Chapter 2

Pharmacokinetics

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KEY TERMS AND DEFINITIONS

Bioavailability (F)—the fraction of the administered dose that is available to the systemic circulation. Units are expressed as a fraction in decimal form (eg, 4/5 = 0.8) or percentage (eg, 80%).

Clearance (CL)—the volume of serum, plasma, or blood that has all of the drug removed per unit of time by the eliminating organ. Total body clearance is the sum of the clearances of all the eliminating organs. Units are expressed as volume per time (eg, mL/hour).

Dosage regimen—how much drug will be given how often when multiple doses of the drug will be given (eg, 10 mg every day).

Elimination rate constant (*k*; it may also be signified as *ke* or *kd*)—the fraction of drug removed from the blood in a given time. Units are expressed as a fraction per time.

First-pass drugs—drugs that have a large fraction of the active drug metabolized in the liver as it passes through the liver before reaching the systemic circulation.

Half-life ($t_{1/2}$)—the time it takes for one half of the drug to be removed from the body. Units are in time (usually hours).

Prodrug—a drug that has to be converted into an active form by the body, usually by an enzyme in the liver.

Route of administration—the method used to give the drug to the patient during treatment.

Steady state (ss)—the point in therapy when the amount of drug administered exactly replaces the amount of drug removed. Steady state is never technically achieved, but

DOI 10.37573/9781585286638.002

for clinical purposes, five half-lives, which is when 97% of steady state is achieved, is considered to be at steady state. Units are in time.

Systemic—having a distribution or effect throughout the body.

Therapeutic range—a statistical range of desirable drug concentrations, for which the *majority* of patients show an effective therapeutic response with minimal drug-related side effects.

Volume of distribution—describes the volume into which the drug distributes in the body. Units are expressed in volume (mL or L).

LEARNING OBJECTIVES

After completing this chapter, you should be able to

1. Define pharmacokinetics and relate its principles to the work of a pharmacy technician.
2. Relate the route of administration to the actions of a drug and define at least eight routes of administration.
3. Define absorption, distribution, metabolism, and excretion and describe the relevance of each of these.
4. Discuss how pharmacokinetics contributes to choosing dosage regimens.
5. Relate pharmacokinetic principles to the prediction of drug interactions.

When using medication, the first concern is *the effect of that medication on the body*. Pharmacokinetics is the study of the *body's effect on the medication*. As soon as a drug is introduced to the body, it goes on a trip through the body on its way to elimination. Mathematical models can be used to predict this "trip" and, therefore, determine how much drug will be in the body at any time. When certain concentrations cause predictable outcomes or effects ("pharmacodynamics"), the models can be used to set target levels (concentrations) to produce the desired effects of drugs in patients. These principles are applied to improve patient outcomes.

Using pharmacokinetics, the pharmacist can properly evaluate measured drug concentrations and design good **dosage regimens** for patients. These dosage regimens are intended to increase efficacy while avoiding toxicity in patients treated with medications. In addition, pharmacokinetic principles help to predict and avoid drug-drug and drug-disease interactions.

ROUTES OF ADMINISTRATION

There are several methods of giving drugs to patients, commonly called **routes of administration**. While some routes are created for convenience, others may be needed due to a patient's or drug's limitations or characteristics. The routes of administration are reviewed in the following section.

Oral Route

The oral (PO) route of administration is the most commonly prescribed route, as well as the route most associated with taking medications. Oral medications are beneficial for individuals taking medications on a daily basis, and medication for oral use can easily be carried along for dosing throughout the day. However, not all drugs can be given orally because of the rigorous journey from administration to site of action.

After being swallowed, a drug in a capsule, tablet, or liquid travels down the esophagus and into the stomach. Once it enters the stomach it comes in contact with various digestive enzymes and stomach fluids that are acidic in nature. The acidic environment, enzymes, and physical mixing require that the medication be formulated to withstand the conditions or it could be rendered ineffective. Most absorption of drugs occurs in the small intestine. The finger-like villi found there increase the surface area, improving the chances for drugs and nutrients to be absorbed. When the drug is absorbed it enters the gut wall, which contains drug-metabolizing enzymes and efflux pumps. If the drug makes it through the gut wall without being metabolized, it will travel via the bloodstream to the liver before finally making it to the **systemic** circulation. By going through the gut wall and liver before reaching the systemic circulation, some drugs are significantly metabolized before reaching the site of action. This is called the first-pass effect. Not all drugs can be given orally because they all cannot "survive" this rigorous journey.

Some drugs given orally are formulated to release their contents slowly. This may be done for many reasons. In these cases, the drug may have "sustained release" or "controlled release" in the name of the preparation. Some preparations may also have a coating ("enteric coating"), which will protect the drug from being destroyed in the journey to the

absorption site. These types of medications should never be crushed or chewed or split unless the product is specifically formulated and labeled to allow this. Otherwise, the patient could be at risk for toxicity from the entire dose being available at once or lack of efficacy if the drug is destroyed.

Sublingual and Buccal

These medications are formulated to be given through the mucosa in the mouth. Sublingual (SL) administration designates administration under the tongue, and in buccal administration, the drug is placed between the gums and the cheek. This type of formulation is not chewed or swallowed but placed in the mouth to dissolve. These routes of administration provide quicker absorption and, for some drugs, greater **bioavailability**, because the drug is absorbed directly into the bloodstream without going to the gut and liver first, thereby avoiding the first-pass elimination. After the medication is dissolved and absorbed, it is immediately available in the bloodstream, which may lead to a quicker onset of action than would occur with an oral dose. An example of an SL product is the Nitrostat® tablet. These are administered if a patient is experiencing chest pain due to angina. The formulation allows for an abrupt onset of action that will quickly diminish the chest pain.

Inhalation

Inhalation (INH) affords local delivery of the drug directly to the lungs or nasal passages. Following INH, an aerosolized or powdered drug can be available quickly and completely to the lungs, the nasal passages, and/or the blood vessels in these areas. This is beneficial for patients with respiratory illnesses, who can have the drug delivered to the site of action without exposing the whole body to its effects. Many drugs for the treatment of asthma or chronic obstructive pulmonary disease (COPD) come in a form to be inhaled to deliver the drug to the site of action without exposing the whole body to the drug. The INH route may also be used for the systemic delivery of drugs that cannot be given orally. Examples of this are the nasal spray of calcitonin used to deliver a bone hormone for the treatment of osteoporosis and immediate-release insulin given by oral inhalation for the treatment of type one diabetes mellitus.

Rectal

The rectal (PR) route of administration is not one most patients prefer, but it does have a place in therapy. Suppositories are solid medication dosage forms that are given rectally and may be advantageous for patients who are vomiting or for patients who are not conscious and do not have intravenous (IV) access, as well as if needed for local action. Enemas are liquid dosage forms delivered rectally; most are intended to act locally. Most medications in suppositories will not go through the liver and therefore will not have the first-pass effect.

Vaginal

While the vaginal (PV) route of administration is also not highly used, it is beneficial for local treatment of vaginal conditions. Formulations that may be used include vaginal suppositories, creams, and even some tablets. Patients who benefit from PV administration include those being treated for vaginal infections, menopause, and infertility.

Topical

Topical application includes preparations intended for use directly on the skin (dermal), into the eye (ophthalmic), into the ear (otic), and into the nose (nasal). This route is quite common and there are a variety of products available for topical administration, with subtle differences. Preparations made for direct application to the skin include creams, ointments, lotions, gels, shampoos, and solutions. Both creams and ointments have oil bases, but ointments have higher oil content than creams and provide a protective layer on top of the skin. Lotions and gels have a water base and are more easily spread on top of the skin. Solutions contain the highest liquid content and are most readily absorbed through the skin. Shampoos are soap solutions intended for use on the head and body. Both ophthalmic and otic preparations come in solutions and suspensions. A suspension is different than a solution because a suspension suspends small particles of an insoluble drug in a liquid that is usually water based. It is a good way to administer a drug that is insoluble in water. A solution, in contrast, has a soluble drug dispersed in a solvent, which is also usually water based. It is important to realize that there is a difference between them because the use of some preparations may not be appropriate for a given medical condition. For example, solutions may contain alcohol, whereas suspensions do not, and, therefore, otic drops formulated into a solution should not be used in a patient with a ruptured eardrum due to the risk of worsening the injury because of the alcohol. Ophthalmic preparations are specially formulated for comfort and safety of sensitive eye tissues and must be sterile to prevent infection.

Topical nasal preparations are commonly drops or gels that are applied directly into the nose. The nasal route is beneficial for patients suffering from allergies as the drug is delivered directly to the site of the symptoms.

ALERT!

While ophthalmic dosage forms are sometimes prescribed for or used in the ear, otic drops are never appropriate for use in the eye. ONLY DRUGS FORMULATED FOR THE EYE SHOULD BE ADMINISTERED INTO THE EYE.

Intravenous/Intramuscular/ Subcutaneous Injections

Injection routes of administration deliver the medication directly into the vein (IV), muscle (IM), or subcutaneous (SUBQ) tissue of the patient. Injection methods require delivery by a needle. Because the drugs bypass the gastrointestinal (GI) tract, lack of absorption and destruction in the journey to the systemic circulation is not an issue for IV medications, and is less problematic for IM formulations than for those administered PO.

PRACTICE POINT

All injectable dosage forms must be sterile.

Transdermal

The application of patches is considered transdermal drug delivery. After a patch is applied to unbroken skin, the drug travels across the layers of skin and is absorbed by the body. This route is beneficial because of the ease of administration of the drug. Also, while most oral medications require everyday dosing, patches allow for multiple-day and longer dosing. For a patient who is unable to take pain medications due to effects on the GI system, the transdermal application allows the administration of an effective analgesic without many of the adverse effects associated with the oral form. Transdermal dosage forms are described in more detail in Chapter 32.

ALERT!

Transdermal patches should never be cut or altered unless labeled as safe for cutting. The delayed-release structure of the patch will be compromised and the patient at risk for getting the total dose quickly, which could be very dangerous for the patient.

ADME (ABSORPTION, DISTRIBUTION, METABOLISM, EXCRETION): A TRIP THROUGH THE BODY

Absorption

If a drug is given by any route other than intravenously, it must first be absorbed. For the drug, the trip from the site of administration to the systemic circulation can be difficult. Medications taken orally must pass through and withstand the conditions of the stomach and then travel to the small intestine for absorption. There are enzymes found in the wall of the small intestine that can metabolize (break down or change) the drug. Also, in the wall of the small intestine, there are pumps that can transport the drug back into the GI tract. After absorption, the drug must travel to the liver, where it again may be metabolized. With routes of administration other than IV, it is possible that not all of the drug given will be available to the body. The percent of medication available to the body from a given dose is known as the drug's bioavailability. This is a property specific to each drug and depends on many factors, including dosage form and route of administration. If the drug is able to bypass the absorption step, as with those given intravenously, drug absorption is not an issue and the bioavailability of the drug is 100%. Some drugs are so highly affected before reaching the systemic circulation that it is not useful to give them by the oral route. In most cases, however, a larger dose can be given when administered orally to overcome any decrease in bioavailability related to poor absorption or the first-pass effect (described in the section on Metabolism that follows). Drug-drug and drug-food interactions can occur at many points in the absorption process (details are described later on in the section on Drug and Disease Interactions).

Distribution

Distribution describes the process by which the drug is spread throughout the body and to what extent it is concentrated in various tissues. This property is also unique to each drug, as some drugs distribute widely throughout the body and have large distributions and others do not travel much

beyond the bloodstream and therefore have small distributions. Common sites of distribution are the blood, muscles, fat tissue, bones, and organs. These may become important when treating certain conditions that require the drug to penetrate tissues to be effective. Besides this, the **volume of distribution** of a drug also helps pharmacists determine the rate at which the drug is removed from the body. Drugs having a larger volume of distribution will take longer to be eliminated from the body, whereas drugs with smaller volumes of distribution will take less time to be removed.

Metabolism

As soon as drugs enter the body, elimination begins. Some drugs need to be changed into a new compound to enhance their elimination. Metabolism is the process by which the drug is broken down or changed by various enzyme systems. The compounds formed as a result of the interaction between the drug and enzymes are known as metabolites. Metabolites may be *active* (with a therapeutic effect) or *inactive* (with little or no therapeutic effect) when compared to their precursors (the original drug compounds) and *some* may even be responsible for toxic side effects. Some drugs are inactive until they are activated by being metabolized. These are called **prodrugs**. Recall that drugs taken orally are absorbed and transported to the liver before reaching the rest of the body. This is an important safeguard built into our bodies, to ensure than anything eaten must go through the liver for possible metabolism before being utilized by the body. This, however, may result in significant metabolism of drugs before reaching the site of action. This is called the first-pass effect because drugs taken orally must "first pass" through the liver before reaching the systemic circulation. If a drug intended for systemic effect is highly eliminated by the first pass, (ie, nitroglycerin, lidocaine), it may be ineffective when given orally and, therefore, should be given via a "non-first-pass route" such as SL or IV.

Several liver enzymes are responsible for the metabolism of drugs. They are categorized into two groups: phase I and phase II enzyme systems. The most common phase I drug-metabolizing enzymes are known collectively as the cytochrome P450 enzymes, sometimes abbreviated CYP P450 (pronounced "sip P four-fifty"). The CYP P450 family of enzymes includes a large number of individual enzymes. Other enzyme systems that can metabolize drugs include phase II enzymes, which act by conjugating (chemically combining) drugs with glucuronic acid or glutathione, or modifying the drug by the transfer of methyl, acetyl, or sulfa groups from donor compounds. Most enzymes can be upregulated and downregulated by inducing or inhibiting the enzymes. There are drugs and diseases that can induce and inhibit enzymes. This is a major source of drug and disease interactions (as described later in the section on Drug and Disease Interactions).

There are also some enzymes that are genetically controlled and could exist in greater or lesser amounts in individual patients. For example, if a patient has a large amount of enzymes available to metabolize a drug, he or she will be a fast metabolizer and will have a more rapid **clearance** of the drug. In this case, the patient may suffer from a lack of efficacy because of this genetically determined increase in the enzyme. This patient would possibly need a higher dose of the drug compared to patients without this genetic trait. On the other hand, slow metabolizers would have genetically less enzyme available and would need lower doses of drugs metabolized by that enzyme. Pharmacogenomics is a relatively new and exciting field of study that examines how to accurately predict and react to such potential over- or under-dosing of drugs based upon the genetic make-up of the patient. Tests are available to predict the genetic types for some critical metabolizing enzymes. This information can be utilized to determine if some drugs can or should be used, and to help tailor the proper dosages of drugs to ensure that they are safe and effective. Chapter 3 examines this field in detail.

Excretion

Excretion is the process by which the drug and its metabolites are eliminated from the body. The main routes of excretion are through the urine and feces. Drugs may also exit the body through exhalation and sweating but to a much lesser extent. How readily drugs and metabolites are excreted in the urine or feces is dependent on their physiochemical properties and the function of the excreting organ. A drug excreted primarily by the kidneys will likely require dose adjustment for a patient with kidney failure. If the dose is not adjusted, the concentration of the drug may increase to a range that is toxic to the patient. Similarly, if two drugs are cleared by the same mechanism, one drug may be preferentially eliminated over another, resulting in hindering the elimination of the other drug. This may result in an increased concentration of the drug that had its elimination reduced. There are even drug interactions that can occur in the kidneys (as described in the section on Drug and Disease Interactions).

PHARMACOKINETIC MODELING

Mathematical models can be used to predict concentrations of drug in the body and when they will occur. If there is a known effect that is targeted and related to drug

concentration, dosage regimens can be designed to deliver a given concentration-time profile. Most drugs are eliminated in a *log linear* fashion. This may sound complicated, but it simply means that, instead of a drug being removed by a certain number of milligrams or grams each minute or hour, a given fraction or percentage of the drug is removed each hour. For example, 50% of the drug may be removed per hour. In this case, after 1 hour 50% would be left, after 2 hours 25% would be left, after 3 hours 12.5% would remain, etc. The amount of time it takes for half of the drug to be removed is called the **half-life**. The half-life is a measure of how long the drug hangs around in the body and is, therefore, an important element in determining how often a drug should be given. The shorter the half-life, the more often the drug must be given and vice versa. Half-life also determines how long it takes for the drug to reach a **steady state**. Steady state is a state of equilibrium that occurs when the drug administered replaces the drug removed. It takes four or five half-lives to reach a "clinical" steady state.

The line formed by a plot of drug concentrations after administration versus time will be curved, if the drug follows what is termed a linear, "one-compartment" model (see **Figure 2-1**). If the same drug concentrations versus time are plotted on a log linear plot or the log normal (ln) concentration versus time is plotted, the resulting line will be straight.

To determine the half-life and **elimination rate constant (*k*)**, the slope of the elimination line must be determined. The elimination rate constant (*k*) is a measure of the fraction of the drug that is removed per unit of time. The units for half-life are in terms of time (hours, minutes, etc.). The units for the elimination rate constant will be the inverse of half-life, per unit of time (per hour, etc.). This is because it is signifying the fraction of removal in that time. The elimination rate constant (*k*) is the slope of the straight line formed in the log linear plot in Figure 2-1. Therefore, a simple "rise over run" method can be used to determine the elimination rate constant (*k*):

$$k = \frac{rise}{run} = \frac{\ln C_2 - \ln C_1}{t_2 - t_1} \qquad \text{Eq. 1}$$

The elimination rate constant (*k*) is closely related to the half-life.

$$t_{1/2} = \frac{0.693}{k} \qquad \text{Eq. 2}$$

These equations are complex but pharmacy technicians are not usually expected to do such calculations. The important point to take from them is that removal of a drug from the body is often described using numbers (the elimination rate constant and, more commonly, the half-life) that give us an idea of how long it takes to remove the drug and how long it takes to reach a steady state. This will influence how frequently a drug must be dosed.

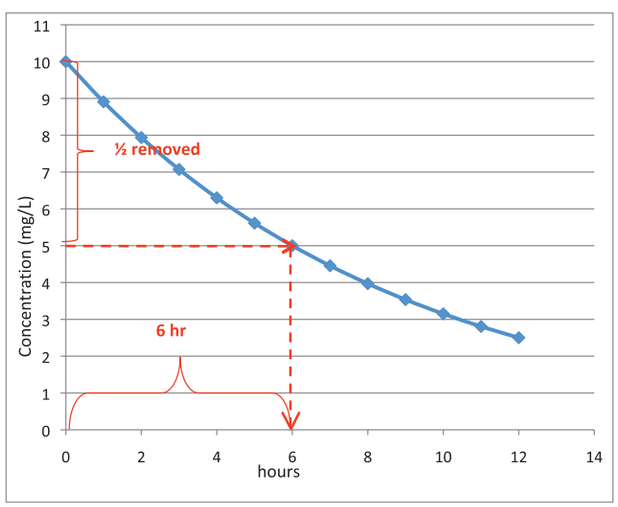

FIGURE 2-1. Concentrations after a dose given where it takes 6 hours for half of the drug to be removed; therefore, the half-life of this drug is 6 hours.

DOSAGE REGIMEN DESIGN

A dosage regimen is how much drug will be given in a period of time when multiple doses of the drug will be given (eg, 10 mg every day). It is usually designed to ensure that the drug concentrations resulting from the dosage regimen will be within the **therapeutic range**. The therapeutic range is a range of concentrations that describes the best chance for the patient to achieve therapeutic efficacy and avoid toxicity. The dosage regimen is made up of two parts, the dose rate (how much drug is given per unit of time) and the dosing interval (how often the drug is given).

Determination of the Dosing Rate

The dosing rate can be defined as the amount of drug given per unit of time. For example, if a drug's dosage regimen is 10 mg once daily, the dose rate would be 10 mg per day. However, if the drug were given 10 mg twice daily, the dose rate would be 20 mg per day. Pharmacists are able to determine an ideal dose rate for a given patient if some parameters

are known. The ideal dosing rate will be targeting a chosen average concentration at steady state (Css,avg). This is as it states, the average concentration measured over the dosing interval once at steady state. This concentration will likely be toward the middle of the therapeutic range.

$$C_{ss,\,avg} = \frac{F \times DR}{CL} \qquad \text{Eq. 3}$$

The average concentration over a dosing interval at steady state ($C_{ss,avg}$) is determined by the clearance (CL), bioavailability (F), and dose rate (DR) of the drug given. While bioavailability is important in most routes of administration, it is not necessary to consider it when determining a dosing rate for a drug given intravenously. (Recall that the bioavailability of these drugs is 100%.)

Once the drug is at steady state and assuming that the F and CL remain constant, the average concentration at steady state will be proportional to the amount of drug given per unit of time (dose rate). Therefore, if the concentration is too low, the dose rate can be increased proportionally to raise the concentration to the target range. If the concentration is too high, the dose rate should be proportionally lowered to ensure that the patient doesn't suffer from toxicity. This is only true for drugs that exhibit linear clearance. This is when a given fraction of the drug is removed per unit of time.

There are some drugs that are eliminated in a nonlinear fashion. In this case, an amount of drug is removed per unit of time, not a fraction of the drug per unit of time. Drugs that are eliminated this way will have a clearance that is concentration dependent. The $C_{ss,avg}$ will not be proportional to the dose rate in this case. Phenytoin (Dilantin®), a drug used for seizures, is cleared this way. If the dose rate of phenytoin is doubled, the resulting concentration would be much more than double. This is a concern as it could result in toxicity.

Determination of the Dose Interval

The dose interval is how often the drug is given (ie, daily, twice a day, etc.). The longer the dosing interval, the more variation there will be in the concentrations over the dosing interval. For most drugs, the goal is to minimize the difference between the maximum concentration (C_{max}) achieved, usually at or near the beginning of the dosing interval, and the minimum concentration (C_{min}) achieved at the end of the dosing interval. The longer the dosing interval, the larger the difference between C_{max} and C_{min}. Figure 2-2 demonstrates the difference when giving 150 mg every 12 hours (blue line) compared to giving 75 mg every 6 hours (red line). The amounts given per time are the same (12.5 mg/hr), so the patient will get the same amount of drug per time (same dose rate) but the C_{max} and C_{min} will differ.

As a rule of thumb, dosing every one or two half-lives works well for most drugs. Since it takes one half-life to eliminate half the drug, this means that there will be half (one half-life) or a quarter (two half-lives) of the drug at the end of the dosing interval when compared to the beginning of the dosing interval. Therefore, drugs with longer half-lives can be given less often. This is usually desirable to improve patient adherence to the dosage regimen.

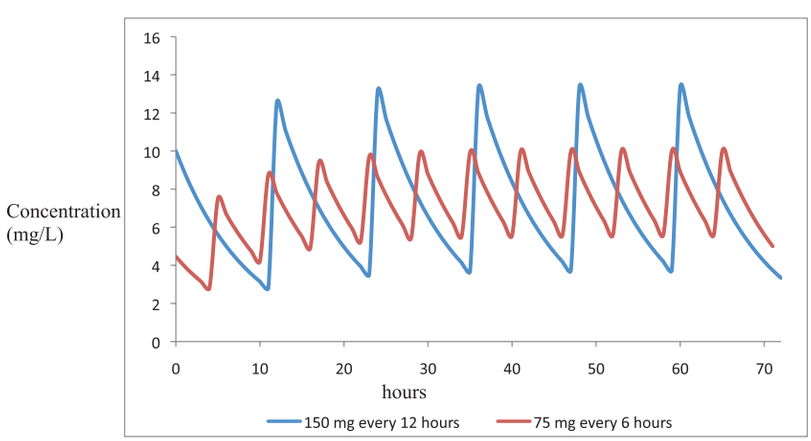

FIGURE 2-2. Concentration time curves when giving the same dose rate but differing dose intervals. Half-life is 6 hours.

MONITORING

One of the benefits of applying pharmacokinetics to patient drug regimens is the ability of the pharmacist to monitor drug concentrations that correlate with drug effects, both therapeutic and toxic. These concentrations can be measured through blood draws. Of course, determining whether a patient has either subtherapeutic or toxic drug effects is not determined by a drug concentration level alone. Drug concentration should always be viewed in the context of the patient's signs and symptoms. If the concentrations are too high, indicating possible toxicity, is the patient exhibiting signs and symptoms of toxicity? If the concentrations are too low, is the patient showing signs of lack of efficacy? Once this has been established, calculations can be utilized to estimate concentrations at any time after a drug is given. For most drugs a log linear relationship allows any concentration to be determined when one concentration and the half-life (or the elimination rate constant, *k*) are known.

$$C_t = C_0 e^{-\frac{0.693}{t\frac{1}{2}} \times t} \text{ or } C_t = C_0 e^{-k \times t} \qquad \text{Eq. 4}$$

where C_t = concentration that occurs *t* amount of time after C_0

C_0 = concentration that occurs "*t*" amount of time before C_t

*t*½ = half-life

k = elimination rate constant

t = amount of time between C_t and C_0

e^{-kt} = fraction of drug remaining at time *t*

Note: equation 4 is a rearrangement of equation 1.

$$k = \frac{rise}{run} = \frac{\ln C_2 - \ln C_1}{t_2 - t_1}$$

$$k(\Delta t) = \ln C_2 - \ln C_1$$

$$\ln C_2 = \ln C_1 - k(\Delta t)$$

anti-log each side

$$C_2 = C_1 \bullet e^{-k\Delta t}$$

These equations look challenging, but they are very useful. For example, if it is known that a drug has a therapeutic range from 5 mg/L to 20 mg/L, a dosage regimen can be designed to keep the concentrations within that range. If the *t*½ of the drug is known to be 6 hours and a concentration is measured 8 hours after the drug is given and is found to be 7.94 mg/L, it can be determined when the concentration will fall below 5 mg/L and the next dose must be administered.

$$C_t = c_0 e^{-\frac{0.693}{t\frac{1}{2}}t}$$

$$5\frac{mg}{L} = \frac{7.94mg}{L} e^{-\frac{0.693}{6hr}t}$$

When solved for *t*: *t* = 4 hr.

Thus, the concentration will fall to 5 mg/L in 4 hours, which will be 12 hours after the drug is given. This drug should be dosed every 12 hours to stay within the therapeutic range (Figure 2-3).

Utilizing pharmacokinetic modeling in choosing the proper dosing regimen for a patient can result in better

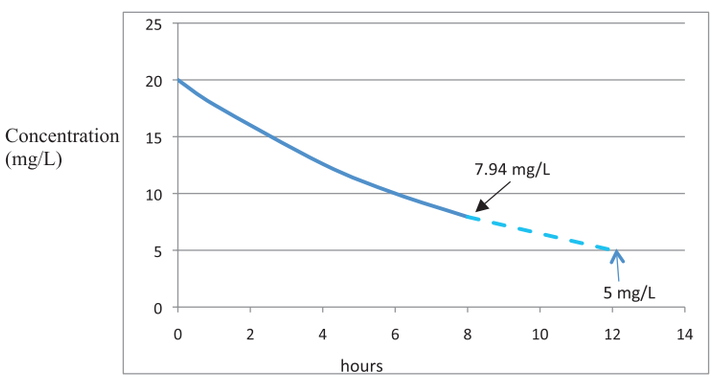

FIGURE 2-3. Concentration-time curve demonstrating the determination of when the next dose should be given.

TABLE 2-1. Representative Drugs with Narrow Therapeutic Range

Central Nervous System	Cardiovascular
Acetaminophen	Digoxin
Amitriptyline	Disopyramide
Carbamazepine	Flecainide
Desipramine	Lidocaine
Ethosuximide	Procainamide
Imipramine	Quinidine
Lithium	
Nortriptyline	
Phenobarbital	
Phenytoin	
Primidone	
Valproic acid/divalproex	
Antibiotics	**Immunologic/ Immunosuppressive**
Amikacin	Cyclosporine
Chloramphenicol	Methotrexate
Gentamicin	Sirolimus
Tobramycin	Tacrolimus

patient care because there is more confidence in predicting a regimen that will be effective while avoiding toxicity. This is based on the *C*ss,avg, *C*ss,max, and *C*ss,min all being within the therapeutic range. Drugs with relatively small ("narrow") therapeutic ranges are the ones that most commonly require drug level monitoring and specialized dosing because the differences between the *C*max that is needed to avoid toxicity and the *C*min that is needed to ensure efficacy is small. These are also the drugs that are highly vulnerable to drug, food, and disease interactions. A representative list of these drugs can be found in Table 2-1.

DRUG AND DISEASE INTERACTIONS

Drug Interactions in Absorption

Absorption can be increased or decreased depending on disease states, the drugs, or the foods that are administered at the same time. This can pose a problem for individuals who have multiple disease states requiring the use of multiple medications. Absorption drug interactions may result in either more or less drug being absorbed and, therefore, leave some therapies possibly toxic and some possibly ineffective. It is important to understand that drug, food, and disease interactions do not just happen when an interfering drug or food is added but the reverse effect will often happen when the drug or food is stopped.

One such interaction occurs when drugs given orally bind with other compounds, decreasing their ability to be absorbed. An example of this is ciprofloxacin (Cipro®), an antibiotic. When calcium is given with oral ciprofloxacin, it will decrease the amount of ciprofloxacin available for absorption. This could result in suboptimal concentrations of this antibiotic, possibly resulting in therapeutic failure. If you add the auxiliary label that says do not take with antacids, this is likely the reason why.

When grapefruit or grapefruit juice comes into contact with the intestinal tract, it can decrease the effectiveness of some of the enzymes in the intestinal wall. By decreasing the enzyme activity, drugs that are subject to this enzyme can have an increase in the amount of drug that is bioavailable or the amount that makes it to the systemic circulation. This increase in bioavailability will increase the concentration of drug in the body, possibly putting the patient at risk for toxicity. An example of this drug-food interaction happens with grapefruit juice and a group of cholesterol-lowering medications called statins, as well as with cyclosporine, an immunosuppressant used to block the rejection of transplanted organs.

These are only a few examples of many types of interactions that can occur in the process of absorption. There are many others. These are most significant for drugs with small therapeutic ranges (Table 2-1).

Drug Interactions in Metabolism

Metabolism may also be the source of drug-disease, drug-drug, and drug-food interactions. Recall from earlier discussion, the importance of the CYP P450 system of enzymes. Many, but not all, drugs require metabolism by these enzymes to become active or inactive. There are many drugs that can induce or inhibit CYP P450 enzymes. If an enzyme inhibitor of the CYP P450 3A4 enzyme, such as fluconazole (Diflucan®), is added to the regimen of a patient who is already taking a drug like phenytoin (Dilantin®) that is metabolized by this system, the phenytoin will not be metabolized as quickly and will increase the concentration of the phenytoin, putting the patient at risk for toxicity. Conversely, if erythromycin, a CYP P450 3A4 inducer is added to the regimen of a patient on phenytoin, the clearance of phenytoin will increase, causing a decrease in the concentration of phenytoin. This could result in therapeutic failure.

Enzymes that metabolize drugs can be induced or inhibited by other drugs and diseases. Recall that genetic predispositions for being fast and slow metabolizers will

also enter into the determination of the dosing regimen for metabolized drugs. A more detailed discussion can be found in chapter 3.

Drug Interactions in Excretion

When a patient who has kidney disease is taking a drug for which the body relies on the kidneys for elimination, it would be expected that the clearance would decrease. This would result in an increase in the amount of drug in the body, possibly putting the patient at risk for toxicity unless the dose rate is decreased.

There are drug interactions that can occur as well. Some drugs are eliminated by utilizing transport systems or "carriers" that move them from the blood into the nephron and out of the body in the urine. Drugs may compete with each other for the carrier taking them from the blood into the nephron. If two drugs are competing for the same carrier, one may be preferentially carried into the nephron and one left behind. The one left behind will not be cleared, thereby decreasing drug clearance and increasing concentrations and half-life. This drug interaction is utilized for a beneficial therapeutic effect when probenecid is added to the regimen of a patient who is already on penicillin. The probenecid will be preferentially carried into the nephron leaving the penicillin behind, purposefully increasing the concentrations and duration ($t½$) of the antibiotic penicillin. There are other similar drug interactions that are not always considered to be beneficial.

There are also drug interactions associated with changes in the pH of the urine that could increase or decrease the clearance of a drug eliminated in the urine. If a patient with renal impairment is taking a drug that is cleared by the kidneys, the patient is at risk for toxicity. Adding or stopping a drug that affects the carrier of another drug for secretion into the nephron could alter the clearance of drugs susceptible to these interactions.

Knowing about all these interactions will be helpful to ensure that patients are properly warned or advised by the pharmacist. However, it is ultimately the pharmacist's role to evaluate the situation and confer with the prescriber for suggested changes in the dosing regimen or warn the patient about potential problems.

SUMMARY

Pharmacokinetics provides an important set of tools for pharmacists to ensure that their patients have optimal dosage regimens. Utilization of these concepts can help pharmacists predict and avoid the possible dangerous effects of drug-drug, drug-food, and drug-disease interactions and, therefore, avoid possible problems of inefficacy or toxicity. It is important to recognize that utilizing drug concentrations and pharmacokinetics is only a tool. This information must be coupled with clinical information and evidence in order to get a true picture of the patient. Understanding and using these principles will result in better outcomes in patients.

REVIEW QUESTIONS

1. You see that one of your patients is buying some St. John's Wort OTC (over-the-counter) for depression. You want to be sure that there are no drug interactions. You recall the pharmacist saying that this drug can be an enzyme inhibitor. What should you do?
2. A patient is well controlled on a drug that is totally cleared by the kidneys, and then the patient becomes renally impaired. Is the patient at risk? What will this mean for the patient's drug regimen?
3. A patient is on a drug that has a half-life of 8 hours. How long will it take for the patient to reach steady state?
4. The concentration after an IV dose is given is 80 mg/L. Twenty-four hours later the concentration of this drug is measured to be 10 mg/L. What is the half-life of this drug? If the therapeutic range of this drug is 20–80 mg/L, how often should the drug be given?
5. A patient on an antihypertensive medication has had a change in her insurance coverage, which means the patient must change brands of her blood pressure medication. The patient would be happy with this because it is much cheaper for her. However, it is known that this brand of the drug has a lower bioavailability. How would this likely affect the clearance, volume, half-life, and concentrations of this drug in your patient? What dosage regimen changes should be recommended?
6. A patient is taking 200 mg twice daily of a drug called "Nemo" for cholesterol lowering. The average target concentration is 10 mg/L. The patient's cholesterol has not improved, and the average concentration is measured to be 5 mg/L. What dosage regimen changes should be recommended? (Assume the patient is at steady state and that F and CL are stable. "Nemo" is a linearly cleared drug.)
7. How could pharmacokinetic principles be used to help determine how often a drug is given to a patient?
8. How might pharmacokinetic principles be used to anticipate drug interactions?