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The Science and
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21st EDITION



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21ST EDITION

Remington

**The Science and Practice
of Pharmacy**



LIPPINCOTT WILLIAMS & WILKINS

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Preface to the Twenty-First Edition

For over 100 years and throughout 20 previous editions, *Remington: The Science and Practice of Pharmacy* has stood as the definitive text and reference source of all aspects of the science and practice of pharmacy. In this new edition, you will find a text that is practice-oriented while maintaining its traditionally reliable coverage of scientific aspects. The 21st edition keeps pace with the changes in pharmacy curriculum and professional pharmacy practice in general.

In the years since the first publication of *Remington's Pharmaceutical Sciences*, there have been many changes in the field of pharmacy and pharmacy practice. Although this edition of *Remington* maintains the general philosophy of previous editions, several changes have been made to present fresh and new information and to take advantage of the advances made in recent years. Each section of the book has been critically reviewed and revised to reflect the emerging trends in the field. The overall organization of the book is the same as the previous editions.

The biggest change in the 21st edition is in the *Pharmacy Practice* section. This section has been reorganized and expanded to reflect the changing realities of contemporary practice. The integration of new scientific information into clinical practice is often difficult, and one of the key purposes of this section is to help clinicians translate these scientific advances into clinical practice and care of patients. This section brings the reader up to date on the latest trends and approaches. New chapters have been added that cover the areas of:

- The application of ethical principles to practice dilemmas
- Statistics applied to pharmacy practice
- Technology and automation
- Professional communication
- Medication errors
- Re-engineering pharmacy practice
- Management of special risk medicines
- Specialization of pharmacy practice
- Disease state management
- Emergency patient care
- Wound care

The *Pharmaceutical and Medicinal Agents* section is the most very useful part of the book in terms of core drug information. For this edition, we've added more than 100 new drug monographs, and the previously existing material has been up-

dated. We realize that this is a section that is nearly impossible to keep current, and we've tried to include as many new drugs as possible. Because of space constraints, we were limited to the most important or most widely used drugs.

Another significant addition to this edition is the expansion of the *Pharmacodynamics and Pharmacokinetics* section to include the new, growing area of Pharmacogenomics. This chapter highlights many of the important advances including: practical applications and technological considerations, molecular diagnostics for optimizing drug therapy, and pharmacogenomics and drug development.

Many people were involved in creating this edition. I am grateful to all the Section Editors and authors for their skillful review of the literature and for incorporating their own unique perspectives and experience into their chapters. With this edition, we welcome five new Section Editors. They represent a wide geographic diversity and spectrum of experience. We also have approximately 100 new authors who represent over 32 universities as well as positions in governmental agencies and private industry.

I also gratefully acknowledge the extensive contributions of the authors and Section Editors of previous editions of *Remington* for laying the foundation for the current volume. I recognize that we all stand upon the shoulders of giants and are supported by those leaders who taught and inspired many previous generations.

I especially thank Alfonso R Gennaro, PhD for his continued support. Dr. Gennaro was *Remington* editor for the past four editions. No one is more familiar with *Remington* than he is. Dr. Gennaro has been instrumental in the creation and review of the drug monographs. Ensuring scientific accuracy is critical in a book such as *Remington*, and he has been very generous with his time and expertise in this area.

A heartfelt thanks also goes to Mr. John Hoover, author and indexer, who has been involved with *Remington* since the 1960s and has provided editorial guidance at every step of the process.

It is a pleasure and honor to work on a book with such a long and rich tradition.

Randy Hendrickson
Editor

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Clinical Pharmacokinetics and Pharmacodynamics

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In Chapter 58, the basic principles of pharmacokinetics were presented. Clinical pharmacokinetics is the discipline in which basic pharmacokinetic principles are applied to the development of rational dosage regimens. In this chapter, the concepts of pharmacokinetics are placed into perspective with the development of individualized drug dosage regimens. The clinical significance of drug absorption, distribution, and elimination and influence of disease states on these processes are emphasized. Examples are given of the ways pharmacokinetic principles can be applied in the calculation and adjustment of dosage regimens designed to fit the pharmacokinetic and pharmacodynamic properties of drugs and specific disease states that alter drug disposition. The principles of therapeutic drug monitoring and the rational use of this clinical science in the management of patients also are discussed.

Overview of Clinical Pharmacokinetics

The application of pharmacokinetic principles to patient care can aid the clinician in making rational drug use decisions. However, knowing the relationship between the time course of drug concentration and the pharmacologic effect is critical to the application of pharmacokinetic principles and the interpretation of plasma drug concentrations in the patient care setting.

As a general rule traditional pharmacokinetic research is an intensive study of a limited number of subjects resulting in very precise pharmacokinetic and pharmacodynamic parameter estimates. Clinical pharmacokinetics, on the other hand, is usually limited to very few and sometimes no plasma drug concentrations, requiring the clinician to make an educated guess about key elements of drug disposition and the drug use process. In the research setting, it is common to obtain 10 or more samples for drug concentration measurements within a single dosing interval. In the clinical setting, it is uncommon to obtain more than two or three samples for a patient during a hospitalization or within a year for ambulatory care patients.

Therefore, understanding the usual manner in which drugs are absorbed, distributed, and eliminated as well as the known factors that alter drug disposition and which of these elements is most likely to be altered in the individual patient is key to the clinician's ability to effectively use pharmacokinetics. A basic knowledge of pharmacokinetics provides guidance to the clinician when selecting a drug product, dosing regimen, the anticipated onset of drug effect, and determining an appropriate sampling strategy if drug concentrations are to be obtained.

Drugs with Narrow Versus Wide Therapeutic Range

The therapeutic range is a concentration range that is likely to result in the desired clinical or therapeutic response with an acceptable risk or likelihood of developing a toxic response. For every drug, there is a therapeutic range, but it is those drugs in which the minimum concentration that is likely to result in the desired drug effect is relatively close to the higher drug concentration that is likely to result in a toxic response. The therapeutic index is the ratio of the maximum desired concentration relative to the minimum desired concentration. The application of pharmacokinetic principles may be limited in the use of some drugs. Drugs that have a wide therapeutic index may not require precise dose adjustments when drug disposition is altered and a simple approximation may be satisfactory to limit the probability of toxicity and assure efficacy. Other drugs may have a complex series of biological events that result in an obscure relationship between the pharmacologic effects and the drug dose or drug concentration making it difficult to apply the usual pharmacokinetic principles to the daily care of a patient.

Drugs with a narrow therapeutic range, however, tend to lend themselves to careful dose adjustments and plasma drug concentration monitoring to help ensure optimal patient outcomes. For those drugs that are monitored with plasma drug concentrations, there is usually a *Normal Therapeutic Range* that attempts to define the drug concentrations where the benefit to risk ratio is optimal (Fig 59-1). While the *Normal Therapeutic Range* is important, it is only a guide, and it is the patient and not the drug concentration that is therapeutic or toxic. There are patients with an optimal clinical outcome whose plasma drug concentrations fall outside the usual range and others who develop unacceptable side effects or toxicities when drug concentrations are within or even below the usual *Therapeutic Range*.

Plasma Protein Binding and the Therapeutic Range

One potential factor that can change the *Normal Therapeutic Range* is alterations in plasma protein binding. In most cases, clinical laboratories use assay procedures that measure and report the total plasma drug concentration, ie, the drug concentration that is bound to plasma protein and the unbound plasma drug concentration. It is only the unbound drug in plasma that can cross into the tissue where the receptors are located.

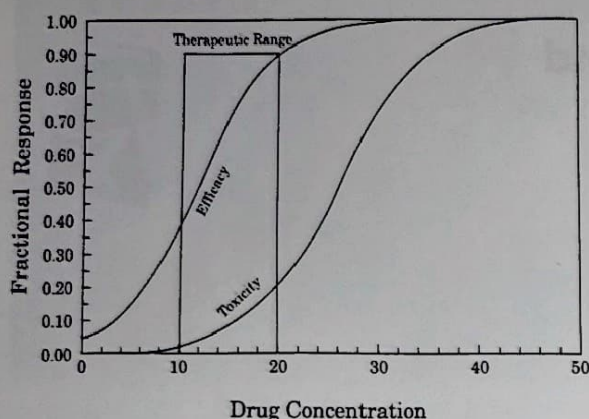


Figure 59-1. "Normal therapeutic range." The "normal therapeutic range" defines the region of drug concentrations where the probability of a positive therapeutic response is good and the risk for development of a significant dose-related adverse effect is acceptable. For most agents the normal therapeutic range is quite wide, however, for certain agents there is a relatively narrow therapeutic range and monitoring of drug concentrations may be necessary to maximize the potential for efficacy and minimize the risk of toxicity.

Therefore, it is the unbound drug concentration that is proportional to the tissue and receptor drug concentration and the pharmacodynamic response (Fig 59-2). Any change in plasma protein binding would be expected to alter the potential for any plasma drug concentration, reported as both bound and unbound drug, to result in a toxic or therapeutic response. Many drugs have significant binding to plasma proteins and the relationship between the unbound drug concentration and the total drug concentration is referred to as the free fraction or f_u .

$$f_u = \frac{\text{Unbound Drug Concentration}}{\text{Total Drug Concentration}} \quad (1)$$

or

$$\text{Unbound Drug Concentration} = (f_u)(\text{Total Drug Concentration}) \quad (2)$$

Any factor that alters plasma protein binding will result in an altered free fraction (f_u). Therefore, when interpreting assayed drug concentrations with altered plasma binding, the clinician should make some type of adjustment when using the assayed drug concentration.

One approach is to calculate a normal plasma binding drug concentration:

Normal Plasma Binding
Drug Concentration

$$= \left(\frac{f_u'}{f_u} \right) \left(\frac{\text{Assayed Drug Concentration}}{\text{Altered Plasma Binding}} \right) \quad (3)$$

and then compare the normal plasma binding drug concentration to the normal therapeutic range to evaluate the drug's potential for either efficacy or toxicity.

An alternative approach is to calculate an adjusted therapeutic range:

$$\text{Adjusted Therapeutic Range} = \left(\frac{f_u}{f_u'} \right) (\text{Normal Therapeutic Range}) \quad (4)$$

and compare this adjusted therapeutic range to the assayed drug concentration with altered plasma binding to evaluate the drug's potential for either efficacy or toxicity.

In any case for drugs with high plasma binding, care should be taken in the interpretation of assayed drug concentration. Most weak acid drugs with high plasma binding (eg, phenytoin) are bound almost exclusively to albumin. The most commonly encountered reasons for alterations in plasma binding for these drugs are hypoalbuminemia, end stage renal failure or dialysis and displacement by other drugs. Basic compounds tend to have a more complex plasma-binding pattern and extensive binding to a number of plasma proteins including alpha-1-acid-glycoprotein, other globulins and albumin is common.

In addition to plasma binding alterations, clinical conditions can change a patient's response to a given dose or drug concentration. As an example, a change in renal function can change a patient's ability to eliminate drugs whose route of elimination is via the kidneys (eg, aminoglycoside antibiotics). The addition of a new drug that either inhibits the elimination or metabolism (eg, amiodarone when added to a patient receiving digoxin) or induces metabolism (eg, carbamazepine inducing the metabolism of warfarin) can alter the relationship between the drug dosing regimen and the resultant drug concentrations and drug effect. In addition, alterations in electrolyte or acid base balance might alter the potential of a drug to produce toxicity (eg, hypokalemia in a patient receiving digoxin). While the normal therapeutic range is usually thought of as fixed upper and lower boundaries, there are many situations that require the clinician to make adjustments in dosing regimens and target drug concentrations. Knowing both the drug's pharmacokinetic and pharmacodynamic characteristics allow the clinician to design drug regimens that have an optimal chance of producing a beneficial outcome for the patient.

Absorption, Distribution, and Elimination

In the application of pharmacokinetics to the clinical practice setting, the ability to estimate a patient's absorption, distribution, and elimination characteristics is an important step in initiating drug therapy. For many drugs, clinicians simply learn the "usual" dose and use that dose for all patients. In a number of situations, knowing the principles behind the usual dose allows the clinician to make adjustments in drug therapy for those patients where therapeutic problems, toxicity or lack of efficacy, are likely to occur.

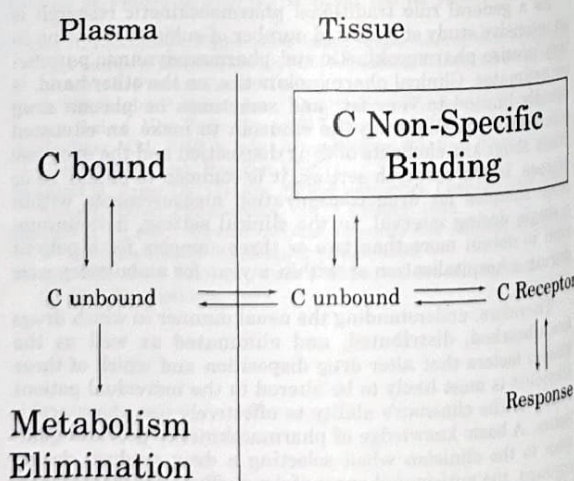


Figure 59-2. Note that it is the unbound drug concentration ($C_{unbound}$) that is able to cross into the tissue and equilibrate with the tissue binding sites and the drug receptor. While C_{bound} may be a significant percentage of the plasma drug pool, in most cases very little drug is in plasma and therefore C_{bound} represents relatively little of the total drug in the body.

Absorption/Bioavailability

The absorption of a drug is a key element in determining a drug-dosing regimen. The extent of absorption is referred to as bioavailability and is usually expressed as either a fraction (F) or percent of an administered drug that is available to produce a pharmacologic effect. An F value of 1 represent 100% of an administered dose is bioavailable. Most drugs when given by the intravenous route are assumed to be 100% bioavailable (F of 1.0). Absorption by other routes of administration (oral, rectal, etc) may or may not be complete. A number of factors influence the bioavailability of a drug.

To be orally absorbed, drugs must have a reasonable degree of water solubility so that they can dissolve in the gastrointestinal (GI) fluids. In addition, they must also have some lipid solubility characteristics so that the drug can cross the lipid membranes of the cell wall in the GI tract and enter the general circulation and eventually cross the cell walls of other tissues in the body. Aminoglycoside antibiotics are an example of a drug class whose water solubility is so high (lipid solubility very low) that they are not absorbed to any significant extent when administered by the oral route and must be given parenterally to achieve systemic effects.

Drugs that are unstable in the GI tract may have low bioavailability because they are broken down or decompose before they can be absorbed. The proton pump inhibitors (eg, omeprazole) are an example of a drug class that is unstable in the gastric acid and are administered orally as an enteric-coated tablet. In addition, although some drugs are absorbed, they are metabolized by the enzymes in the gut wall or the liver prior to reaching the systemic circulation. Lidocaine is an example of a drug that is metabolized so extensively as it passes through the liver following oral absorption that effective systemic effects require parenteral administration. Extensive hepatic metabolism following oral absorption is referred to as a *First Pass Effect* (see Chapter 58 *Hepatic Clearance*). Recently a greater appreciation for the impact of drug transporters on oral bioavailability of a number of compounds has been realized. In particular, the xenobiotic transporter P-glycoprotein has been shown to significantly affect the oral bioavailability of cyclosporine and other large hydrophobic compounds. Similar to the knowledge gained by studying the CYP450 enzymes responsible for metabolism of commonly prescribed drugs, knowledge of the substrate specificity of P-glycoprotein is integral to predicting the bioavailability of drugs that are substrates for this transporter.

Bioavailability or F, refers only to the extent of absorption. The rate of drug absorption can also be an important factor in drug administration. Extended release tablets and capsules are often designed for the drug to be slowly released from the dosage form so that drug absorption is relatively constant over the entire dosing interval. As a result these types of oral dosage forms tend to produce relatively little fluctuation in the plasma drug concentrations within a dosing interval. While this may be ideal for a drug with a narrow therapeutic index, these drug products may not be useful when relatively rapid drug onset is desired. In addition the drug release characteristics are usually designed to be consistent with a specific dosing interval. If a drug product is designed to be absorbed over 12 hours, extending the dosing interval to 24 hours may result in unacceptable swings in plasma concentrations.

Patients with certain gastrointestinal diseases may have a very short gastrointestinal transit time and thereby limiting the use of some extended release drug products. One example of a slowly absorbed drug with a limited bioavailability is phenytoin in the newborn. While not designed as an extended release product, phenytoin is so limited in its water solubility that several hours are required for complete absorption following oral administration. The newborn child has such a short GI transit time that when infants are changed from parenteral to equal oral doses of phenytoin, the plasma concentrations almost always decline dramatically because of a limited oral bioavailability.

Volume of Distribution (V)

Following absorption, drugs distribute throughout the body. Each drug has its own characteristics that result in an apparent volume of distribution (V) and can be expressed mathematically as:

$$\text{Volume of Distribution} = \frac{\text{Amount of Drug in the Body}}{\text{Plasma Concentration}}$$

or

$$V = \frac{\text{Amount of Drug in the Body}}{C} \quad (5)$$

where V is the volume of distribution and C is the plasma drug concentration. As can be seen from the equation above, volume of distribution is the volume required to account for the drug assuming the tissues have the same concentration as plasma. Volume of distribution is an important pharmacokinetic parameter when calculating the loading dose required to rapidly increase the plasma drug concentration to some desired concentration:

$$\text{Loading Dose} = \frac{C(V)}{F}$$

where C is the desired plasma concentration and F the bioavailability. In some cases, there may be drug already present and only a partial or incremental loading dose is needed to achieve the desired C_{Target} .

$$\text{Incremental Loading Dose} = \frac{(C_{\text{Target}} - C_{\text{Initial}})(V)}{F} \quad (6)$$

In the above equation C_{Target} is the desired concentration following and C_{Initial} is the drug concentration just prior to the incremental loading dose.

Body Composition and Volume of Distribution

Volume of distribution is most often reported as L/kg. The applicability of this L/kg value assumes that the physical characteristics of the patient are similar to the study population. Patients who are obese, emaciated, or have extensive third spacing of fluid (ascites or edema) may have an altered volume of distribution based on total body weight. Therefore some assessment of body composition is important when making initial estimates of V.

OBESE VERSUS IDEAL BODY WEIGHT—When patients are obese the most common approach is to calculate the patient's Ideal Body Weight (IBW):

$$\text{IBW}_{\text{males}} = 50 \text{ kg} + 2.3(\text{Height in inches} > 60) \quad (7)$$

$$\text{IBW}_{\text{females}} = 45 \text{ kg} + 2.3(\text{Height in inches} > 60) \quad (8)$$

IBW in the above equations is in kg, and it is this weight that is generally assumed to represent a "non-obese" weight. When the volume of distribution is known to correspond best to ideal or non-obese weight, it is the IBW that should be used for obese patients. As a practical approach, if a patient who weighs more than their IBW, most clinicians consider the patient to be clinically obese only if the patient is greater than 120% of their IBW:

$$\text{Clinically Obese} = \left(\frac{\text{Patient's Weight}}{\text{IBW}} \right) 100 > 120 \quad (9)$$

There are a few drugs that either part or all of the excess adipose weight in the clinically obese patient is used in calculating the apparent volume of distribution. Care should be taken to

carefully evaluate the patient's weight as well as the characteristics of the specific drug in question.

EXCESS THIRD SPACE FLUID (EDEMA AND ASCITES)—Some patients have extensive edema or ascites. This fluid accumulates in the interstitial space between the vasculature and the intracellular compartment or the peritoneal cavity. The degree to which a patient's vascular volume and/or intracellular volume can change is limited. Therefore, in most cases, significant changes in body water occur in the intraperitoneal and interstitial or third space. Depending on the drug's distribution characteristics the presence of third space fluid may alter how the apparent volume of distribution is calculated. In most cases, the presence of third space fluid is evaluated by changes in weight, with 1 kg of weight gain representing 1 liter of third space fluid. Alternatively, an experienced clinician can often approximate in patients with ascites or edema the number of excess third space liters present.

One method that can be used to account for any third space fluid is to calculate the contribution that one would expect for each liter (kg) of excess edema or ascites. The apparent V for each liter can be calculated by multiplying the fraction of unbound drug in plasma (f_u) times the number of liters of excess third space fluid.

$$V_{\text{Excess 3rd space fluid}} = (f_u)(\text{Liters of Excess 3rd Space Fluid}) \quad (10)$$

The units of V are liters. The liters of excessive third space fluid gain are usually estimated by subtracting the patient's current weight from their usual weight in kilograms. Care should be taken to evaluate whether or not the weight gain is in fact excess third space fluid. Usually this is accomplished by determining the time course of the weight gain. Muscle mass and adipose weight gain generally takes many months, but third space weight gain can occur over weeks, days, or even a few hours. The presence of or change in the patient's edema or ascites is also a factor that should be considered when estimating excess third space fluid weight. As an example, a patient who gains 10 kg of weight in 2 days may have been initially dehydrated and simply replaced a fluid deficit rather than have gained 10 L of excess third space fluid. On the other hand if the patient has extensive edema before gaining the 10 kg, the amount of excess third space fluid may be much more than the most recent 10 kg weight gain would suggest.

In most cases the amount of excess fluid gained is in the range of 5 to 10 L and is seldom more than 20 L. Because the contribution of 5 to 20 L is not significant for most drugs, the weight used in calculating the volume of distribution need only consider the patient's usual weight. However, if the volume of distribution is small and plasma protein binding is low (f_u approaches 1), then excess third spacing of fluid should be considered in the calculation. This would be accomplished by first calculating the patient's weight without the excess third space weight and using the *non-excess third space weight* to calculate the patient's V in the usual way. In addition, Equation 10 above can be used to determine the additional contribution of $V_{\text{Excess 3rd space fluid}}$. The sum of these two values would be the most reasonable value to use for the patient's volume of distribution.

Digoxin and aminoglycoside antibiotics are two drugs that represent the extremes. Digoxin has a f_u of approximately 0.9 and a V of approximately 500 L (7 L/Kg). If a patient accumulated 10 liters of excessive third space fluid, the increase in V would only be 9 L [ie, (0.9) (Liters of Excess 3rd Space Fluid)]. This increase in V is less than 2% of the total volume of distribution and therefore not clinically significant. It is important to note that the patient's weight without the excess third space fluid should be used to calculate the volume of distribution for digoxin and most other drugs with a large volume of distribution. Aminoglycoside antibiotics also have a f_u of approximately 0.9 but the usual V is approximately 15 to 20 liters. Therefore, the increase in V of 9 L associated with 10 liters of excess third space fluid would be significant and would be incorporated in the calculation of V .

Two Compartment Volume Of Distribution

While it is often useful to think of the body as a single compartment, in reality we are made of hundreds if not thousands of individual spaces into which a drug distributes. However, for most drugs the volume of distribution can be conceptualized into two individual compartments. An initial first volume (V_1) consisting of plasma and other rapidly equilibrating tissues and a second more slowly equilibrating volume (V_2) (Fig 59-3).

LOCATION OF TARGET ORGAN—The two-compartment model has two important clinical implications. First is related to the location of the target organ for clinical response (therapeutic or toxic). Some drugs have an end organ for clinical response (efficacy or toxicity) that equilibrates very rapidly with plasma. Therefore, large doses administered rapidly into the smaller first compartment will result in elevated drug concentrations and have the potential for causing drug toxicity. It is also possible to give a smaller first dose that achieves an initial therapeutic concentration and response that is quickly lost as the drug concentration declines during distribution into the larger volume. Drugs whose target organ respond as though it were located in the initial volume of distribution must be administered in such a way as to avoid the transiently elevated drug concentrations during the administration process. This is most common when drugs are administered by the intravenous route. Most drugs have a maximum recommended rate of infusion. Usually this rate is designed to allow drug distribution to take place as the drug is being infused. Occasionally it is recommended to divide a dose into portions that are administered at set intervals, again allowing for distribution to be completed before the next part of the dose is administered. For some drugs, the intravenous administration rate has to be controlled because of an agent in the injectable dosage form that has the potential for toxicity. As an example, penicillin is most commonly available as the potassium salt. While rapid injection of penicillin itself can be potentially harmful, it is the potassium that is probably the most dangerous and the reason for controlling the infusion rate of IV potassium penicillin. When drugs

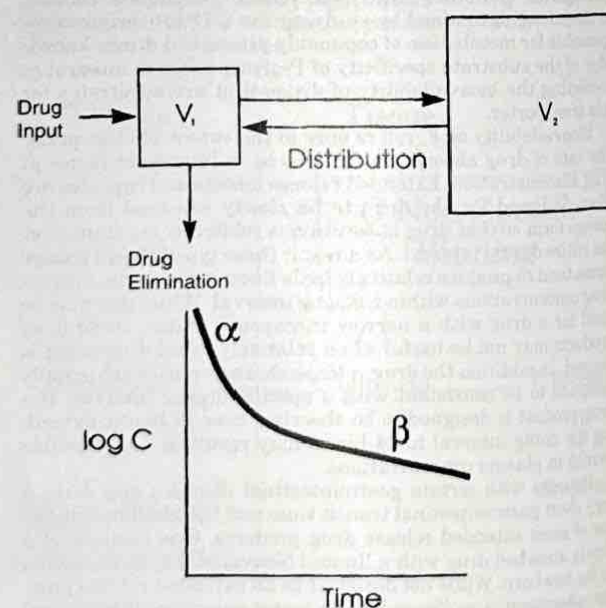
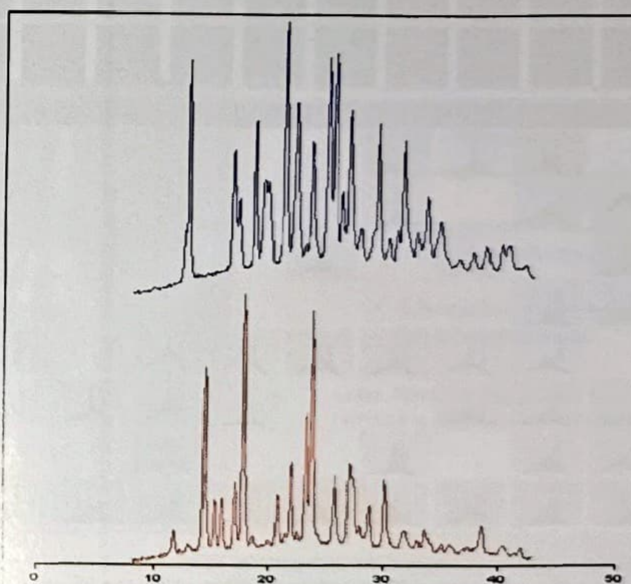


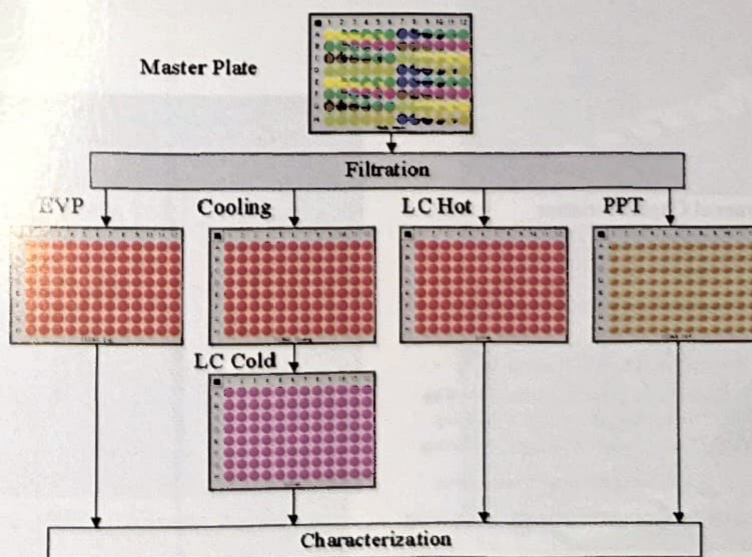
Figure 59-3. Drug first enters the body into V_1 . The initial rapid decrease in drug concentration (α phase) is primarily due to drug moving into the larger more slowly equilibrating V_2 , the more slowly declining drug concentrations (β phase) are primarily due to drug being eliminated from the body.



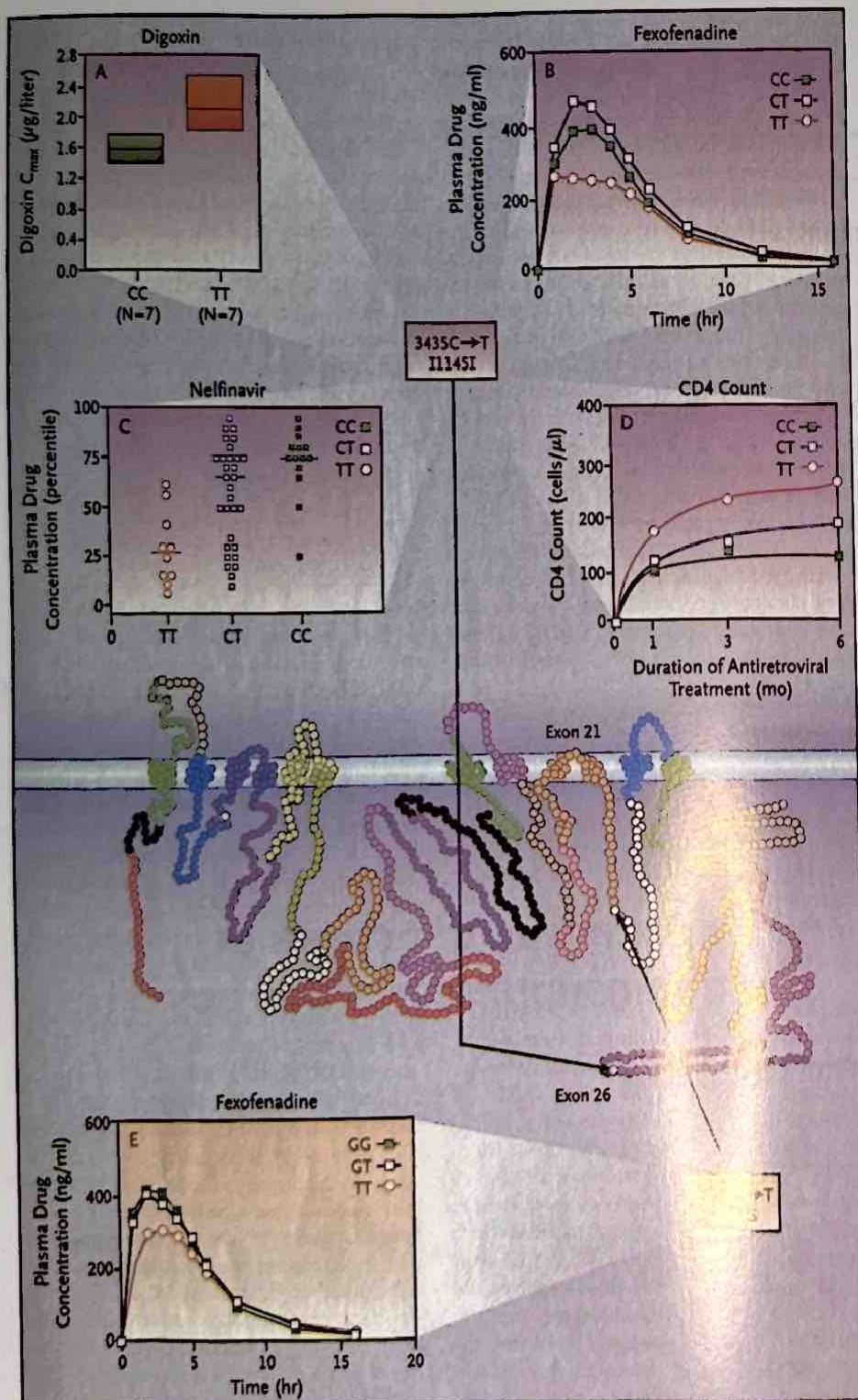
Color Plate 1. Figure 34-32. The 3-dimensional molecular structure of d,l-propranolol hydrochloride provides information about the molecular conformation and bonding whereas the its packing arrangement within the crystallographic unit cell is useful in understanding the physical properties of the crystalline form.



Color Plate 2. Figure 34-35. The x-ray powder diffraction patterns of two polymorphic forms of d,l-propranolol hydrochloride indicate differences in molecular arrangements within their different crystal lattices.



Color Plate 3. Figure 34-44. Design for the crystallization process for polymorphic form screening demonstrates hot filtration of the crystallization solution and its transfer to three crystallization plates and two plates for solubility determination.



Color Plate 23. Figure 62-3. Functional consequences of genetic polymorphisms in the human p-glycoprotein transporter gene (*MDR1* or *ABCB1*). The schematic of the human P-glycoprotein was adapted from Kim RB, Leake BF, Choo EF, et al. *Clin Pharmacol Ther* 2001; 70: 189, with each circle representing an amino acid and each color a different exon encoding the corresponding amino acids. Two SNPs in the human *ABCB1* gene have been associated with altered drug disposition (Panels A,B,C,E) or altered drug effects (Panel D) in humans. The synonymous SNP in exon 26 (nucleotide 3435 C>T SNP), has been associated with higher digoxin oral bioavailability in patients homozygous for the T nucleotide¹⁶⁷ (Panel A), but lower plasma concentrations after oral doses of fexofenadine¹⁷⁰ (Panel B) and nelfinavir¹⁷¹ (Panel C). This SNP has also been linked to better CD4 cell recovery in HIV infected patients treated with nelfinavir and other antiretroviral agents (Panel D).¹⁷¹ The SNP at nucleotide 2766 (G>T) has been associated with lower fexofenadine plasma concentrations in patients homozygous for the T nucleotide at position 2766 (Panel E).¹⁷⁰ Panels A-E have been adapted from the original reports of Kim RB, Leake BF, Choo EF, et al. *Clin Pharmacol Ther* 2001; 70: 189; Hoffmeyer S, Burk O, von Richter O, et al. *Proc Natl Acad Sci U S A* 2000; 97: 3473; and Fellay J, Marzolini C, Meaden ER, et al. *Lancet* 2002; 359: 30. (From Evans WE, McLeod HL. *N Engl J Med* 2003; 348: 538).

are administered orally, the absorption process is usually sufficiently slow so that elevated concentrations in the initial volume of distribution are limited. Digoxin and lithium are two exceptions, but fortunately both drugs have the end organ or response located in the tissue compartment and the transiently elevated concentrations in the initial volume of distribution do not result in an augmented clinical response.

For drugs that have the end organ for response in the deeper more slowly equilibrating volume, administration rate is not usually very critical. Digoxin is an example of a drug where the end organ for response, in this case the myocardium, is in the deep compartment. However, it is still a common clinical practice to divide large loading doses because digoxin has a significant potential for toxicity. The loading doses are divided so that the patient can be evaluated and the remaining part of the loading dose withheld if adverse events are observed.

Clearance

Clearance (CL) is a measure of the body's potential to eliminate drug. Clearance is expressed as volume/time and can be thought of as the proportionality constant between the average steady-state drug concentration ($C_{ss\text{ ave}}$) and the rate of drug administration. At steady state the rate of drug administration must equal the rate of drug elimination.

$$\text{Rate of Administration} = \text{Rate of Elimination}$$

$$\text{Rate of Administration} = (CL)(C_{ss\text{ ave}})$$

If the Rate of Administration is expressed as $F \text{ Dose}/\tau$, where F is the bioavailability, Dose is the amount of drug administered, and τ is the interval between doses we have the following:

$$F \text{ Dose}/\tau = (CL)(C_{ss\text{ ave}}) \quad (11)$$

This equation can be rearranged to calculate the desired dose necessary to achieve a desired $C_{ss\text{ ave}}$ if CL and F are known and a dosing interval τ is selected.

$$\text{Dose} = \frac{(CL)(C_{ss\text{ ave}})(\tau)}{F} \quad (12)$$

Alternatively, if a dose has been prescribed, the anticipated $C_{ss\text{ ave}}$ can be calculated.

$$C_{ss\text{ ave}} = \frac{F \text{ Dose}/\tau}{CL} \quad (13)$$

Clearance is often expressed as L/day, L/hr, or mL/min. To allow adjustment for size, clearance values are usually expressed as L/hr per kg or L/hr per m^2 . There is some evidence that clearance values are best adjusted using surface area of m^2 , but in clinical practice this is usually limited to patients who are substantially different from the usual 70 kg or $1.73 m^2$ adult, and there is no representative patient population for a more direct comparison.

The two primary elimination pathways are elimination of unchanged drug by the renal route and hepatic metabolism.

CREATININE CLEARANCE (CL_{CR}) AND RENAL CLEARANCE (CL_{Renal})—Renal elimination parallels renal function, and the most common measure of renal function is creatinine clearance (CL_{CR}). The equation by Cockcroft and Gault is the most common method of estimating CL_{CR} or renal function:

$$\text{CL}_{CR} \text{ for males (mL/min)} = \frac{(140 - \text{Age})(\text{Weight})}{(72)(\text{SCr}_{ss})} \quad (14)$$

$$\text{CL}_{CR} \text{ for females (mL/min)} = (0.85) \frac{(140 - \text{Age})(\text{Weight})}{(72)(\text{SCr}_{ss})} \quad (15)$$

where age is in years, weight in kg, and SCr_{ss} is the steady-state plasma creatinine in mg/dL. There are a number of assumptions inherent in the above equations. First is that the plasma creatinine is stable and not rising or falling (ie, at steady state and the patient not receiving dialysis), and the second is that the patient's muscle mass is average for his/her age, weight, and sex. In obese patients, IBW should be used in the equation to calculate CL_{CR}. Also if a patient has extensive third spacing of fluid, that weight should not be included in the patient's weight, and for those patients who weigh less than their IBW, their actual and not IBW should be used.

Once a patient's CL_{CR} is known or estimated, then maintenance dose adjustments can be made based on the degree of renal impairment and the fraction of the total clearance that is renal. In addition, the impact of adding to a patient's regimen a drug that can inhibit the secretion or reabsorption of a renally eliminated drug should be considered.

In some instances, it is appropriate to collect urine to directly measure creatinine clearance. The urine is collected usually over a 24-hour period, the creatinine concentration in plasma is measured, and the patient's creatinine clearance calculated by the following equation:

$$\text{CL}_{CR} (\text{mL/min}) = \frac{(U)(V)}{(P)} \quad (16)$$

where U is the urine concentration of creatinine in mg/dL, V is the urine volume in mL divided by the collection time in minutes. In the above equation, P is in units of mg/dL and is analogous to the value of SCr_{ss} in Equation 14 or 15 above. The value of $(U)(V)$ is the production rate of creatinine and analogous to the 140 - Age, Weight and 72 in Equations 14 and 15. The advantage of obtaining a urine collection to measure creatinine clearance is that it is a direct measurement and does not make an assumption about creatinine production as do the methods that do not utilize a urine collection (eg, Equations 14 and 15).

There are two major disadvantages of 24-hour urine collections for creatinine clearance. The first and most obvious is that the information required to make clinical decisions may be unacceptably delayed because of the time required to collect the patient's urine. The second is that urine collections are often inaccurate. It is common for patients and even health care professionals to inadvertently discard a portion of the urine during the collection process or on occasion to collect for longer than the time listed on the collection document.

Whenever a creatinine collection is obtained, it is important to evaluate whether or not the collection appears to be adequate or complete. Although there are a number of methods that could be used, the most straightforward is to compare the CL_{CR} from the 24-hour urine collection to the CL_{CR} calculated from Equation 14 or 15 above. If the two values are in close agreement, it is usually a good indication that the patient is average in terms of their muscle mass, creatinine production, and the collection was properly obtained. However, if the two values are substantially different, one of the values is more likely to be the better estimate of the patient's renal function. Because both the urine collection and Equations 14 and 15 use the same value for the plasma creatinine, the difference has to be in either the accuracy of the 24-hour urine collection or the inherent assumptions in Equations 14 or 15 about the patient's muscle mass and creatinine production.

In most cases where there are significant differences, the 24-hour collection CL_{CR} is lower than the value calculated by Equation 14 or 15. This is because the most common error is either not collecting all of the urine in the 24-hour collection period or that Equations 14 or 15 over-predicts the patient's muscle mass and creatine production. Therefore if the patient has a reasonably normal body stature and muscle mass, it is likely that Equation 14 or 15 would be the better estimate of the patient's renal function. On the other hand, if a patient is very thin and emaciated with a lower than average muscle mass, it is likely that the 24-hour collection is the better estimate of the patient's

renal function. There are other possibilities, but the examples above are the most common scenarios.

Once creatinine clearance is known, CL_{Renal} can be calculated by multiplying the patient's creatinine clearance by a "factor" or ratio of the usual drug clearance to CL_{Cr} . As an example, procainamide CL_{Renal} is about 3 times CL_{Cr} and so a patient's creatinine clearance would be multiplied by 3 to obtain an estimate of renal clearance for procainamide. Aminoglycosides have a CL_{Renal} that is approximately equal to CL_{Cr} while the factor for phenobarbital is so small that CL_{Cr} is not considered in calculating the clearance of phenobarbital.

HEPATIC CLEARANCE ($CL_{Hepatic}$)—Hepatic metabolism or $CL_{Hepatic}$ usually represents the conversion of active drug into a more polar and inactive compound by changing one or more of the functional groups on the compound. Hepatic clearance is a function of both the number and the quality of the hepatic enzymes. Clearly there are a number of factors that influence the liver's ability to metabolize drugs. Genetic composition as well as environmental factors and disease play a role in a patient's hepatic metabolic capabilities. Currently genetic profiles are not commonly available, but there are a number of drugs that are known to either inhibit or induce hepatic metabolism and we are learning more about which enzymes are responsible.

Accurate assessment of hepatic function and a patient's ability to metabolize drugs is difficult. Elevated plasma enzymes such as alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (Alk Phos) represent ongoing liver damage but are a poor reflection of function. More direct but still relatively unreliable predictors of hepatic dysfunction and decreased drug metabolism are an increased plasma bilirubin (Bili), decreased plasma albumin (Alb), and an increased prothrombin time (PT). These three biological indicators are useful in that they each represent a metabolic function of the liver. However, there are a number of factors that influence each of these laboratory tests. As an example, a patient with a low plasma albumin may have a gastroenteropathy or nephritis and have a low albumin because of a protein wasting problem and not because of decreased hepatic synthesis. Similarly, a high PT may be due to warfarin and not a reflection of a patient's hepatic metabolic capacity for drugs. Patients with severe liver failure and cirrhosis would be expected to have an elevated bilirubin and prothrombin time as well as a decreased plasma albumin. However, the presence of these abnormal laboratory test, even in the face of obvious liver disease, are not always good predictors of the extent to which a patient's ability to metabolize drugs will be decreased. Similarly congestive heart failure is known to be associated with decreased metabolism of a number of drugs. The exact mechanism of this disease-drug interaction is not known but is assumed to be secondary to either decreased hepatic blood flow or an increase in portal pressure and thereby a decrease in the ability of the hepatic enzymes to function properly.

In most clinical settings, when there is evidence of significant hepatic dysfunction the tendency is to assume that the patient's hepatic capacity is approximately half normal. Clearly this "yes" or "no" approach to estimating the presence and the extent of hepatic disease on drug metabolism leaves much to be desired. Unfortunately, with few exceptions, this is the state of the art in clinical pharmacokinetics with regard to hepatic metabolism.

OTHER CLEARANCE MECHANISMS—Renal elimination of unchanged drug and hepatic metabolism are the most common routes of elimination. However, on occasion other elimination pathways play an important role. As an example, succinylcholine is hydrolyzed and inactivated (cleared from the body in a pharmacokinetic sense) by butyrylcholinesterase enzymes located in the liver and to a significant extent in the circulating in plasma. There are other examples of in-vivo and in-vitro drug interactions that essentially act as a clearance mechanism. Aminoglycoside antibiotics with a primary amine group (eg, gentamicin) can form a covalent bond with beta-

lactam antibiotics (eg, penicillin) and as a result the aminoglycoside is inactivated. This interaction is not very rapid, and significant inactivation of an aminoglycoside antibiotic only occurs when the aminoglycoside and beta-lactam antibiotic are mixed in the same IV bag or in-vivo when the two drugs are administered to a patient with end-stage renal failure. In these types of patients, the additional "clearance" can be equivalent to as much as 5 mL/min. Other potential routes of elimination are via dialysis, either hemo- or peritoneal. Some drugs are significantly removed by dialysis and care should be taken to adjust the initial dosing regimen for patients with very poor renal function and to determine if any supplemental doses would be required because of the dialysis process.

The overall approach to using pharmacokinetics and assessment of a patient's renal and hepatic function needs to be combined with the urgency of the clinical situation, the available options, and the consequences of either drug toxicity or a therapeutic failure.

Drug-Drug Interactions

With today's trend towards polypharmacy, drug-drug interactions are common and can result in therapeutic misadventures. Care should be taken to evaluate how adding or removing a drug from a patient's regimen will affect the absorption, distribution, and elimination of the other drugs the patient may be taking. Knowing the direction of the interaction (ie, increase or decrease), the time course of the onset, and the magnitude of the interaction are all important considerations when evaluating drug-drug interaction. Understanding the specifics of a drug-drug interaction helps the clinician know how and when to monitor the patient and the probable adjustments in the dosing regimen that will be necessary. As an example, both quinidine and amiodarone will approximately double a patient's steady state digoxin concentration. The doubling in the steady state digoxin concentration is due to the fact that quinidine and amiodarone both reduce by half the total clearance of digoxin, however, quinidine has a half-life of about 6 hours and accumulates to steady state within 1 day. In addition, quinidine reduces the volume of distribution digoxin, and as a result digoxin concentrations will increase rapidly within 24 hours following the initiation of quinidine therapy. Amiodarone, on the other hand, has a very long half-life and appears to have little influence on the volume of distribution for digoxin. Therefore, the increase in digoxin concentrations following the addition of amiodarone occurs over 1 to 2 weeks. Understanding these differences in how quinidine and amiodarone affect digoxin's volume of distribution vs. clearance helps to explain the difference in clinical management when either quinidine or amiodarone are added to a patient's therapy. When quinidine is initiated, a daily dose of digoxin is usually withheld to blunt the rapid rise in digoxin due to the decrease in volume of distribution, and the maintenance dose is halved to compensate for the reduction in clearance in an attempt to maintain the same digoxin concentration at steady state. In contrast, when amiodarone is added to a patient's regimen, the usual practice is to simply reduce the digoxin maintenance dose in half to compensate for the reduction in clearance.

Again knowing which parameter is affected, in which direction the parameter will be altered, and the time course as well as the expected magnitude of the change will provide the clinician with a logical approach to dealing with the drug-drug interaction.

Elimination Rate Constant (K) and Half-Life ($t_{1/2}$)

In physical chemistry, the K or rate constant is the independent parameter that controls the rate of change in a reaction. In the physiologic model used in clinical pharmacokinetics, CL and V

are the independent parameters and the relationship of CL to V that controls the rate of change of drug in the body. The fractional rate of change or K constant has the units of inverse time, usually hours⁻¹ or days⁻¹ and its relationship to CL and V is represented in the following equation.

$$K = \frac{CL}{V} \quad (17)$$

or

$$CL = (K)(V) \quad (18)$$

Note that although Equation 18 appears to represent CL as a function of K and V, it is Equation 17 that represents the true dependence of K on CL and V.

Half-life is a common clinical tool and is related to K or CL and V in the following way:

$$t_{1/2} = \frac{0.693}{K} \quad (19)$$

and

$$t_{1/2} = \frac{0.693 V}{CL} \quad (20)$$

The half-life of a drug is the time required for half of the drug to be eliminated from the body or the time required for a drug concentration to decline by half (Fig 59-4). This definition assumes a single compartment volume of distribution and that CL and V are constant values, independent of dose or concentration. The utility of half-life is in estimating the rate of change of drug within the body. When a drug is administered at a consistent dosing rate, the drug will accumulate to 50% of steady state after one $t_{1/2}$, 75% after 2 $t_{1/2}$ and after 3.3 $t_{1/2}$'s will be at 90% of the final steady-state or plateau value. Similarly during decline, after one $t_{1/2}$ 50% will be eliminated (50% remaining), after two $t_{1/2}$'s 75% will be eliminated (25% remaining) and after 3.3 $t_{1/2}$'s 90% will be eliminated (10% remaining). The equation that predicts drug accumulation towards steady-state assuming continuous input (see PK models section) is as follows:

$$C_t = \frac{(F)(Dose/\tau)}{CL} (1 - e^{-Kt}) \quad (21)$$

where $\frac{(F)(Dose/\tau)}{CL}$ represents the eventual C_{ss} ave, and $(1 - e^{-Kt})$ represents the fraction of steady-state achieved after t hours of

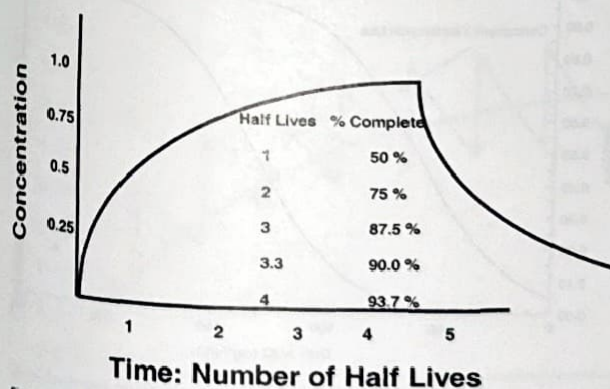


Figure 59-4. Drug Accumulation and Decline. The ascending curve represents drug concentration accumulating towards steady-state and the descending curve represents drug concentration declining after the drug is discontinued. After one $t_{1/2}$ the drug is at 50% of steady-state, two $t_{1/2}$'s 75% and 3.3 $t_{1/2}$'s 90% of steady-state. In the declining phase the drug concentration declines to half of the previous concentration in each $t_{1/2}$ after 3.3 $t_{1/2}$'s 90% of the drug will have been eliminated.

input at a rate of $(F)(Dose/\tau)$. Alternatively the concentration of drug remaining some time t later can be expressed by the following:

$$C_2 = (C_1)(e^{-Kt}) \quad (22)$$

where C_1 is the initial concentration, e^{-Kt} is the fraction remaining at t hours later, and C_2 is the remaining concentration. Equation 22 assumes that CL and V are constant, that the V behaves as a one-compartment model and that there is no additional drug input between C_1 and C_2 . Clearly an equation can become complex when it is composed of a series of equations representing the concentration at C_1 . Take for example a drug that is infused for 10 hours and then the infusion is discontinued and 5 hours later a drug concentration is to be calculated. This could be accomplished by using Equation 21 to calculate the concentration (C_1) at the end of the 10-hour infusion and then substituting that value for C_1 in Equation 22 and calculating the value of C_2 5 hours later. Alternatively Equations 21 and 22 could be combined as follows:

$$C_2 = \frac{(F)(Dose/\tau)}{CL} (1 - e^{-K \cdot 10 \text{ hours}})(e^{-K \cdot 5 \text{ hours}}) \quad (23)$$

Either approach is reasonable, but equations can become somewhat complex depending on the number of dose manipulations that are made and the time when the drug concentration is to be calculated.

INDIVIDUALIZED DRUG DOSING REGIMENS

The goal of clinical PK/PD is to develop individualized drug therapy regimens to maximize the likelihood of therapeutic success. The doses utilized in clinical practice typically are derived from phase II/III clinical trials in which the safety and efficacy of an agent are evaluated. The information from clinical trials as well as preclinical work from animal and in-vitro studies provides data on the doses necessary to obtain concentrations in the "usual therapeutic range." As discussed previously, the therapeutic range defines the range of concentrations in which most patients have a therapeutic effect and a low incidence of toxicity; however, for drugs exhibiting a narrow therapeutic index, it may be necessary to more precisely define the dosage regimen for an individual based on (1) patient factors (severity of disease), (2) concentrations achievable at site of drug action (distribution, elimination), and (3) the level of sensitivity to the drug (pharmacodynamics). For example, it is widely recognized that higher doses of the aminoglycoside antibiotics are necessary in the treatment of sepsis versus a urinary tract infection. The high mortality rate from sepsis requires early aggressive therapy in order to control the infection before serious end organ damage occurs. Higher doses are also necessary where penetration into the site of the infection is reduced (ie, pneumonia or meningitis), whereas lower doses would be appropriate when renal function is compromised. These differences can be characterized and are based on knowledge of the pharmacokinetics of the drug being administered. Over the past decade, our understanding of the pharmacodynamics of drugs has improved significantly. This recognition stemmed from the observation that despite achievement of concentrations in the desired range, not all patients exhibit the same clinical response. Subsequently, a number of studies have evaluated the relationship between measures of drug exposure (C_{max}, AUC), measures of disease sensitivity (eg, minimum inhibitory concentration for bacteria), and clinical outcomes (efficacy and toxicity). For the aminoglycoside antibiotics, it has been shown that the bactericidal activity and clinical improvement is correlated with the peak to MIC ratio (Fig 59-5). According to this analysis, the probability of normalizing the temperature and leukocyte count is maximized when the peak/MIC ratio exceeds 10. Therefore, higher doses would be necessary for