration at therapeutic levels (direct effect), but cause death (exaggerated effect of respiratory depression) at increased dose levels. This is an extension of the intended therapeutic effect of central nervous system (CNS) depression.
- Multiple concurrent adverse, or side, effects occurring at therapeutic dosage levels. For example, the administration of certain antihistamines for hay fever, intended to antagonize histamine action at H_1-histaminic receptors in the respiratory system, can also bind to H_3-histaminic receptors in the CNS and cause drowsiness. In this case, the drowsiness is a concurrent side effect, not an intended response. ADEs are discussed in detail in Chapter 5.

Median Effective Dose or Lethal Dose

The dose of a drug required to produce a desired response in 50% of the individuals within the same population is the median effective dose (ED50), as shown in Figure 2-6. If death is the measured end point, the ED50 is expressed as the median lethal dose (LD50). A steep dose–response curve indicates a narrow dosage range between minimal and maximal effects. Consequently, the risk for toxic or even lethal dosage levels can be greater because of the narrower dosage range. Similarly, the median toxic dose (TD50) is the dose of a drug that produces a specific toxic response in 50% of the individuals within the same population. These concepts are used during drug development to determine the safety of doses. Fortunately, laboratory animals are used to determine the LD50 in drug research centers! The relative safety of a drug for humans is extrapolated from animal data and clinical data during new drug's clinical trials.

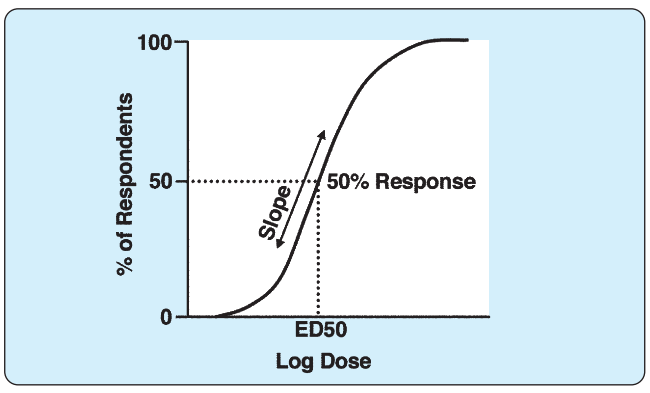

Figure 2-6 Effective Dose in 50% of Subjects.

Therapeutic Index

When evaluating potential therapeutic agents, dose–response curves provide valuable information relative to their safety. The margin of safety of a drug is expressed by the Therapeutic Index (TI). For example, if the slope of the dose–response curve is steep, it indicates a narrow range between dosages that produce minimal and maximal effects, or between a safe dose and a toxic dose (Fig. 2-7). Using the dose–response

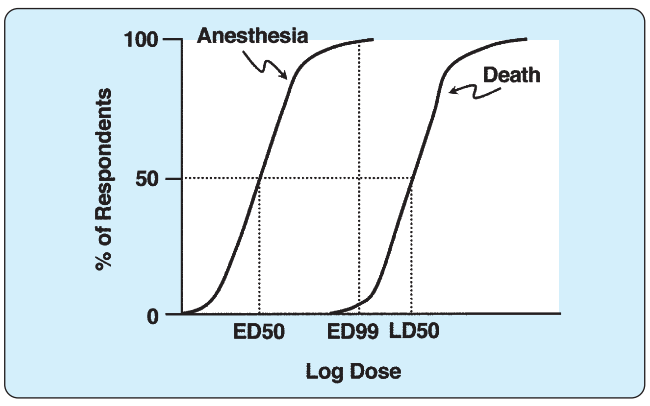

Figure 2-7 ED50 and LD50. The margin of safety of a drug may be expressed by its therapeutic index, the actual ratio of LD50 and ED50, or by comparing the 99% dose–response curve for the therapeutic effect with the curve for the toxic effect.

curve, the risk of a toxic effect may also be calculated and expressed as the drug's TI. The TI is the actual ratio of the LD50 and ED50 (LD50/ED50). The same concept applies to any toxic effect in that the higher the numerical value of this ratio (or the higher the TI), the safer the drug. The margin of safety also may be established by comparing 99% dose–response curve for the therapeutic effect to the curve for a toxic or lethal effect (Fig. 2-7). The farther apart these two curves are, the wider the margin of safety.

Self-Study Review

3. Describe the steps a drug follows after being delivered to body cells.
4. List seven features of receptors.
5. Describe the features of the four types of chemical bonds between a drug molecule and the complementary receptor. Which type is most common in drug–receptor complexes?
6. Define the roles of *affinity* and *intrinsic activity* in drug action. Which is related to potency?
7. What is the difference in the effect of a weak agonist when compared to a partial agonist? Identify both in a log dose curve illustration.
8. Describe the relationship of *efficacy* and the *ceiling dose* concept.
9. Compare the *ceiling dose* with the *threshold dose*.
10. Define *ED50* and *LD50*.
11. What is the *therapeutic index* (TI), and how is it used? What is the formula to determine the TI, and what is the significance of a high number?

PHARMACOKINETICS

Pharmacokinetics deals with the movement of drugs through the body. Therefore, pharmacokinetics relates to a drug's absorption; distribution in the body, including to the site of action; metabolism to prepare the drug for removal from the body; and excretion, where the drug is ultimately removed from the body and its effect is terminated. As drugs progress through these various phases within the body to be delivered to their sites of action and, ultimately, to be eliminated from the body, they must pass through biologic barriers (e.g., cell walls, blood vessels) in various tissues.

Passage across Biologic Membranes

To produce an effect, most drugs must pass through cell membranes to gain access to their receptor(s). Passage through biologic membranes affects the amount of the drug that reaches the site of action and influences the time it takes the drug to get to the site of action. The physicochemical properties that influence the movement of drug molecules across biologic membranes are molecular size, lipid solubility, and the degree of ionization (a function of the pH of the environment and pK_a of the drug). In an acid environment, an acidic drug exists mainly in the nonionized form. Nonionized molecules are lipid soluble and pass through biologic membranes easily. In the same acid environment, a basic drug exists mainly in the ionized form. Ionized drugs are water soluble and must pass through water pores of the biologic membrane or be transported through the membrane by specialized transport mechanisms. These movements are accomplished in a variety of ways.

Filtration

Small, water-soluble substances may pass through aqueous channels or water pores in cell membranes by a process known as *filtration*. Larger water-soluble molecules are in the ionized form and are blocked from moving through small water pore openings. They must rely on specialized transport mechanisms (discussed below) to move through the biologic membrane.

Passive Diffusion

Most drugs are weak acids or weak bases, and drug molecules are too large to pass through most aqueous channels. However, as a function of their lipid solubility, the nonpolar (nonionized) forms of these drugs readily can cross biologic membranes by *passive diffusion* along a concentration gradient (from high concentration to low concentration) until equilibrium is reached across the membrane. Therefore, nonionized lipid-soluble molecules can easily pass through biologic membranes.

Specialized Transport Mechanisms

Large ionized, water-soluble drug molecules require more complex processes to cross biologic membranes. These include facilitated diffusion and active transport mechanisms.

Facilitated Diffusion

The concept of *facilitated diffusion* assumes that the drug forms a complex with a component of the cell membrane on one side. The complex is then carried through the membrane, the drug is released, and the carrier returns to the original surface to repeat the process. Vitamins are known to participate in facilitated diffusion, furnishing the energy to carry large, water-soluble drug molecules across membranes. Facilitated diffusion does not require energy and does not proceed against a concentration gradient. One example is the movement of glucose across cell membranes; it is thought to be *facilitated* by insulin. Another example is that some water-insoluble substances, such as fat-soluble vitamins (vitamins A, D, E, and K), are engulfed by the cell membrane and are released unchanged in the cytoplasm by a process known as *endocytosis*, a form of facilitated diffusion.

Active Transport

Active transport is the movement of drug molecules across biologic membranes against both a concentration and an electrochemical gradient. This activity requires energy. The

BOX 2-2. Factors That Influence Absorption

- Degree of ionization
- Formulation (liquid or solid)
- Concentration
- Circulation to area
- Area of absorptive surface
- Route of administration

transfer of some drugs through biologic membranes in the kidneys and intestines relies on an active transport mechanism.

Absorption

Regardless of the process by which a drug moves through biologic membranes, it first must be dissolved in the fluids encircling the cells. For this reason, a drug must have some degree of both lipid and water solubility—water solubility to get it to the cell, and lipid solubility to get it through the cell membrane. Factors that influence the rate of absorption of drugs include

- the degree of ionization and pH of tissues;
- the formulation of the drug (liquid or solid);
- the drug's concentration (the greater the concentration of a drug, the faster the rate of absorption);
- circulation to the area (the greater the blood flow to tissue, the faster the rate of absorption);
- the area of absorptive surface (the greater the area to which the drug is exposed, the faster the rate of absorption);
- the route of administration (ROA; Box 2-2).

Degree of Ionization

As mentioned earlier, the ionized form of a drug tends to be more water soluble, and nonionized forms tend to be more lipid soluble. Biologic membranes are composed of

- layers of lipid material and proteins that allow for passage of lipid-soluble molecules;
- small openings or water pores that allow for the passage of water-soluble molecules.

Consequently, the nonpolar, nonionized form of a drug will diffuse across biologic membranes more readily than its polar, ionized form. This phenomenon has clinical implications. For example, if the patient is taking an antacid, which increases the pH of the stomach and upper small intestine, the administration of a weak acid (such as aspirin) may result in increased ionization and poor absorption of the aspirin, giving less-than-optimal pain relief.

pK_a and Ionization

The pH of the area affects drugs' degrees of ionization. Drugs will be ionized or nonionized primarily as a function of their pK_a and the pH of the environment. The *pK_a* is defined as that pH at which a drug is 50% ionized and 50% nonionized. For example, in the highly acidic environment of the stomach, drugs with a low pK_a will exist primarily in their nonionized forms (weak acids in an acidic environment). Ionization occurs when different charges (acids mixed with bases) exist together. Similarly, in the small intestine where the pH is more basic, the same drugs with a low pK_a will be more ionized.

Formulation of Drug

The form in which a drug is administered can affect the rate of absorption. To illustrate this point, let us consider the form in which a drug is administered to a patient. Aqueous formulations of drugs (such as Alka-Seltzer) do not require time to dissolve after oral administration and, therefore, will cover a wider area of the absorptive surface in the gastrointestinal (GI) tract much faster than a tablet, which must go through stages of a dissolving process. In general, the liquid formulation results in an increased rate of absorption of the drug (and more rapid onset of action) than solid formulations of the same drug.

Enteric Coating

Drugs can be modified in various ways that result in delayed absorption. Enteric-coated formulations delay dissolution of tablets until they have moved from the stomach into the upper small intestine, thereby reducing adverse gastric side effects.

Other Modifications

A strategy involved in formulating intraoral topical agents is to combine them with an insoluble agent. This strategy prevents agents applied to the oral mucosa from dissolving in saliva and being removed (e.g., corticosteroid mixed with an insoluble agent [Kenalog in Orabase]). New doseforms and delivery systems are being developed every day. For example, in 2006 the Food and Drug Administration (FDA) approved the very first inhaled insulin, a drug formerly only administered by injection.

Drug Concentration

Highly concentrated drugs are absorbed faster than the same drugs in low concentrations. Absorption of drugs through skin and mucosa by passive diffusion is proportional to the drugs' concentration and lipid solubility. This concept is discussed further when ROAs are presented.

Circulation to Area

The greater the blood flow to tissue, the faster the rate of absorption. Organs with significant blood flow include the heart, the GI tract, and the liver. This concept is illustrated in the discussion related to ROAs.

Area of Absorptive Surface

The upper small intestine has a large surface area and is the site of absorption for most orally administered drugs. Drugs

BOX 2-3. Routes of Administration

Enteral
- oral
- rectal

Parenteral
- various injections
- inhalation
- topical (sublingual, drops, patches, intrasulcus)

must pass through the wall of the small intestine and be absorbed into the bloodstream to be distributed to the body tissues and their receptors.

Routes of Administration

ROAs are classified as **enteral** or **parenteral**. Enteric drugs are placed directly into the GI tract by oral or rectal administration and must pass through the liver before distribution to the site of action. This reduces the bioavailability of some drugs by a process called *first-pass metabolism*. Parenteral drugs bypass the GI tract and include various injection, inhalation, and topical routes, such as direct application to the skin or mucosa and sublingual administration (Box 2-3).

Enteral

The oral route is the safest, most common, most convenient, and most economical method of drug administration. It is also the most unpredictable route because many factors can affect the rate of absorption between the GI tract (Box 2-4).

The rectal route, which is a form of enteric drug administration, may be useful in young children who have trouble swallowing tablet doseforms, and for unconscious or vomiting patients. However, absorption with this route is unpredictable. When a drug is administered enterally, its rate of absorption into the systemic circulation is influenced by

- the inherent characteristics of the drug (lipid soluble, water soluble, molecular weight, pK_a of the drug);
- the pH of the GI tract, which can change the ionization characteristics of a drug molecule;
- the presence of food in the stomach, which slows the rate of absorption because the drug competes for absorption with food components in the GI mucosa;
- gastric motility, which can move the drug through the intestines so fast that it does not have time for complete absorption;
- the degree of splanchnic blood flow (blood flow through intestinal viscera)—i.e., the intestinal viscera have a large surface area and significant vascularity;
- patient compliance in taking the prescribed drug regimen.

BOX 2-4. Features of the Oral Route

- Safest route
- Most common route
- Most convenient route
- Most economical route
- Most unpredictable route

First-Pass Effect

The close anatomical relationship between the liver and the GI tract, and the abundant blood supply of these organs, has important effects on the bioavailability of some drugs. Because the liver is situated between enteric sites of absorption and the systemic circulation, it can profoundly influence the amount of drug in circulation when the drug is administered orally—an action that has been described as the *first-pass effect*. A drug given orally is absorbed mainly in the upper small intestine and enters the splanchnic circulation supplying that mucosa. Rectally administered drugs are absorbed via the lower intestinal mucosa. Within the circulation, the drug molecules attach to plasma proteins, called *albumin*. Drugs bind at various ratios to plasma proteins. When the drug binds at a 90:10 ratio, this means that 90% of the molecules are bound to albumin and 10% exist in an unbound form. Albumin serves to carry the molecule in the circulation to be distributed to the site of action. The protein-bound drug is protected from metabolism as the blood moves through the liver. Drugs that are removed efficiently from the liver during "first pass" will have a low bioavailability. Consequently, only that fraction of the drug that reaches the systemic circulation after first-pass metabolism is bioavailable to its receptor site.

Parenteral

Parenteral drugs bypass the GI tract and include various injectable routes, such as intravenous (IV), subcutaneous (SC), intramuscular (IM); inhalation; and topical routes. This ROA often is used for agents susceptible to degradation in the GI tract and those adversely affected by hepatic first-pass metabolism.

Intravenous Administration

The IV route provides for accurate and immediate deposition of drugs into the circulation, bypassing the absorption phase. The effect is rapid, with almost immediate onset of action. This route is considered to be the most predictable ROA. The IV route often is used in emergency situations. The dose of injected drugs can be adjusted to the patient's response; however, once a drug is injected, there is no recall. This makes the IV route less safe than the oral route, where absorption can be manipulated. Sterile formulations of soluble substances and an aseptic technique are required. Local irritation, often referred to as *injection site reactions*, and damage to the inner blood vessel wall can result in thromboembolic complications (Box 2-5).

BOX 2-5. Features of IV Route

- Bypasses absorption, causing immediate effect
- Most predictable route
- Used in emergency situations
- Less safe than oral route
- Injection site reactions are possible

Subcutaneous Injection

Following SC injection, a drug's rate of absorption into the bloodstream is slow and sufficiently constant to provide a sustained effect. The incorporation of a vasoconstrictor into a drug formulation, such as in a local anesthetic agent used in dentistry, can further retard the rate of absorption. Local tissue irritation characterized by sloughing, necrosis, and severe pain are potential complications. Insulin is administered by SC injection.

Intramuscular Injection

The IM injection allows for rapid absorption of aqueous solutions into the bloodstream. Oily or other nonaqueous formulations may provide for slow, constant absorption. This is another example that illustrates the role of drug formulation in the drug's absorption. Substances considered too irritating to administer by IV and SC routes in some instances may be given intramuscularly. The IM injection is usually given in the deltoid or gluteal muscle.

Other Parenteral-Injectable Routes

Intradermal, intrathecal, and intraperitoneal routes are other types of parenteral ROAs given by injection. The tuberculosis skin test uses the intradermal route.

Inhalation

Inhaled drugs are considered to be delivered topically—the drug is inhaled and attaches to pulmonary tissues, where absorption occurs. This direct topical absorption also has an advantage over enteric administration because it circumvents the metabolic first-pass breakdown in the liver. The large pulmonary absorptive surface in the lungs allows for rapid access of gaseous, volatile agents to the circulation. Drugs administered by inhalation may act locally or they may cross the alveoli, enter the circulation, and act at the appropriate receptor site. Concentration is controlled at the alveolar level because most of these drugs are exhaled immediately. Asthma often is treated with inhaled drugs.

Topical Application

This ROA is used to apply drugs directly to tissue. It includes those placed sublingually, supplied via patches, inserted by drops in the eyes or ears, or placed within the gingival sulcus. Absorption of drugs through skin and mucosa by passive diffusion is proportional to their concentration and lipid solubility. Drugs' concentrations may be increased for topical products because the skin is a barrier to absorption. Warnings related to applying topical anesthetic agents include

- limiting the area of application in order to reduce the absorption of these concentrated local anesthetic agents;
- avoiding placement of an occlusive dressing;
- avoiding application over abraded areas or where skin is not intact;
- considering the allergic potential.

Systemic adverse effects can occur if occlusive dressings are placed over the drug or if the drug is applied to abraded or inflamed areas. In these situations, the concentrated drug is absorbed more easily, leading to overdose. For unexplained reasons, the topical ROA is more likely to cause allergic drug reactions.

Sublingual

Topical application of a drug placed under the tongue is absorbed into the lingual venous system through nonkeratinized mucosa. Because venous drainage from the mouth flows into the superior vena cava, and because of the rich vascularity of the oral area, sublingually administered drugs enter the circulation quickly. This direct absorption also has an advantage over enteric administration because it circumvents the metabolic first-pass breakdown in the liver. Absorption of many drugs is immediate, and this ROA is often used when a rapid response is needed, such as when nitroglycerin is used to treat anginal pain.

Transdermal Patch

Transdermal delivery systems are designed to provide for a slow, continued release of medication. The patch is applied to the skin, eliminating the need for multiple doses of the drug. Most patches consist of several layers: An adhesive to stick to the skin, a membrane to control the rate of drug release, a reservoir where the drug is placed, and a backing that keeps the drug from evaporating. Common adverse effects with patches include local erythema and irritation. These are minimized by rotating the location of the patch when it is reapplied. Patches are changed daily, every few days, or weekly, depending on the specific drug.

Other Topical Routes

The recent introduction of locally applied antimicrobial agents into the gingival sulcus utilizes a polymer-based formulation. This keeps the antimicrobial product from leaving the area and increases the duration of the effect. This is discussed in detail in Chapter 9.

Self-Study Review

12. Describe the stages a drug goes through from the time of administration to the elimination of the drug.
13. Compare the features of ionized molecules with those of nonionized forms as the molecule moves through tissues to cause an effect.

14. What is the role of specialized transport mechanisms in moving drug molecules across the membrane? Give an example of a specialized transport vehicle.
15. Identify three factors that affect the absorption of a drug.
16. From where in the GI tract are most drugs absorbed?
17. Describe how taking a drug that alters the pH of the stomach can affect the absorption of a drug.
18. Describe two means to alter a drug's absorption through modifying the formulation.
19. Identify features of enteral and parenteral ROAs.
20. How does food in the stomach affect drug absorption?
21. Describe how the first-pass effect influences the onset of drug action.
22. List parenteral routes and identify the route used in most emergency situations.
23. What is the most predictable ROA?
24. What are the precautions to follow when using topical agents?

Distribution of Drugs

Drug absorption is a prerequisite for establishing adequate plasma levels. Next, drugs must reach their target organ(s) in therapeutic concentrations to produce effects. Drug distribution is achieved primarily through the circulatory system. In most cases, the therapeutic effect of a drug in tissues correlates well with the concentration in the circulation.

Tissues and organs vary greatly in their abilities to absorb various drugs and in the proportion of systemic blood flow that they receive. Highly perfused organs, such as the liver, kidney, heart, and CNS, tend to receive the drug within minutes of absorption. Muscles, most viscera, skin, and fat may require a longer amount of time before equilibrium is achieved. When the patient has excess body fat, those drugs that tend to accumulate in fat are slowly released from these fat stores, which can result in high blood levels when multiple doses of the drug are taken. *Redistribution* may affect the duration of a drug effect. For example, if a drug of high lipid solubility accumulates rapidly in the brain and then is redistributed to other tissues, the drug effects in the brain are reduced. The distribution of drugs—their ability to cross biologic membranes and leave the vascular compartment, and ultimately to accumulate in tissues and at their sites of action—relies on the same factors that affect absorption (i.e., molecular weight, concentration in plasma, lipid solubility, pH of the vascular compartment, and pK_a of the drug). In addition, in the circulation, many drugs are bound to plasma proteins and, therefore, are unable to bind to therapeutic receptors.

Plasma Protein Binding

The capacity of tissues (i.e., muscle and fat) to bind and store drugs increases the tendency of drugs to leave the vascular compartment, but this tendency is counteracted to some extent by plasma protein (albumin) binding of drugs. Plasma protein binding is a nonselective process. Many drugs compete with each other and with endogenous substances for albumin-binding sites. Plasma protein binding tends to reduce the availability of drugs for diffusion into target organs because, in general, *only the free or unbound drug is capable of crossing biologic membranes.* Because highly protein-bound drugs cannot leave the circulation, their rate of metabolism and excretion also is reduced. The therapeutic consequence of this phenomenon is taken into consideration when drug dosages are determined. Highly protein-bound drugs, such as aspirin, are also an important mechanism for some drug–drug interactions. When administered concurrently with another drug, highly bound drugs will compete for albumin-binding sites, and the drug with the greatest affinity (e.g., aspirin) will tend to "bump" the other drug off the albumin receptor, effectively increasing its free, unbound form. The increased blood level of the free drug molecules can lead to increased therapeutic and/or toxic effects, even though the drug was administered in therapeutic doses.

Blood–Brain Barrier

The distribution of drugs to the CNS and cerebrospinal fluid is restricted by the blood–brain barrier. However, cerebral blood flow is the only limiting factor associated with highly lipid-soluble, uncharged (nonpolar) drugs.

Placenta as a Barrier

In a pregnant woman, drugs pass across the placenta by simple diffusion (once again, as a function of their concentration in plasma, molecular weight, lipid solubility, pH of the vascular compartment, and their pK_a). The result is that the fetus becomes medicated along with the mother. This is the reason for the restriction of drugs, except prenatal vitamins, during pregnancy.

Metabolism

Rarely does a drug enter the body and leave it without modification. A number of organs (liver, kidneys, GI tract, skin, lungs) are capable of metabolizing drugs using a variety of enzymatic reactions. However, the liver contains the greatest diversity and quantity of metabolic enzymes, and the majority of drug metabolism occurs there. The liver preferentially metabolizes highly lipophilic drugs, rendering the drugs in their metabolite state and inactive, although some drug metabolites maintain a degree of pharmacologic activity. The kidneys easily eliminate the metabolite form, which is ionized (water soluble). These enzymatic reactions, classified as Phase I and Phase II processes, are collectively referred to as *biotransformation* and can alter drugs in four different ways:

1. Convert an active drug to an inactive drug
2. Convert an active drug to an active or toxic metabolite
3. Convert an inactive drug to an active drug
4. Convert an unexcretable (more lipophilic) drug into an excretable (more hydrophilic) metabolite

Phase I Reactions

A drug's chemical structure is modified through oxidation, reduction, or hydrolysis, which require very little energy. The most commonly used pathway is the hepatic microsomal cytochrome P450 (CYP450) enzyme system, which oxidizes lipophilic molecules. Some drugs are biotransformed by CYP450-independent oxidation, hydrolysis, or reduction. These reactions are not limited to the hepatic endoplasmic reticulum. A practical example is the hydrolysis of ester and amide local anesthetic agents and the oxidation of epinephrine, which may be hydrolyzed or oxidized, respectively, at their sites of administration within tissues, thereby limiting their systemic toxicity.

Phase II Reactions

The chemical structure of a drug is modified by conjugation to a large polar endogenous molecule. Some metabolites of Phase I reactions can undergo additional Phase II metabolism. In contrast to a Phase I reaction, Phase II biotransformation almost always results in inactivation of the parent drug. Virtually all Phase II metabolites are pharmacologically inactive.

Cytochrome P450 Induction and Inhibition

The CYP450 enzyme system can be induced to increase drug metabolism or inhibited to reduce the rate of a drug's metabolism, and it is responsible for many adverse drug–drug interactions. For example, chronic ethanol toxicity induces the metabolism of barbiturates, whereas acute ethanol toxicity inhibits the metabolism of barbiturates. Alcohol and barbiturates are additive CNS depressants. These potential drug–drug interactions are the basis for the "DO NOT DRINK ALCOHOL WITH THIS DRUG" warning on a barbiturate prescription. Other drugs (erythromycin, omeprazole, cimetidine, ciprofloxacin) inhibit CYP450 enzymes and decrease the metabolism of many other drugs. This increases the drugs' blood levels and effectively increases their therapeutic and/or toxic effects.

Excretion

Renal excretion is the most common and important mechanism of *drug elimination* from the body. Biotransformation prepares the molecule, and the kidney eliminates it via urination. Consequently, following biotransformation, drugs are intrinsically hydrophilic (ionized) and are excreted more readily than lipophilic (nonionized) compounds. A relatively small number of drugs are excreted primarily in the GI tract via the bile, and only minor quantities are excreted through respiratory (exhalation) and dermal routes (perspiration). Lactation is responsible for minor amounts of drug excretion.

Glomerular Filtration, Tubular Secretion, and Reabsorption from the Tubular Lumen

Renal blood flow represents about 25% of total systemic circulation. Therefore, afferent arterioles in the kidney constantly bring free, unbound, and plasma-protein–bound drugs into the glomeruli. The glomerulus is the primary location for drug elimination to occur. Typically, only the free drug is filtered by the glomeruli. A drug may be filtered at the renal glomerulus or secreted into the proximal tubule, and, subsequently, either may be reabsorbed into the tubular lumen and returned to the circulation or may be excreted into the urine where, via urination, it is removed from the body (Fig. 2-8).

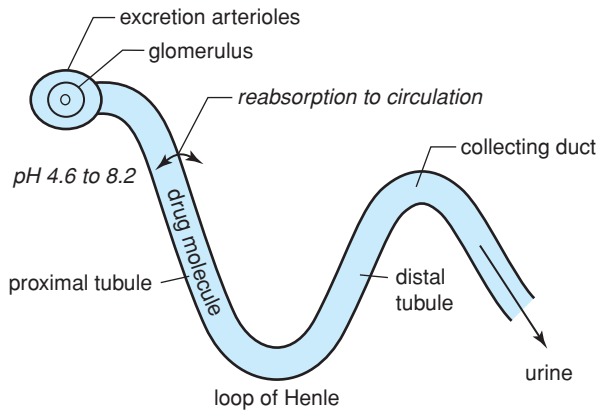

Figure 2-8 Elimination of a Drug in the Kidney

The mechanism includes these processes:

- Glomerular filtration depends on renal blood flow, glomerular filtration rate, and plasma protein binding. Reduced renal blood flow, reduced glomerular filtration rate, and increased plasma protein binding all contribute to reduced drug elimination.
- Active tubular secretion facilitates the movement of the drug from the bloodstream into the renal tubular fluid by a nonselective carrier system for organic ions. Some drugs, such as penicillin, aspirin, and probenecid, are actively secreted at the proximal tubule and compete with each other for the same secretory transport mechanisms.
- Passive tubular reabsorption of nonionized drugs results in net passive reabsorption. Although reabsorption can decrease the elimination rate of drugs, many drugs exhibit pH trapping in the distal tubules and are efficiently eliminated in the urine. When drugs need to be retained in the body, the pH of the urine can be manipulated. By alkalinizing the urine (via administration of sodium bicarbonate), the plasma level of weak acids can be decreased; alternatively, by acidifying the urine (via administration of ammonium chloride), the plasma level of weak bases can be decreased.

In summary, drug molecules are removed from the circulation into renal proximal tubules by the glomeruli, or they may be secreted into renal proximal tubules from peritubular capillaries and, if not reabsorbed in the collecting tubules of the kidney, excreted in the urine. Although the kidneys excrete most drugs via glomerular filtration, there are other mechanisms whereby the body eliminates drugs.

Enterohepatic Recirculation

Some metabolites formed in the liver are excreted via the bile into the intestinal tract to be eliminated in the feces. If these metabolites are subsequently hydrolyzed and

reabsorbed from the gut (a process called *enterohepatic recirculation*), drug action can be re-established. One could say this is the body's contribution to recycling! Enterohepatic recirculation can result in a significant delay in the elimination of drugs from the body.

Exhalation

Pulmonary excretion is important mainly for the elimination of anesthetic gases and vapors.

Other Mechanisms

Drugs can be excreted in lactation and are potential sources of unwanted pharmacologic effects in nursing infants. Other routes, such as saliva, sweat, and tears, are quantitatively unimportant.

Half-Life of a Drug

The removal of most drugs from the body follows exponential or first-order kinetics. Assuming a relatively uniform distribution of a drug within the body (considered to be a single compartment), first-order kinetics implies that a constant fraction (%) of the drug is eliminated per unit time. The rate of exponential kinetics may be expressed by its constant (k), the fractional change per unit time, or its **half-life** (expressed as $t_{1/2}$), which is the time required for the plasma concentration of a drug to decrease by 50%. This occurs in several ways, such as

- the distribution half-life, which represents the rapid decline in plasma–drug concentration as 50% of the drug is distributed throughout the body;
- the elimination half-life, which reflects the time required to excrete 50% of the drug from the system.

Following the administration of multiple therapeutic dosages of a drug at time intervals equal to or shorter than the drug's half-life, a plateau level of drug accumulates. This is called **steady-state concentration** and involves over four half-lives. For example, if the $t_{1/2}$ of a drug is 1 hour, then it will require the administration of four therapeutic doses at 1-hour intervals to reach steady state (Fig. 2-9). The plateau represents a rate of drug administration that is equal to the rate of drug elimination. Consequently, fluctuations in the plasma concentration of drugs occur as a function of the dosage interval and the drug's elimination half-life. Assuming first-order kinetics, it takes approximately four half-lives to eliminate a drug from the body. The elimination of some drugs (such as alcohol) may follow zero-order kinetics, implying that a constant amount of the drug is eliminated per unit time. In this case, the enzymes that metabolize the drug become saturated and cannot absorb more drug, resulting in a constant amount of drug being metabolized per unit of time. Small changes in the dose of drugs with this type of kinetics can lead to large serum concentrations and increase the risk for toxicity.

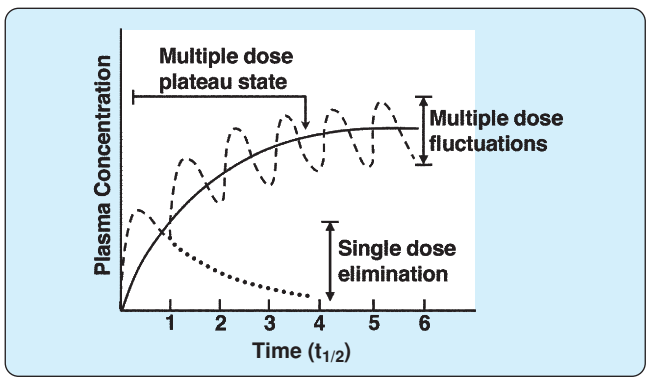

Figure 2-9 Drug Half-Life. This shows the effects of dosing on plasma concentration.

Self-Study Review

25. Describe features of distribution that affect a drug molecule reaching the receptor.
26. What is the role of albumin in the blood?
27. Identify the organ responsible for most drug metabolism.
28. Describe the four ways drugs are altered during biotransformation.
29. What are the differences between Phase I reactions and Phase II reactions in biotransformation?
30. Which enzyme system is the primary pathway for drug metabolism?
31. In which organ are most drugs excreted? What is the primary area of the organ where this occurs?
32. Describe the process of drug excretion.
33. Define a drug's half-life.

CONCLUSION

After initial administration of a drug, there is a period of time before any perceptible effect of the drug is observed in the patient. The time of onset is determined mainly by the rate and degree of absorption. The effect increases with time until the drug reaches the peak effect. Movement through biologic membranes and drug redistribution influences the peak effect. The effect diminishes as the drug is metabolized and eliminated from the body. The duration of action is affected primarily by the rate of inactivation and excretion of the drug by the liver and kidneys. The onset of action, the peak effect, and the duration of action are all dependent upon the dose administered—i.e., the larger the dose, the shorter the time to reach the peak effect, and the longer the duration of action. An important clinical use of time-effect relationships involves multiple dosing schedules over a period of time that depends on the drug's half-life. To eliminate adverse events, the dosage schedule must be designed to avoid giving more drug than has been eliminated since the last dose.

P1: SFL
LWBK088-02 Pickett-3870G LWBK088-Pickett.cls
Printer: R.R. Donnelley China
June 9, 2008 13:31

CLINICAL APPLICATION EXERCISES (CAE)

Exercise 1. During the review of the health history, it is noted that the patient lists Tums as a current over-the-counter (OTC) medication. The current appointment is for periodontal débridement of one quadrant. The diagnosis of the case is severe chronic periodontal disease, and a recommendation will be made for "saltwater rinse in evening, plus OTC medication for pain relief." How will the current drug history information affect your recommendation for pain relief?

Exercise 2. During oral examination, your patient gasps, clutches his chest, and cries out in pain. He reports taking anticholesterol medication due to a recently identified problem with high cholesterol. You tell the receptionist to call 911, and you secure the medical emergency kit. What ROA should be used to get the vasodilating drug to the coronary arteries quickly?

Exercise 3. Your patient is an elderly, overweight person who presents to the office in pain. The dentist decides to prescribe a narcotic agent. What considerations are important in determining dosage, and why?