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CLINICAL PHARMACOKINETIC AND PHARMACODYNAMIC CONCEPTS

INTRODUCTION

Clinical pharmacokinetics is the discipline that applies pharmacokinetic concepts and principles in humans in order to design individualized dosage regimens which optimize the therapeutic response of a medication while minimizing the chance of an adverse drug reaction. Pharmacokinetics is the study of the *absorption*, *distribution*, *metabolism,* and *excretion* of drugs.[1] When drugs are given extravascularly (e.g., orally, intramuscularly, applied to the skin via a transdermal patch, etc.), *absorption* must take place for the drug molecules to reach the systemic circulation. In order to be absorbed, the drug molecules must pass through several physiological barriers before reaching the vascular system. For example, when a medication is given orally, the drug dosage form must release drug molecules via dissolution, and the molecules must pass through the various layers of the gastrointestinal tract where they enter capillaries. *Distribution* occurs when drug molecules that have entered the vascular system pass from the bloodstream into various tissues and organs such as the muscle or heart. *Metabolism* is the chemical conversion of the drug molecule, usually by an enzymatically mediated reaction, into another chemical entity referred to as a *metabolite.* The metabolite may have the same, or different, pharmacological effect as the parent drug, or even cause toxic side effects. *Excretion* is the irreversible removal of drug from the body and commonly occurs via the kidney or biliary tract.

Pharmacodynamics is the relationship between drug concentration and pharmacological response. It is extremely important for clinicians to realize that the change in drug effect is usually not proportional to the change in drug dose or concentration (Figure 1-1). For example, when a drug dose or concentration is increased from a baseline value, the increase in pharmacological effect is greater when the initial dose or concentration is low compared to the change in drug effect observed when the initial dose or concentration is high. Thus, the

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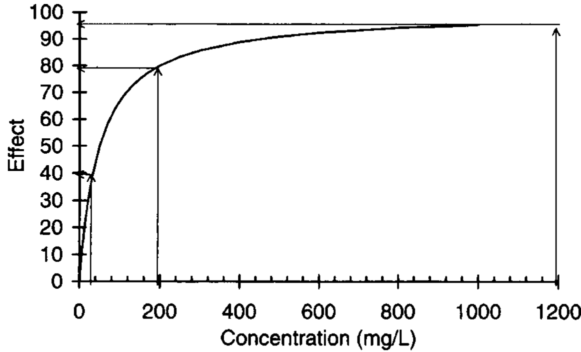

FIGURE 1-1 The relationship between drug concentration and response is usually a hyperbolic function: Effect = $(E_{max} \cdot C)/(EC_{50} + C)$, where E_{max} is the maximum effect and EC_{50} is the drug concentration where the drug effect equals $E_{max}/2$. After a dosage change is made and drug concentrations increase, the drug effect does not change proportionally. Further, the increase in pharmacological effect is greater when the initial concentration is low compared to the change in drug effect observed when the initial concentration is high. In this graph, the drug effect changes ~50% (from ~40 to 80 units) with a fivefold increase in concentrations at low levels (from ~40 to 200 mg/L), but only ~20% (from ~80 to 95 units) when the same five-fold increase in concentrations is made at high concentrations (from ~200 to 1000 mg/L).

increase in pharmacological effect that one observes in a patient as the dose is increased is subject to the law of diminishing returns and will eventually reach a maximum. The reason that most drugs follow this pattern is because their pharmacological effect is produced by forming a complex with a drug receptor. Once the drug-receptor complex is formed, the pharmacological effect is expressed. Often, toxic side effects of drugs follow the same type of dose- or concentration-response relationship, albeit shifted to the right on the dose or concentration axis. In clinical situations, patients may need to tolerate some side effects in order to obtain the maximal pharmacological effect of the agent.

LINEAR VERSUS NONLINEAR PHARMACOKINETICS

When drugs are given on a constant basis, such as a continuous intravenous infusion or an oral medication given every 12 hours, serum drug concentrations increase until the rate of drug administration equals the rate of drug metabolism and excretion. At that point, serum drug concentrations become constant during a continuous intravenous infusion or exhibit a repeating pattern over each dosage interval for medications given at a scheduled time (Figure 1-2). For example, if theophylline is given as a continuous infusion at a rate of 50 mg/h, theophylline serum concentrations will increase until the removal of theophylline via hepatic metabolism and renal excretion equals 50 mg/h. If cyclosporine is given orally at a dose of 300 mg every 12 hours, cyclosporine blood concentrations will follow a repeating pattern over the dosage interval which will increase after a dose is given (due to drug absorption from the gastrointestinal tract) and decrease after absorption is complete. This repeating pattern continues and eventually drug concentrations for each dosage interval become superimposable when the amount of cyclosporine absorbed into

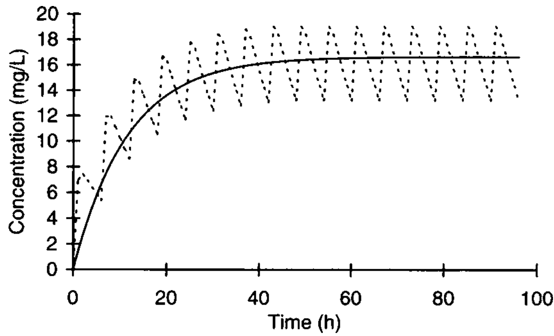

FIGURE 1-2 When medications are given on a continuous basis, serum concentrations increase until the rate of drug administration equals the elimination rate. In this case, the solid line shows serum concentrations in a patient receiving intravenous theophylline at a rate of 50 mg/h (solid line) and oral theophylline 300 mg every 6 hours (*dashed line*). Since the oral dosing rate (dose/dosage interval = 300 mg/6 h = 50 mg/h) equals the intravenous infusion rate, the drug accumulation patterns are similar. For the intravenous infusion, serum concentrations increase in a smooth pattern until steady state is achieved. During oral dosing, the serum concentrations oscillate around the intravenous profile, increasing during drug absorption and decreasing after absorption is complete and elimination takes place.

the body from the gastrointestinal tract equals the amount removed by hepatic metabolism over each dosage interval. Regardless of the mode of drug administration, when the rate of drug administration equals the rate of drug removal, the amount of drug contained in the body reaches a constant value. This equilibrium condition is known as *steady state* and is extremely important in clinical pharmacokinetics because usually steady-state serum or blood concentrations are used to assess patient response and compute new dosage regimens.

If a patient is administered several different doses until steady state is established, and steady-state serum concentrations are obtained from the patient after each dosage level, it is possible to determine a pattern of drug accumulation (Figure 1-3). If a plot of steady-state concentration versus dose yields a straight line, the drug is said to follow *linear pharmacokinetics*. In this situation, steady-state serum concentrations increase or decrease proportionally with dose. Therefore, if a patient has a steady-state drug concentration of 10 μg/mL at a dosage rate of 100 mg/h, the steady-state serum concentration will increase to 15 μg/mL if the dosage rate is increased to 150 mg/h (e.g., a 50% increase in dose yields a 50% increase in steady-state concentration).

While most drugs follow linear pharmacokinetics, in some cases drug concentrations do not change proportionally with dose. When steady-state concentrations change in a disproportionate fashion after the dose is altered, a plot of steady-state concentration versus dose is not a straight line and the drug is said to follow *nonlinear pharmacokinetics*. When steady-state concentrations increase more than expected after a dosage increase, the most likely explanation is that the processes removing the drug from the body have become saturated. This phenomenon is known as *saturable* or *Michaelis-Menten pharmacokinetics*. Both phenytoin[2] and salicylic acid[3] follow Michaelis-Menten pharmacokinetics. When steady-state concentrations increase less than expected after a dosage increase, there are two typical explanations. Some drugs, such as valproic acid[4] and disopyramide,[5] saturate plasma

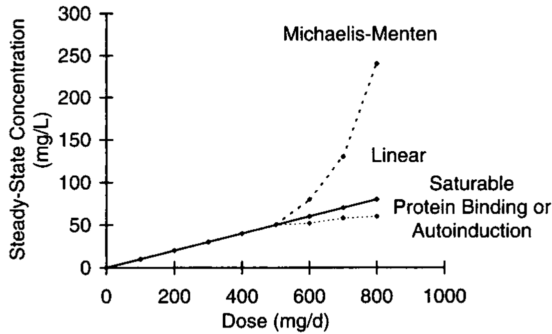

FIGURE 1-3 When doses are increased for most drugs, steady-state concentrations increase in a proportional fashion leading to linear pharmacokinetics (*solid line*). However, in some cases proportional increases in steady-state concentrations do not occur after a dosage increase. When steady-state concentrations increase more than expected after a dosage increase (*upper dashed line*), Michaelis-Menten pharmacokinetics may be taking place. If steady-state concentrations increase less than expected after a dosage increase (*lower dashed line*), saturable plasma protein binding or autoinduction are likely explanations.

protein binding sites so that as the dosage is increased steady-state serum concentrations increase less than expected. Other drugs, such as carbamazepine,[6] increase their own rate of metabolism from the body as dose is increased so steady-state serum concentrations increase less than anticipated. This process is known as *autoinduction* of drug metabolism. In either case, the relationship between steady-state concentration and dose for drugs that follow nonlinear pharmacokinetics is fraught with significant intersubject variability. Drugs that exhibit nonlinear pharmacokinetics are oftentimes very difficult to dose correctly.

Steady-state serum concentrations/dose plots for medications are determined in humans early during the drug development process. Because of this, by the time a new drug is available for general use it is usually known if the drug follows linear or nonlinear pharmacokinetics, and it is not necessary to determine this relationship in individual patients. Thus, the clinician treating a patient knows whether to anticipate linear or nonlinear pharmacokinetics and can assume the appropriate situation when adjusting drug doses. Dealing with drugs that follow linear pharmacokinetics is more straightforward and relatively easy. If a patient has been taking a medication long enough for steady state to have been established, and it is determined that a dosage adjustment is necessary because of lack of drug effect or the presence of drug toxicity, steady-state drug concentrations will change in proportion to dose for drugs that follow linear pharmacokinetics. For example, if a patient is taking sustained-release procainamide 1000 mg every 12 hours for the treatment of a cardiac arrhythmia, but is still having the arrhythmia, a clinician could obtain a steady-state procainamide serum concentration. If the procainamide concentration was too low (e.g., 4 μg/mL before the next dose), a dosage increase could help suppress the arrhythmia. Using linear pharmacokinetic principles, one could determine that a dosage increase to 1500 mg every 12 hours would increase the steady-state procainamide serum concentration to 6 μg/mL (e.g., new steady-state concentration = (new dose/old dose) × old steady-state concentration; new steady-state concentration = (1500 mg/1000 mg) × 4 μg/mL = 6 μg/mL).

CLEARANCE

Clearance (Cl) is the most important pharmacokinetic parameter because it determines the maintenance dose (MD) that is required to obtain a given steady-state serum concentration (Css): MD = Css · Cl. If one knows the clearance of a drug, and wants to achieve a certain steady-state serum concentration, it is easy to compute the required maintenance dose. Target steady-state concentrations are usually chosen from previous studies in patients that have determined minimum effective concentrations and maximum concentrations that produce the desired pharmacological effect but avoid toxic side effects. This range of steady-state concentrations is known as the *therapeutic range* for the drug. The therapeutic range should be considered as an initial guideline for drug concentrations in a specific patient; drug dose and steady-state concentrations should then be titrated and individualized based on therapeutic response. For example, the therapeutic range for theophylline is generally accepted as 10–20 μg/mL for the treatment of asthma with concentrations of 8–12 μg/mL considered as a reasonable starting point. If it were known that the theophylline clearance for a patient equaled 3 L/h and the desired steady-state theophylline serum concentration was 10 μg/mL, the theophylline maintenance dose to achieve this concentration would be 30 mg/h (10 μg/mL = 10 mg/L; MD = Css · Cl; MD = 10 mg/L · 3 L/h = 30 mg/h).

The definition of clearance is the volume of serum or blood completely cleared of the drug per unit time. Thus, the dimension of clearance is volume per unit time, such as L/h or mL/min. The liver is most often the organ responsible for drug metabolism while in most cases the kidney is responsible for drug elimination. The gastrointestinal wall, lung, and kidney can also metabolize some drugs, and some medications are eliminated unchanged in the bile. Drug metabolism is characterized as Phase I reactions, which oxidize drug molecules, and Phase II reactions, which form glucuronide or sulfate esters with drug molecules. In either case, the resulting metabolite is more water soluble than the parent drug, and is more likely to be eliminated in the urine.

The majority of drug metabolism is catalyzed by enzymes contained in the microsomes of hepatocytes known as the cytochrome P-450 (CYP) enzyme system. This family of enzymes is very important to understand because specific enzymes are responsible for the metabolism of each drug entity. Once it is known that a patient is deficient in one of the enzymes, usually because the clearance of a known drug substrate is very low resulting in high steady-state serum concentrations for a low to moderate dose, it can be inferred that all drugs metabolized by that enzyme will have a low clearance, and doses of other drugs that are substrates of the enzyme may be empirically reduced. If a metabolic drug interaction occurs between one medication and another known to be a substrate for a specific enzyme, it can be assumed that a drug interaction will occur between that drug and other substrates of the same enzyme. The enzymes are classified using a series of numbers and letters, and indicate how closely related the enzymes are to each other using amino acid sequencing. As an example of the classification scheme, the enzyme known as CYP3A4 is named because it is part of the cytochrome P-450 family, the major family group is "3," the subfamily group within the family is "A," and the specific, individual enzyme within the subfamily is "4." Thus, using this scheme, one can tell that CYP2C9 and CYP2E1 belong to the same family, and CYP2C9 and CYP2C19 belong to the same subfamily and are closely related, but are different enzymes. Table 1-1

TABLE 1-1 Cytochrome P-450 Enzymes, Substrates, Inhibitors, and Inducers[7, 8]

CYTOCHROME P-450 ENZYME	SUBSTRATES	INHIBITORS	INDUCERS
CYP1A2	Acetaminophen	Atazanavir	Barbiturates
	Caffeine	Cimetidine	Carbamazepine
	Clomipramine	Ciprofloxacin	Charcoal-broiled meat
	Imipramine	Enoxacin	Omeprazole
	Nortriptyline	Erythromycin	Phenobarbital
	Ondansetron	Fluvoxamine	Primidone
	Phenacetin	Interferon	Rifampin
	Tacrine	Mexiletine	Tobacco/Marijuana
Smoke			
	Theophylline	Tacrine	
	(R)-Warfarin	Zileuton	
	Zileuton		
CYP2B6	Bupropion	Thiotepa	Phenobarbital
	Cyclophosphamide	Ticlopidine	Rifampin
PM:	Ifosfamide		
~4% Caucasians			
CYP2C9	Candesartan	Amiodarone	Aminoglutethimide
	Celecoxib	Atazanavir	Barbiturates
PM:	Chlorpropamide	Clopidogrel	Carbamazepine
~7% Caucasians	Diclofenac	Cotrimoxazole	Phenobarbital
	Dronabinol	Delavirdine	Phenytoin
	Glipizide	Disulfiram	Primidone
	Glyburide	Efavirenz	Rifampin
	Ibuprofen	Fluconazole	
	Losartan	Fluvastatin	
	Naproxen	Fluvoxamine	
	Phenytoin	Imatinib	
	Piroxicam	Isoniazid	
	Sulfamethoxazole	Leflunomide	
	Tolbutamide	Metronidazole	
	Torsemide	Miconazole	
	Valsartan	Sulfamethoxazone	
	(S)-Warfarin	Sulfinpyrazole	
		Voriconazole	
		Zafirlukast	
CYP2C19	Amitriptyline	Chloramphenicol	Barbiturates
	Carisoprodol	Cimetidine	Phenytoin
PM:	Citalopram	Clopidogrel	Rifampin
~4% Caucasians	Clomipramine	Delavirdine	St. John's Wort
~20% Japanese & Chinese	Desmethyldiazepam	Efavirenz	
	Diazepam	Felbamate	
	Hexobarbital	Fluconazole	
	Imipramine	Felbamate	
	Lansoprazole	Fluoxetine	
	(S)-Mephenytoin	Fluvoxamine	
	Nelfinavir	Isoniazid	
	Omeprazole	Modafinil	
	Pantoprazole	Omeprazole	
	Phenytoin	Oxcarbazepine	

(*Continued*)

TABLE 1-1 (*Continued*)

CYTOCHROME P-450 ENZYME	SUBSTRATES	INHIBITORS	INDUCERS
CYP2C19 *(continued)*	Primidone Propranolol Sertraline Voriconazole (R)-Warfarin	Ticlopidine Voriconazole	
CYP2D6 PM: ~8% Caucasians ~3% African-Americans ~1% Japanese & Chinese	Amitriptyline Carvedilol Chlorpromazine Clomipramine Codeine Debrisoquin Desipramine Dextromethorphan Encainide Flecainide Fluoxetine Fluvoxamine Haloperidol Hydrocodone Imipramine Maprotiline Methamphetamine (S)-Metoprolol Mexiletine Nortriptyline Oxycodone Paroxetine Perhexiline Perphenazine Propafenone Propranolol Risperidone Sertraline Sparteine Thioridazine Timolol Tramadol Trazodone Venlafaxine	Amiodarone Bupropion Chloroquine Chlorpheniramine Chlorpromazine Cimetidine Cinacalcet Clemastine Diphenhydramine Duloxetine Fluoxetine Haloperidol Hydroxyzine Imatinib Paroxetine Perphenazine Promethazine Propafenone Propoxyphene Quinidine Ritonavir Sertraline Terbinafine Thioridazine Tripelennamine	
CYP2E1	Acetaminophen Chlorzoxazone Enflurane Ethanol Halothane Isoflurane Theophylline	Disulfiram	Ethanol Isoniazid

(*Continued*)

TABLE 1-1 Cytochrome P-450 Enzymes, Substrates, Inhibitors, and Inducers[7, 8] (*Continued*)

CYTOCHROME P-450 ENZYME	SUBSTRATES	INHIBITORS	INDUCERS
CYP3A family (includes 3A4, 3A5, 3A7)	Alfentanil	Amiodarone	Aminoglutethimide
	Alprazolam	Amprenavir	Barbiturates
	Amiodarone	Aprepitant	Bexarotene
	Amlodipine	Atazanavir	Bosetan
	Astemizole	Clarithromycin	Carbamazepine
	Atorvastatin	Danazole	Dexamethasone
	Bepridil	Darunavir	Efavirenz
	Bromocriptine	Delavirdine	Modafinil
	Buspirone	Diltiazem	Nevirapine
	Carbamazepine	Erythromycin	Oxcarbazepine
	Cerivastatin	Fluconazole	Phenobarbital
	Chlorpheniramine	Fluvoxamine	Phenytoin
	Cilostazol	Grapefruit Juice	Primidone
	Cisapride	Imatinib	Rifabutin
	Clarithromycin	Indinavir	Rifampin
	Clonazepam	Isoniazid	St. John's Wort
	Clopidogrel	Itraconazole	Troglitazone
	Cyclosporine	Ketoconazole	
	Delavirdine	Mifepristone	
	Dexamethasone	Miconazole	
	Diazepam	Nefazodone	
	Diltiazem	Nelfinavir	
	Disopyramide	Norfloxacin	
	Donepezil	Quinupristin	
	Doxorubicin	Ritonavir	
	Erythromycin	Saquinavir	
	Ethinyl Estradiol	Tamoxifen	
	Etoposide	Telithromycin	
	Felodipine	Troleandomycin	
	Fentanyl	Verapamil	
	Finasteride	Voriconazole	
	Flurazepam	Zafirlukast	
	Hydrocortisone		
	Indinavir		
	Isradipine		
	Itraconazole		
	Ketoconazole		
	Lansoprazole		
	Lidocaine		
	Loratadine		
	Losartan		
	Lovastatin		
	Methylprednisolone		
	Midazolam		
	Nefazodone		
	Nelfinavir		
	Nicardipine		
	Nifedipine		
	Nimodipine		

(*Continued*)

TABLE 1-1 (*Continued*)

CYTOCHROME P-450 ENZYME	SUBSTRATES	INHIBITORS	INDUCERS
CYP3A family (includes 3A4, 3A5, 3A7) *(continued)*	Nisoldipine Nitrendipine Oxycodone Pioglitazone Prednisolone Prednisone Progesterone Quinidine Quinine Rifabutin Ritonavir Salmeterol Saquinavir Sildenafil Simvastatin Sirolimus Sufentanil Tacrolimus Telithromycin Teniposide Terfenadine Testosterone Theophylline Topiramate Triazolam Troleandomycin Vardenafil Verapamil Vinblastine Vincristine Voriconazole Zalepion Ziprasidone Zolpidem Zonisamide		

lists the cytochrome P-450 enzymes responsible for the majority of drug oxidative metabolism in humans along with examples of known substrates, inhibitors, and inducers.[7, 8] Some ethnic groups are deficient in certain enzyme families to a varying extent, and this information is included. P-glycoprotein (PGP) is a transport protein responsible for the active secretion of drugs into the bile, urine, and gastrointestinal tract. Table 1-2 lists PGP substrates, inhibitors, and inducers.[8]

The kidney eliminates drugs by glomerular filtration and tubular secretion in the nephron. Once drug molecules have entered the urine by either of these processes, it is possible that the molecules may reenter the blood via a process known as *tubular reabsorption.* Glomerular filtration and, usually, tubular reabsorption are passive processes. *Tubular secretion* is an active process usually mediated by a transport molecule which

TABLE 1-2 P-Glycoprotein Substrates, Inhibitors, and Inducers[8]

SUBSTRATES	INHIBITORS	INDUCERS
Atorvastatin	Amiodarone	Carbamazepine
Azithromycin	Clarithromycin	St. John's Wart
Cetirizine	Cyclosporine	Rifampin
Cyclosporine	Diltiazem	
Daunorubicin	Erythromycin	
Desloratadine	Grapefruit juice	
Digoxin	Indinavir	
Diltiazem	Itraconazole	
Doxorubicin	Ketoconazole	
Erythromycin	Nicardipine	
Etoposide	Nelfinavir	
Fexofenadine	Propafenone	
Indinavir	Quinidine	
Loperamide	Ritonavir	
Nelfinavir	Saquinavir	
Ondansetron	Tacrolimus	
Paclitaxel	Tamoxifen	
Quinidine	Testosterone	
Rifampin	Verapamil	
Ritonavir		
Saquinavir		
Tacrolimus		
Verapamil		
Vinblastine		
Vincristine		

facilitates the transfer of drug across the kidney tubule. The majority of drug tubular secretion takes place in the proximal tubule of the nephron while tubular reabsorption usually takes place in the distal tubule of the nephron.

The clearance for an organ, such as the liver or kidney, that metabolizes or eliminates drugs is determined by the blood flow to the organ and the ability of the organ to metabolize or eliminate the drug.[9] Liver blood flow (LBF) and renal blood flow (RBF) are each ~ 1–1.5 L/min in adults with normal cardiovascular function. The ability of an organ to remove or extract the drug from the blood or serum is usually measured by determining the extraction ratio (ER), which is the fraction of drug removed by the organ, and is computed by measuring the concentrations of the drug entering (C_{in}) and leaving (C_{out}) the organ: $ER = (C_{in} - C_{out})/C_{in}$. Liver or renal blood flow and the extraction ratio for a drug are rarely measured in patients. However, the extraction ratio is oftentimes determined during the drug development process, and knowledge of this parameter can be extremely useful in determining how the pharmacokinetics of a drug will change during a drug interaction or if a patient develops hepatic, renal, or cardiac failure.

The drug clearance for an organ is equal to the product of the blood flow to the organ and the extraction ratio of the drug. Therefore, hepatic clearance (Cl_H) for a drug would be determined by taking the product of liver blood flow and the hepatic extraction ratio (ER_H) for the drug ($Cl_H = LBF \cdot ER_H$), and renal clearance (Cl_R) for a medication would be determined by multiplying renal blood flow and the renal extraction ratio for the agent ($Cl_R = RBF \cdot ER_R$). For example, verapamil has a hepatic extraction ratio of 90% ($ER_H = 0.90$).

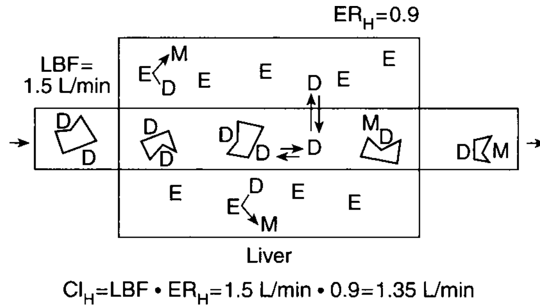

FIGURE 1-4 This schematic depicts the liver (*large box*) with the blood vessel supplying blood to it. When drug molecules (*D*) enter an organ (blood flows from left to right) that clears the drug, they may be bound to plasma proteins (*trapezoid shapes*) or exist in the unbound state. The unbound or "free" drug molecules are in equilibrium with the bound drug in the blood and unbound drug in the tissue. Drug-protein complexes are usually too big to diffuse across biologic membranes into tissues. Drug molecules that have entered hepatic tissue may encounter an enzyme (*E*) that metabolizes the drug. When this occurs the drug is chemically converted to a metabolite (*M*) which can diffuse back into the blood and leave the liver along with drug molecules that were not metabolized. The clearance of drug is equal to the blood flow to the organ (*LBF*) times the extraction ratio (ER_H) for the organ.

For patients with normal liver blood flow (LBF = 1.5 L/min), hepatic clearance would be expected to equal 1.35 L/min ($Cl_H = LBF \cdot ER_H$, $Cl_H = 1.5\ L/min \cdot 0.90 = 1.35\ L/min$; Figure 1-4). The total clearance for a drug is the sum of the individual clearances for each organ that extracts the medication. For example, the total clearance (Cl) for a drug that is metabolized by the liver and eliminated by the kidney is the sum of hepatic and renal clearance for the agent: $Cl = Cl_H + Cl_R$.

Hepatic Clearance

The physiologic determinates of hepatic clearance have been extensively studied.[9–11] Another way to think of hepatic clearance is to recognize that its value is a function of the intrinsic ability of the enzyme to metabolize a drug (intrinsic clearance); the fraction of drug present in the bloodstream that is not bound to cells or proteins, such as albumin, α_1-acid glycoprotein, or lipoproteins, but is present in the unbound, or "free," state (unbound fraction of drug); and liver blood flow. The *intrinsic clearance* (Cl'_{int}) is the inherent ability of the enzyme to metabolize the drug and is the quotient of the Michaelis-Menten constants V_{max} (maximum rate of drug metabolism) and Km (drug concentration at which the metabolic rate equals $V_{max}/2$; $Cl'_{int} = V_{max}/Km$) for the unbound drug. The unbound fraction of drug in the blood or serum (f_B) is the unbound drug concentration divided by the total (bound + unbound) drug concentration. The relationship between the three physiological factors and hepatic drug clearance is:

$$Cl_H = \frac{LBF \cdot (f_B \cdot Cl'_{int})}{LBF + (f_B \cdot Cl'_{int})}$$

Fortunately, most drugs have a large hepatic extraction ratio ($ER_H \geq 0.7$) or a small hepatic extraction ratio ($ER_H \leq 0.3$), and the relationship is simplified in these situations.

For drugs with a low hepatic extraction ratio, hepatic clearance is mainly a product of the free fraction of the drug in the blood or serum and intrinsic clearance: $Cl_H = f_B \cdot Cl'_{int}$. In this case, drug interactions that displace drug molecules bound to proteins will increase the fraction of unbound drug in the blood ($\uparrow f_B$); more unbound drug molecules will be able to leave the vascular system (drug-protein complexes are far too big to exit the vascular system) and enter hepatocytes where the additional unbound drug will be metabolized and hepatic drug clearance will increase. Additionally, drug interactions that inhibit or induce the cytochrome P-450 enzyme system (decreasing or increasing Cl'_{int}, respectively) will change the hepatic clearance of the medication accordingly. The hepatic clearance of drugs with low extraction ratios does not change much when liver blood flow decreases secondary to liver or cardiac disease. Examples of drugs with low hepatic extraction ratios are valproic acid, phenytoin, and warfarin.

For drugs with high hepatic extraction ratios, hepatic clearance is mainly a function of liver blood flow: $Cl_H = LBF$. The rate limiting step for drug metabolism in this case is how much drug can be delivered to the liver because the capacity to metabolize drug is very large. In this case, hepatic clearance is very sensitive to changes in liver blood flow due to congestive heart failure or liver disease. However, the hepatic clearance of drugs with high extraction ratios does not change much when protein binding displacement or enzyme induction or inhibition occurs due to drug interactions. Examples of drugs with high hepatic extraction ratios are lidocaine, morphine, and most tricyclic antidepressants.

Renal Clearance

The physiological determinants of renal clearance are glomerular filtration rate (GFR), the free fraction of drug in the blood or serum (f_B), the clearance of drug via renal tubular secretion (Cl_{sec}), and the fraction of drug reabsorbed in the kidney (FR): $Cl_R = [(f_B \cdot GFR) + Cl_{sec}](1 - FR)$.[12,13] Average glomerular filtration rates in adults with normal renal function are 100–120 mL/min. Since tubular secretion is an active process, it has been described by an equation similar to that used to explain liver metabolism:

$$Cl_{sec} = [RBF \cdot (f_B Cl'_{sec})] / [RBF + (f_B Cl'_{sec})],$$

where Cl'_{sec} is the intrinsic clearance due to active tubular secretion. Thus, the entire equation is:

$$Cl_R = \left[(f_B \cdot GFR) + \frac{RBF \cdot (f_B Cl'_{sec})}{RBF + (f_B Cl'_{sec})} \right] (1 - FR)$$

If the renal clearance of a drug is greater than glomerular filtration rate, it is likely that the drug was eliminated, in part, by active tubular secretion. The aminoglycoside antibiotics and vancomycin are eliminated primarily by glomerular filtration. Digoxin, procainamide, ranitidine, and ciprofloxacin are eliminated by both glomerular filtration and active tubular secretion.

In some cases, glomerular filtration rate and renal tubular secretion function may be measured in patients with renal disease. However, for the purposes of drug dosing, glomerular filtration rate is approximated by measuring or estimating creatinine clearance for a patient. Creatinine is a by-product of muscle metabolism that is eliminated primarily by glomerular filtration.

VOLUME OF DISTRIBUTION

Volume of distribution (V) is an important pharmacokinetic parameter because it determines the loading dose (LD) that is required to achieve a particular steady-state drug concentration immediately after the dose is administered: LD = Css · V (Figure 1-5). However, it is rare to know the exact volume of distribution for a patient because it is necessary to administer a dose on a previous occasion in order to have computed the volume of distribution. Thus, usually an average volume of distribution measured in other patients with similar demographics (age, weight, gender, etc.) and medical conditions (renal failure, liver failure, heart failure, etc.) is used to estimate a loading dose (Figure 1-6). Because of this, most patients will not actually attain steady state after a loading dose, but, hopefully, serum drug concentrations will be high enough so that the patient will experience the pharmacological effect of the drug.

The volume of distribution is a hypothetical volume that relates drug serum concentrations to the amount of drug in the body. Thus, the dimension of volume of distribution is in volume units, such as L or mL. At any given time after drug has been absorbed from extravascular sites and the serum and tissue drug concentrations are in equilibrium, the serum concentration for a drug (C) is equal to the quotient of the amount of drug in the body (A_B) and the volume of distribution: $C = A_B/V$. The volume of distribution can be

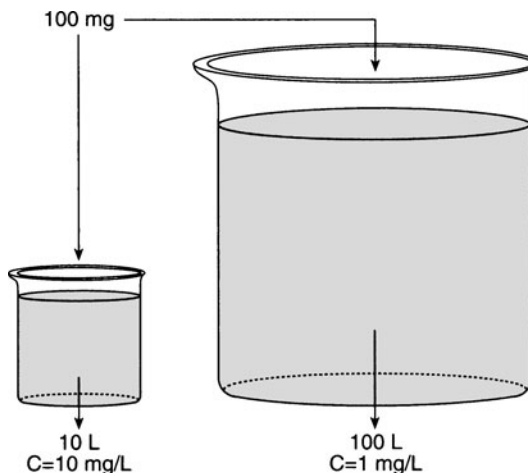

FIGURE 1-5 The volume of distribution (*V*) is a hypothetical volume that is the proportionality constant which relates the concentration of drug in the blood or serum (*C*) and the amount of drug in the body (A_B): $A_B = C \cdot V$. It can be thought of as a beaker of fluid representing the entire space that drug distributes into. In this case, one beaker, representing a patient with a small volume of distribution, contains 10 L while the other beaker, representing a patient with a large volume of distribution, contains 100 L. If 100 mg of drug is given to each patient, the resulting concentration will be 10 mg/L in the patient with the smaller volume of distribution, but 1 mg/L in the patient with the larger volume of distribution. If the minimum concentration needed to exert the pharmacological effect of the drug is 5 mg/L, one patient will receive a benefit from the drug while the other will have a subtherapeutic concentration.

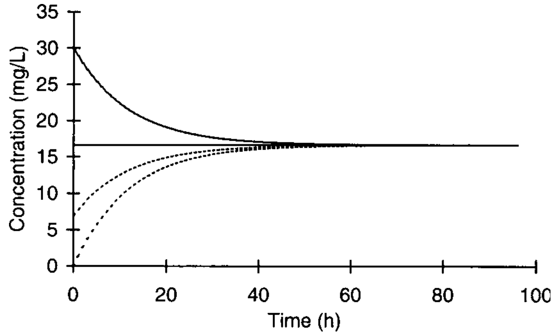

FIGURE 1-6 If the volume of distribution (*V*) is known for a patient, it is possible to administer a loading dose (*LD*) that will attain a specified steady-state drug concentration (*Css*): LD = Css · V. This example depicts the ideal loading dose given as an intravenous bolus dose followed by a continuous intravenous infusion (*solid line* starting at 16 mg/L) so steady state is achieved immediately and maintained. If a loading dose was not given and a continuous infusion started (*dashed line* starting at 0 mg/L), it would take time to reach steady-state concentrations, and the patient may not experience an effect from the drug until a minimum effect concentration is achieved. This situation would not be acceptable for many clinical situations where a quick onset of action is needed. Since the volume of distribution is not known for a patient before a dose is given, clinicians use an average volume of distribution previously measured in patients with similar demographics and disease states to compute loading doses. When this is done, the patient's volume of distribution may be smaller than average and result in higher than expected concentrations (*solid line* starting at 30 mg/L) or larger than average and result in lower than expected concentrations (*dotted line* starting at 7 mg/L). In these cases, it still takes 3–5 half-lives to reach steady-state, but therapeutic drug concentrations are achieved much sooner than giving the drug by intravenous infusion only.

very small if the drug is primarily contained in the blood (warfarin V = 5–7 L), or very large if the drug distributes widely in the body and is mostly bound to bodily tissues (digoxin V = 500 L).

The physiologic determinates of volume of distribution are the actual volume of blood (V_B) and size (measured as a volume) of the various tissues and organs of the body (V_T). Therefore, a larger person, such as a 160-kg football player, would be expected to have a larger volume of distribution for a drug than a smaller person, such as a 40-kg grandmother. How the drug binds in the blood or serum compared to the binding in tissues is also an important determinate of the volume of distribution for a drug. For example, the reason warfarin has such a small volume of distribution is that it is highly bound to serum albumin so that the free fraction of drug in the blood (f_B) is very small. Digoxin has a very large volume of distribution because it is very highly bound to tissues (primarily muscle) so that the free fraction of drug in the tissues (f_T; f_T = unbound drug concentration in the tissue/total tissue drug concentration) is very small. The equation that relates all of these physiologic determinates to the volume of distribution is:[14]

$$V = V_B + \frac{f_B}{f_T} V_T$$

This equation can help clinicians understand why a drug has a large or small volume of distribution, or why the volume of distribution might change under various circumstances. An example is how the volume of distribution changes when plasma protein binding drug interactions occur. If a drug that is highly bound to plasma proteins is given to a patient, and then a second drug that is also highly bound to the same plasma protein is given concurrently, the second drug will compete for plasma protein binding sites and displace the first drug from the protein. In this case, the free fraction in the serum of the first drug will increase ($\uparrow f_B$), resulting in an increased volume of distribution: $\uparrow V = V_B + (\uparrow f_B/f_T)V_T$.

HALF-LIFE AND ELIMINATION RATE CONSTANT

When drugs that follow linear pharmacokinetics are given to humans, serum concentrations decline in a curvilinear fashion (Figure 1-7). When the same data is plotted on a semilogarithmic axis, serum concentrations decrease in a linear fashion after drug absorption and distribution phases are complete (Figure 1-8). This part of the curve is known as the *elimination phase*. The time that it takes for serum concentrations to decrease by $^1/_2$ in the elimination phase is a constant and is called the *half-life* ($t_{1/2}$). The half-life describes how quickly drug serum concentrations decrease in a patient after a medication is administered, and the dimension of half-life is time (hour, minute, day, etc.). Another common measurement used to denote how quickly drug serum concentrations decline in a patient is the elimination rate constant (k_e). The dimension for the elimination rate constant is reciprocal time ($hour^{-1}$, $minute^{-1}$, day^{-1}, etc.). If the amount of drug in the body is known, the elimination rate for the drug can be computed by taking the product of the elimination rate constant and the amount of drug in the body (A_B): elimination rate = $A_B \cdot k_e$. The half-life and elimination rate constant are related to each other by the following equation, so it is easy to compute one once the other is known: $t_{1/2} = 0.693/k_e$. The elimination rate constant can also be measured graphically by computing the slope of the log concentration

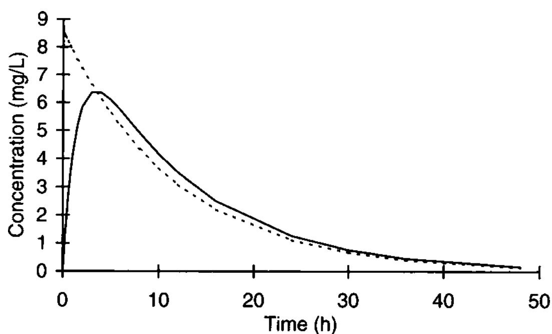

FIGURE 1-7 Serum concentration/time profile for a patient receiving 300 mg of theophylline orally (*solid line*) and by intravenous bolus (*dashed line*). If this data is plotted on rectilinear axes, serum concentrations decline in a curvilinear fashion in both cases. When the drug is given orally, serum concentrations initially increase while the drug is being absorbed and decline after drug absorption is complete.

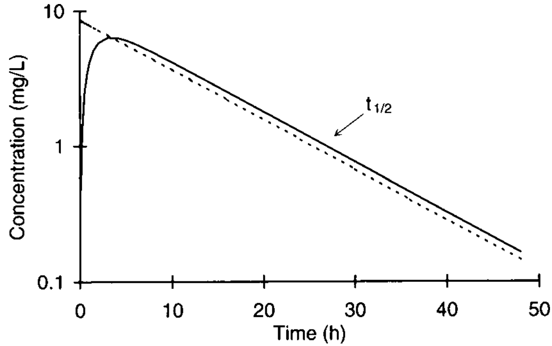

FIGURE 1-8 Serum concentration/time profile for a patient receiving 300 mg of theophylline orally (*solid line*) and by intravenous bolus (*dashed line*). If this data is plotted on semilogarithmic axes, serum concentrations decline in a straight line in both cases. When the drug is given orally, serum concentrations initially increase while the drug is being absorbed and decline after drug absorption is complete. This same data set is plotted in Figure 1-7 on rectilinear axes.

versus time graph during the elimination phase: using $\log_{10}$, $k_e/2.303 = -(\log C_1 - \log C_2)/(t_1 - t_2)$; or, using natural logarithms, $k_e = -(\ln C_1 - \ln C_2)/(t_1 - t_2)$.

The half-life is important because it determines the time to steady state during the continuous dosing of a drug and the dosage interval. The approach to steady-state serum concentrations is an exponential function. If a drug is administered on a continuous basis for 3 half-lives, serum concentrations are ~90% of steady-state values; on a continuous basis for 5 half-lives, serum concentrations equal ~95% of steady-state values; or on a continuous basis for 7 half-lives, serum concentrations achieve ~99% of steady-state values (Figure 1-9). Generally, drug serum concentrations used for pharmacokinetic monitoring can be safely measured after 3–5 estimated half-lives because most drug assays

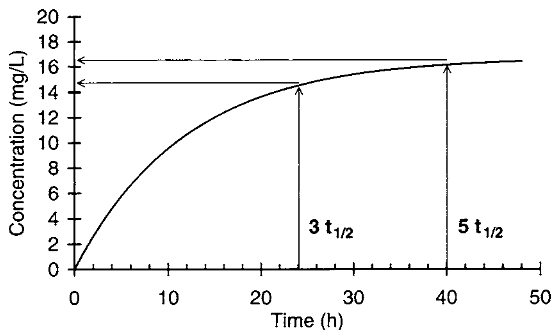

FIGURE 1-9 Serum concentration/time graph for a drug that has a half-life equal to 8 hours. The arrows indicate concentrations at 3 half-lives (24 hours, ~90% of Css) and at 5 half-lives (40 hours, ~95% of Css). Since most drug assays have 5–10% measurement error, serum concentrations obtained between 3–5 half-lives after dosing commenced can be considered to be at steady state for clinical purposes and used to adjust drug doses.

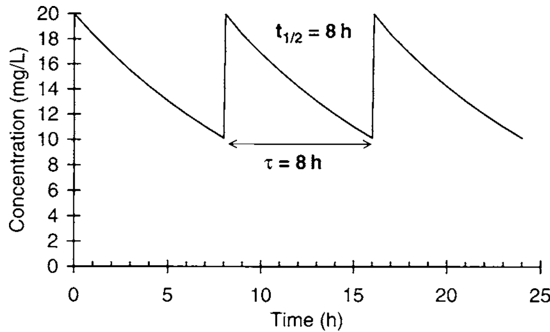

FIGURE 1-10 The dosage interval for a drug is determined by the half-life of the agent. In this case, the half-life of the drug is 8 hours, and the therapeutic range of the drug is 10–20 mg/L. In order to ensure that maximum serum concentrations never go above and minimum serum concentrations never go below the therapeutic range, it is necessary to give the drug every 8 hours (τ = dosage interval).

have 5–10% measurement error. It should be noted that the half-life for a drug in a patient is not usually known, but is estimated using values previously measured during pharmacokinetic studies conducted in similar patients.

The dosage interval for a drug is also determined by the half-life of the medication. For example, if the therapeutic range of a drug is 10–20 mg/L, the ideal dosage interval would not let maximum serum concentrations exceed 20 mg/L or allow the minimum serum concentration to go below 10 mg/L (Figure 1-10). In this case, the dosage interval that would produce this steady-state concentration/time profile would be every half-life. After a dose is given, the maximum serum concentration would be 20 mg/L. In 1 half-life the serum concentration would be 10 mg/L, and the next dose would be administered to the patient. At steady state this serum concentration/time profile would be repeated after each dose. During drug development, it is very common to use the drug half-life as the initial dosage interval for the new drug compound until the pharmacodynamics of the agent can be determined.

The half-life and elimination rate constant are known as *dependent parameters* because their values depend on the clearance (Cl) and volume of distribution (V) of the agent: $t_{1/2} = (0.693 \cdot V)/Cl$, $k_e = Cl/V$. The half-life and elimination rate constant for a drug can change either because of a change in clearance or a change in the volume of distribution. Because the values for clearance and volume of distribution depend solely on physiological parameters and can vary independently of each other, they are known as *independent parameters*.

MICHAELIS-MENTEN OR SATURABLE PHARMACOKINETICS

Drugs that are metabolized by the cytochrome P-450 enzymes and other enzyme systems may undergo Michaelis-Menten or saturable pharmacokinetics. This is the type of non-linear pharmacokinetics that occurs when the number of drug molecules overwhelms or

saturates the enzyme's ability to metabolize the drug.[2,3] When this occurs, steady-state drug serum concentrations increase in a disproportionate manner after a dosage increase (Figure 1-3). In this case the rate of drug removal is described by the classic Michaelis-Menten relationship that is used for all enzyme systems: rate of metabolism = $(V_{max} \cdot C)/(Km + C)$, where V_{max} is the maximum rate of metabolism, C is the substrate concentration, and Km is the substrate concentration where the rate of metabolism = $V_{max}/2$.

The clinical implication of Michaelis-Menten pharmacokinetics is that the clearance of a drug is not a constant as it is with linear pharmacokinetics, but is concentration- or dose-dependent. As the dose or concentration increases, the clearance rate (Cl) decreases as the enzyme approaches saturable conditions: $Cl = V_{max}/(Km + C)$. This is the reason concentrations increase disproportionately after a dosage increase. For example, phenytoin follows saturable pharmacokinetics with average Michaelis-Menten constants of V_{max} = 500 mg/d and Km = 4 mg/L. The therapeutic range of phenytoin is 10–20 mg/L. As the steady-state concentration of phenytoin increases from 10 mg/L to 20 mg/L, clearance decreases from 36 L/d to 21 L/d [$Cl = V_{max}/(Km + C)$; Cl = (500 mg/d) / (4 mg/L + 10 mg/L) = 36 L/d; Cl = (500 mg/d)/(4 mg/L + 20 mg/L) = 21 L/d]. Unfortunately, there is so much interpatient variability in Michaelis-Menten pharmacokinetic parameters for a drug (typically V_{max} = 100–1000 mg/d and Km = 1–10 mg/L for phenytoin) that dosing drugs which follow saturable metabolism is extremely difficult.

The volume of distribution (V) is unaffected by saturable metabolism and is still determined by the physiological volume of blood (V_B) and tissues (V_T) as well as the unbound concentration of drug in the blood (f_B) and tissues (f_T): $V = V_B + (f_B/f_T)V_T$. Also, half-life ($t_{1/2}$) is still related to clearance and volume of distribution using the same equation as for linear pharmacokinetics: $t_{1/2} = (0.693 \cdot V)/Cl$. However, since clearance is dose- or concentration-dependent, half-life also changes with dosage or concentration changes. As doses or concentrations increase for a drug that follows Michaelis-Menten pharmacokinetics, clearance decreases and half-life becomes longer for the drug: $\uparrow t_{1/2} = (0.693 \cdot V)/\downarrow Cl$. The clinical implication of this finding is that the time to steady state (3–5 $t_{1/2}$) is longer as the dose or concentration is increased for a drug that follows saturable pharmacokinetics.

Under steady-state conditions the rate of drug administration equals the rate of drug removal. Therefore, for a drug that is solely removed by metabolism via one enzyme system, the Michaelis-Menten equation can be used to compute the maintenance dose (MD) required to achieve a target steady-state serum concentration (Css):

$$MD = \frac{V_{max} \cdot Css}{Km + Css}$$

When the therapeutic range for a drug is far below the Km value for the enzymes that metabolize the drug Css, this equation simplifies to: $MD = (V_{max}/Km)Css$ or, since V_{max}/Km is a constant, $MD = Cl \cdot Css$. Therefore, when Km >> Css, drugs that are metabolized follow linear pharmacokinetics. When the therapeutic range for a drug is far above the Km value for the enzyme system that metabolizes the drug, the rate of metabolism becomes a constant equal to V_{max}. Under these conditions only a fixed amount of drug is metabolized because the enzyme system is completely saturated and cannot increase its

metabolic capacity. This situation is also known as *zero-order pharmacokinetics*. *First-order pharmacokinetics* is another name for linear pharmacokinetics.

Based on these facts, it can be seen that any drug that is metabolized by enzymes undergoes Michaelis-Menten pharmacokinetics. But, the therapeutic ranges of most drugs are far below the Km for the enzymes that metabolize the agent. Because of this, most medications that are metabolized follow linear pharmacokinetics. However, even in these cases saturable drug metabolism can occur in drug overdose cases where the drug concentration far exceeds the therapeutic range for the medication.

BIOAVAILABILITY

When a drug is administered extravascularly, the entire dose may not enter the systemic circulation. For example, an orally administered tablet may not completely dissolve so that part of the dose is eliminated in the stool, or a transdermal patch may not release the entire dose before it is removed from the skin. The fraction of the administered dose that is delivered to the systemic circulation is known as the *bioavailability* for the drug and dosage form. When medications are given orally, intramuscularly, subcutaneously, or by other extravascular routes, the drug must be absorbed across several biologic membranes before entering the vascular system. In these cases, drug serum concentrations rise while the drug is being absorbed into the bloodstream, reach a maximum concentration (C_{max}) when the rate of drug absorption equals the rate of drug elimination, and eventually decrease according to the half-life of the drug. The phase of the curve over which absorption takes place is known as the *absorption phase*, and the time that the maximum concentration occurs is called T_{max} (Figure 1-11).

If a medication is given orally, drug molecules must pass through several organs before entering the systemic circulation. During absorption from the gastrointestinal tract, the drug molecules will encounter enzymes that may metabolize the agent (primarily

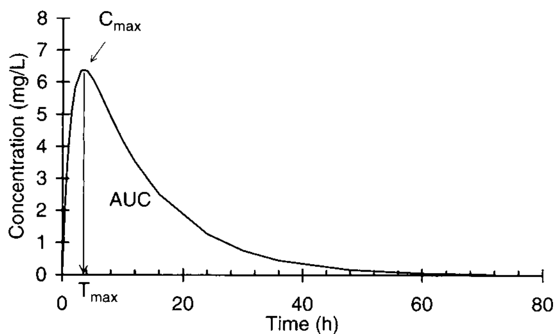

FIGURE 1-11 Area under the serum concentration/time curve (*AUC*), the maximum concentration (*C_{max}*), and the time that the maximum concentration occurs (*T_{max}*) are considered primary bioavailability parameters. When the AUC, C_{max}, and T_{max} are the same within statistical limits for two dosage forms of the same drug, the dosage forms are considered to be bioequivalent.

CYP3A4 substrates since ~90% of cytochrome P-450 contained in the gut wall is CYP3A4) or even pump the drug back into the lumen and prevent absorption from taking place (primarily P-glycoprotein substrates). Once drug molecules are absorbed from the gastrointestinal tract, they enter the portal vein. The portal vein and hepatic artery together supply blood to the liver, and the sum of portal vein (~$^2/_3$ total LBF) and hepatic artery (~$^1/_3$ total LBF) blood flows make up liver blood flow (LBF) which equals ~1–1.5 L/min. If the drug is hepatically metabolized, part of the drug may be metabolized by the liver even though the majority of the drug was absorbed from the gastrointestinal tract. Drugs that are substrates for CYP3A4 and CYP2D6 are particularly susceptible to presystemic metabolism by the liver. Blood leaving the liver via the hepatic vein enters the inferior vena cava, and will eventually be pumped through the lung by the right side of the heart before entering the left side of the heart and being pumped into the arterial system. To a lesser extent, some drugs are metabolized by the lung or irreversibly eliminated into expired air.

The loss of drug from these combined processes is known as presystemic metabolism or the first-pass effect. Since the entire oral dose that was absorbed must take this route before entering the systemic vascular system, large amounts of drug can be lost via these processes. For example, the oral bioavailability of both propranolol (a substrate for CYP2D6 and CYP2C19) and verapamil (a substrate for CYP3A4 and P-glycoprotein) is about ~10% even though the oral dosage forms for each agent release 100% of the drug into the gastrointestinal tract.

For drugs that follow linear pharmacokinetics, bioavailability is measured by comparing serum concentrations achieved after extravascular and intravenous doses in the same individual. Rather than compare drug concentrations at each time point, a composite of drug concentrations over time is derived by measuring the total area under the serum concentration time curve (AUC) for each route of administration (Figure 1-11). If the extravascular and intravenous doses are the same, the bioavailability for a drug can be calculated by taking the ratio of the AUCs for each route of administration. For example, if 10 mg of a drug were administered to a subject on two separate occasions by intravenous (IV) and oral (PO) routes of administration, the bioavailabilty (F) would be computed by dividing the AUC after oral administration (AUC_{PO}) by the AUC after intravenous administration (AUC_{IV}): $F = AUC_{PO}/AUC_{IV}$. If it is not possible to administer the same dose intravenously and extravascularly because poor absorption or presystemic metabolism yields serum concentrations that are too low to measure, the bioavailability calculation can be corrected to allow for different size doses for the different routes of administration: $F = (AUC_{PO}/AUC_{IV})(D_{IV}/D_{PO})$, where D_{IV} is the intravenous dose and D_{PO} is the oral dose.

Bioequivalence

When the patent expires for drug entities, generic drugs are manufactured that are less expensive than brand name products. This is because the drug company manufacturing the generic drug does not have to prove that the drug is safe and effective since those studies were done by the pharmaceutical company producing the brand name drug. Although it is not a requirement for generic drug products to be marketed by a pharmaceutical company, a desirable attribute of a generic drug dosage form is that it produce the same serum concentration/time profile as its brand name counterpart. When it meets

this requirement, the generic drug product is said to be *bioequivalent* to the brand name drug. In theory, it should be possible to substitute a bioequivalent generic drug dosage form for a brand name product without a change in steady-state drug serum concentrations or therapeutic efficacy.

Bioequivalence is achieved when the serum concentration/time curve for the generic and brand name drug dosage forms are deemed indistinguishable from each other using statistical tests. Concentration/time curves are superimposable when the area under the total serum concentration/time curve (AUC), maximum concentration (C_{max}), and time that the maximum concentration occurs (T_{max}) are identical within statistical limits. In order to achieve the Food and Drug Administration's (FDA) definition of oral bioequivalance and be awarded an "AB" rating in the FDA publication *Approved Drug Products with Therapeutic Equivalence Evaluations* (also known as *The Orange Book*), the pharmaceutical company producing a generic drug product must administer single doses or multiple doses of the drug until steady state is achieved using both the generic and brand name drug dosage forms to a group of 18–24 humans and prove that the AUC (from time = 0 to infinity after a single dose, or over the dosage interval at steady state), C_{max}, and T_{max} values are statistically identical for the two dosage forms. The ratio of the area under the serum concentration/time curves for the generic ($AUC_{generic}$) and brand name (AUC_{brand}) drug dosage forms is known as the *relative bioavailability* ($F_{relative}$) since the reference AUC is derived from the brand name drug dosage form: $F_{relative} = AUC_{generic}/AUC_{brand}$. Many states allow the substitution of generic drugs for brand name drugs if the prescriber notes on the prescription order that generic substitution is acceptable, and the generic drug dosage form has an AB rating.

PROBLEMS

1. Define the following terms:

- **a.** absorption
- **b.** distribution
- **c.** metabolism
- **d.** elimination
- **e.** steady state
- **f.** linear or first-order pharmacokinetics
- **g.** nonlinear pharmacokinetics
- **h.** saturable or Michaelis-Menten pharmacokinetics
- **i.** autoinduction
- **j.** therapeutic range
- **k.** zero-order pharmacokinetics
- **l.** bioavailability
- **m.** bioequivalent
- **n.** clearance
- **o.** volume of distribution
- **p.** half-life
- **q.** elimination rate constant

2. Two new antibiotics are marketed by a pharmaceutical manufacture. Reading the package insert, you find the following information:

DOSE	CURACILLIN STEADY-STATE CONCENTRATIONS (mg/L)	BETTERMYCIN STEADY-STATE CONCENTRATIONS (mg/L)
0	0	0
100	15	25
250	37.5	62.5
500	75	190
1000	150	510

What type of pharmacokinetics do each of these drugs follow?

3. A patient with liver failure and a patient with heart failure need to be treated with a new antiarrhythmic drug. You find a research study that contains the following information for Stopabeat in patients similar to the ones you need to treat: normal subjects: clearance = 45 L/h, volume of distribution = 175 L; liver failure: clearance = 15 L/h, volume of distribution = 300 L; heart failure: clearance = 30 L/h, volume of distribution = 100 L. Recommend an intravenous loading dose (LD) and continuous intravenous infusion maintenance dose (MD) to achieve a steady-state concentration of 10 mg/L for your two patients based on this data and estimate the time it will take to achieve steady-state conditions.

4. After the first dose of gentamicin is given to a patient with renal failure, the following serum concentrations are obtained:

TIME AFTER DOSAGE ADMINISTRATION (HOUR)	CONCENTRATION (μg/mL)
1	7.7
24	5.6
48	4.0

Compute the half-life and the elimination rate constant for this patient.

5. Average values of Michaelis-Menten pharmacokinetic parameters for phenytoin in adults are V_{max} = 500 mg/d and Km = 4 mg/L. What are the expected average doses of phenytoin that would produce steady-state concentrations at the lower and upper limits of the therapeutic range (10–20 mg/L)?

6. A new immunosuppresant, Noreject, is being studied in the renal transplant clinic where you work. Based on previous studies, the following area under the serum concentration/time curves (AUC) were measured after single doses of 10 mg in renal transplant patients: intravenous bolus AUC = 1530 mg · h/L, oral capsule AUC = 1220 mg · h/L, oral liquid AUC = 1420 mg · h/L. What is the bioavailability of the oral capsule and oral liquid? What is the relative bioavailability of the oral capsule compared to the oral liquid?