CHAPTER 2

Pharmacokinetics

OVERVIEW

Pharmacokinetics is the study of drug disposition in the body and focuses on the changes in drug plasma concentration. For any given drug and dose, the plasma concentration of the drug will rise and fall according to the rates of three processes: absorption, distribution, and elimination. Absorption of a drug refers to the movement of drug into the bloodstream, with the rate dependent on the physical characteristics of the drug and its formulation. Distribution of a drug refers to the process of a drug leaving the bloodstream and going into the organs and tissues. Elimination of a drug from the blood relies on two processes: biotransformation (metabolism) of a drug to one or more metabolites, primarily in the liver; and the excretion of the parent drug or its metabolites, primarily by the kidneys. The relationship between these processes is shown in Figure 2–1.

DRUG ABSORPTION

Drug absorption refers to the passage of drug molecules from the site of administration into the circulation. The process of drug absorption applies to all routes of administration, except for the topical route, where drugs are applied directly on the target tissue, and intravenous administration, where the drug is already in the circulation. Drug absorption requires that drugs cross one or more layers of cells and cell membranes. Drugs injected into the subcutaneous tissue and muscle bypass the epithelial barrier and are more easily absorbed through spaces between capillary endothelial cells. In the gut, lungs, and skin, drugs must first be absorbed through a layer of epithelial cells that have tight junctions. For this reason, drugs face a greater barrier to absorption after oral administration than after parenteral administration.

Processes of Absorption

Most drugs are absorbed by passive diffusion across a biologic barrier and into the circulation. The rate of absorption is proportional to the drug concentration gradient across the barrier and the surface area available for absorption at that site, known as Fick’s Law. Drugs can be absorbed passively through cells either by lipid diffusion or by aqueous diffusion. Lipid diffusion is a process in which the drug dissolves in the lipid components of the cell membranes. This process is facilitated by a high degree of lipid solubility of the drug. Aqueous diffusion occurs by passage through aqueous pores in cell membranes. Because aqueous diffusion is restricted to drugs with low molecular weights, many drugs are too large to be absorbed by this process.

A few drugs are absorbed by active transport or by facilitated diffusion. Active transport requires a carrier molecule and a form of energy, provided by hydrolysis of the terminal high-energy phosphate bond of ATP. Active transport can transfer drugs against a concentration gradient. For example, the antineoplastic drug, 5-fluorouracil, undergoes active transport. Facilitated diffusion also requires a carrier molecule, but no energy is needed. Thus drugs or substances cannot be transferred against a concentration gradient but diffuse faster than without a carrier molecule present. Some cephalosporin antibiotics, such as cephalixin, undergo facilitated diffusion by an oligopeptide transporter protein located in intestinal epithelial cells.

Effect of pH on Absorption of Weak Acids and Bases

Many drugs are weak acids or bases that exist in both ionized and non-ionized forms in the body. Only the non-ionized form of these drugs is sufficiently soluble in membrane lipids to cross cell membranes (Box 2-1). The ratio of the two forms at a particular site influences the rate of absorption and is also a factor in distribution and elimination.

The protonated form of a weak acid is non-ionized, whereas the protonated form of a weak base is ionized. The ratio of the protonated form to the nonprotonated form of these drugs can be calculated using the Henderson-Hasselbalch equation (see Box 2-1). The pKa is the negative log of the ionization constant, particular for each acidic or basic drug. At a pH equal to the pKₐ, equal amounts of the protonated and nonprotonated forms are present. If the pH is less than the pKₐ, the protonated form predominates. If the pH is greater than the pKₐ, the nonprotonated form predominates.

In the stomach, with a pH of 1, weak acids and bases are highly protonated. At this site, the non-ionized form of weak acids (pKₐ = 3–5) and the ionized form of weak bases
(pKₐ = 8–10) will predominate. Hence, weak acids are more readily absorbed from the stomach than are weak bases. In the intestines, with a pH of 7, weak bases are also mostly ionized, but much less so than in the stomach, and weak bases are absorbed more readily from the intestines than from the stomach.

However, weak acids can also be absorbed more readily from the intestines than from the stomach, despite their greater ionization in the intestines, because the intestines have a greater surface area than the stomach for absorption of the non-ionized form of a drug, and this outweighs the influence of greater ionization in the intestines.

**DRUG DISTRIBUTION**

Drugs are distributed to organs and tissues via the circulation, diffusing into interstitial fluid and cells from the circulation. Most drugs are not uniformly distributed throughout total body water, and some drugs are restricted to the extracellular fluid or plasma compartment. Drugs with sufficient lipid solubility can simply diffuse through membranes into cells. Other drugs are concentrated in cells by the phenomenon of ion trapping, which is described further below. Drugs can also be actively transported into cells. For example, some drugs are actively transported into hepatic cells, where they may undergo enzymatic biotransformation. In the intestines, drug transport by P-glycoprotein (Pgp) in the blood-to-lumen direction leads to a secretion of various drugs into the intestinal tract, thereby serving as a detoxifying mechanism. The Pgp proteins also remove many drugs from tissues throughout the body, including anticancer agents. Inhibition of Pgp by amiodarone, erythromycin, propranolol, and other agents can increase tissue levels of these drugs and augment their pharmacologic effects.

**Factors Affecting Distribution**

**Organ Blood Flow**

The rate at which a drug is distributed to various organs after a drug dose is administered depends largely on the proportion of cardiac output received by the organs. Drugs are rapidly distributed to highly perfused tissues, namely the brain, heart, liver, and kidney, and this enables a rapid onset of action of drugs affecting these tissues. Drugs are distributed more slowly to less perfused tissues such as skeletal muscle and even more slowly to those with the lowest blood flow, such as skin, bone, and adipose tissue.

**Plasma Protein Binding**

Almost all drugs are reversibly bound to plasma proteins, primarily albumin, but also lipoproteins, glycoproteins, and β globulins. The extent of binding depends on the affinity of a particular drug for protein-binding sites and ranges from less than 10% to as high as 99% of the plasma concentration. As the free (unbound) drug diffuses into interstitial fluid and cells, drug molecules dissociate from plasma proteins to maintain the equilibrium between free drug and bound drug. In general, acid drugs bind to albumin and basic drugs to glycoproteins and β globulins.

Plasma protein binding is saturable, and a drug can be displaced from binding sites by other drugs that have a high affinity for such sites. However, most drugs are not used at high enough plasma concentrations to occupy the vast number of plasma protein binding sites. There are a few agents that may cause drug interactions by competing for plasma protein binding sites, as highlighted in Chapter 4.

**Molecular Size**

Molecular size is a factor affecting the distribution of extremely large molecules, such as those of the anticoagulant heparin. Heparin is largely confined to the plasma compartment, although it does undergo some biotransformation in the liver.

**Lipid Solubility**

Lipid solubility is a major factor affecting the extent of drug distribution, particularly to the brain, where the blood-brain barrier restricts the penetration of polar and ionized molecules. The barrier is formed by tight junctions between the capillary endothelial cells and also by the glial cells that surround the capillaries, which inhibit the penetration of polar molecules into brain neurons.

**DRUG BIOTRANSFORMATION**

Drug biotransformation and excretion are the two processes responsible for the decline of the plasma drug concentration over time. Both of these processes contribute to the
Weak acids (HA) donate a proton (H⁺) to form anions (A⁻), whereas weak bases (B) accept a proton to form cations (HB⁺). For weak acids, the protonated form is nonionized. For weak bases, the protonated form is ionized.

Only the non-ionized form of a drug can readily penetrate cell membranes.

The pKₐ of a weak acid or weak base is the pH at which there are equal amounts of the protonated form and the nonprotonated form. The Henderson-Hasselbalch equation can be used to determine the ratio of the two forms:

$$\log\left(\frac{\text{protonated form}}{\text{Nonprotonated form}}\right) = \text{pK}_a - \text{pH}$$

For salicylic acid, which is a weak acid with a pKₐ of 3, log [HA]/[A⁻] is 3 minus the pH. At a pH of 2, then, log [HA]/[A⁻] = 3 - 2 = 1. Therefore, [HA]/[A⁻] = 10/1.

For amphetamine, which is a weak base with a pKₐ of 10, log [HB⁺]/[B] is 10 minus the pH. At a pH of 8, then, log [HB⁺]/[B] = 10 - 8 = 2. Therefore, [HB⁺]/[B] = 100/1.
elimination of active drug from the body, and as discussed later in the chapter, clearance is a measure of the rate of elimination. Biotransformation, or drug metabolism, is the enzyme-catalyzed conversion of drugs to their metabolites. Most drug biotransformation takes place in the liver, but drug-metabolizing enzymes are found in many other tissues, including the gut, kidneys, brain, lungs, and skin.

Role of Drug Biotransformation

The fundamental role of drug-metabolizing enzymes is to inactivate and detoxify drugs and other foreign compounds (xenobiotics) that can harm the body. Drug metabolites are usually more water soluble than is the parent molecule and, therefore, they are more readily excreted by the kidneys. No particular relationship exists between biotransformation and pharmacologic activity. Some drug metabolites are active, whereas others are inactive. Many drug molecules undergo attachment of polar groups, a process called conjugation, for more rapid excretion. As a general rule, most conjugated drug metabolites are inactive, but a few exceptions exist.

Formation of Active Metabolites

Many pharmacologically active drugs, such as the sedative-hypnotic agent diazepam (Valium), are biotransformed to active metabolites. Some agents, known as prodrugs, are administered as inactive compounds and then biotransformed to active metabolites. This type of agent is usually developed because the prodrug is better absorbed than its active metabolite. For example, the antiglaucoma agent dipivefrin (Propine) is a prodrug that is converted to its active metabolite, epinephrine, by corneal enzymes after topical ocular administration. Orally administered prodrugs, such as the antihypertensive agent enalapril (Vasotec), are converted to their active metabolite by hepatic enzymes during their first pass through the liver.

First-Pass Biotransformation

Drugs that are absorbed from the gut reach the liver via the hepatic portal vein before entering the systemic circulation (Fig. 2–2). Many drugs, such as the antihypertensive agent felodipine (Plendil), are extensively converted to inactive metabolites during their first pass through the gut wall and liver, and have low bioavailability (see below) after oral administration. This phenomenon is called the first-pass effect. Drugs administered by the sublingual or rectal route undergo less first-pass metabolism and have a higher degree of bioavailability than do drugs administered by the oral route.

Phases of Drug Biotransformation

Drug biotransformation can be divided into two phases, each carried out by unique sets of metabolic enzymes. In many cases, phase I enzymatic reactions create or unmask a chemical group required for a phase II reaction. In some cases, however, drugs bypass phase I biotransformation and go directly to phase II. Although some phase I drug metabolites are pharmacologically active, most phase II drug metabolites are inactive.

Phase I Biotransformation

Phase I biotransformation includes oxidative, hydrolytic, and reductive reactions (Fig. 2–3).

OXIDATIVE REACTIONS. Oxidative reactions are the most common type of phase I biotransformation. They are catalyzed by enzymes isolated in the microsomal fraction of liver homogenates (the fraction derived from the endoplasmic reticulum) and by cytoplasmic enzymes.

The microsomal cytochrome P450 (CYP) monooxygenase system is a family of enzymes that catalyzes the biotransformation of drugs with a wide range of chemical structures. The microsomal monooxygenase reaction requires the following: CYP (a hemoprotein); a flavoprotein that is reduced by nicotinamide adenine dinucleotide phosphate (NADPH), called NADPH CYP reductase; and membrane lipids in which the system is embedded. In the drug-oxidizing reaction, one atom of oxygen is used to form a hydroxylated metabolite of a drug, as shown in Figure 2–4, whereas the other atom of oxygen forms water when combined with electrons contributed by NADPH. The hydroxylated metabolite may be the end product of the reaction or serve as an intermediate that leads to the formation of another metabolite.
The most common chemical reactions catalyzed by CYP enzymes are aliphatic hydroxylation, aromatic hydroxylation, N-dealkylation, and O-dealkylation.

Many CYP isozymes have been identified and cloned, and their role in metabolizing specific drugs elucidated. Each isozyme catalyzes a different but overlapping spectrum of oxidative reactions. Most drug biotransformation is catalyzed by three CYP families named CYP1, CYP2, and CYP3. The different CYP families are likely related by gene duplication and each family is divided into subfamilies, also clearly related by homologous protein sequences. The CYP3A subfamily catalyzes more than half of all microsomal drug oxidations.

Many drugs alter drug metabolism by inhibiting or inducing CYP enzymes, and drug interactions can occur when these drugs are administered concurrently with other drugs that are metabolized by CYP (see Chapter 4). Two examples of inducers of CYP are the barbiturate, phenobarbital, and the antitubercular drug, rifampin. The inducers stimulate the transcription of genes encoding CYP enzymes, resulting in increased messenger RNA (mRNA) and protein synthesis. Drugs that induce CYP enzymes activate the binding of nuclear receptors to enhancer domains of CYP genes, increasing the rate of gene transcription.

A few drugs are oxidized by cytoplasmic enzymes. For example, ethanol is oxidized to aldehyde by alcohol dehydrogenase, and caffeine and the bronchodilator theophylline are metabolized by xanthine oxidase. Other cytoplasmic oxidases include monoamine oxidase, a site of action for some psychotropic medications.

HYDROLYTIC REACTIONS. Esters and amides are hydrolyzed by a variety of enzymes. These include cholinesterase and other plasma esterases that inactivate choline esters, local anesthetics, and drugs such as esmolol (Brevibloc), an agent for the treatment of tachycardia that blocks cardiac β1-adrenergic receptors. There are few CYP enzymes that carry out hydrolytic reactions.

REDUCTIVE REACTIONS. Reductive reactions are less common than are oxidative and hydrolytic reactions. Chloramphenicol, an antimicrobial agent, and a few other drugs are partly metabolized by a hepatic nitro reductase, and this process involves CYP enzymes. Nitroglycerin, a vasodilator, undergoes reductive hydrolysis catalyzed by glutathione-organic nitrate reductase.

Phase II Biotransformation

In phase II biotransformation, drug molecules undergo conjugation reactions with an endogenous substance such as acetate, glucuronate, sulfate, or glycine (Fig. 2–5). Conjugation enzymes, which are present in the liver and other tissues, join various drug molecules with one of these endogenous substances to form water-soluble metabolites that are more easily excreted. Except for microsomal glucuronosyltransferases, these enzymes are located in the
### Description | Reaction | Examples
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**Oxidative reactions**  
Aliphatic hydroxylation  
\[ R-CH_2CH_3 \rightarrow R-CHCH_3 \]  
Ibuprofen, pentobarbital, and tolbutamide

Aromatic hydroxylation  
\[ \text{苯} \rightarrow \text{苯} + \text{酚} \]  
Phenobarbital, phenytoin, and propranolol

\[ R \rightarrow NHCH_3 \rightarrow R \rightarrow NH_2 + CH_2O \]  
Codeine, imipramine, and theophylline

\[ R \rightarrow OCH_3 \rightarrow R \rightarrow OH + CH_2O \]  
Codeine, dextromethorphan, and indomethacin

\[ R \rightarrow NHCH_3 \rightarrow R \rightarrow NH_2 + CH_2O \]  
Amphetamine and diazepam

\[ R \rightarrow NHCH_3 \rightarrow R \rightarrow NH_2 + CH_2O \]  
Chlorpheniramine

\[ R \rightarrow NH \rightarrow R \rightarrow N-OH \]  
Chlorpromazine and cimetidine

\[ R \rightarrow S \rightarrow R \rightarrow S=O \]  
Chlorpromazine and cimetidine

**Hydrolytic reactions**  
Amide hydrolysis  
\[ R \rightarrow COOH + R_2 \rightarrow NH_2 \]  
Lidocaine and procainamide

Ester hydrolysis  
\[ R \rightarrow COOH + R_2 \rightarrow OH \]  
Aspirin, esmolol, and procaaine

**Reductive reactions**  
Nitro reduction  
\[ \text{硝基} \rightarrow \text{铵} \]  
Chloramphenicol

\[ R \rightarrow O\text{NO}_2 \rightarrow R \rightarrow OH + \text{NO}_2^- \]  
Nitroglycerin

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*Figure 2-3. Phase I drug biotransformation. Many drugs are biotransformed by oxidative, hydrolytic, or reductive reactions and then undergo conjugation with endogenous substances. A few drugs bypass phase I reactions and directly enter phase II biotransformation.*
Binds to the oxidized form of P450 (i.e., Fe$^{3+}$). Second, the drug P450 and water are produced.

Four steps are involved in the CYP reaction: First, the drug substrate interacts with oxygen. Fourth, the oxidized drug (metabolite) is reduced by CYP reductase, using electrons donated by the reduced form of NADPH. Third, the drug-reduced form of P450 [i.e., Fe$^{2+}$] interacts with oxygen. Fourth, the oxidized drug (metabolite) and water are produced.

...cytoplasm. Most conjugated drug metabolites are pharmacologically inactive.

**GLUCURONIDE FORMATION.** Glucuronide formation, the most common conjugation reaction, utilizes glucuronyltransferases to conjugate a glucuronate molecule with the parent drug molecule.

**ACETYLATION.** Acetylation is accomplished by N-acetyltransferase enzymes that utilize acetyl coenzyme A (acetyl CoA) as a source of the acetate group.

**SULFATION.** Sulfotransferases catalyze the conjugation of several drugs, including the vasodilator minoxidil and the potassium-sparing diuretic triamterene, whose sulfate metabolites are pharmacologically active.

**Pharmacogenomics**

Since the completion of the human genome, it is now fully realized that there is a great degree of individual variation, called *polymorphism*, in the genes coding for drug-metabolizing enzymes. Modern genetic studies were triggered by rare fatalities in children being treated for leukemia using the thiopurine agent, 6-mercaptopurine (6-MP). It was discovered that the children died as a result of drug toxicity because they expressed a faulty variant of thiopurine methyltransferase, the enzyme that metabolizes 6-MP.

**Variations in Acetyltransferase Activity**

Individuals exhibit slow or fast acetylation of some drugs because of genetically determined differences in N-acetyltransferase. Slow acetylators (SAs) were first identified by neuropathic effects of isoniazid, a drug to treat tuberculosis. These patients had higher plasma levels of isoniazid compared to other patients classified as rapid acetylators (RAs). The SA phenotype is autosomal recessive, although there are more than 20 allelic variants of the gene for N-acetyltransferase identified. In individuals with one wild-type enzyme and one faulty variant, an intermediate phenotype is observed. The *distribution* of these phenotypes varies from population to population. About 15% of Asians, 50% of Caucasians and Africans, and more than 80% of Middle Eastern populations have the SA phenotype. Other drugs that may cause toxicity in the SA patient are sulfonamide antibiotics, the antiarrhythmic agent procainamide, and the antihypertensive agent hydralazine.

**Variations in CYP2D6 and CYP2C19 Activity**

Variations in oxidation of some drugs have been attributed to genetic differences in certain CYP enzymes. Genetic polymorphisms of CYP2D6 and CYP2C19 enzymes are well characterized, and human populations of “extensive metabolizers” and “poor metabolizers” have been identified. These differences are caused by more than 70 identified variants in the CYP2D6 gene and more than 25 variants of the CYP2C19 genes, resulting from point mutations, deletions, or additions; gene rearrangements, or deletion or duplication of the entire gene. This gives rise to an increase, reduction, or complete loss of enzyme activity and to different levels of enzyme expression that result in *altered rates* of enzymatic reactions.

Most individuals are extensive metabolizers of CYP2D6 substrates, but 10% of Caucasians and a smaller fraction of Asians and Africans are poor metabolizers of substrates for CYP2D6. Psychiatric patients who are poor metabolizers of CYP2D6 drugs have been found to have a higher rate of adverse drug reactions than those who are extensive metabolizers because of higher psychotropic drug plasma levels. In addition, poor metabolizers of CYP2D6 drugs have a reduced ability to metabolize codeine to morphine sufficiently to obtain adequate pain relief when codeine is administered for analgesia.

Poor metabolizers of CYP2C19 substrates have higher plasma levels of proton pump inhibitors, such as omeprazole (PRILOSEC), whereas some extensive metabolizers of CYP2C19 drugs require larger doses of omeprazole to treat peptic ulcer.

**Other Variations in Drug Metabolism Enzymes**

About 1 of 3000 individuals exhibits a familial atypical cholinesterase that will not metabolize succinylcholine, a neuromuscular blocking agent, at a normal rate. Affected individuals are subject to prolonged apnea after receiving the usual dose of the drug. For this reason, patients should be screened for atypical cholinesterase before receiving succinylcholine.
There are many more polymorphisms in both phase I and phase II metabolic enzymes. With more than 30 families of drug-metabolizing enzymes, all with genetic variants, a major development in pharmacotherapy will be the individual tailoring of drug and dose to each patient’s genomic identity.

**DRUG EXCRETION**

Excretion is the removal of drug from body fluids and occurs primarily in the urine. Other routes of excretion from the body include in bile, sweat, saliva, tears, feces, breast milk, and exhaled air.

**Renal Drug Excretion**

Most drugs are excreted in the urine, either as the parent compound or as a drug metabolite. Drugs are handled by the kidneys in the same manner as are endogenous substances, undergoing processes of glomerular filtration, active tubular secretion, and passive tubular reabsorption. The amount of drug excreted is the sum of the amounts filtered and secreted minus the amount reabsorbed. The relationship between these processes, the rate of drug excretion, and renal clearance is shown in Box 2-2.

**Glomerular Filtration**

Glomerular filtration is the first step in renal drug excretion. In this process, the free drug enters the renal tubule as a dissolved solute in the plasma filtrate (see Box 2-2). If a drug has a large fraction bound to plasma proteins, as is the case with the anticoagulant warfarin, it will have a low rate of glomerular filtration.

**Active Tubular Secretion**

Some drugs, particularly weak acids and bases, undergo active tubular secretion by transport systems located primarily in proximal tubular cells. This process is competitively inhibited by other drugs of the same chemical class. For example, the secretion of penicillins and other weak acids is inhibited by probenecid, an agent used to treat gout.

Active tubular secretion is not affected by plasma protein binding. This is due to the equilibrium of free drug and bound drug such that when free drug is actively transported across the renal tubule, this fraction of free drug is replaced by a fraction that dissociates from plasma proteins.

**Passive Tubular Reabsorption**

The extent to which a drug undergoes passive reabsorption across renal tubular cells and into the circulation depends on the lipid solubility of the drug. Drug biotransformation facilitates drug elimination by forming polar drug metabolites that are not as readily reabsorbed as the less-polar parent molecules.

Most nonelectrolytes, including ethanol, are passively reabsorbed across tubular cells. Ionized weak acids and bases are not reabsorbed across renal tubular cells, and they are more rapidly excreted in the urine than are non-ionized drugs that undergo passive reabsorption. The proportion of ionized and non-ionized drugs is affected by renal tubular...
**PH**, which can be manipulated to increase the excretion of a drug after a drug overdose (Box 2–3).

### Biliary Excretion and Enterohepatic Cycling

Many drugs are excreted in the bile as the parent compound or a drug metabolite. Biliary excretion favors compounds with molecular weights that are higher than 300 and with both polar and lipophilic groups; smaller molecules are excreted only in negligible amounts. Conjugation, particularly with glucuronate, increases biliary excretion.

Numerous conjugated drug metabolites, including both the glucuronate and sulfate metabolites of steroids, are excreted in the bile. After the bile empties into the intestines, a fraction of the drug may be reabsorbed into the circulation and eventually return to the liver. This phenomenon is called **enterohepatic cycling** (Fig. 2–6). Excreted conjugated drugs can be hydrolyzed back to the parent drug by intestinal bacteria, and this facilitates the drug’s reabsorption. Thus, biliary excretion eliminates substances from the body only to the extent that enterohepatic cycling is incomplete, that is, when some of the excreted drug is not reabsorbed from the intestine.
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Other Routes of Excretion

Sweat and saliva represent minor routes of excretion for some drugs. In pharmacokinetic studies, saliva measurements are sometimes used because the saliva concentration of a drug often reflects the intracellular concentration of the drug in target tissues.

QUANTITATIVE PHARMACOKINETICS

To derive and use expressions for pharmacokinetic parameters, the first step is to establish a mathematical model that accurately relates the plasma drug concentration to the rates of drug absorption, distribution, and elimination. The one-compartment model is the simplest model of drug disposition, but the two-compartment model provides a more accurate representation of the pharmacokinetic behavior of many drugs (Fig. 2–7). With the one-compartment model, drug undergoes absorption into the blood according to the rate constant, $k_a$, and elimination from the blood with a rate constant, $k_e$. In the two-compartment model, drugs are absorbed into the central compartment (blood), distributed from the central compartment to the peripheral compartment (the tissues), and eliminated from the central compartment. Regardless of the model used, rate constants can be determined for each process and used to derive expressions for other pharmacokinetic parameters, such as the elimination half-life ($t_{1/2}$) of a drug. In this section, the most important parameters of pharmacokinetics are explained in greater detail.

Drug Plasma Concentration Curves

Figure 2–8A shows a standardized drug plasma concentration curve over time after oral administration of a typical drug. The Y-axis is a linear scale of drug plasma concentration.

**Box 2–3  Urine Acidification and Alkalization in the Treatment of Drug Overdose**

If a drug or other compound is a weak acid or base, its degree of ionization and rate of renal excretion will depend on its $pK_a$ and on the pH of the renal tubular fluid. The rate of excretion of a weak acid can be accelerated by alkalining the urine, whereas the rate of excretion of a weak base can be accelerated by acidifying the urine. These procedures have been used to enhance the excretion of drugs and poisons, but they are not without risk to the patient, and their benefits have been established for only a few drugs.

To make manipulation of the urine pH worthwhile, a drug must be excreted to a large degree by the kidneys. The short-acting barbiturates (e.g., secobarbital) are eliminated almost entirely via biotransformation to inactive metabolites, so modification of the urine pH has little effect on their excretion. In contrast, phenobarbital is excreted to a large degree by the kidneys, so urine alkalization is useful in treating an overdose of this drug. Urine acidification to enhance the elimination of weak bases (e.g., amphetamine), has been largely abandoned because it does not significantly increase the elimination of these drugs and poses a serious risk of metabolic acidosis.

In cases involving an overdose of aspirin or other salicylate, alkalization of the urine produces the dual benefits of increasing drug excretion and counteracting the metabolic acidosis that occurs with serious aspirin toxicity. For patients suffering from phenobarbital overdose or from herbicide 2,4-dichlorophenoxyacetic acid poisoning, alkalization of the urine is also helpful: this is accomplished by administering sodium bicarbonate intravenously every 3 to 4 hours to increase the urinary pH to 7–8.

**Figure 2–6. Enterohepatic cycling.** Drugs and drug metabolites with molecular weights higher than 300 may be excreted via the bile, stored in the gallbladder, delivered to the intestines by the bile duct, and then reabsorbed into the circulation. This process reduces the elimination of a drug and prolongs its half-life and duration of action in the body.
concentration, often in μg/mL or mg/L, and the X-axis is a time scale, usually in hours. Parameters of the plasma drug concentration curve are the maximum concentration ($C_{\text{max}}$), the time needed to reach the maximum ($T_{\text{max}}$), the minimum effective concentration (MEC), and the duration of action. A measure of the total amount of drug during the time course is given by the area under the curve (AUC). These measures are useful for comparing the bioavailability of different pharmaceutical formulations or of drugs given by different routes of administration.

Bioavailability (F)

Bioavailability is defined as the fraction (F) of the administered dose of a drug that reaches the systemic circulation in an active form. As shown in Figure 2–8B, the oral bioavailability of a particular drug is determined by dividing the AUC of an orally administered dose of the drug (AUCoral) by the AUC of an intravenously administered dose of the same drug (AUCiv). By definition, an intravenously administered drug has 100% bioavailability. The bioavailability of drugs administered intramuscularly or via other routes can be determined in the same manner as the bioavailability of drugs administered orally.

The bioavailability of orally administered drugs is of particular concern because it can be reduced by many pharmaceutical and biologic factors. Pharmaceutical factors include the rate and extent of tablet disintegration and drug dissolution. Biologic factors include the effects of food, which can sequester or inactivate a drug; the effects of gastric acid, which can inactivate a drug; and the effects of gut and liver enzymes, which can metabolize a drug during its absorption and first pass through the liver. The CYP3A4 isozyme found in intestinal enterocytes and hepatic cells is a particularly important catalyst of first-pass drug metabolism. CYP3A4 works in conjunction with Pgp (described in the section titled “Drug Distribution”) as the 3A4 isozyme located in enterocytes inactivates drugs transported into the intestinal lumen by Pgp.

Volume of Distribution

The volume of distribution ($V_d$) is defined as the volume of fluid in which a drug would need to be dissolved to have the same concentration as it does in plasma. The $V_d$ does not represent the volume in a particular body fluid compartment (Fig. 2–9A); instead, as shown in Figure 2–9B, it is an apparent volume that represents the relationship between the dose of a drug and the resulting plasma concentration of the drug.

Calculation of $V_d$

After intravenous drug administration, the plasma drug concentration falls rapidly at first, as the drug is distributed from the central compartment to the peripheral compartment. The $V_d$ is calculated by dividing the dose of a drug given intravenously by the plasma drug concentration immediately after the distribution phase (α). As shown in Figure 2–9C, this drug concentration can be determined by extrapolating the plasma drug concentration back to time
zero from the linear part of the elimination phase (β). Note that the Y-axis in this case is plotted on a log scale so that the exponential elimination phase is converted to a straight line. The plasma drug concentration at time zero ($C_0$) represents the plasma concentration of a drug that would be obtained if it were instantaneously dissolved in its $V_d$. The equation for calculating $V_d$ is rearranged to determine the dose of a drug that is required to establish a specified plasma drug concentration (see below).

**Interpretation of $V_d$**

Although the $V_d$ does not correspond to an actual body fluid compartment, it does provide a measure of the extent of distribution of a drug. A low $V_d$ that approximates plasma volume or extracellular fluid volume usually indicates that the drug’s distribution is restricted to a particular compartment (the plasma or extracellular fluid). The anticoagulant warfarin has a $V_d$ of about 8 L, which reflects a high degree of plasma protein binding. When the $V_d$ of a drug is equivalent to total body water (about 40 L, as occurs with ethanol), this usually indicates that the drug has reached the intracellular fluid as well.

Some drugs have a $V_d$ that is much larger than total body water. A large $V_d$ may indicate that the drug is concentrated intracellularly, with a resulting low concentration in the plasma. Many weak bases, such as the antidepressant fluoxetine (Prozac), have a large $V_d$ (40–55 L) because of the phenomenon of intracellular ion trapping. Weak bases are less ionized within plasma than they are within cells because intracellular fluid usually has a lower pH than extracellular fluid. After a weak base diffuses into a cell, a larger fraction is ionized in the more acidic intracellular fluid. This restricts its diffusion out of a cell and results in a large $V_d$.

A large $V_d$ may also result from sequestration into fat tissue, such as occurs with the antimalarial agent chloroquine.

**Drug Clearance**

Clearance ($Cl$) is the most fundamental expression of drug elimination. It is defined as the volume of body fluid (blood) from which a drug is removed per unit of time. Whereas the clearance of a particular drug is constant, it is important to note that the amount of drug contained in the clearance volume will vary with the plasma drug concentration.

**Renal Clearance.** Renal clearance can be calculated as the renal excretion rate divided by the plasma drug concentration (see Box 2-2). Drugs that are eliminated primarily by glomerular filtration, with little tubular secretion or reabsorption, will have a renal clearance that is approximately equal to the creatinine clearance, which is normally about 100 mL/min in an adult. A renal drug clearance that is higher than the creatinine clearance indicates that the drug is a substance that undergoes tubular secretion. A renal drug clearance that is lower than the creatinine clearance suggests that the drug is highly bound to plasma proteins or that it undergoes passive reabsorption from the renal tubules.

**Hepatic Clearance.** Hepatic clearance is more difficult to determine than renal clearance. This is because hepatic drug elimination includes the biotransformation and biliary excretion of parent compounds. For this reason, hepatic clearance is usually determined by multiplying hepatic blood flow by the arteriovenous drug concentration difference.

**SINGLE DOSE PHARMACOKINETICS**

**First-Order Kinetics**

Most drugs exhibit first-order kinetics, in which the rate of drug elimination (amount of drug eliminated per unit time) is proportional to the plasma drug concentration and follows an exponential decay function. Note that the rate of
Drug elimination is not the same as the elimination rate constant, \( k_e \) (fraction of drug eliminated per unit time). A few drugs (e.g., ethanol) exhibit zero-order kinetics, in which the rate of drug elimination is constant and independent of plasma drug concentration (see Fig. 2–10B). For drugs that exhibit first-order kinetics, the plasma drug concentration can be determined from the dose of a drug and its clearance. Because the plasma drug concentration is often correlated with the magnitude of a drug’s effect, it is possible to use pharmacokinetic expressions to determine and adjust drug dosages to achieve a desired therapeutic effect (see below).

The following principles pertain to first-order kinetics: A drug’s rate of elimination is equal to the plasma drug concentration multiplied by the drug clearance; the elimination rate declines as the plasma concentration declines (see Fig. 2–10A); and the half-life and clearance of the drug remain constant as long as renal and hepatic function do not change.

**Elimination Half-Life \( t_{1/2} \)**

Elimination half-life \( (t_{1/2}) \) is the time required to reduce the plasma drug concentration by 50%. It can be calculated from the elimination rate constant, but it is usually determined from the plasma drug concentration curve (Fig. 2–11). The half-life can also be expressed in terms of the drug’s clearance and volume of distribution, indicating that the drug’s half-life will change when either of these factors is altered. The formula for relating half-life to clearance and volume of distribution is given in the legend of Figure 2–11. Disease, age, and other physiologic variables can alter drug clearance or volume of distribution and thereby change the elimination half-life (see Chapter 4).

**Zero-Order Kinetics**

The following principles pertain to zero-order kinetics: The rate of drug elimination is constant (see Fig. 2–10B); the drug’s elimination half-life is proportional to the plasma drug concentration; the clearance is inversely proportional to the drug concentration; and a small increase in dosage can produce a disproportionate increase in the plasma drug concentration.

In many cases, the reason that the rate of drug elimination is constant is that the elimination process becomes saturated. This occurs, for example, at most plasma concentrations of ethanol. In some cases, drugs exhibit zero-order elimination when high doses are administered, which occurs, for example, with aspirin and the anticonvulsant...
phenytoin (DILANTIN) or when a hepatic or renal disease has impaired the drug elimination processes.

**CONTINUOUS DOSE AND MULTIPLE DOSE KINETICS**

### Drug Accumulation and the Steady-State Principle

When a drug that exhibits first-order pharmacokinetics is administered to a patient continuously or intermittently, the drug will accumulate until it reaches a plateau or steady-state plasma drug concentration.

**Figure 2–10.** The kinetic order of drugs. In first-order kinetics (A), the rate of drug elimination is proportional to the plasma drug concentration. In zero-order kinetics (B), the rate of drug elimination is constant. The kinetic order of a drug is derived from the exponent, $n$, in the following expression:

\[
\frac{\Delta [\text{Drug}]}{\Delta t} = k_e [\text{Drug}]^n
\]

where $\Delta$ represents change, $[\text{Drug}]$ represents the plasma drug concentration, and $t$ is time. If $n$ is 1, then $\Delta[\text{Drug}]/\Delta t$ is proportional to $[\text{Drug}]$. If $n$ is 0, then $\Delta[\text{Drug}]/\Delta t$ is constant ($k_e$), because $[\text{Drug}]^0$ equals 1.

### Figure 2–11. Drug half-life and clearance.

The elimination half-life ($t_{1/2}$) is the time required to reduce the plasma drug concentration ($C$) by 50%. The formula is as follows:

\[
t_{1/2} = \frac{0.693}{k_e}
\]

where 0.693 is the natural logarithm of 2, and $k_e$ is the elimination rate constant. The half-life is often determined from the plasma drug concentration curve shown here. The clearance (Cl) is the volume of fluid from which a drug is eliminated per unit of time. It can be calculated as the product of the volume of distribution, $V_d$, and $k_e$. If $0.693/t_{1/2}$ is substituted for $k_e$, the equation is as follows:

\[
Cl = 0.693 \frac{V_d}{t_{1/2}}
\]

Thus, a drug’s clearance is directly proportional to its volume of distribution and is inversely proportional to its half-life.

The basis for this accumulation to a steady state is shown in Figure 2–12. When the drug is first administered, the rate of administration is much greater than the rate of elimination, because the plasma concentration is so low. As the drug continues to be administered, the rate of drug elimination gradually increases, whereas the rate of administration...
remains constant. Eventually, as the plasma concentration rises sufficiently, the rate of drug elimination equals the rate of drug administration. At this point, the steady-state equilibrium is achieved.

**Time Required to Reach the Steady-State Condition**

Drug accumulation to a steady state is a first-order process and therefore obeys the rule that half of the process is completed in a defined time. Because the time to reach the steady state is dependent on the time it takes for the rate of drug elimination to equal the rate of drug administration, the time to reach the steady state is a function of the elimination half-life of the drug. Any first-order process requires about five half-lives to be completed; thus the time to reach the steady-state drug concentration is about five drug half-lives. If the half-life of a drug changes, then the time required to reach the steady state also changes. Note that the time required to reach the steady state is independent both of the drug dose and the rate or frequency of drug administration.

**Steady-State Drug Concentration**

The steady-state drug concentration depends on the drug dose administered per unit of time and on the half-life of the drug. Figure 2–13 illustrates typical plasma concentration curves after drugs are administered continuously or intermittently. If the dose is doubled, the steady-state concentration is also doubled (Fig. 2–13A). Likewise, if the half-life is doubled, the steady-state concentration is doubled (Fig. 2–13B).

A drug administered intermittently will accumulate to a steady state at the same rate as a drug given by continuous infusion, but the plasma drug concentration will fluctuate as each dose is absorbed and eliminated. The average steady-state plasma drug concentration with intermittent intravenous administration will be the same as if the equivalent dose were administered by continuous infusion (Fig. 2–13C). A comparison of the steady-state drug levels following continuous intravenous infusion, multiple oral doses, and a single oral dose is shown in Figure 2–13D. With intermittent oral administration, the bioavailability of the drug will also influence the steady-state plasma concentration.

**Dosage Calculations**

The methods for calculating both the loading dose and the maintenance dose are given in Box 2–4.

**Loading Dose**

A loading dose, or priming dose, is given to rapidly establish a therapeutic plasma drug concentration. The loading dose can be calculated by multiplying the volume of distribution by the desired plasma drug concentration. The loading dose, which is larger than the maintenance dose, is generally administered as a single dose, but it can be divided into fractions that are given over several hours. A divided loading dose is sometimes used for drugs that are more toxic, for example, digitalis glycosides used to treat congestive heart failure.

**Maintenance Dose**

A maintenance dose is given to establish or maintain the desired steady-state plasma drug concentration. For drugs given intermittently, the maintenance dose is one of a series of doses administered at regular intervals. The amount of drug to be given is based on the principle that at the steady state, the rate of drug administration equals the rate of drug elimination. To determine the rate of drug elimination, the drug clearance is multiplied by the average steady-state plasma drug concentration. The maintenance dose is then calculated as the rate of drug elimination multiplied by the dosage intervals. If the drug is administered orally, its bioavailability must also be included in the equation.
Figure 2–13. Plasma drug concentrations after continuous or intermittent drug administration. (A) The steady-state plasma drug concentration is proportional to the dose administered per unit of time. (B) The steady-state plasma drug concentration is directly proportional to the half-life (and is inversely related to clearance). (C) The average steady-state concentration is the same for intermittent infusion as it is for continuous infusion. With intermittent drug administration, however, the plasma concentrations fluctuate between doses, and the size of fluctuations increases as the dosage interval increases. (D) Plasma drug concentrations after intermittent oral administration are affected by the rates of drug absorption, distribution, and elimination. If only one dose is given, the peak in plasma drug concentration is followed by a continuous decline in the curve.
**BOX 2-4 DRUG DOSAGE CALCULATIONS**

**Loading Dose**

The loading dose, or priming dose, of a drug is determined by multiplying the **volume of distribution** ($V_d$) of the drug by the **desired plasma drug concentration** (desired C). (This information can be found in the medical literature.) For theophylline, for example, the estimated $V_d$ for an adult weighing 70 kg is 35 L, and the desired C is 15 mg/L. The calculation is as follows:

\[
\text{Loading dose} = V_d \times C = 35L \times 15\text{mg/L} = 525\text{mg}
\]

As is discussed in Chapter 4 (see Table 4-5), the patient’s age can affect the $V_d$ and, therefore, should be considered in determining the appropriate loading dose for a particular patient.

**Maintenance Dose**

Calculations of the maintenance dose must take into consideration the **intended frequency of drug administration**. With intermittent administration, the fluctuations in C increase as the dosage interval increases. A two-fold fluctuation in C will occur when the dosage interval is equal to the drug’s half-life. This is because the C will fall 50% between doses. For many drugs, the half-life is a convenient and acceptable dosage interval.

The maintenance dose is designed to establish or maintain a **desired steady-state C**. The amount of drug to be given is based on the principle that at the steady state, the rate of drug administration equals the rate of drug elimination. The rate of elimination is equal to the clearance multiplied by the steady-state drug concentration. For example, if the steady-state gentamicin concentration is 2 mg/L and the clearance for gentamicin is 100 mL/min (0.1 L/min), then the elimination rate is 0.1 L/min ÷ 2 mg/L = 0.2 mg/min. If the drug is to be administered every 8 hours, then the dosage would be calculated as follows:

\[
\text{Maintenance dose} = \text{Hourly rate} \times \text{dosage interval in hours} = 0.2\text{mg/min} \times 60\text{ minutes in an hour} \times 8\text{ hours} = 96\text{ mg every 8 hours}
\]

If a drug is to be administered orally, the calculated dose must be divided by the fractional bioavailability to determine the administered dose.

**Dosage Adjustment Using Pharmacokinetic Values**

First, choose the target C and administer the initial dose on the basis of the standard published values (general population values) for clearance or $V_d$. Second, measure the patient’s plasma drug levels and calculate the patient’s $V_d$ and clearance. Third, revise the dosage based on the patient’s $V_d$ and clearance.

**SUMMARY OF IMPORTANT POINTS**

- Most drugs are absorbed by passive diffusion across or between cells. The rate of passive diffusion of a drug across cell membranes is proportional to the drug’s lipid solubility and the surface area available for absorption. Only the non-ionized form of weak acids and bases is lipid soluble.
- The ratio of the ionized form to the non-ionized form of a weak acid or base can be determined from the pKₐ of the drug and the pH of the body fluid in which the drug is dissolved.
- The distribution of a drug is influenced by organ blood flow and by the plasma protein binding, molecular size, and lipid solubility of the drug. Only drugs with high lipid solubility can penetrate the blood-brain barrier.
- The volume of distribution is the volume of fluid in which a drug would need to be dissolved to have the same concentration in that volume as it does in plasma. It is calculated by dividing the drug dose by the plasma drug concentration at time zero.
- Many drugs are biotransformed before excretion. Drug metabolites can be pharmacologically active or inactive. Phase I reactions include oxidative, reductive, and hydrolytic reactions, whereas phase II reactions conjugate a drug with an endogenous substance. The CYP enzymes located in the endoplasmic reticulum of liver cells are the most important oxidative metabolic enzymes.
- Most drugs are excreted in the urine, either as the parent compound or as drug metabolites, and undergo the processes of glomerular filtration, active tubular secretion, and passive tubular reabsorption. The renal clearance of a drug can be calculated by dividing the renal excretion rate by the plasma drug concentration.
- Most drugs exhibit first-order kinetics, in which the rate of drug elimination is proportional to the plasma drug concentration at any given time. If drug elimination mechanisms (biotransformation and excretion) become saturated, a drug can exhibit zero-order kinetics, in which the rate of drug elimination is constant.
- In first-order kinetics, a drug’s half-life and clearance are constant as long as physiologic elimination processes are constant. The half-life is the time required for the plasma drug concentration to decrease by 50%. The clearance is the volume of plasma from which a drug is eliminated per unit of time.
- The oral bioavailability of a drug is the fraction of the administered dose that reaches the circulation in an active form. It is determined by dividing the AUC after oral administration by the AUC after intravenous administration. Factors that reduce bioavailability include incomplete tablet disintegration and first-pass and gastric inactivation of a drug.
With continuous or intermittent drug administration, the plasma drug concentration increases until it reaches a steady-state condition, in which the rate of drug elimination is equal to the rate of drug administration. It takes about four to five drug half-lives to achieve the steady-state condition.

The steady-state drug concentration can be calculated as the dose per unit of time divided by the clearance, and this equation can be rearranged to determine the dose per unit of time required to establish a specified steady-state drug concentration.

A loading dose is a single or divided dose given to rapidly establish a therapeutic plasma drug concentration. The dose can be calculated by multiplying the volume of distribution by the desired plasma drug concentration.

Review Questions

1. If food decreases the rate but not the extent of the absorption of a particular drug from the gastrointestinal tract, then taking the drug with food will result in a smaller
   (A) area under the plasma drug concentration time curve
   (B) maximal plasma drug concentration
   (C) time at which the maximal plasma drug concentration occurs
   (D) fractional bioavailability
   (E) total clearance

2. If a drug exhibits first-order elimination, then
   (A) the elimination half-life is proportional to the plasma drug concentration
   (B) the drug is eliminated at a constant rate
   (C) hepatic drug metabolizing enzymes are saturated
   (D) drug clearance will increase if the plasma drug concentration increases
   (E) the rate of drug elimination (mg/min) is proportional to the plasma drug concentration

3. After a person ingests an overdose of an opioid analgesic, the plasma drug concentration is found to be 32 mg/L. How long will it take to reach a safe plasma concentration of 2 mg/L if the drug’s half-life is 6 hours?
   (A) 12 hours
   (B) 24 hours
   (C) 48 hours
   (D) 72 hours
   (E) 1 week

4. What dose of a drug should be injected intravenously every 8 hours to obtain an average steady-state plasma drug concentration of 5 mg/L if the drug’s volume of distribution is 30 L and its clearance is 8 L/h?
   (A) 40 mg
   (B) 80 mg

5. The volume of distribution of a drug will be greater if the drug
   (A) is more ionized inside cells than in plasma
   (B) is administered very rapidly
   (C) is highly ionized in plasma
   (D) has poor lipid solubility
   (E) has a high molecular weight

Answers and Explanations

1. The answer is B: the maximal plasma drug concentration. If the rate of drug absorption is reduced, then the maximal plasma drug concentration will be less because more time will be available for drug distribution and elimination while the drug is being absorbed. Moreover, the time at which the maximal plasma drug concentration occurs will increase. If the extent of drug absorption (fraction absorbed) does not change, then the area under the curve and fractional bioavailability will not change.

2. The answer is E: the rate of drug elimination (mg/min) is proportional to the plasma drug concentration. In first-order elimination, drug half-life and clearance do not vary with the plasma drug concentration, but the rate of drug elimination (quantity per time) is proportional to plasma drug concentration at any time.

3. The answer is B: 24 hours. The half-life is the time required to reduce the plasma drug concentration 50%. In this case, it will take four drug half-lives, or 24 hours, to reduce the plasma level from 32 to 2 mg/L.

4. The answer is D: 320 mg. The dose required to establish a target plasma drug concentration is calculated by multiplying the clearance by the target concentration and dosage interval. In this case, it is 5 mg/L × 8 L/h × 8 hours = 320 mg.

5. The answer is A: is more ionized inside cells than in plasma. When a drug is more ionized inside cells, the drug becomes sequestered in the cells and the volume of distribution can become quite large. This is called ion-trapping.

SELECTED READINGS