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Pharmacokinetics: The Dynamics of Drug Absorption, Distribution, Metabolism, and Elimination

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In order to understand and control the therapeutic action of drugs in the human body, one must know how much drug will reach the site(s) of drug action and when this will occur. The absorption, distribution, metabolism (biotransformation), and elimination of drugs are the processes of *pharmacokinetics* (Figure 2–1). Understanding and employing pharmacokinetic principles can increase the probability of therapeutic success and reduce the occurrence of adverse drug effects in the body.

PHYSICOCHEMICAL FACTORS IN TRANSFER OF DRUGS ACROSS MEMBRANES

The absorption, distribution, metabolism, excretion, and action of a drug all involve its passage across cell membranes. Mechanisms by which drugs cross membranes and the physicochemical properties of molecules and membranes that influence this transfer are critical to understanding the disposition of drugs in the human body. The characteristics of a drug that predict its movement and availability at sites of action are its molecular size and structural features, degree of ionization, relative lipid solubility of its ionized and non-ionized forms, and its binding to serum and tissue proteins. In most cases, a drug must traverse the plasma membranes of many cells to reach its site of action. Although barriers to drug movement may be a single layer of cells (intestinal epithelium) or several layers of cells and associated extracellular protein (skin), the plasma membrane represents the common barrier to drug distribution.

Cell Membranes. The plasma membrane consists of a bilayer of amphipathic lipids with their hydrocarbon chains oriented inward to the center of the bilayer to form a continuous hydrophobic phase and their hydrophilic heads oriented outward. Individual lipid molecules in the bilayer vary according to the particular membrane and can move laterally and organize themselves with cholesterol (e.g., sphingolipids), endowing the membrane with fluidity, flexibility, organization, high electrical resistance, and relative impermeability to highly polar molecules. Membrane proteins embedded in the bilayer serve as structural anchors, receptors, ion channels, or transporters to transduce electrical or chemical signaling pathways and provide selective targets for drug actions. In contrast to earlier proposals that cell membranes are fluid and thus proteins collide in an unordered fashion, we now understand that membranes are highly ordered and compartmented (Pinaud et al., 2009; Singer, 2004). These proteins may be associated with caveolin and sequestered within caveolae; they may be excluded from caveolae; or they may be organized in signaling domains rich in cholesterol and sphingolipid not containing caveolin or other scaffolding proteins (i.e., lipid rafts).

Cell membranes are relatively permeable to water either by diffusion or by flow resulting from hydrostatic or osmotic differences across the membrane, and bulk flow of water can carry with it drug molecules. However, proteins with drug molecules bound to them are too large and polar for this type of membrane passage to occur. Transmembrane movement of drug generally is limited to unbound drug; thus drug-protein complexes constitute an inactive reservoir of drug that can influence both therapeutic as well as unwanted drug effects. Paracellular passage through intercellular gaps is sufficiently large that transfer across capillary endothelium is generally limited by blood flow and not by other factors. As described later, such membrane passage is an important factor in filtration across the glomerulus in the kidney. Important exceptions exist in such capillary diffusion; "tight" intercellular junctions are present in specific tissues, and paracellular passage in them is limited. Capillaries of the central nervous system (CNS) and a variety of epithelial tissues have tight junctions. Bulk flow of water can carry with it small water-soluble substances, but bulk-flow transfer is limited when the molecular mass of the solute exceeds 100–200 Da. Accordingly, most large lipophilic drugs must pass through the cell membrane itself (Figure 2–2).

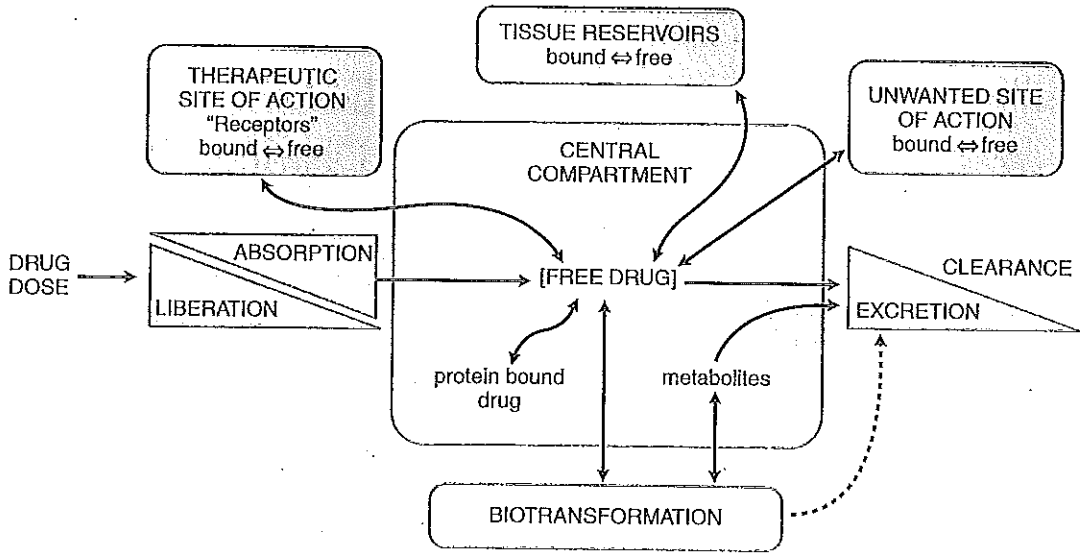

Figure 2–1 *The interrelationship of the absorption, distribution, binding, metabolism, and excretion of a drug and its concentration at its sites of action.* Possible distribution and binding of metabolites in relation to their potential actions at receptors are not depicted.

Passive Flux Across Membranes. Drugs cross membranes either by passive processes or by mechanisms involving the active participation of components of the membrane. In passive transfer, the drug molecule usually penetrates by diffusion along a concentration gradient by virtue of its solubility in the lipid bilayer. Such transfer is directly proportional to the magnitude of the concentration gradient across the membrane, to the lipid-water partition coefficient of the drug, and to the membrane surface area exposed to the drug. The greater the partition coefficient, the higher is the concentration of drug in the membrane and the faster is its diffusion. After a steady state is attained, the concentration of the unbound drug is the same on both sides of the membrane if the drug is a non-electrolyte. For ionic compounds, the steady-state concentrations depend on the electrochemical gradient for the ion and on differences in pH across the membrane, which will influence the state of ionization of the molecule disparately on either side of the membrane and can effectively trap drug on one side of the membrane.

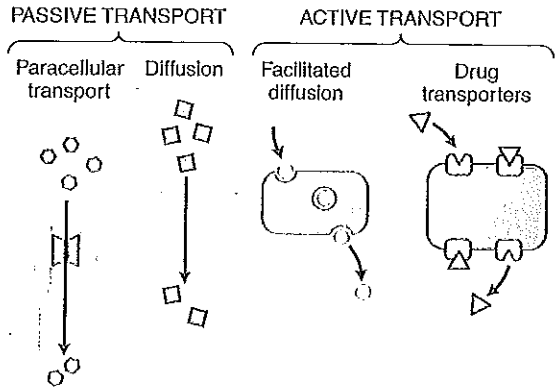

Figure 2–2. *The variety of ways drugs move across cellular barriers in their passage throughout the body.*

Weak Electrolytes and the Influence of pH. Many drugs are weak acids or bases that are present in solution as both the non-ionized and ionized species. The non-ionized molecules usually are more lipid soluble and can diffuse readily across the cell membrane. In contrast, the ionized molecules usually are less able to penetrate the lipid membrane because of their low lipid solubility, and passage will depend on the leakiness of the membrane related to the membrane's electrical resistance. Therefore, the transmembrane distribution of a weak electrolyte is influenced by its pK_a and the pH gradient across the membrane. The pK_a is the pH at which half the drug (weak acid or base electrolyte) is in its ionized form.

To illustrate the effect of pH on distribution of drugs, the partitioning of a weak acid ($pK_a = 4.4$) between plasma (pH = 7.4) and gastric juice (pH = 1.4) is depicted in Figure 2–3. Assume that the gastric mucosal membrane behaves as a simple lipid barrier with a high electrical resistance that is permeable only to the lipid-soluble, non-ionized form of the acid. The ratio of non-ionized to ionized drug at each pH is readily calculated from the Henderson-Hasselbalch equation:

$$\log \frac{[\text{protonated form}]}{[\text{unprotonated form}]} = pK_a - \text{pH} \quad \text{(Equation 2–1)}$$

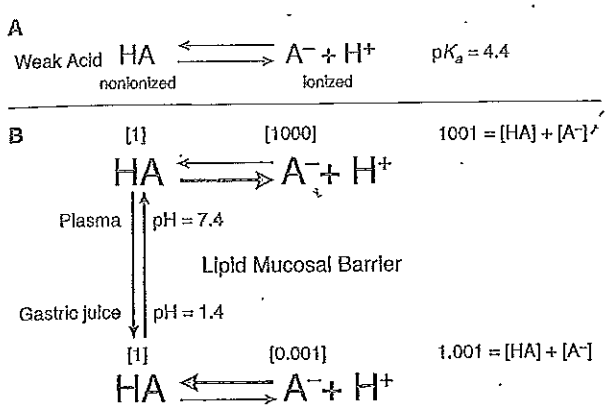

Figure 2–3 *Influence of pH on the distribution of a weak acid between plasma and gastric juice separated by a lipid barrier.*
A. The dissociation of a weak acid, $pK_a = 4.4$.
B. Dissociation of the weak acid in plasma (pH 7.4) and gastric acid (pH 1.4). The uncharged from, HA, equibrates across the membrane. Blue numbers in brackets show relative concentrations of HA and A^-.

This equation relates the pH of the medium around the drug and the drug's acid dissociation constant (pK_a) to the ratio of the protonated (HA or BH^+) and unprotonated (A^- or B) forms, where $HA \leftrightarrow A^- + H^+$ ($K_a = [A^-][H^+]/[HA]$) describes the dissociation of an acid, and $BH^+ \leftrightarrow B + H^+$ ($K_a = [B][H^+]/[BH^+]$) describes the dissociation of the protonated form of a base.

In the example of Figure 2–3, the ratio of nonionized to ionized drug in plasma is 1:1000; in gastric juice, the ratio is 1:0.001, as given in brackets in Figure 2–3. The total concentration ratio between the plasma and the gastric juice therefore would be 1000:1 if such a system came to a steady state. For a weak base with a pK_a of 4.4 (e.g., chlordiazepoxide), the ratio would be reversed, as would the thick horizontal arrows in Figure 2–3, which indicate the predominant species at each pH. Accordingly, at steady state, an acidic drug will accumulate on the more basic side of the membrane and a basic drug on the more acidic side.

Common ionizable groups on drug molecules are carboxylic acids (pK_a~4.5) and primary amino groups (pK_a~9.5), but myriad others are possible. Resonance structures and electron withdrawing groups can change the pK_a, and many compounds have multiple ionizable groups; thus, pK_a values vary over a broad range. Furthermore, some drugs contain quaternary amines with a permanent positive change. One consequence of a drug being ionized at physiological pH is illustrated by the relative lack of sedative effects of second generation histamine H_1 antagonists: second generation antihistamines are ionized molecules (less lipophilic) that cross the blood-brain barrier poorly compared to first generation agents (uncharged at pH 7.4). The effects of net charge are observable elsewhere in the body, in the kidney tubules, for instance. Urine pH can vary over a ride range, from 4.5 to 8. As urine pH drops (as $[H^+]$ increases), weak acids (A^-) and weak bases (B) will exist to a greater extend in their protonated forms (HA and BH^+); the reverse is true as pH rises, where A^- and B will be favored. In the kidney tubules where a lipid soluble (uncharged) drug can be reabsorbed by passive diffusion, excretion of the drug can be promoted by altering the pH of the urine to favor the ionized state (A^- or BH^+). Thus, alkaline urine favors excretion of weak acids; acid urine favors excretion of weak bases. Elevation of urine pH (by giving sodium bicarbonate) will promote urinary excretion of weak acids such as aspirin (pK_a~3.5) and urate (pK_a~5.8). This principle of *ion trapping* is an important process in drug distribution.

These considerations have obvious implications for the absorption and excretion of many drugs, as will be discussed more specifically. The establishment of concentration gradients of weak electrolytes across membranes with a pH gradient is a physical process and does not require an active electrolyte transport system. All that is necessary is a membrane preferentially permeable to one form of the weak electrolyte and a pH gradient across the membrane. The establishment of the pH gradient, however, is an active process.

Carrier-Mediated Membrane Transport. While passive diffusion through the bilayer is dominant in the disposition of most drugs, carrier-mediated mechanisms also play an important role. *Active transport* is characterized by a direct requirement for energy, movement against an electrochemical gradient, saturability, selectivity, and competitive inhibition by co-transported compounds. Na^+,K^+-ATPase is an important example of an active transport mechanism that is a therapeutic target of digoxin in the treatment of heart failure (Chapter 28). Secondary active transport uses the electrochemical energy stored in a gradient to move another molecule against a concentration gradient; e.g., the Na^+–Ca^{2+} exchange protein uses the energy stored in the Na^+ gradient established by the Na^+, K^+-ATPase mechanism to export cytosolic Ca^{2+} and maintain it at a low basal level, ~100 nM in most cells (Chapter 3); similarly, the Na^+-dependent glucose transporters SGLT1 and SGLT2 move glucose across membranes of gastrointestinal (GI) epithelium and renal tubules by coupling glucose transport to downhill Na^+ flux.

Facilitated diffusion describes a carrier-mediated transport process in which there is no input of energy, and therefore enhanced movement of the involved substance is down a chemical gradient as in the permeation of glucose across a muscle cell membrane mediated by the insulin-sensitive glucose transporter GLUT4. Such mechanisms, which may be highly selective for a specific conformational structure of a drug, are involved in the transport of endogenous

compounds whose rate of transport by passive diffusion otherwise would be too slow (Figure 5–4). In other cases, they function as exporters, creating a barrier to prevent the intracellular accumulation of potentially toxic substances. Pharmacologically important transporters may mediate either drug uptake or efflux and often facilitate vectorial transport across polarized cells. An important efflux transporter is the P-glycoprotein encoded by the multidrug resistance-1 (*MDR1*) gene (Table 5–4). P-glycoprotein localized in the enterocyte limits the oral absorption of transported drugs because it exports compounds back into the lumen of the GI tract subsequent to their absorption by passive diffusion. The P-glycoprotein also can confer resistance to some cancer chemotherapeutic agents (Chapters 60-63). Transporters and their roles in drug action are presented in detail in Chapter 5.

DRUG ABSORPTION, BIOAVAILABILITY, AND ROUTES OF ADMINISTRATION

Absorption is the movement of a drug from its site of administration into the central compartment (Figure 2–1) and the extent to which this occurs. For solid dosage forms, absorption first requires dissolution of the tablet or capsule, thus liberating the drug. The clinician is concerned primarily with bioavailability rather than absorption. *Bioavailability* is a term used to indicate the fractional extent to which a dose of drug reaches its site of action or a biological fluid from which the drug has access to its site of action. For example, a drug given orally must be absorbed first from the GI tract, but net absorption may be limited by the characteristics of the dosage form, the drug's physicochemical properties, by intestinal metabolism, and by transporter export back into the intestinal lumen. The absorbed drug then passes through the liver, where metabolism and biliary excretion may occur before the drug enters the systemic circulation. Accordingly, a fraction of the administered and absorbed dose of drug will be inactivated or diverted in the intestine and liver before it can reach the general circulation and be distributed to its sites of action. If the metabolic or excretory capacity of the liver and the intestine for the drug is large, bioavailability will be reduced substantially (*first-pass effect*). This decrease in availability is a function of the anatomical site from which absorption takes place; other anatomical, physiological, and pathological factors can influence bioavailability (described later), and the choice of the route of drug administration must be based on an understanding of these conditions. Moreover, knowledge of drugs that undergo significant metabolism or require active transport across the intestinal and hepatic membranes instructs our understanding of adverse events in therapeutics, since some drugs are substrates for the same drug metabolizing enzymes or drug transporters and thus compete for metabolism and transport.

Oral (Enteral) Versus Parenteral Administration. Often there is a choice of the route by which a therapeutic agent may be administered, and knowledge of the advantages and disadvantages of the different routes of administration is then of primary importance. Some characteristics of the major routes employed for systemic drug effect are compared in Table 2–1.

Oral ingestion is the most common method of drug administration. It also is the safest, most convenient, and most economical. Disadvantages to the oral route include limited absorption of some drugs because of their physical characteristics (e.g., low water solubility or poor membrane permeability), emesis as a result of irritation to the GI mucosa, destruction of some drugs by digestive enzymes or low gastric pH, irregularities in absorption or propulsion in the presence of food or other drugs, and the need for cooperation on the part of the patient. Such cooperation is frequently not forthcoming, since tolerating certain oral medications means accepting unwanted effects, such as GI pain, which may require use of an alternate route of administration (Cosman, 2009). In addition, drugs in the GI tract may be metabolized by the enzymes of the intestinal flora, mucosa, or liver before they gain access to the general circulation.

Parenteral injection of drugs has certain distinct advantages over oral administration. In some instances, parenteral administration is essential for the drug to be delivered in its active form, as in the case of monoclonal antibodies such as infliximab, an antibody directed against tumor necrosis factor α (TNF α) used in the treatment of rheumatoid arthritis. Availability usually is more rapid, extensive, and predictable when a drug is given by injection. The effective dose can therefore be delivered more accurately. In emergency therapy and when a patient is unconscious, uncooperative, or unable to retain anything given by mouth, parenteral therapy may be a necessity. The injection of drugs, however, has its disadvantages: asepsis must be maintained, and this is of particular concern when drugs are given over time, such as in intravenous or intrathecal administration; pain may accompany the injection; and it is sometimes difficult for patients to perform the injections themselves if self-medication is necessary.

Oral Administration. Absorption from the GI tract is governed by factors such as surface area for absorption, blood flow to the site of absorption, the physical state of the drug (solution, suspension, or solid dosage form), its water solubility, and the drug's concentration at the site of absorption. For drugs given in solid form, the rate of dissolution may limit their absorption, especially drugs of low aqueous solubility. Since most drug absorption from the GI tract occurs by passive diffusion, absorption is favored when the drug is in the nonionized and more lipophilic form. Based on the pH-partition concept (Figure 2–3), one would predict that drugs that are weak acids would be better absorbed from the stomach (pH 1-2) than from the upper intestine (pH 3-6), and vice versa for weak bases. However, the epithelium of the stomach is lined with a thick mucus layer, and its surface area is small; by contrast, the villi of the upper intestine provide an extremely large surface area (~200 m^2). Accordingly, the rate of absorption of a drug from the intestine will be greater than that from the stomach even if the drug is predominantly ionized in the intestine and largely non-ionized in the stomach. Thus, any factor that accelerates gastric emptying (recumbent position, right side)

Table 2–1

Some Characteristics of Common Routes of Drug Administration[a]

ROUTE	ABSORPTION PATTERN	SPECIAL UTILITY	LIMITATIONS AND PRECAUTIONS
Intravenous	Absorption circumvented Potentially immediate effects Suitable for large volumes and for irritating substances, or complex mixtures, when diluted	Valuable for emergency use Permits titration of dosage Usually required for high-molecular-weight protein and peptide drugs	Increased risk of adverse effects Must inject solutions *slowly* as a rule Not suitable for oily solutions or poorly soluble substances
Subcutaneous	Prompt from aqueous solution Slow and sustained from repository preparations	Suitable for some poorly soluble suspensions and for instillation of slow-release implants	Not suitable for large volumes Possible pain or necrosis from irritating substances
Intramuscular	Prompt from aqueous solution Slow and sustained from repository preparations	Suitable for moderate volumes, oily vehicles, and some irritating substances Appropriate for self-administration (e.g., insulin)	Precluded during anticoagulant therapy May interfere with interpretation of certain diagnostic tests (e.g., creatine kinase)
Oral ingestion	Variable, depends on many factors (*see* text)	Most convenient and economical; usually more safe	Requires patient compliance Bioavailability potentially erratic and incomplete

[a]*See* text for more complete discussion and for other routes.

will be likely to increase the rate of drug absorption (Queckenberg and Fuhr, 2009), whereas any factor that delays gastric emptying is expected to have the opposite effect, regardless of the characteristics of the drug. Gastric motor activity and gastric emptying rate are governed by neural and humoral feedback provided by receptors found in the gastric musculature and proximal small intestine. In healthy individuals, gastric emptying rate is influenced by a variety of factors including the caloric content of food; volume, osmolality, temperature, and pH of ingested fluid; diurnal and inter-individual variation; metabolic state (rest/exercise); and the ambient temperature. Such factors will influence ingested drug absorption. Gastric emptying is influenced in women by the effects of estrogen (i.e., slower than in men for premenopausal women and those taking estrogen replacement therapy).

Drugs that are destroyed by gastric secretions and low pH or that cause gastric irritation sometimes are administered in dosage forms with an enteric coating that prevents dissolution in the acidic gastric contents. These pharmacologically inactive coatings, often of cellulose polymers, have a threshold of dissolution between pH 5 and 6. Enteric coatings are useful for drugs such as aspirin, which can cause significant gastric irritation in many patients, and for presenting a drug such as mesalamine to sites of action in the ileum and colon (Figure 47–4).

Controlled-Release Preparations. The rate of absorption of a drug administered as a tablet or other solid oral dosage form is partly dependent on its rate of dissolution in GI fluids. This is the basis for *controlled-release, extended-release, sustained-release,* and *prolonged-action* pharmaceutical preparations that are designed to produce slow, uniform absorption of the drug for 8 hours or longer. Such preparations are offered for medications in all major drug categories. Potential advantages of such preparations are reduction in the frequency of administration of the drug as compared with conventional dosage forms (often with improved compliance by the patient), maintenance of a therapeutic effect overnight, and decreased incidence and/or intensity of both undesired effects (by dampening of the peaks in drug concentration) and nontherapeutic blood levels of the drug (by elimination of troughs in concentration) that often occur after administration of immediate-release dosage forms.

Many controlled-release preparations fulfill these expectations and may be preferred in some therapeutic situations (e.g., therapy for depression [Nemeroff, 2003] and ADHD [Manos et al., 2007]) or treatment with dihydropyridine Ca^{2+} entry blockers (Chapters 26-28). However, such products do have drawbacks: variability of the systemic concentration achieved may be greater for controlled-release than for immediate-release dosage forms; the dosage form may fail; and "dose dumping" with resulting toxicity can occur because the total dose of drug in a controlled-release preparation may be several times the amount contained in the conventional preparation, although current regulatory approval requirements generally preclude such occurrences. Controlled-release dosage forms are most appropriate for drugs with short half-lives ($t_{1/2}$ <4 hours) or in selected patient

groups such as those receiving anti-epileptics (Bialer, 2007; Pellock et al., 2004). So-called controlled-release dosage forms are sometimes developed for drugs with long $t_{1/2}$ values (>12 hours). These usually more expensive products should not be prescribed unless specific advantages have been demonstrated. The availability of controlled-release dosage forms of some drugs can lead to abuse, as in the case of controlled-release oxycodone marketed as OXYCONTIN. Crushing and snorting the delayed-release tablets results in a rapid release of the drug, increased absorption, and high peak serum concentrations (Aquina et al., 2009).

Sublingual Administration. Absorption from the oral mucosa has special significance for certain drugs despite the fact that the surface area available is small. Venous drainage from the mouth is to the superior vena cava, bypassing the portal circulation and thereby protecting the drug from rapid intestinal and hepatic first-pass metabolism. For example, nitroglycerin is effective when retained sublingually because it is non-ionic and has very high lipid solubility. Thus, the drug is absorbed very rapidly. Nitroglycerin also is very potent; absorption of a relatively small amount produces the therapeutic effect ("unloading" of the heart; Chapter 27).

Transdermal Absorption. Not all drugs readily penetrate the intact skin. Absorption of those that do is dependent on the surface area over which they are applied and their lipid solubility because the epidermis behaves as a lipid barrier (Chapter 65). The dermis, however, is freely permeable to many solutes; consequently, systemic absorption of drugs occurs much more readily through abraded, burned, or denuded skin. Inflammation and other conditions that increase cutaneous blood flow also enhance absorption. Toxic effects sometimes are produced by absorption through the skin of highly lipid-soluble substances (e.g., a lipid-soluble insecticide in an organic solvent). Absorption through the skin can be enhanced by suspending the drug in an oily vehicle and rubbing the resulting preparation into the skin. Because hydrated skin is more permeable than dry skin, the dosage form may be modified or an occlusive dressing may be used to facilitate absorption. Controlled-release topical patches have become increasingly available, including nicotine for tobacco-smoking withdrawal, scopolamine for motion sickness, nitroglycerin for angina pectoris, testosterone and estrogen for replacement therapy, various estrogens and progestins for birth control, and fentanyl for pain relief.

Rectal Administration. Approximately 50% of the drug that is absorbed from the rectum will bypass the liver; the potential for hepatic first-pass metabolism thus is less than that for an oral dose; furthermore, a major drug metabolism enzyme, CYP3A4, is present in the upper intestine but not in the lower intestine. However, rectal absorption can be irregular and incomplete, and certain drugs can cause irritation of the rectal mucosa. The use of special mucoadhesive microspheres may increase the number of medications that can be given by the rectal route (Patil and Sawant, 2008).

Parenteral Injection. The major routes of parenteral administration are intravenous, subcutaneous, and intramuscular. Absorption from subcutaneous and intramuscular sites occurs by simple diffusion along the gradient from drug depot to plasma. The rate is limited by the area of the absorbing capillary membranes and by the solubility of the substance in the interstitial fluid. Relatively large aqueous channels in the endothelial membrane account for the indiscriminate diffusion of molecules regardless of their lipid solubility. Larger molecules, such as proteins, slowly gain access to the circulation by way of lymphatic channels.

Drugs administered into the systemic circulation by any route, excluding the intra-arterial route, are subject to possible first-pass elimination in the lung prior to distribution to the rest of the body. The lungs serve as a temporary storage site for a number of agents, especially drugs that are weak bases and are predominantly non-ionized at the blood pH, apparently by their partition into lipid. The lungs also serve as a filter for particulate matter that may be given intravenously, and they provide a route of elimination for volatile substances.

Intravenous. Factors limiting absorption are circumvented by intravenous injection of drugs in aqueous solution because bioavailability is complete and rapid. Also, drug delivery is controlled and achieved with an accuracy and immediacy not possible by any other procedure. In some instances, as in the induction of surgical anesthesia, the dose of a drug is not predetermined but is adjusted to the response of the patient. Also, certain irritating solutions can be given only in this manner because the drug, if injected slowly, is greatly diluted by the blood. There are both advantages and disadvantages to the use of this route of administration. Unfavorable reactions can occur because high concentrations of drug may be attained rapidly in both plasma and tissues. There are therapeutic circumstances where it is advisable to administer a drug by bolus injection (small volume given rapidly, e.g., tissue plasminogen activator immediately following an acute myocardial infarction) and other circumstances where slower administration of drug is advisable, such as the delivery of drugs by intravenous "piggyback" (e.g., antibiotics). Intravenous administration of drugs warrants close monitoring of the patient's response. Furthermore, once the drug is injected, there is often no retreat. Repeated intravenous injections depend on the ability to maintain a patent vein. Drugs in an oily vehicle, those that precipitate blood constituents or hemolyze erythrocytes, and drug combinations that cause precipitates to form must not be given by this route.

Subcutaneous. Injection into a subcutaneous site can be done only with drugs that are not irritating to tissue; otherwise, severe pain, necrosis, and tissue sloughing may occur. The rate of absorption following subcutaneous injection of a drug often is sufficiently constant and slow to provide a sustained effect. Moreover, altering the period over which a drug is absorbed may be varied intentionally, as is accomplished with insulin for injection using particle size, protein complexation, and pH to provide short-acting (3-6 hours), intermediate-acting (10-18 hours), and long-acting (18-24 hours) preparations. The incorporation of a vasoconstrictor agent in a solution of a drug to be injected subcutaneously also retards absorption. Thus, the injectable local anesthetic lidocaine incorporates epinephrine into the dosage form. Absorption of drugs implanted under the skin in a solid pellet form occurs slowly over a period of weeks or months; some hormones (e.g., contraceptives) are administered effectively in this manner, and implantable devices (e.g., a plastic rod delivering etonogestrel) can provide effective contraception for 3 years (Blumenthal et al., 2008).

Intramuscular. Drugs in aqueous solution are absorbed quite rapidly after intramuscular injection depending on the rate of blood flow to the injection site. This may be modulated to some extent by local heating, massage, or exercise. For example, while absorption of insulin generally is more rapid from injection in the arm and

abdominal wall than the thigh, jogging may cause a precipitous drop in blood sugar when insulin is injected into the thigh rather than into the arm or abdominal wall because running markedly increases blood flow to the leg. A hot bath accelerates absorption from all these sites owing to vasodilation. Generally, the rate of absorption following injection of an aqueous preparation into the deltoid or vastus lateralis is faster than when the injection is made into the gluteus maximus. The rate is particularly slower for females after injection into the gluteus maximus. This has been attributed to the different distribution of subcutaneous fat in males and females and because fat is relatively poorly perfused. Very obese or emaciated patients may exhibit unusual patterns of absorption following intramuscular or subcutaneous injection. Slow, constant absorption from the intramuscular site results if the drug is injected in solution in oil or suspended in various other repository (depot) vehicles. Antibiotics often are administered in this manner. Substances too irritating to be injected subcutaneously sometimes may be given intramuscularly.

Intra-arterial. Occasionally, a drug is injected directly into an artery to localize its effect in a particular tissue or organ, such as in the treatment of liver tumors and head/neck cancers. Diagnostic agents sometimes are administered by this route (e.g., technetium-labeled human serum albumin). Intra-arterial injection requires great care and should be reserved for experts. The dampening, first-pass, and cleansing effects of the lung are not available when drugs are given by this route.

Intrathecal. The blood-brain barrier and the blood-cerebrospinal fluid (CSF) barrier often preclude or slow the entrance of drugs into the CNS. Therefore, when local and rapid effects of drugs on the meninges or cerebrospinal axis are desired, as in spinal anesthesia or treatment of acute CNS infections, drugs sometimes are injected directly into the spinal subarachnoid space. Brain tumors also may be treated by direct intraventricular drug administration. More recent developments include special targeting of substances to the brain via receptor-mediated transcytosis (Jones and Shusta, 2007) and modulation of tight junctions (Matsuhisa et al., 2009).

Pulmonary Absorption. Provided that they do not cause irritation, gaseous and volatile drugs may be inhaled and absorbed through the pulmonary epithelium and mucous membranes of the respiratory tract. Access to the circulation is rapid by this route because the lung's surface area is large. The principles governing absorption and excretion of anesthetic and other therapeutic gases are discussed in Chapter 19. In addition, solutions of drugs can be atomized and the fine droplets in air (aerosol) inhaled. Advantages are the almost instantaneous absorption of a drug into the blood, avoidance of hepatic first-pass loss, and in the case of pulmonary disease, local application of the drug at the desired site of action. For example, owing to the ability to meter doses and create fine aerosols, drugs can be given in this manner for the treatment of allergic rhinitis or bronchial asthma (Chapter 36). Pulmonary absorption is an important route of entry of certain drugs of abuse and of toxic environmental substances of varied composition and physical states. Both local and systemic reactions to allergens may occur subsequent to inhalation.

Topical Application

Mucous Membranes. Drugs are applied to the mucous membranes of the conjunctiva, nasopharynx, oropharynx, vagina, colon, urethra, and urinary bladder primarily for their local effects. Occasionally, as in the application of synthetic anti-diuretic hormone to the nasal mucosa, systemic absorption is the goal. Absorption through mucous membranes occurs readily. In fact, local anesthetics applied for local effect sometimes may be absorbed so rapidly that they produce systemic toxicity.

Eye. Topically applied ophthalmic drugs are used primarily for their local effects (Chapter 64). Systemic absorption that results from drainage through the nasolacrimal canal is usually undesirable. Because drug that is absorbed via drainage is not subject to first-pass intestinal and hepatic metabolism, unwanted systemic pharmacological effects may occur when β adrenergic receptor antagonists or corticosteroids are administered as ophthalmic drops. Local effects usually require absorption of the drug through the cornea; corneal infection or trauma thus may result in more rapid absorption. Ophthalmic delivery systems that provide prolonged duration of action (e.g., suspensions and ointments) are useful additions to ophthalmic therapy. Ocular inserts, such as the use of pilocarpine-containing inserts for the treatment of glaucoma, provide continuous delivery of small amounts of drug. Very little is lost through drainage; hence systemic side effects are minimized.

Novel Methods of Drug Delivery

Drug-eluting stents and other devices are being used to target drugs locally and minimize systemic exposure. The systemic toxicity of potentially important compounds can be decreased significantly by combination with a variety of drug carrier vehicles that modify distribution. For example, linkage of the cytotoxic agent calicheamicin to an antibody directed to an antigen found on the surface of certain leukemic cells can target the drug to its intended site of action, improving the therapeutic index of calicheamicin.

Recent advances in drug delivery include the use of biocompatible polymers with functional monomers attached in such a way as to permit linkage of drug molecules to the polymer. A drug-polymer conjugate can be designed to be a stable, long-circulating prodrug by varying the molecular weight of the polymer and the cleavable linkage between the drug and the polymer. The linkage is designed to keep the drug inactive until it released from the backbone polymer by a disease-specific trigger, typically enzyme activity in the targeted tissue that delivers the active drug at or near the site of pathology. Nanoparticles are offering new opportunities for diagnosis, targeted drug delivery, and imaging of clinical effect (Prestidge et al., 2010; Sajja et al., 2009).

Bioequivalence

Drug products are considered to be pharmaceutical equivalents if they contain the same active ingredients and are identical in strength or concentration, dosage form, and route of administration. Two pharmaceutically equivalent drug products are considered to be *bioequivalent* when the rates and extents of bioavailability of the active ingredient in the two products are not significantly different under suitable test conditions. In the past, dosage forms of a drug from different manufacturers and even different lots of preparations from a single manufacturer sometimes differed in their bioavailability. Such differences were seen primarily among oral dosage forms of poorly soluble, slowly absorbed drugs such as the urinary anti-infective, metronidazole (FLAGYL). When first introduced, the generic form was not bioequivalent because the generic manufacturer was not able to mimic the proprietary process used to microsize the drug for absorption initially. Differences in crystal form, particle size, or other

physical characteristics of the drug that are not rigidly controlled in formulation and manufacture affect disintegration of the dosage form and dissolution of the drug and hence the rate and extent of drug absorption.

The potential non-equivalence of different drug preparations has been a matter of concern (Meredith, 2009). However, no prospective clinical study has shown an FDA-approved generic drug product to yield significantly different therapeutic effects, even when testing published anecdotal reports of non-equivalence. Because of the legitimate concern of clinicians and the financial consequences of generic prescribing, this topic will continue to be actively addressed. Generic versus brand name prescribing is further discussed in connection with drug nomenclature and the choice of drug name in writing prescription orders (Appendix I).

DISTRIBUTION OF DRUGS

Following absorption or systemic administration into the bloodstream, a drug distributes into interstitial and intracellular fluids. This process reflects a number of physiological factors and the particular physicochemical properties of the individual drug. Cardiac output, regional blood flow, capillary permeability, and tissue volume determine the rate of delivery and potential amount of drug distributed into tissues. Initially, liver, kidney, brain, and other well-perfused organs receive most of the drug; delivery to muscle, most viscera, skin, and fat is slower, and this second distribution phase may require minutes to several hours before the concentration of drug in tissue is in equilibrium with that in blood. The second phase also involves a far larger fraction of body mass (e.g., muscle) than does the initial phase and generally accounts for most of the extravascularly distributed drug. With exceptions such as the brain, diffusion of drug into the interstitial fluid occurs rapidly because of the highly permeable nature of the capillary endothelial membrane. Thus, tissue distribution is determined by the partitioning of drug between blood and the particular tissue. Lipid solubility and transmembrane pH gradients are important determinants of such uptake for drugs that are either weak acids or bases. However, in general, ion trapping associated with transmembrane pH gradients is not large because the pH difference between tissue and blood (~7.0 versus 7.4) is small. The more important determinant of blood-tissue partitioning is the relative binding of drug to plasma proteins and tissue macromolecules that limits the concentration of free drug.

Plasma Proteins. Many drugs circulate in the bloodstream bound to plasma proteins. Albumin is a major carrier for acidic drugs; α_1-acid glycoprotein binds basic drugs. Nonspecific binding to other plasma proteins generally occurs to a much smaller extent. The binding is usually reversible; covalent binding of reactive drugs such as alkylating agents occurs occasionally. In addition to the binding of drugs to carrier proteins such as albumin, certain drugs may bind to proteins that function as specific hormone carrier proteins, such as the binding of estrogen or testosterone to sex hormone–binding globulin or the binding of thyroid hormone to thyroxin-binding globulin.

The fraction of total drug in plasma that is bound is determined by the drug concentration, the affinity of binding sites for the drug, and the number of binding sites. Mass-action relationships determine the unbound and bound concentrations (described later). At low concentrations of drug (less than the plasma protein binding dissociation constant), the fraction bound is a function of the concentration of binding sites and the dissociation constant. At high drug concentrations (greater than the dissociation constant), the fraction bound is a function of the number of binding sites and the drug concentration. Therefore, plasma binding is a nonlinear, saturable process. For most drugs, the therapeutic range of plasma concentrations is limited; thus, the extent of binding and the unbound fraction are relatively constant. The percentage values listed for protein binding in Appendix II refer to binding in the therapeutic range unless otherwise indicated. The extent of plasma protein binding also may be affected by disease-related factors. For example, hypoalbuminemia secondary to severe liver disease or nephrotic syndrome results in reduced binding and an increase in the unbound fraction. Also, conditions resulting in the acute-phase reaction response (e.g., cancer, arthritis, myocardial infarction, Crohn's disease) lead to elevated levels of α_1-acid glycoprotein and enhanced binding of basic drugs. Changes in protein binding due to disease states and drug-drug interactions are clinically relevant mainly for a small subset of so-called high-clearance drugs of narrow therapeutic index (described later) that are administered intravenously, such as lidocaine (Benet and Hoener, 2002). When changes in plasma protein binding occur in patients, unbound drug rapidly equilibrates throughout the body and only a transient significant change in unbound plasma concentration will occur. Only drugs that show an almost instantaneous relationship between free plasma concentration and effect (e.g., anti-arrhythmics) will show a measureable effect. Thus, unbound plasma drug concentrations will really exhibit significant changes only when either drug input or clearance of unbound drug occurs, as a consequence of metabolism or active transport. A more common problem resulting from competition of drugs for plasma protein-binding sites is misinterpretation of measured concentrations of drugs in plasma because most assays do not distinguish free drug from bound drug.

Importantly, binding of a drug to plasma proteins limits its concentration in tissues and at its site of action because only unbound drug is in equilibrium across membranes. Accordingly, after distribution equilibrium is achieved, the concentration of active, unbound drug in intracellular water is the same as that in plasma except when carrier-mediated transport is involved. Binding of a drug to plasma protein also limits the drug's glomerular filtration because this process does not immediately change the concentration of free drug in the plasma (water is also filtered). However, plasma protein binding generally does not limit renal tubular secretion or

biotransformation because these processes lower the free drug concentration, and this is followed rapidly by dissociation of drug from the drug-protein complex, thereby reestablishing equilibrium between bound and free drug. Drug transport and metabolism also are limited by binding to plasma proteins, except when these are especially efficient, and drug clearance, calculated on the basis of unbound drug, exceeds organ plasma flow.

Tissue Binding. Many drugs accumulate in tissues at higher concentrations than those in the extracellular fluids and blood. For example, during long-term administration of the anti-malarial agent quinacrine, the concentration of drug in the liver may be several thousand times that in the blood. Such accumulation may be a result of active transport or, more commonly, binding. Tissue binding of drugs usually occurs with cellular constituents such as proteins, phospholipids, or nuclear proteins and generally is reversible. A large fraction of drug in the body may be bound in this fashion and serve as a reservoir that prolongs drug action in that same tissue or at a distant site reached through the circulation. Such tissue binding and accumulation also can produce local toxicity, as in the case of the accumulation of the aminoglycoside antibiotic gentamicin in the kidney and vestibular system.

Fat as a Reservoir. Many lipid-soluble drugs are stored by physical solution in the neutral fat. In obese persons, the fat content of the body may be as high as 50%, and even in lean individuals fat constitutes 10% of body weight; hence fat may serve as a reservoir for lipid-soluble drugs. For example, as much as 70% of the highly lipid-soluble barbiturate thiopental may be present in body fat 3 hours after administration, when plasma concentrations are negligible and no anesthetic effects are measurable. Fat is a rather stable reservoir because it has a relatively low blood flow. However, among highly lipophilic drugs (e.g., remifentanil and some β blockers), the degree of lipophilicity does not predict their distribution in obese individuals.

Bone. The tetracycline antibiotics (and other divalent metal-ion chelating agents) and heavy metals may accumulate in bone by adsorption onto the bone crystal surface and eventual incorporation into the crystal lattice. Bone can become a reservoir for the slow release of toxic agents such as lead or radium into the blood; their effects thus can persist long after exposure has ceased. Local destruction of the bone medulla also may lead to reduced blood flow and prolongation of the reservoir effect because the toxic agent becomes sealed off from the circulation; this may further enhance the direct local damage to the bone. A vicious cycle results, whereby the greater the exposure to the toxic agent, the slower is its rate of elimination. The adsorption of drug onto the bone crystal surface and incorporation into the crystal lattice have therapeutic advantages for the treatment of osteoporosis. Phosphonates such as sodium etidronate bind tightly to hydroxyapatite crystals in mineralized bone matrix. However, unlike naturally occurring pyrophosphates, etidronate is resistant to degradation by pyrophosphatases and thus stabilizes the bone matrix.

Redistribution. Termination of drug effect after withdrawal of a drug usually is by metabolism and excretion but also may result from redistribution of the drug from its site of action into other tissues or sites. Redistribution is a factor in terminating drug effect primarily when a highly lipid-soluble drug that acts on the brain or cardiovascular system is administered rapidly by intravenous injection or by inhalation. A good example of this is the use of the intravenous anesthetic thiopental, a highly lipid-soluble drug. Because blood flow to the brain is so high, the drug reaches its maximal concentration in brain within a minute of its intravenous injection. After injection is concluded, the plasma concentration falls as thiopental diffuses into other tissues, such as muscle. The concentration of the drug in brain follows that of the plasma because there is little binding of the drug to brain constituents. Thus, in this example, the onset of anesthesia is rapid, but so is its termination. Both are related directly to the concentration of drug in the brain.

CNS and Cerebrospinal Fluid. The distribution of drugs into the CNS from the blood is unique. One reason for this is that the brain capillary endothelial cells have continuous tight junctions; therefore, drug penetration into the brain depends on transcellular rather than paracellular transport. The unique characteristics of brain capillary endothelial cells and pericapillary glial cells constitute the blood-brain barrier. At the choroid plexus, a similar blood-CSF barrier is present, except that it is epithelial cells that are joined by tight junctions rather than endothelial cells. The lipid solubility of the nonionized and unbound species of a drug is therefore an important determinant of its uptake by the brain; the more lipophilic a drug, the more likely it is to cross the blood-brain barrier. This situation often is used in drug design to alter drug distribution to the brain; e.g., the so-called second-generation antihistamines, such as loratadine, achieve far lower brain concentrations than do agents such as diphenhydramine and thus are nonsedating. Drugs may penetrate into the CNS by specific uptake transporters normally involved in the transport of nutrients and endogenous compounds from blood into the brain and CSF.

Another important factor in the functional blood-brain barrier involves membrane transporters that are efflux carriers present in the brain capillary endothelial cell and capable of removing a large number of chemically diverse drugs from the cell. MDR1 (P-gp) and the organic anion–transporting polypeptide (OATP) are two of the more notable of these. The effects of these exporters are to dramatically limit access of the drug to the tissue expressing the efflux transporter. Together, P-gp and the OATP family export a large array of structurally

diverse drugs (see Chapter 5 and Maeda et al., 2008). Expression of OATP isoforms and their polymorphic forms in the GI tract, liver, and kidney, as well as the blood-brain barrier, has important implications for drug absorption and elimination, as well as tissue penetration. Expression of these efflux transporters accounts for the relatively restricted pharmacological access to the brain and other tissues such as the testes, where drug concentrations may be below those necessary to achieve a desired effect despite adequate blood flow. This situation occurs with HIV protease inhibitors and with loperamide, a potent, systemically active opioid that lacks the central effects characteristic of other opioids (Chapter 19). Efflux transporters that actively secrete drug from the CSF into the blood also are present in the choroid plexus (see Chapter 5 for details of the contribution of drug transporters to barrier function). Drugs also may exit the CNS along with the bulk flow of CSF through the arachnoid villi. In general, the blood-brain barrier's function is well maintained; however, meningeal and encephalic inflammation increase local permeability. Recently, blood-brain barrier disruption has emerged as a strategy in the treatment of certain brain tumors such as primary CNS lymphomas (Angelov et al., 2009).The goal of this treatment is to enhance delivery of chemotherapy to the brain tumor while maintaining cognitive function that is often damaged by conventional radiotherapy.

Placental Transfer of Drugs. The transfer of drugs across the placenta is of critical importance because drugs may cause anomalies in the developing fetus. Administered immediately before delivery, as is often the case with the use of tocolytics in the treatment of preterm labor, they also may have adverse effects on the neonate. Lipid solubility, extent of plasma binding, and degree of ionization of weak acids and bases are important general determinants in drug transfer across the placenta. The fetal plasma is slightly more acidic than that of the mother (pH 7.0-7.2 versus 7,4), so that ion trapping of basic drugs occurs. As in the brain, P-gp and other export transporters are present in the placenta and function to limit fetal exposure to potentially toxic agents. The view that the placenta is an absolute barrier to drugs is, however, inaccurate, in part because a number of influx transporters are also present (Weier et al., 2008). The fetus is to some extent exposed to all drugs taken by the mother.

EXCRETION OF DRUGS

Drugs are eliminated from the body either unchanged by the process of excretion or converted to metabolites. Excretory organs, the lung excluded, eliminate polar compounds more efficiently than substances with high lipid solubility. Lipid-soluble drugs thus are not readily eliminated until they are metabolized to more polar compounds.

The kidney is the most important organ for excreting drugs and their metabolites. Substances excreted in the feces are principally unabsorbed orally ingested drugs or drug metabolites excreted either in the bile or secreted directly into the intestinal tract and not reabsorbed. Excretion of drugs in breast milk is important not because of the amounts eliminated, but because the excreted drugs are potential sources of unwanted pharmacological effects in the nursing infant (Buhimschi and Weiner, 2009). Excretion from the lung is important mainly for the elimination of anesthetic gases (Chapter 19).

Renal Excretion. Excretion of drugs and metabolites in the urine involves three distinct processes: glomerular filtration, active tubular secretion, and passive tubular reabsorption. Changes in overall renal function generally affect all three processes to a similar extent. Even in healthy persons, renal function is not constant. In neonates, renal function is low compared with body mass but matures rapidly within the first few months after birth. During adulthood, there is a slow decline in renal function, ~1% per year, so that in elderly patients a substantial degree of functional impairment may be present.

The amount of drug entering the tubular lumen by filtration depends on the glomerular filtration rate and the extent of plasma binding of the drug; only unbound drug is filtered. In the proximal renal tubule, active, carrier-mediated tubular secretion also may add drug to the tubular fluid. Transporters such as P-gp and the multidrug-resistance–associated protein type 2 (MRP2), localized in the apical brush-border membrane, are responsible for the secretion of amphipathic anions and conjugated metabolites (such as glucuronides, sulfates, and glutathione adducts), respectively (Chapters 5 and 6). Solute carrier transporters that are more selective for organic cationic drugs are involved in the secretion of organic bases. Membrane transporters, mainly located in the distal renal tubule, also are responsible for any active reabsorption of drug from the tubular lumen back into the systemic circulation; however, most such reabsorption occurs by non-ionic diffusion.

In the proximal and distal tubules, the non-ionized forms of weak acids and bases undergo net passive reabsorption. The concentration gradient for back-diffusion is created by the reabsorption of water with Na^+ and other inorganic ions. Since the tubular cells are less permeable to the ionized forms of weak electrolytes, passive reabsorption of these substances depends on the pH. When the tubular urine is made more alkaline, weak acids are largely ionized and thus are excreted more rapidly and to a greater extent. When the tubular urine is made more acidic, the fraction of drug ionized is reduced, and excretion is likewise reduced. Alkalinization and acidification of the urine have the opposite effects on the excretion of weak bases. In the treatment of drug poisoning, the excretion of some drugs can be hastened by appropriate alkalinization or acidification of the urine. Whether alteration of urine pH results in a significant change in drug elimination depends on the extent and persistence of the pH change and the contribution of pH-dependent passive reabsorption to total drug elimination. The effect is greatest for weak acids and bases with pK_a values in the range of urinary pH (5-8). However, alkalinization of urine can produce a 4-6-fold increase in excretion of a relatively strong acid such as salicylate when urinary pH is changed

from 6.4 to 8.0 and the fraction of non-ionized drug is reduced from 1% to 0.04%.

Biliary and Fecal Excretion. Transporters are also present in the canalicular membrane of the hepatocyte, and these actively secrete drugs and metabolites into bile. P-gp and BCRP (breast cancer resistance protein, or ABCG2) transport a plethora of amphipathic lipid-soluble drugs, whereas MRP2 is mainly involved in the secretion of conjugated metabolites of drugs (e.g., glutathione conjugates, glucuronides, and some sulfates). Ultimately, drugs and metabolites present in bile are released into the GI tract during the digestive process. Because secretory transporters also are expressed on the apical membrane of enterocytes, direct secretion of drugs and metabolites may occur from the systemic circulation into the intestinal lumen. Subsequently, drugs and metabolites can be reabsorbed back into the body from the intestine, which, in the case of conjugated metabolites such as glucuronides, may require their enzymatic hydrolysis by the intestinal microflora. Such enterohepatic recycling, if extensive, may prolong significantly the presence of a drug (or toxin) and its effects within the body prior to elimination by other pathways. For this reason, drugs may be given orally to bind substances excreted in the bile. In the case of mercury poisoning, for example, a resin can be administered orally that binds with dimethyl mercury excreted in the bile, thus preventing reabsorption and further toxicity.

Enterohepatic recycling also can be an advantage in the design of drugs. Ezetimibe is the first of a class of drugs that specifically reduces the intestinal absorption of cholesterol (Lipka, 2003). The drug is absorbed into the intestinal epithelial cell, where it is believed to interfere with the sterol transporter system, preventing both free cholesterol and plant sterols (phytosterols) from being transported into the cell from the intestinal lumen. The drug is absorbed rapidly and glucuronidated to an active metabolite in the intestinal cell before secretion into the blood. Absorbed ezetimibe is avidly taken up by the liver from the portal blood and excreted into the bile, resulting in low peripheral blood concentrations. The glucuronide conjugate is hydrolyzed and absorbed, and is equally effective in inhibiting sterol absorption. This enterohepatic recycling is responsible for a $t_{1/2}$ in the body of >20 hours. The principal benefit is a reduction in low-density lipoprotein cholesterol (see Chapter 31 and Dembowki and Davidson, 2009).

Excretion by Other Routes. Excretion of drugs into sweat, saliva, and tears is quantitatively unimportant. Elimination by these routes depends mainly on diffusion of the non-ionized lipid-soluble form of drugs through the epithelial cells of the glands and depends on the pH. Drugs excreted in the saliva enter the mouth, where they are usually swallowed. The concentration of some drugs in saliva parallels that in plasma. Saliva therefore may be a useful biological fluid in which to determine drug concentrations when it is difficult or inconvenient to obtain blood. The same principles apply to excretion of drugs in breast milk. Since milk is more acidic than plasma, basic compounds may be slightly concentrated in this fluid; conversely, the concentration of acidic compounds in the milk is lower than in plasma. Non-electrolytes, such as ethanol and urea, readily enter breast milk and reach the same concentration as in plasma, independent of the pH of the milk. Thus, the administration of drugs to breast-feeding women carries the general caution that the suckling infant will be exposed to some extent to the medication and/or its metabolites. In certain cases, such as treatment with the β blocker atenolol, the infant may be exposed to significant amounts of drug (Ito and Lee, 2003). Although excretion into hair and skin is quantitatively unimportant, sensitive methods of detection of drugs in these tissues have forensic significance.

METABOLISM OF DRUGS

The lipophilic characteristics of drugs that promote their passage through biological membranes and subsequent access to their sites of action hinder their excretion from the body. Renal excretion of unchanged drug is a major route of elimination for 25–30% of drugs administered to humans. The majority of therapeutic agents are lipophilic compounds filtered through the glomerulus and reabsorbed into the systemic circulation during passage through the renal tubules. The metabolism of drugs and other xenobiotics into more hydrophilic metabolites is essential for their elimination from the body, as well as for termination of their biological and pharmacological activity. In general, biotransformation reactions generate more polar, inactive metabolites that are readily excreted from the body. However, in some cases, metabolites with potent biological activity or toxic properties are generated. Many of the enzyme systems that transform drugs to inactive metabolites also generate biologically active metabolites of endogenous compounds, as in steroid biosynthesis. Understanding drug metabolism has spawned the new disciplinary focus of pharmacogenetics, which offers the promise that understanding the expression and activities of specific metabolizing enzyme isoforms in a given individual will permit the clinician to tailor treatments, particularly in chemotherapy (Dawood and Leyland-Jones, 2009), to maximize therapeutic outcomes and minimize risks of toxicity or drug-drug interactions.

Drug metabolism or biotransformation reactions are classified as either phase I functionalization reactions or phase II biosynthetic (conjugation) reactions. Phase I reactions introduce or expose a functional group on the parent compound such as occurs in hydrolysis reactions. Phase I reactions generally result in the loss of pharmacological activity, although there are examples of retention or enhancement of activity. In rare instances, metabolism is associated with an altered pharmacological activity. *Prodrugs* are pharmacologically inactive compounds designed to maximize the amount of the active species that reaches its site of action. Inactive prodrugs are converted rapidly to biologically active metabolites often by the hydrolysis of an ester or amide linkage. Such is the case with a number of angiotensin-converting enzyme (ACE) inhibitors employed in the management of high blood pressure. Enalapril, for instance, is relatively inactive until converted by esterase activity to the diacid enalaprilat. If not excreted rapidly into the urine, the products of

phase I biotransformation reactions then can react with endogenous compounds to form a highly water-soluble conjugate.

Phase II conjugation reactions lead to the formation of a covalent linkage between a functional group on the parent compound or phase I metabolite and endogenously derived glucuronic acid, sulfate, glutathione, amino acids, or acetate. These highly polar conjugates generally are inactive and are excreted rapidly in the urine and feces. An example of an active conjugate is the 6-glucuronide metabolite of morphine, which is a more potent analgesic than its parent.

The enzyme systems involved in the biotransformation of drugs are localized primarily in the liver, although every tissue examined has some metabolic activity. Other organs with significant metabolic capacity include the GI tract, kidneys, and lungs. Following oral administration of a drug, a significant portion of the dose may be metabolically inactivated in either the intestinal epithelium or the liver before the drug reaches the systemic circulation. This so-called first-pass metabolism significantly limits the oral availability of highly metabolized drugs. Within a given cell, most drug-metabolizing activity is found in the smooth endoplasmic reticulum and the cytosol, although drug biotransformations also can occur in the mitochondria, nuclear envelope, and plasma membrane. The enzyme systems involved in phase I reactions are located primarily in the endoplasmic reticulum, whereas the phase II conjugation enzyme systems are mainly cytosolic. Often, drugs biotransformed through a phase I reaction in the endoplasmic reticulum are conjugated at this same site or in the cytosolic fraction of the same cell in a sequential fashion. These biotransforming reactions are carried out by CYPs (cytochrome P450 isoforms) and by a variety of transferases. These enzyme families, the major reactions they catalyze, and their roles in drug metabolism and adverse drug responses are presented in detail in Chapter 6.

CLINICAL PHARMACOKINETICS

The fundamental tenet of clinical pharmacokinetics is that a relationship exists between the pharmacological effects of a drug and an accessible concentration of the drug (e.g., in blood or plasma). This relationship has been documented for many drugs and is of benefit in the therapeutic management of patients. For some drugs, no clear or simple relationship has been found between pharmacological effect and concentration in plasma, whereas for other drugs, routine measurement of drug concentration is impractical as part of therapeutic monitoring. In most cases, as depicted in Figure 2–1, the concentration of drug at its sites of action will be related to the concentration of drug in the systemic circulation. The pharmacological effect that results may be the clinical effect desired, a toxic effect, or in some cases an effect unrelated to the known therapeutic efficacy or toxicity. Clinical pharmacokinetics attempts to provide both a quantitative relationship between dose and effect and a framework within which to interpret measurements of concentrations of drugs in biological fluids and their adjustment through changes in dosing for the benefit of the patient. The importance of pharmacokinetics in patient care is based on the improvement in therapeutic efficacy and the avoidance of unwanted effects that can be attained by application of its principles when dosage regimens are chosen and modified.

The four most important parameters governing drug disposition are *bioavailability*, the fraction of drug absorbed as such into the systemic circulation; *volume of distribution,* a measure of the apparent space in the body available to contain the drug based on how much is given versus what is found in the systemic circulation; *clearance,* a measure of the body's efficiency in eliminating drug from the systemic circulation; and *elimination* $t_{1/2}$, a measure of the rate of removal of drug from the systemic circulation. We will deal with each of these parameters in turn, and will explore mathematical relationships that use them to describe the time course of plasma drug accumulation and to design dosage regimens based on physiologic and pathophysiologic variables of individual patients.

Clearance

Clearance is the most important concept to consider when designing a rational regimen for long-term drug administration. The clinician usually wants to maintain steady-state concentrations of a drug within a *therapeutic window* or range associated with therapeutic efficacy and a minimum of toxicity for a given agent. Assuming complete bioavailability, the steady-state concentration of drug in the body will be achieved when the rate of drug elimination equals the rate of drug administration. Thus:

$$\text{Dosing rate} = CL \cdot C_{ss} \qquad \text{(Equation 2–2)}$$

where CL is clearance of drug from the systemic circulation and C_{ss} is the steady-state concentration of drug. If the desired steady-state concentration of drug in plasma or blood is known, the rate of clearance of drug by the patient will dictate the rate at which the drug should be administered.

The concept of clearance is extremely useful in clinical pharmacokinetics because its value for a particular drug usually is constant over the range of concentrations encountered clinically. This is true because systems for elimination of drugs such as metabolizing enzymes and transporters usually are not saturated, and thus the absolute rate of elimination of the drug is essentially a linear function of its concentration in plasma. That is, the elimination of most drugs follows first-order kinetics, where a constant fraction of drug in the body is eliminated per unit of time. If mechanisms for elimination of a given drug become saturated, the kinetics approach zero order, in which a constant amount of drug is eliminated per unit of time.

Under such a circumstance, clearance (CL) will vary with the concentration of drug, often according to the equation

$$CL = v_m/(K_m + C) \qquad \text{(Equation 2–3)}$$

where K_m represents the concentration at which half the maximal rate of elimination is reached (in units of mass/volume) and v_m is equal to the maximal rate of elimination (in units of mass/time). Thus, clearance is derived in units of volume/time. This equation is analogous to the Michaelis-Menten equation for enzyme kinetics. Design of dosage regimens for drugs with zero-order elimination kinetics is more complex than when elimination is first-order (described later).

Principles of drug clearance are similar to those of renal physiology, where, e.g., creatinine clearance is defined as the rate of elimination of creatinine in the urine relative to its concentration in plasma. At the simplest level, clearance of a drug is its rate of elimination by all routes normalized to the concentration of drug C in some biological fluid where measurement can be made:

$$CL = \text{rate of elimination}/C \qquad \text{(Equation 2–4)}$$

Thus, when clearance is constant, the rate of drug elimination is directly proportional to drug concentration. Note that clearance does not indicate how much drug is being removed, but rather the volume of biological fluid such as blood or plasma from which drug would have to be completely removed to account for the clearance per unit of body weight (e.g., mL/min per kg). Clearance can be defined further as blood clearance (CL_b), plasma clearance (CL_p), or clearance based on the concentration of unbound drug (CL_u), depending on the measurement made (C_b, C_p, or C_u).

Clearance of drug by several organs is additive. Elimination of drug from the systemic circulation may occur as a result of processes that occur in the kidney, liver, and other organs. Division of the rate of elimination by each organ by a concentration of drug (e.g., plasma concentration) will yield the respective clearance by that organ. Added together, these separate clearances will equal systemic clearance:

$$CL_{renal} + CL_{hepatic} + CL_{other} = CL \qquad \text{(Equation 2–5)}$$

Other routes of elimination could include loss of drug in saliva or sweat, secretion into the GI tract, volatile elimination from the lung, and metabolism at other sites such as skin. Note that changes in clearance in one organ will change the overall calculation; thus, renal failure alters CL for drugs excreted unchanged from the plasma.

Systemic clearance may be determined at steady state by using Equation 2–2. For a single dose of a drug with complete bioavailability and first-order kinetics of elimination, systemic clearance may be determined from mass balance and the integration of Equation 2–4 over time:

$$CL = \text{Dose}/AUC \qquad \text{(Equation 2–6)}$$

where AUC is the total area under the curve that describes the measured concentration of drug in the systemic circulation as a function of time (from zero to infinity), as in Figure 2–6.

Examples. The plasma clearance for the antibiotic cephalexin is 4.3 mL/min/kg, with 90% of the drug excreted unchanged in the urine. For a 70-kg man, the clearance from plasma would be 301 mL/min, with renal clearance accounting for 90% of this elimination. In other words, the kidney is able to excrete cephalexin at a rate such that the drug is completely removed (cleared) from ~270 mL of plasma every minute (renal clearance = 90% of total clearance). Because clearance usually is assumed to remain constant in a medically stable patient (e.g., no acute decline in kidney function), the rate of elimination of cephalexin will depend on the concentration of drug in the plasma (Equation 2–4).

The β adrenergic receptor antagonist propranolol is cleared from the blood at a rate of 16 mL/min/ kg (or 1120 mL/min in a 70-kg man), almost exclusively by the liver. Thus, the liver is able to remove the amount of propranolol contained in 1120 mL of blood in 1 minute. Even though the liver is the dominant organ for elimination, the plasma clearance of some drugs exceeds the rate of blood flow to this organ. Often this is so because the drug partitions readily into red blood cells (RBCs) and the rate of drug delivered to the eliminating organ is considerably higher than expected from measurement of its concentration in plasma. The relationship between plasma (subscript p; acellular) and blood (subscript b; all components) clearance at steady state is given by

$$\frac{CL_p}{CL_b} = \frac{C_b}{C_p} = 1 + H\left[\frac{C_{rbc}}{C_p} - 1\right] \qquad \text{(Equation 2–7)}$$

Clearance from the blood therefore may be estimated by dividing the plasma clearance by the drug's blood-to-plasma concentration ratio, obtained from knowledge of the hematocrit ($H = 0.45$) and the red cell to plasma concentration ratio. In most instances, the blood clearance will be less than liver blood flow (1.5 L/min) or, if renal excretion also is involved, the sum of the blood flows to each eliminating organ. For example, the plasma clearance of the immunomodulator, tacrolimus, ~2 L/min, is more than twice the hepatic plasma flow rate and even exceeds the organ's blood flow despite the fact that the liver is the predominant site of this drug's extensive metabolism. However, after taking into account the extensive distribution of tacrolimus into red cells, its clearance from the blood is only ~63 mL/min, and it is actually a low- rather than high-clearance drug, as might be interpreted from the plasma clearance value alone. Sometimes, however, clearance from the blood by metabolism exceeds liver blood flow, and this indicates extrahepatic metabolism. In the case of the β_1 receptor antagonist, esmolol, the blood clearance value (11.9 L/min) is greater than cardiac output (~5.3 L/min) because the drug is metabolized efficiently by esterases present in red blood cells.

A further definition of clearance is useful for understanding the effects of pathological and physiological variables on drug elimination, particularly with respect to an individual organ. The rate of presentation of drug to the organ is the product of blood flow (Q) and the arterial drug concentration (C_A); and the rate of exit of drug from the organ is the product of blood flow and the venous drug concentration (C_V). The difference between these rates at steady state is the rate of drug elimination by that organ:

$$\begin{aligned}\text{Rate of elimination} &= Q \cdot C_A - Q \cdot C_V \\ &= Q(C_A - C_V)\end{aligned} \qquad \text{(Equation 2–8)}$$

Division of Equation 2–8 by the concentration of drug entering the organ of elimination C_A yields an expression for clearance of the drug by the organ in question:

$$CL_{organ} = Q\left[\frac{C_A - C_V}{C_A}\right] = Q \cdot E \qquad \text{(Equation 2–9)}$$

The expression $(C_A - C_V)/C_A$ in Equation 2–9 can be referred to as the *extraction ratio (E)* of the drug. While not employed in general medical practice, calculations of a drug's extraction ratio(s) are useful for modeling the effects of disease of a given metabolizing organ on clearance and in the design of ideal therapeutic properties of drugs in development.

Hepatic Clearance. The concepts developed in Equation 2–9 have important implications for drugs that are eliminated by the liver. Consider a drug that is removed efficiently from the blood by hepatic processes—metabolism and/or excretion of drug into the bile. In this instance, the concentration of drug in the blood leaving the liver will be low, the extraction ratio will approach unity, and the clearance of the drug from blood will become limited by hepatic blood flow. Drugs that are cleared efficiently by the liver (e.g., drugs in Appendix II with systemic clearances >6 mL/min/kg, such as diltiazem, imipramine, lidocaine, morphine, and propranolol) are restricted in their rate of elimination not by intra-hepatic processes but by the rate at which they can be transported in the blood to the liver.

Additional complexities also may be considered. For example, the equations presented earlier do not account for drug binding to components of blood and tissues, nor do they permit an estimation of the intrinsic capacity of the liver to eliminate a drug in the absence of limitations imposed by blood flow, termed *intrinsic clearance*. In biochemical terms and under first-order conditions, intrinsic clearance is a measure of the ratio of the Michaelis-Menten kinetic parameters for the eliminating process (i.e., v_m/K_m) and thus reflects the maximum metabolic or transport capability of the clearing organ. Extensions of the relationships of Equation 2–9 to include expressions for protein binding and intrinsic clearance have been proposed for a number of models of hepatic elimination (Hallifax and Houston, 2009). Models indicate that when the capacity of the eliminating organ to metabolize the drug is large in comparison with the rate of presentation of drug to the organ, clearance will approximate the organ's blood flow. By contrast, when the drug-metabolizing capacity is small in comparison with the rate of drug presentation, clearance will be proportional to the unbound fraction of drug in blood and the drug's intrinsic clearance. Appreciation of these concepts allows understanding of a number of possibly puzzling experimental results. For example, enzyme induction or hepatic disease may change the rate of drug metabolism in an isolated hepatic microsomal enzyme system but not change clearance in the whole animal. For a drug with a high extraction ratio, clearance is limited by blood flow, and changes in intrinsic clearance owing to enzyme induction or hepatic disease should have little effect. Similarly, for drugs with high extraction ratios, changes in protein binding owing to disease or competitive binding interactions by other drugs should have little effect on clearance. Conversely, changes in intrinsic clearance and protein binding will affect the clearance of drugs with low intrinsic clearances such as warfarin, and thus extraction ratios, but changes in blood flow will have little effect.

Renal Clearance. Renal clearance of a drug results in its appearance in the urine. In considering the impact of renal disease on the clearance of a drug, complications that relate to filtration, active secretion by the kidney tubule, and reabsorption from it must be considered along with blood flow. The rate of filtration of a drug depends on the volume of fluid that is filtered in the glomerulus and the unbound concentration of drug in plasma, because drug bound to protein is not filtered. The rate of secretion of drug by the kidney will depend on the drug's intrinsic clearance by the transporters involved in active secretion as affected by the drug's binding to plasma proteins, the degree of saturation of these transporters, and the rate of delivery of the drug to the secretory site. In addition, processes involved in drug reabsorption from the tubular fluid must be considered. The influences of changes in protein binding and blood flow and in the number of functional nephrons are analogous to the examples given earlier for hepatic elimination.

DISTRIBUTION

Volume of Distribution. Volume is a second fundamental parameter that is useful in considering processes of drug disposition. The volume of distribution (V) relates the amount of drug in the body to the concentration of drug (C) in the blood or plasma depending on the fluid measured. This volume does not necessarily refer to an identifiable physiological volume but rather to the fluid volume that would be required to contain all of the drug in the body at the same concentration measured in the blood or plasma:

$$\text{Amount of drug in body}/V = C \quad \text{or} \quad V = \text{amount of drug in body}/C \qquad \text{(Equation 2–10)}$$

A drug's volume of distribution therefore reflects the extent to which it is present in extravascular tissues and not in the plasma. It is reasonable to view V as an imaginary volume, since for many drugs the volume of distribution exceeds the known volume of any and all body compartments. For example, the value of V for the highly lipophilic anti-malarial chloroquine is some 15,000 L, yet the plasma volume of a typical 70-kg man is 3 L, blood volume is ~5.5 L, extracellular fluid volume outside the plasma is 12 L, and the volume of total-body water is ~42 L.

Many drugs exhibit volumes of distribution far in excess of these values. For example, if 500 μg of the cardiac glycoside digoxin were in the body of a 70-kg subject, a plasma concentration of ~0.75 ng/mL would be observed. Dividing the amount of drug in the body by the plasma concentration yields a volume of distribution for digoxin of ~667 L, or a value ~15 times greater than the total-body volume of a 70-kg man. In fact, digoxin distributes preferentially to muscle and adipose tissue and to its specific receptors (Na^+,K^+-ATPase), leaving a very small amount of drug in the plasma to be measured. For drugs that are bound extensively to plasma proteins

but that are not bound to tissue components, the volume of distribution will approach that of the plasma volume because drug bound to plasma protein is measurable in the assay of most drugs. In contrast, certain drugs have high volumes of distribution even though most of the drug in the circulation is bound to albumin because these drugs are also sequestered elsewhere.

The volume of distribution may vary widely depending on the relative degrees of binding to high-affinity receptor sites, plasma and tissue proteins, the partition coefficient of the drug in fat, and accumulation in poorly perfused tissues. As might be expected, the volume of distribution for a given drug can differ according to patient's age, gender, body composition, and presence of disease. Total-body water of infants younger than 1 year of age, for example, is 75–80% of body weight, whereas that of adult males is 60% and that of females is 55%.

Several volume terms are used commonly to describe drug distribution, and they have been derived in a number of ways. The volume of distribution defined in Equation 2–10 considers the body as a single homogeneous compartment. In this one-compartment model, all drug administration occurs directly into the central compartment, and distribution of drug is instantaneous throughout the volume (V). Clearance of drug from this compartment occurs in a first-order fashion, as defined in Equation 2–4; that is, the amount of drug eliminated per unit of time depends on the amount (concentration) of drug in the body compartment. Figure 2–4A and Equation 2–11 describe the decline of plasma concentration with time for a drug introduced into this central compartment:

$$C = [\text{dose}/V][e^{-kt}] \qquad \text{(Equation 2–11)}$$

where k is the rate constant for elimination that reflects the fraction of drug removed from the compartment per unit of time. This rate constant is inversely related to the $t_{1/2}$ of the drug [$kt_{1/2} = 0.693 = \ln 2$].

The idealized one-compartment model discussed earlier does not describe the entire time course of the plasma concentration. That is, certain tissue reservoirs can be distinguished from the central compartment, and the drug concentration appears to decay in a manner that can be described by multiple exponential terms (Figure 2–4B).

Rate of Distribution. The multiple exponential decay observed for a drug that is eliminated from the body with first-order kinetics results from differences in the rates at which the drug equilibrates to and within tissues. The rate of equilibration will depend on the ratio of the perfusion of the tissue to the partition of drug into the tissue. In many cases, groups of tissues with similar perfusion-partition ratios all equilibrate at essentially the same rate such that only one apparent phase of distribution is seen (rapid initial fall of concentration of intravenously injected drug, as in Figure 2–4B). It is as though the drug starts in a "central" volume (Figure 2–1), which

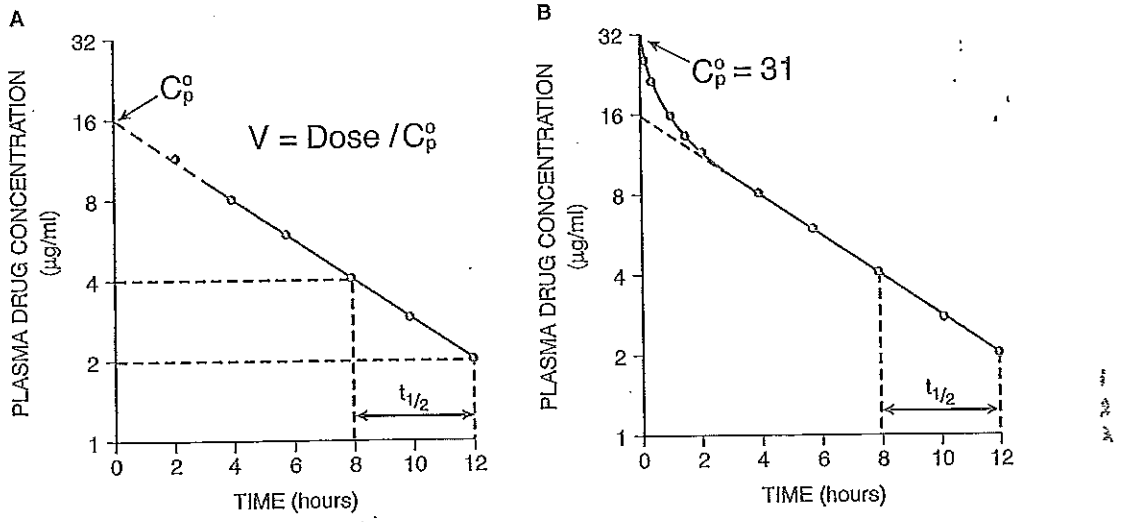

Figure 2–4 *Plasma concentration-time curves following intravenous administration of a drug (500 mg) to a 70-kg patient.* A. Drug concentrations are measured in plasma at 2-hour intervals following drug administration. The semi-logarithmic plot of plasma concentration (C_p) versus time appears to indicate that the drug is eliminated from a single compartment by a first-order process (Equation 2–11) with a $t_{1/2}$ of 4 hours ($k = 0.693/t_{1/2} = 0.173\ hr^{-1}$). The volume of distribution (V) may be determined from the value of C_p obtained by extrapolation to $t = 0$ ($C_p^o = 16\ \mu g/mL$). Volume of distribution (Equation 2–10) for the one-compartment model is 31.3 L, or 0.45 L/kg ($V = \text{dose}/C_p^o$). The clearance for this drug is 90 mL/min; for a one-compartment model, $CL = kV$. B. Sampling before 2 hours indicates that in fact the drug follows multi-exponential kinetics. The terminal disposition $t_{1/2}$ is 4 hours, clearance is 84 mL/min (Equation 2–6), V_{area} is 29 L (Equation 2–11), and V_{ss} is 26.8 L. The initial or "central" distribution volume for the drug ($V_1 = \text{dose}/C_p^o$) is 16.1 L. The example chosen indicates that multicompartment kinetics may be overlooked when sampling at early times is neglected. In this particular case, there is only a 10% error in the estimate of clearance when the multicompartment characteristics are ignored. For many drugs, multicompartment kinetics may be observed for significant periods of time, and failure to consider the distribution phase can lead to significant errors in estimates of clearance and in predictions of the appropriate dosage. Also, the difference between the "central" distribution volume and other terms reflecting wider distribution is important in deciding a loading dose strategy.

consists of plasma and tissue reservoirs that are in rapid equilibrium with it, and distributes to a "final" volume, at which point concentrations in plasma decrease in a log-linear fashion with a rate constant of k (Figure 2–4B). The multicompartment model of drug disposition can be viewed as though the blood and highly perfused lean organs such as heart, brain, liver, lung, and kidneys cluster as a single central compartment, whereas more slowly perfused tissues such as muscle, skin, fat, and bone behave as the final compartment (the tissue compartment).

If the pattern or ratio of blood flow to various tissues changes within an individual or differs among individuals, rates of drug distribution to tissues also will change. However, changes in blood flow also may cause some tissues that were originally in the "central" volume to equilibrate sufficiently more slowly so as to appear only in the "final" volume. This means that central volumes will appear to vary with disease states that cause altered regional blood flow (such as would be seen in cirrhosis of the liver). After an intravenous bolus dose, drug concentrations in plasma may be higher in individuals with poor perfusion (e.g., shock) than they would be if perfusion were better. These higher systemic concentrations may in turn cause higher concentrations (and greater effects) in tissues such as brain and heart, whose usually high perfusion has not been reduced by the altered hemodynamic state. Thus, the effect of a drug at various sites of action can vary depending on perfusion of these sites.

Multicompartment Volume Terms. Two different terms have been used to describe the volume of distribution for drugs that follow multiple exponential decay. The first, designated V_{area}, is calculated as the ratio of clearance to the rate of decline in concentration during the elimination (final) phase of the logarithmic concentration versus time curve:

$$V_{area} = \frac{CL}{k} = \frac{dose}{k \cdot AUC} \qquad \text{(Equation 2–12)}$$

The estimation of this parameter is straightforward, and the volume term may be determined after administration of a single dose of drug by the intravenous or oral route (where the value for the dose must be corrected for bioavailability). However, another multicompartment volume of distribution term may be more useful, especially when the effect of disease states on pharmacokinetics is to be determined. The volume of distribution at steady state (V_{ss}) represents the volume in which a drug would appear to be distributed during steady state if the drug existed throughout that volume at the same concentration as that in the measured fluid (plasma or blood). V_{ss} also may be appreciated as shown in Equation 2–13, where V_c is the volume of distribution of drug in the central compartment and V_T is the volume term for drug in the tissue compartment:

$$V_{ss} = V_C + V_T \qquad \text{(Equation 2–13)}$$

Although V_{area} is a convenient and easily calculated parameter, it varies when the rate constant for drug elimination changes, even when there has been no change in the distribution space. This is so because the terminal rate of decline of the concentration of drug in blood or plasma depends not only on clearance but also on the rates of distribution of drug between the "central" and "final" volumes. V_{ss} does not suffer from this disadvantage. The value of V_{area} will always be greater than V_{ss}. As will be described, the extent of this difference will depend on the difference in $t_{1/2}$ observed during a dosing interval at steady state versus the value found for the terminal $t_{1/2}$. V_{ss} can only be determined accurately if the drug is given intravenously.

Steady State. Equation 2–2 (dosing rate = CL · C_{ss}) indicates that a steady-state concentration eventually will be achieved when a drug is administered at a constant rate. At this point, drug elimination (the product of clearance and concentration; Equation 2–4) will equal the rate of drug availability. This concept also extends to regular intermittent dosage (e.g., 250 mg of drug every 8 hours). During each interdose interval, the concentration of drug rises with absorption and falls by elimination. At steady state, the entire cycle is repeated identically in each interval (Figure 2–5). Equation 2–2

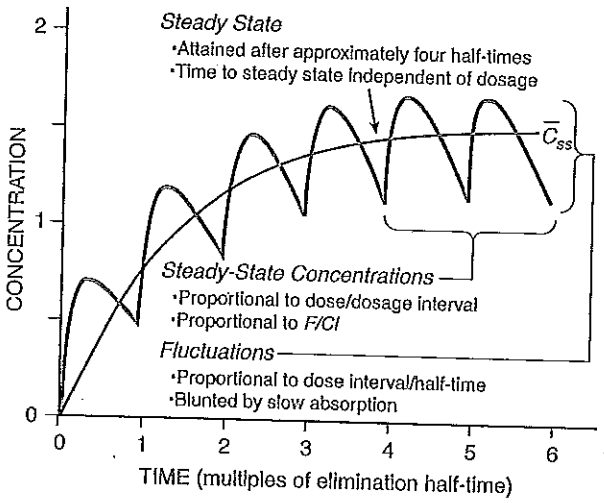

Figure 2–5 *Fundamental pharmacokinetic relationships for repeated administration of drugs.* The blue line is the pattern of drug accumulation during repeated administration of a drug at intervals equal to its elimination half-time when drug absorption is 10 times as rapid as elimination. As the rate of absorption increases, the concentration maxima approach 2 and the minima approach 1 during the steady state. The black line depicts the pattern during administration of equivalent dosage by continuous intravenous infusion. Curves are based on the one-compartment model. Average concentration ($\bar{C}_{ss}$) when the steady state is attained during intermittent drug administration is

where F is fractional bioavailability of the dose and T is dosage interval (time). By substitution of infusion rate for $F \cdot$ dose/T, the formula is equivalent to Equation 2–2 and provides the concentration maintained at steady state during continuous intravenous infusion.

still applies for intermittent dosing, but it now describes the average steady-state drug concentration ($\bar{C}_{ss}$) during an interdose interval.

Half-Life. The $t_{1/2}$ is the time it takes for the plasma concentration to be reduced by 50%. For a one-compartment model (Figure 2–4A), $t_{1/2}$ may be determined readily by inspection and used to make decisions about drug dosage. However, as indicated in Figure 2–4B, drug concentrations in plasma often follow a multi-exponential pattern of decline, reflecting the changing amount of drug in the body. When using pharmacokinetics to calculate drug dosing in disease, note in Equation 2-14 that $t_{1/2}$ changes as a function of both clearance and volume of distribution.

$$t_{1/2} \cong 0.693 \cdot V_{ss}/CL \qquad \text{(Equation 2–14)}$$

This $t_{1/2}$ reflects the decline of systemic drug concentrations during a dosing interval at steady-state as depicted in Figure 2–5.

Examples of the marked differences in terminal versus steady-state $t_{1/2}$ (which reflect the difference between V_{area} and V_{ss}) are gentamicin and indomethacin. A terminal $t_{1/2}$ of 53 hours is observed for gentamicin (versus the steady-state value of 2-3 hours); biliary cycling probably is responsible for the 120-hour terminal value for indomethacin (compared to the steady-state value of 2.4 hours). The appreciation of longer terminal $t_{1/2}$ values for some medications may relate to their accumulation in tissues during chronic dosing or shorter periods of high-dose treatment. Such is the case for gentamicin, where the terminal $t_{1/2}$ is associated with renal and ototoxicities. The relevance of a particular $t_{1/2}$ may be defined in terms of the fraction of the clearance and volume of distribution that is related to each $t_{1/2}$ and whether plasma concentrations or amounts of drug in the body are best related to measures of response.

Clearance is the measure of the body's ability to eliminate a drug; thus, as clearance decreases, owing to a disease process, e.g., $t_{1/2}$ would be expected to increase. However, this reciprocal relationship is valid only when the disease does not change the volume of distribution. For example, the $t_{1/2}$ of diazepam increases with increasing age; however, it is not clearance that changes as a function of age but rather the volume of distribution. Similarly, changes in protein binding of a drug may affect its clearance as well as its volume of distribution, leading to unpredictable changes in $t_{1/2}$ as a function of disease. The $t_{1/2}$ of tolbutamide, e.g., decreases in patients with acute viral hepatitis in a fashion opposite from what one might expect. The disease alters the drug's protein binding in both plasma and tissues, causing no change in volume of distribution but an increase in clearance because higher concentrations of unbound drug are present in the bloodstream.

Although it can be a poor index of drug elimination from the body *per se* (disappearance of drug may be the result of formation of undetected metabolites that have therapeutic or unwanted effects), the $t_{1/2}$ defined in Equation 2–14 provides an approximation of the time required to reach steady state after a dosage regimen is initiated or changed (e.g., four half-lives to reach ~94% of a new steady state) and a means to estimate the appropriate dosing interval (see the later discussion and Sahin and Benet, 2008).

Extent and Rate of Bioavailability

Bioavailability. It is important to distinguish between the rate and extent of drug absorption and the amount of drug that ultimately reaches the systemic circulation. The amount of the drug that reaches the systemic circulation depends not only on the administered dose but also on the fraction of the dose (F) that is absorbed and escapes any first-pass elimination. This fraction is the drug's *bioavailability*. Reasons for incomplete absorption were discussed earlier. Also, as noted previously, if the drug is metabolized in the intestinal epithelium or the liver, or excreted in bile, some of the active drug absorbed from the GI tract will be eliminated before it can reach the general circulation and be distributed to its sites of action.

Knowing the extraction ratio (E_H) for a drug across the liver (Equation 2–9), it is possible to predict the maximum oral availability (F_{max}), assuming that hepatic elimination follows first-order processes:

$$F_{max} = 1 - E_H = 1 - (CL_{hepatic}/Q_{hepatic}) \qquad \text{(Equation 2–15)}$$

Thus, if the hepatic blood clearance for the drug is large relative to hepatic blood flow, the extent of availability will be low when the drug is given orally (e.g., lidocaine or propranolol). This reduction in availability is a function of the physiological site from which absorption takes place, and no modification of dosage form will improve the availability under conditions of linear kinetics. Incomplete absorption and/or intestinal metabolism following oral dosing will, in practice, reduce this predicted maximal value of F.

When drugs are administered by a route that is subject to first-pass loss, the equations presented previously that contain the terms *dose* or *dosing rate* (Equations 2–2, 2–6, 2–11, and 2–12) also must include the bioavailability term F such that the available dose or dosing rate is used. For example, Equation 2–2 is modified to

$$F \cdot \text{dosing rate} = CL \cdot C_{ss} \qquad \text{(Equation 2–16)}$$

where the value of F is between 0 and 1. The value of F varies widely for drugs administered by mouth. Etidronate, a bisphosphonate used to stabilize bone matrix in the treatment of Paget's disease and osteoporosis, has an F of 0.03, meaning that only 3% of the drug appears in the bloodstream following oral dosing. In the case of etidronate,

therapy using oral administration is still useful, and the dose of the drug administered per kilogram is larger than would be given by injection.

Rate of Absorption. Although the rate of drug absorption does not, in general, influence the average steady-state concentration of the drug in plasma, it may still influence drug therapy. If a drug is absorbed rapidly (e.g., a dose given as an intravenous bolus) and has a small "central" volume, the concentration of drug initially will be high. It will then fall as the drug is distributed to its "final" (larger) volume (Figure 2–4B). If the same drug is absorbed more slowly (e.g., by slow infusion), a significant amount of the drug will be distributed while it is being administered, and peak concentrations will be lower and will occur later. Controlled-release oral preparations are designed to provide a slow and sustained rate of absorption in order to produce smaller fluctuations in the plasma concentration-time profile during the dosage interval compared with more immediate-release formulations. A given drug may act to produce both desirable and undesirable effects at several sites in the body, and the rates of distribution of drug to these sites may not be the same. The relative intensities of these different effects of a drug thus may vary transiently when its rate of administration is changed. Since the beneficial, nontoxic effects of drugs are based on knowledge of an ideal or desired plasma concentration range, maintaining that range while avoiding large swings between peak and trough concentrations can improve therapeutic outcome.

Nonlinear Pharmacokinetics

Nonlinearity in pharmacokinetics (i.e., changes in such parameters as clearance, volume of distribution, and $t_{1/2}$ as a function of dose or concentration of drug) usually is due to saturation of either protein binding, hepatic metabolism, or active renal transport of the drug.

Saturable Protein Binding. As the molar concentration of drug increases, the unbound fraction eventually also must increase (as all binding sites become saturated). This usually occurs only when drug concentrations in plasma are in the range of tens to hundreds of micrograms per milliliter. For a drug that is metabolized by the liver with a low intrinsic clearance-extraction ratio, saturation of plasma-protein binding will cause both V and CL to increase as drug concentrations increase; $t_{1/2}$ thus may remain constant (Equation 2–14). For such a drug, C_{ss} will not increase linearly as the rate of drug administration is increased. For drugs that are cleared with high intrinsic clearance-extraction ratios, C_{ss} can remain linearly proportional to the rate of drug administration. In this case, hepatic clearance will not change, and the increase in V will increase the half-time of disappearance by reducing the fraction of the total drug in the body that is delivered to the liver per unit of time. Most drugs fall between these two extremes, and the effects of nonlinear protein binding may be difficult to predict.

Saturable Elimination. In this situation, the Michaelis-Menten equation (Equation 2–3) usually describes the nonlinearity. All active processes are undoubtedly saturable, but they will appear to be linear if values of drug concentrations encountered in practice are much less than K_m. When drug concentrations exceed K_m, nonlinear kinetics are observed. The major consequences of saturation of metabolism or transport are the opposite of those for saturation of protein binding. Saturation of protein binding will lead to increased CL because CL increases as drug concentration increases, whereas saturation of metabolism or transport may decrease CL. When both conditions are present simultaneously, they may virtually cancel each others' effects, and surprisingly linear kinetics may result; this occurs over a certain range of concentrations for salicylic acid, for example.

Saturable metabolism causes oral first-pass metabolism to be less than expected (higher F), and there is a greater fractional increase in C_{ss} than the corresponding fractional increase in the rate of drug administration. The latter can be seen most easily by substituting Equation 2–3 into Equation 2–2 and solving for the steady-state concentration:

$$C_{ss} = \frac{\text{dosing rate} \cdot K_m}{v_m - \text{dosing rate}} \qquad \text{(Equation 2–17)}$$

As the dosing rate approaches the maximal elimination rate (v_m), the denominator of Equation 2–17 approaches zero, and C_{ss} increases disproportionately. Because saturation of metabolism should have no effect on the volume of distribution, clearance and the relative rate of drug elimination decrease as the concentration increases; therefore, the log C_p time curve is concave-decreasing until metabolism becomes sufficiently desaturated and first-order elimination is present. Thus, the concept of a constant $t_{1/2}$ is not applicable to nonlinear metabolism occurring in the usual range of clinical concentrations. Consequently, changing the dosing rate for a drug with nonlinear metabolism is difficult and unpredictable because the resulting steady state is reached more slowly, and importantly, the effect is disproportionate to the alteration in the dosing rate.

The anti-seizure medication phenytoin provides an example of a drug for which metabolism becomes saturated in the therapeutic range of concentrations. Its $t_{1/2}$ is 6-24 hours. For clearance, K_m (5-10 mg/L) is typically near the lower end of the therapeutic range (10-20 mg/L). For some individuals, especially young children and newborns being treated for emergent seizures, K_m may be as low as 1 mg/L. If, for an adult, the target concentration is 15 mg/L and this is attained at a dosing rate of 300 mg/day, then from Equation (2–17), v_m equals 320 mg/day. For such a patient, a dose that is 10% less than optimal (i.e., 270 mg/day) will produce a C_{ss} of 5 mg/L, well below the desired value. In contrast, a dose that is 10% greater than optimal (330 mg/day) will exceed metabolic capacity (by 10 mg/day) and cause a long, slow and unending climb in concentration during which toxicity will occur. Dosage cannot be controlled so precisely (<10% error). Therefore, for patients in whom the target concentration for phenytoin is more than ten times greater than the K_m, alternating between inefficacious therapy and toxicity is almost unavoidable. For a drug such as phenytoin that has a narrow therapeutic index and exhibits nonlinear metabolism, therapeutic drug monitoring (described later) is most important. When the patient is a neonate, appreciation of this concept is of particular concern because signs and symptoms of toxicity are particularly difficult to monitor. In such cases, a pharmacokinetic consult is appropriate.

Design and Optimization of Dosage Regimens

Following administration of a dose of drug, its effects usually show a characteristic temporal pattern (Figure 2–6).

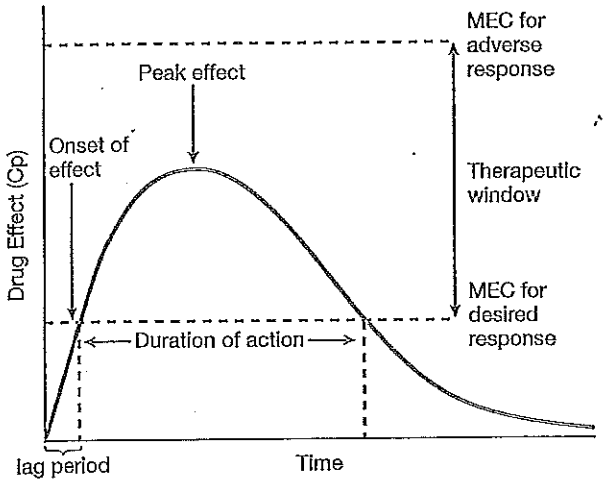

Figure 2–6 *Temporal characteristics of drug effect and relationship to the therapeutic window (e.g., single dose, oral administration).* A lag period is present before the plasma drug concentration (Cp) exceeds the minimum effective concentration (MEC) for the desired effect. Following onset of the response, the intensity of the effect increases as the drug continues to be absorbed and distributed. This reaches a peak, after which drug elimination results in a decline in Cp and in the effect's intensity. Effect disappears when the drug concentration falls below the MEC. Accordingly, the duration of a drug's action is determined by the time period over which concentrations exceed the MEC. An MEC exists for each adverse response, and if drug concentration exceeds this, toxicity will result. The therapeutic goal is to obtain and maintain concentrations within the therapeutic window for the desired response with a minimum of toxicity. Drug response below the MEC for the desired effect will be subtherapeutic; above the MEC for an adverse effect, the probability of toxicity will increase. Increasing or decreasing drug dosage shifts the response curve up or down the intensity scale and is used to modulate the drug's effect. Increasing the dose also prolongs a drug's duration of action but at the risk of increasing the likelihood of adverse effects. Unless the drug is nontoxic (e.g., penicillins), increasing the dose is not a useful strategy for extending the duration of action. Instead, another dose of drug should be given, timed to maintain concentrations within the therapeutic window. The area under the blood concentration-time curve (area under the curve, or AUC, shaded in gray) can be used to calculate the clearance (Equation 2–6) for first-order elimination. The AUC is also used as a measure of bioavailability (defined as 100% for an intravenously administered drug). Bioavailability will be <100% for orally administered drugs, due mainly to incomplete absorption and first-pass metabolism and elimination.

Onset of the effect is preceded by a lag period, after which the magnitude of the effect increases to a maximum and then declines; if a further dose is not administered, the effect eventually disappears as the drug is eliminated. This time course reflects changes in the drug's concentration as determined by the pharmacokinetics of its absorption, distribution, and elimination. Accordingly, the intensity of a drug's effect is related to its concentration above a minimum effective concentration, whereas the duration of the drug's effect reflects the length of time the drug level is above this value. These considerations, in general, apply to both desired and undesired (adverse) drug effects, and as a result, a *therapeutic window* exists that reflects a concentration range that provides efficacy without unacceptable toxicity.

Similar considerations apply after multiple dosing associated with long-term therapy, and they determine the amount and frequency of drug administration to achieve an optimal therapeutic effect. In general, the lower limit of a drug's therapeutic range is approximately equal to the drug concentration that produces about half the greatest possible therapeutic effect, and the upper limit of the therapeutic range is such that no more than 5-10% of patients will experience a toxic effect. For some drugs, this may mean that the upper limit of the range is no more than twice the lower limit. Of course, these figures can be highly variable, and some patients may benefit greatly from drug concentrations that exceed the therapeutic range, whereas others may suffer significant toxicity at much lower values (e.g., with digoxin).

For a limited number of drugs, some effect of the drug is easily measured (e.g., blood pressure, blood glucose) and can be used to optimize dosage using a trial-and-error approach. Even in an ideal case, certain quantitative issues arise, such as how often to change dosage and by how much. These usually can be settled with simple rules of thumb based on the principles discussed (e.g., change dosage by no more than 50% and no more often than every 3-4 half-lives). Alternatively, some drugs have very little dose-related toxicity, and maximum efficacy usually is desired. In such cases, doses well in excess of the average required will ensure efficacy (if this is possible) and prolong drug action. Such a "maximal dose" strategy typically is used for penicillins.

For many drugs, however, the effects are difficult to measure (or the drug is given for prophylaxis), toxicity and lack of efficacy are both potential dangers, or the therapeutic index is narrow. In these circumstances, doses must be titrated carefully, and drug dosage is limited by toxicity rather than efficacy. Thus, the therapeutic goal is to maintain steady-state drug levels within the therapeutic window. For most drugs, the actual concentrations associated with this desired range are not known and need not be known. It is sufficient to understand that efficacy and toxicity generally depend on concentration and how drug dosage and frequency of administration affect the drug level. However, for a small number of drugs for which there is a small (2-3 fold) difference between concentrations resulting in efficacy and toxicity (e.g., digoxin, theophylline, lidocaine, aminoglycosides, cyclosporine, tacrolimus, sirolimus, warfarin, and anticonvulsants), a plasma concentration range associated with effective therapy has been defined. In these cases, a target-level strategy is reasonable, wherein a desired (target) steady-state concentration of the drug (usually in plasma) associated with efficacy and minimal toxicity is chosen, and a dosage is computed that is expected to achieve this value. Drug concentrations are subsequently measured, and dosage is adjusted if necessary to approximate the target more closely (described later).

Maintenance Dose

In most clinical situations, drugs are administered in a series of repetitive doses or as a continuous infusion to maintain a steady-state concentration of drug associated with the therapeutic window. Calculation of the appropriate maintenance dosage is a primary goal. To maintain the chosen steady-state or target concentration, the rate of drug administration is adjusted such that the rate of input equals the rate of loss. This relationship was defined previously in Equations 2–2 and 2–16 and is expressed here in terms of the desired target concentration:

$$\text{Dosing rate} = \text{target } C_p \cdot CL/F \qquad \text{(Equation 2–18)}$$

If the clinician chooses the desired concentration of drug in plasma and knows the clearance and bioavailability for that drug in a particular patient, the appropriate dose and dosing interval can be calculated.

Example. Oral digoxin is to be used as a maintenance dose to gradually "digitalize" a 63 year old, 84-kg patient with congestive heart failure. A steady-state plasma concentration of 0.7-0.9 ng/mL is selected as an appropriate conservative target based on prior knowledge of the action of the drug in patients with heart failure to maintain levels at or belowin the 0.5-1.0 ng/mL range (Bauman et al., 2006). Based on the fact that the patient's creatinine clearance (CL_{Cr}) is 56 mL/min, digoxin's clearance may be estimated from data in Appendix II.

$$\begin{aligned} CL &= 0.88\ CL_{CR} + 0.33\ \text{mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \\ &= 0.88 \times 56/84 + 0.33\ \text{mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \\ &= 0.92\ \text{mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \\ &= 77\ \text{mL} \cdot \text{min}^{-1} = 4.6\ \text{L} \cdot \text{hour}^{-1} \end{aligned}$$

Equation (2–18) then is used to calculate an appropriate dosing rate knowing that the oral bioavailability of digoxin is 70% ($F = 0.7$).

$$\begin{aligned} \text{Dosing rate} &= \text{Target } C_p \cdot CL/F \\ &= 0.75\ \text{ng} \cdot \text{mL}^{-1} \times (0.92/0.7)\ \text{mL} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \\ &= 0.99\ \text{ng} \cdot \text{min}^{-1} \cdot \text{kg}^{-1} \\ &\quad \text{or } 83\ \text{ng} \cdot \text{min}^{-1} \text{ for an 84-kg patient} \\ &\quad \text{or } 83\ \text{ng} \cdot \text{min}^{-1} \times 60\ \text{min} \times 24/24\ \text{hr} \\ &= 0.12\ \text{mg/24 hr} \end{aligned}$$

In practice, the dosing rate would be rounded to the closest dosage size, 0.125 mg/24 hr, which would result in a steady-state plasma concentration of 0.78 ng/mL (0.75 × 125/120). Digoxin is a well characterized example of a drug that is difficult to dose and must be monitored regularly. While guidelines based on calculations of the sort suggested here are useful (Bauman et al., 2006), it is clear that tablet sizes are limiting and tablet sizes intermediate to those available are needed. Since the coefficient of variation for the clearance equation when used for digoxin treatment in this patient group is large (52%), it is common for patients who are not monitored regularly to require hospital admission to adjust medication. Monitoring the clinical status of patients (new or increased ankle edema, inability to sleep in a recumbent position, decreased exercise tolerance) whether accomplished by home health follow up or regular visits to the clinician, is essential to avoid untoward results.

Dosing Interval for Intermittent Dosage. In general, marked fluctuations in drug concentrations between doses are not desirable. If absorption and distribution were instantaneous, fluctuations in drug concentrations between doses would be governed entirely by the drug's elimination $t_{1/2}$. If the dosing interval T were chosen to be equal to the $t_{1/2}$, then the total fluctuation would be 2-fold; this is often a tolerable variation.

Pharmacodynamic considerations modify this. If a drug is relatively nontoxic such that a concentration many times that necessary for therapy can be tolerated easily, the maximal-dose strategy can be used, and the dosing interval can be much longer than the elimination $t_{1/2}$ (for convenience). The $t_{1/2}$ of amoxicillin is ~2 hours, but dosing every 2 hours would be impractical. Instead, amoxicillin often is given in large doses every 8 or 12 hours. For some drugs with a narrow therapeutic range, it may be important to estimate the maximal and minimal concentrations that will occur for a particular dosing interval. The minimal steady-state concentration $C_{ss,min}$ may be reasonably determined by the use of Equation 1–19:

$$C_{ss,\,min} = \frac{F \cdot \text{dose}/V_{ss}}{1 - \exp(-kT)} \cdot \exp(-kT) \qquad \text{(Equation 2–19)}$$

where k equals 0.693 divided by the clinically relevant plasma $t_{1/2}$, and T is the dosing interval. The term $\exp(-kT)$ is, in fact, the fraction of the last dose (corrected for bioavailability) that remains in the body at the end of a dosing interval.

For drugs that follow multi-exponential kinetics and are administered orally, estimation of the maximal steady-state concentration $C_{ss,max}$ involves a complicated set of exponential constants for distribution and absorption. If these terms are ignored for multiple oral dosing, one easily may predict a maximal steady-state concentration by omitting the $\exp(-kT)$ term in the numerator of Equation 2–19 (see Equation 2–20). Because of the approximation, the predicted maximal concentration from Equation 2–20 will be greater than that actually observed.

Example. In the patient with congestive heart failure discussed earlier, an oral maintenance dose of 0.125 mg digoxin per 24 hours was calculated to achieve an average plasma concentration of 0.78 ng/mL during the dosage interval. Digoxin has a narrow therapeutic index, and plasma levels ≤1.0 ng/mL usually are associated with efficacy and minimal toxicity. What are the maximum and minimum plasma concentrations associated with the preceding regimen? This first requires estimation of digoxin's volume of distribution based on available pharmacokinetic data (Appendix II).

$$\begin{aligned} V_{ss} &= 3.1\ CL_{CR} + 3.8\ \text{L} \cdot \text{kg}^{-1} \\ &= 3.1 \times (56/84) + 3.8\ \text{L} \cdot \text{kg}^{-1} \end{aligned}$$

Combining this value with that of digoxin's clearance provides an estimate of digoxin's elimination $t_{1/2}$ in the patient (Equation 2–14).

$$\begin{aligned} t_{1/2} &= 0.693\ V_{ss}/CL \\ &= \frac{0.693 \times 496\ \text{L}}{4.4\ \text{L} \cdot \text{hour}^{-1}} = 75\ \text{hr} = 3.1\ \text{days} \end{aligned}$$

Accordingly, the fractional rate constant of elimination is equal to 0.22 day^{-1} (0.693/3.1 days). Maximum and minimum digoxin plasma concentrations then may be predicted depending on the dosage interval. With T = 1 day (i.e., 0.125 mg given every day):

$$C_{ss,\,max} = \frac{F \cdot \text{dose}/V_{ss}}{1 - \exp(-kT)} = \frac{0.7 \times 0.125 \text{ mg}/496 \text{ L}}{0.2} = 0.88 \text{ ng/mL} \quad \text{(Equation 2–20)}$$

$$C_{ss,\,min} = C_{ss,\,max} \cdot \exp(-kT) = (0.88 \text{ ng/mL})(0.8) = 0.7 \text{ ng/mL} \quad \text{(Equation 2–21)}$$

Thus, the plasma concentrations would fluctuate minimally about the steady-state concentration of 0.78 ng/mL, well within the recommended therapeutic range of 0.5-1.0 ng/mL. In this patient example, twice the daily dose (2 × 0.125 mg) could be given every other day. The average steady-state concentration would remain at 0.78 ng/mL, while the predicted maximum concentration would be 0.98 ng/mL (in Equation 2–20; dose = 0.25 mg and T = 2 days) and the minimum concentration would be 0.62 ng/mL (in Equation 2–21; 0.98 × 0.64). While this result would maintain a therapeutic concentration and avoid large excursions from it between doses, it does not favor patient compliance. Dosing must be compatible with the patient's routine and every other day dosing is problematic in this patient population.

Loading Dose

The *loading dose* is one or a series of doses that may be given at the onset of therapy with the aim of achieving the target concentration rapidly. The appropriate magnitude for the loading dose is

$$\text{Loading dose} = \text{target } C_p \cdot V_{ss}/F \quad \text{(Equation 2–22)}$$

A loading dose may be desirable if the time required to attain steady state by the administration of drug at a constant rate (4 elimination $t_{1/2}$ values) is long relative to the temporal demands of the condition being treated. For example, the $t_{1/2}$ of lidocaine is usually 1-2 hours. Arrhythmias encountered after myocardial infarction obviously may be life-threatening, and one cannot wait 4-8 hours to achieve a therapeutic concentration of lidocaine by infusion of the drug at the rate required to attain this concentration. Hence, use of a loading dose of lidocaine in the coronary care unit is standard.

The use of a loading dose also has significant disadvantages. First, the particularly sensitive individual may be exposed abruptly to a toxic concentration of a drug. Moreover, if the drug involved has a long $t_{1/2}$, it will take a long time for the concentration to fall if the level achieved is excessive. Loading doses tend to be large, and they are often given parenterally and rapidly; this can be particularly dangerous if toxic effects occur as a result of actions of the drug at sites that are in rapid equilibrium with plasma. This occurs because the loading dose calculated on the basis of V_{ss} subsequent to drug distribution is at first constrained within the initial and smaller "central" volume of distribution. It is therefore usually advisable to divide the loading dose into a number of smaller fractional doses that are administered over a period of time. Alternatively, the loading dose should be administered as a continuous intravenous infusion over a period of time. Ideally, this should be given in an exponentially decreasing fashion to mirror the concomitant accumulation of the maintenance dose of the drug, and this is accomplished using computerized infusion pumps.

Example. Accumulation of digitalis ("digitalization") in the patient described earlier is gradual if only a maintenance dose is administered (for at least 12 days, based on $t_{1/2}$ = 3.1 days). A more rapid response could be obtained (if deemed necessary) by using a loading-dose strategy and Equation 2–22. Here a target C_p of 0.9 ng/mL is chosen as a target below the recommended maximum of 1.0 ng/mL.

$$\text{Loading dose} = 0.9 \text{ ng} \cdot \text{mL}^{-1} \times 496 \text{ L}/0.7 = 638 \text{ µg, or } \sim 0.625 \text{ mg}$$

To avoid toxicity, this oral loading dose, would be given as an initial 0.25-mg dose followed by a 0.25-mg dose 6 -8 hours later, with careful monitoring of the patient and the final 0.125-mg dose given 12-14 hours later.

Individualizing Dosage

A rational dosage regimen is based on knowledge of *F*, *CL*, V_{ss}, and $t_{1/2}$ and some information about rates of absorption and distribution of the drug together with potential effects of the disease on these parameters. Recommended dosage regimens generally are designed for an "average" patient; usual values for the important determining parameters and appropriate adjustments that may be necessitated by disease or other factors are presented in Appendix II. This "one size fits all" approach, however, overlooks the considerable and unpredictable inter-patient variability that usually is present in these pharmacokinetic parameters. For many drugs, one standard deviation in the values observed for *F*, *CL*, and V_{ss} is ~20%, 50%, and 30%, respectively. This means that 95% of the time the C_{ss} that is achieved will be between 35% and 270% of the target; this is an unacceptably wide range for a drug with a low therapeutic index. Individualization of the dosage regimen to a particular patient therefore is critical for optimal therapy. The pharmacokinetic principles described earlier provide a basis for modifying the dosage regimen to obtain a desired degree of efficacy with a minimum of unacceptable adverse effects. In situations where the drug's plasma concentration can be measured and related to the therapeutic window, additional guidance for dosage modification is obtained from blood levels taken during therapy and evaluated in a pharmacokinetic consult available in many institutional settings. Such measurement and adjustment are appropriate for many drugs with low therapeutic indices (e.g., cardiac glycosides, anti-arrhythmic agents, anticonvulsants, immunosuppressants, theophylline, and warfarin).

Therapeutic Drug Monitoring

The major use of measured concentrations of drugs (at steady state) is to refine the estimate of *CL/F* for the patient being treated, using Equation 2–16 as rearranged below:

$$CL/F \text{ (patient)} = \text{dosing rate}/C_{ss}\text{(measured)} \quad \text{(Equation 2–23)}$$

The new estimate of *CL/F* can be used in Equation 2–18 to adjust the maintenance dose to achieve the desired target concentration.

Certain practical details and pitfalls associated with therapeutic drug monitoring should be kept in mind. The first of these relates to the time of sampling for measurement of the drug concentration. If intermittent dosing is used, when during a dosing interval should samples be taken? It is necessary to distinguish between two possible uses of measured drug concentrations to understand the possible answers. A concentration of drug measured in a sample taken at virtually any time during the dosing interval will provide information that may aid in the assessment of drug toxicity. This is one type of therapeutic drug monitoring. It should be stressed, however, that such use of a measured concentration of drug is fraught with difficulties because of inter-individual variability in sensitivity to the drug. When there is a question of toxicity, the drug concentration is just one of many items used to interpret the clinical situation.

Changes in the effects of drugs may be delayed relative to changes in plasma concentration because of a slow rate of distribution or pharmacodynamic factors. Concentrations of digoxin, e.g., regularly exceed 2 ng/mL (a potentially toxic value) shortly after an oral dose, yet these peak concentrations do not cause toxicity; indeed, they occur well before peak effects. Thus, concentrations of drugs in samples obtained shortly after administration can be uninformative or even misleading.

The purpose of sampling during supposed steady state is to modify the estimate of *CL/F* and thus the choice of dosage. Early post-absorptive concentrations do not reflect clearance; they are determined primarily by the rate of absorption, the "central" (rather than the steady-state) volume of distribution, and the rate of distribution, all of which are pharmacokinetic features of virtually no relevance in choosing the long-term maintenance dosage. When the goal of measurement is adjustment of dosage, the sample should be taken well after the previous dose, as a rule of thumb, just before the next planned dose, when the concentration is at its minimum. The exceptions to this approach are drugs that are eliminated nearly completely between doses and act only during the initial portion of each dosing interval. If it is questionable whether efficacious concentrations of such drugs are being achieved, a sample taken shortly after a dose may be helpful. On the other hand, if a concern is whether low clearance (as in renal failure) may cause accumulation of drug, concentrations measured just before the next dose will reveal such accumulation and are considerably more useful for this purpose than is knowledge of the maximal concentration. For such drugs, determination of both maximal and minimal concentrations is recommended. These two values can offer a more complete picture of the behavior of the drug in a specific patient (particularly if obtained over more that one dosing period) can better support pharmacokinetic modeling.

A second important aspect of the timing of sampling is its relationship to the beginning of the maintenance-dosage regimen. When constant dosage is given, steady state is reached only after four $t_{1/2}$ have passed. If a sample is obtained too soon after dosage is begun, it will not reflect this state and the drug's clearance accurately. Yet, for toxic drugs, if sampling is delayed until steady state is ensured, the damage may have been done. Some simple guidelines can be offered. When it is important to maintain careful control of concentrations, the first sample should be taken after two $t_{1/2}$ (as calculated and expected for the patient), assuming that no loading dose has been given. If the concentration already exceeds 90% of the eventual expected mean steady-state concentration, the dosage rate should be halved, another sample obtained in another two (supposed) $t_{1/2}$, and the dosage halved again if this sample exceeds the target. If the first concentration is not too high, the initial rate of dosage is continued; even if the concentration is lower than expected, it is usually reasonable to await the attainment of steady state in another two estimated $t_{1/2}$ and then to proceed to adjust dosage as described earlier.

If dosage is intermittent, there is a third concern with the time at which samples are obtained for determination of drug concentrations. If the sample has been obtained just prior to the next dose, as recommended, concentration will be a minimal value, not the mean. However, as discussed earlier, the estimated mean concentration may be calculated by using Equation 2–16.

If a drug follows first-order kinetics, the average, minimum, and maximum concentrations at steady state are linearly related to dose and dosing rate (see Equations 2–16, 2–19, and 2–20). Therefore, the ratio between the measured and desired concentrations can be used to adjust the dose, consistent with available dosage sizes:

$$\frac{C_{ss}\,(\text{measured})}{C_{ss}\,(\text{predicted})} = \frac{\text{Dose (previous)}}{\text{Dose (new)}} \qquad \text{(Equation 2–24)}$$

In the previously described patient given 0.125 mg digoxin every 24 hours, for example, if the measured minimum (trough) steady-state concentration were found to be 0.35 ng/mL rather than the predicted level of 0.7 ng/mL, an appropriate, practical change in the

dosage regimen would be to *increase* the daily dose by 0.125 mg to 0.25-mg digoxin daily.

$$\text{Dose (new)} = \frac{C_{ss}(\text{predicted})}{C_{ss}(\text{measured})} \times \text{Dose (previous)}$$

$$= \frac{0.7}{0.35} \times 0.125 = 0.25 \text{/24 hour}$$

In practice, one would change the dose from the 0.125-mg tablet to the 0.25-mg tablet by providing a new prescription.

Compliance. Ultimately, therapeutic success depends on the patient actually taking the drug according to the prescribed dosage regimen—"Drugs don't work if you don't take them." Noncompliance with the prescribed dosing schedule is a major reason for therapeutic failure, especially in the long-term treatment of heart failure as in our example patient being administered digoxin where the absence of intermediate tablet sizes influences the regimens that can be practically constructed (our patient ultimately required an alternate day or alternate dose schedule). Moreover, treatment of chronic disease using antihypertensive, anti-retroviral, and anticonvulsant agents also represents a compliance problem. When no special efforts are made to address this issue, only about 50% of patients follow the prescribed dosage regimen in a reasonably satisfactory fashion, approximately one-third comply only partly, and about one in six patients is essentially noncompliant (Devabhaktuni and Bangalore 2009). Missed doses are more common than too many doses. The number of drugs does not appear to be as important as the number of times a day doses must be remembered (Ho et al., 2009). Reducing the number of required dosing occasions can improve adherence to a prescribed dosage regimen. Equally important is the need to involve patients in the responsibility for their own health using a variety of strategies based on improved communication regarding the nature of the disease and the overall therapeutic plan (Appendix I).

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