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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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Basic Pharmacokinetics and Pharmacodynamics

Raymond E Galinsky, PharmD
Craig K Svensson, PharmD, PhD



The goal of pharmacotherapy is to provide optimal drug therapy in the treatment or prevention of disease. A major barrier to the achievement of this goal is the large variability in pharmacological effect that is observed following drug administration (Fig 58-1).¹ The ability to implement drug therapy in a safe and rational manner necessitates an understanding of the factors that cause this variability. One of the most important factors is the concentration of drug that is achieved at the site of action.

THE CRITICAL NATURE OF THE CONCENTRATION VERSUS EFFECT RELATIONSHIP

The quantitative response to a drug depends highly on the concentration of drug at the site of action. In most situations, one cannot quantify drug concentration at the actual site of action. Rather, drug concentrations are measured in an easily accessible site that is believed to be in equilibrium with the site of action (eg, blood or one of its components). Figure 58-2² provides a good illustration of a drug whose pharmacological effect is particularly sensitive to changes in blood concentration. Numerous studies have been published that substantiate the critical nature of the concentration-effect relationship for a wide variety of drugs.

It is recognized now that drug therapy may be optimized by designing regimens that account for the concentration of a drug necessary to achieve a desired pharmacological response. However, there is often significant difficulty in achieving such target concentrations. In particular, it often is observed that if a fixed dose of a drug is administered to a group of individuals, the drug concentration measured in plasma can vary widely. For example, the peak concentration of 6-mercaptopurine achieved in a group of 20 patients who received a standard 1 mg/m² dose is shown in Figure 58-3.³ The concentrations ranged from 0 to 660 ng/mL. Taken together, this suggests that variability in drug concentration is a major source of variability in drug effect, and there may be a significant degree of variability among individuals in the drug concentrations produced by a given dose of drug.

A basic understanding of the factors that control drug concentration at the site of action is important for the optimal use of drugs. This is the area of study referred to as *pharmacokinetics*, which is the study of the time course of drug absorption, distribution, metabolism, and elimination.

DRUG CONCENTRATION VERSUS TIME PROFILE

Blood (or its components, plasma or serum) represents the most frequently sampled fluid used to characterize the pharmacoki-

netics of drugs. Drug concentration in the blood is the sum of several processes (Fig 58-4).⁴ Initially, visual characterization of the processes controlling the concentration of drug in the blood can be made by constructing a drug concentration versus time profile (ie, a plot of drug concentration in the blood versus time). As can be seen from Figure 58-5, several useful pieces of information can be derived from such a profile. For example, the time at which the peak concentration occurs can be approximated and the peak concentration quantified. If the minimum concentration needed to maintain a desired effect is known, the onset and duration of effect also can be approximated. While useful information can be drawn casually from a simple graph as depicted in Figure 58-5, a more rigorous description of the pharmacokinetics of a drug is necessary to achieve the accuracy in dosage regimen design required for the safe and effective use of drugs. This higher degree of accuracy necessitates the development of mathematical models for describing the time course of absorption, distribution, metabolism, and elimination.

PHARMACOKINETIC MODELS

One of the primary objectives of pharmacokinetic models is to develop a quantitative method to describe the relationship of drug concentration or amount in the body as a function of time. The complexity of the pharmacokinetic model will vary with the route of administration, the extent and duration of distribution into various body fluids and tissues, the processes of elimination, and the intended application of the pharmacokinetic model. Often, numerous potential mathematical models exist for a particular drug. In such cases, the simplest model that will adequately and accurately describe the pharmacokinetics of the drug is the model that should be chosen.

There are a wide variety of potential uses for pharmacokinetic models, which include

1. Prediction of drug concentration in blood/plasma or tissue.
2. Calculation of a dosage regimen.
3. Quantitative assessment of the effect of disease on drug disposition.
4. Elucidation of the mechanism of disease-induced alterations in drug disposition.
5. Determination of the mechanism for drug-drug interactions.
6. Prediction of drug concentration versus effect relationships.

There are three primary types of pharmacokinetic models: compartmental, noncompartmental, and physiological.

Compartmental models describe the pharmacokinetics of drug disposition by grouping body tissues that are kinetically indistinguishable and describe the transfer of drug between body tissues in terms of rate constants.

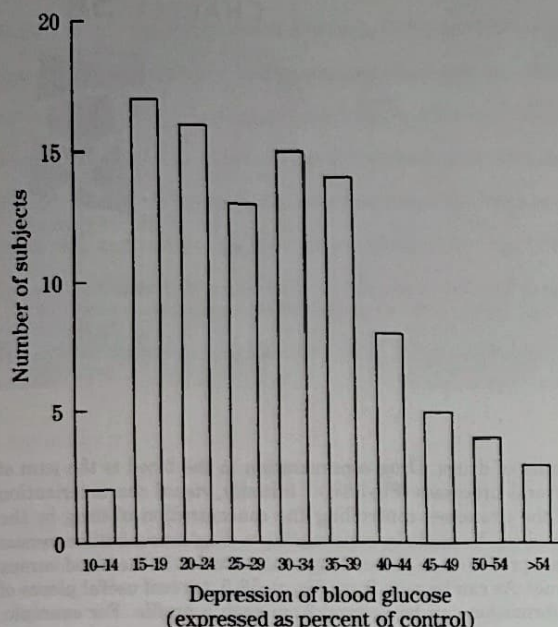


Figure 58-1. Decrease in blood glucose in 97 subjects 30 min after an intravenous dose of 1 g of tolbutamide. Note the large variability observed after the equivalent dose was administered in this group. (Data from Swerdloff RS, et al. *Diabetes* 1967, 16:161.)

Noncompartmental models describe the pharmacokinetics of drug disposition using time- and concentration-averaged parameters.

Physiological models attempt to describe drug disposition in terms of realistic physiological parameters, such as blood flow and tissue-partition coefficients.

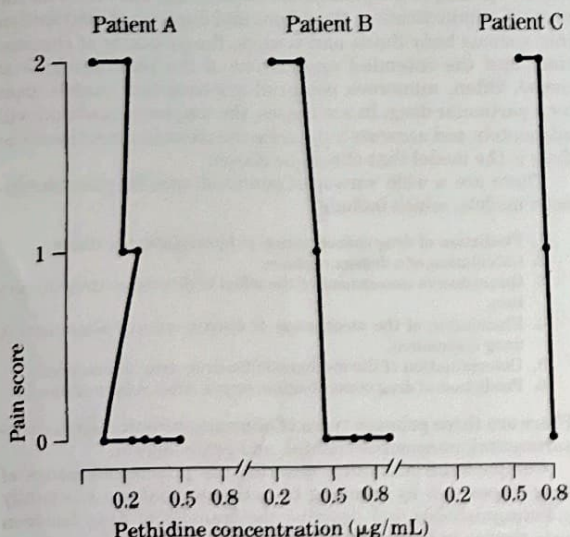


Figure 58-2. Blood-pethidine concentration-response curves for three individual patients, illustrating a typical range in interpatient responses. (From Edwards DJ, et al. *Clin Pharmacokinet* 1982, 7:421.)

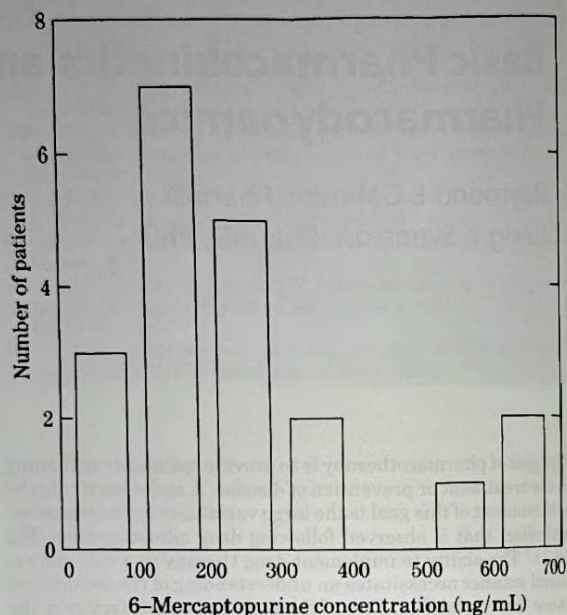


Figure 58-3. Distribution of peak 6-mercaptopurine concentrations achieved in a group of 20 patients receiving an oral dose of 1 mg/m². (Data from Sulh H, et al. *Clin Pharmacol Ther* 1986, 40:604.)

RATES AND ORDERS OF REACTIONS

Many pharmacokinetic models use parameters that are analogous to rate constants in chemical kinetics. For example, consider the case of a drug (D) that is metabolized to a metabolite (M).



This reaction may be described as a function of either the disappearance of the drug or as a function of the appearance of the metabolite. If the *amount* of the drug that is converted to a metabolite is a constant with respect to time, the reaction is said to be *zero-order* and is expressed as

$$\frac{-dD}{dt} = k_0 \quad (1)$$

where K_0 is the zero-order rate constant with units of mass per time (eg, mg/min). A plot of the time-course of the amount of the drug in the body that is converted to a metabolite by zero-order kinetics is shown in Figure 58-6. Integration of Equation 1 yields an equation for a straight line, which describes the amount of the drug in the body at any time (t):

$$\text{Amount}_t = -k_0 t + \text{Amount}_{t=0} = -k_0 t + \text{Dose} \quad (2)$$

Zero-order rate processes typically are found when an enzyme or transport system becomes saturated and the rate process becomes constant and cannot be increased by increases in the concentration of substrate. Zero-order rate processes are typical of constant-rate intravenous infusions and prolonged-release dosage forms.

If the amount of the drug in the body is converted to a metabolite at a rate that is a constant *fraction* of the amount of the drug in the body, the conversion of D to M is said to be a *first-order* reaction described by

$$\frac{dD}{dt} = -kD \quad (3)$$

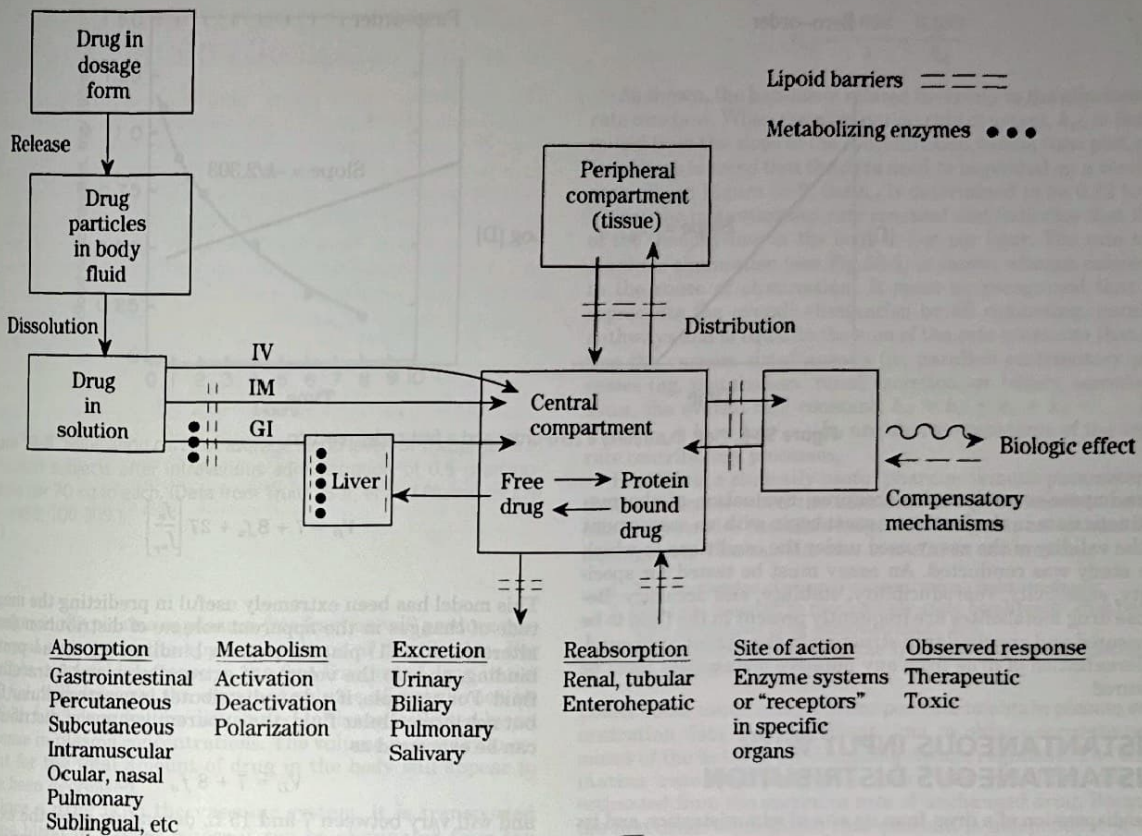


Figure 58-4. Diagram illustrating the factors that influence onset, duration, and intensity of drug effects. Note that the drug must dissolve before being absorbed and that it passes across many lipid barriers and some metabolizing systems before reaching the site of action. (From Barr WH. *Am J Pharm Educ* 1968, 52:958.)

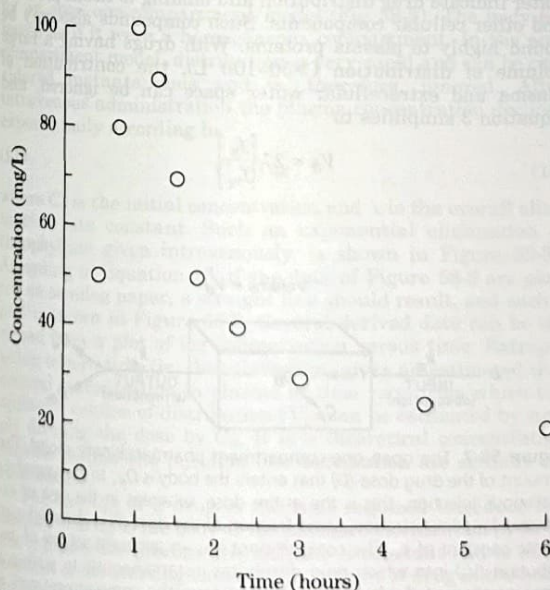


Figure 58-5. Hypothetical plot of drug-concentration data after oral administration of a drug.

where k is the first-order rate constant expressed in units of reciprocal time (eg, min^{-1}). Rearrangement of Equation 3 leads to

$$\frac{dD}{D} = -kdt \quad (4)$$

and integration of this expression yields

$$\int_0^t \frac{dD}{D} \Rightarrow \ln D = -kt + \ln D_0 \quad (5)$$

where $\ln$ is the natural logarithm. This equation also can be expressed in the exponential form

$$D_t = D_0 e^{-kt} \quad (6)$$

Graphically, the integrated form usually is expressed in terms of $\log_{10}$ rather than in natural logarithms (see Fig 58-6):

$$\log D = \frac{-kt}{2.303} + \log D_0 \quad (7)$$

ANALYTICAL CONSIDERATIONS

Any discussion of pharmacokinetics presumes that the drug concentrations can be determined with a high degree of accuracy and precision. One of the most frequent causes of high variability in pharmacokinetic parameters is poor data resulting

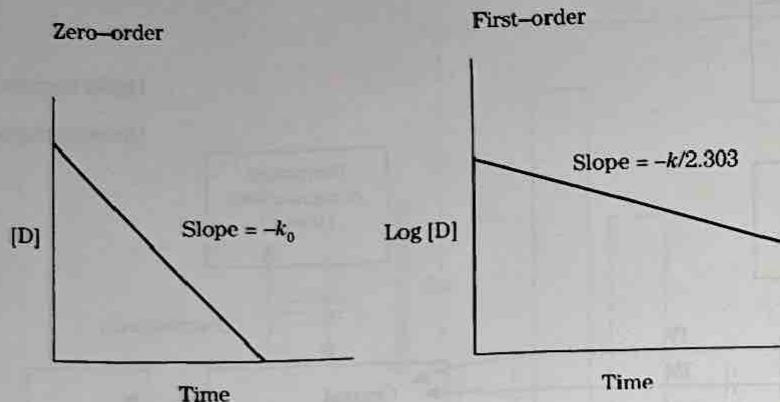


Figure 58-6. Plots illustrating a zero-order and a first-order reaction.

from imprecise analytical procedures. Evaluation of pharmacokinetic data in the literature must begin with an assessment of the validity of the assay used under the conditions in which the study was conducted. An assay must be tested for specificity, sensitivity, reproducibility, stability, and accuracy. Because drug metabolites are frequently present in the fluid to be measured and are similar in structure to the parent compound, differentiation of drug from any putative metabolites must be ensured.

INSTANTANEOUS INPUT WITH INSTANTANEOUS DISTRIBUTION

The disposition of a drug from its site of administration and its distribution and elimination from the body occurs via the vascular system. Most drugs are low-molecular-weight compounds of sufficient lipophilicity that they are able to distribute readily into the intra- and extracellular fluid compartments in the body. The transfer of drug from the circulation to these fluid compartments and then into tissues is called distribution. The pharmacokinetic parameter *volume of distribution* is a proportionality constant that relates drug concentration in a reference fluid, typically plasma, to the amount of drug distributed throughout the body.

$$\text{Volume of distribution } (V_D) = \frac{\text{Amount of drug in body } (D_B)}{\text{Drug concentration } (C_p)} \quad (8)$$

Drugs that distribute widely to tissues will have large volumes of distribution and low plasma concentrations relative to the dose administered, whereas drugs that are highly bound to plasma proteins (eg, warfarin, phenylbutazone) or do not readily enter cells (eg, amikacin) will have low volumes of distribution and high plasma concentrations relative to the administered dose.

Øie and Tozer⁵ have developed a physiological model for expression of the apparent volume of distribution, which takes into account the extracellular water, including plasma- and protein-binding of the drug in both plasma and tissue. For an average 70-kg male, total body water is about 42 L, of which 3 L is plasma and 12 L is extracellular fluid space. Moreover, 55–60% of the albumin in the extracellular space is found outside of plasma. Thus, for drugs that are largely bound to albumin, the apparent volume of distribution can be expressed as

$$V_D = 7 + 8f_u + V_T \left[\frac{f_u}{f_{uT}} \right] \quad (9)$$

where f_u is the fraction of the drug in plasma that is unbound (often referred to as the *free fraction*), f_{uT} is the free fraction of drug in tissue, and V_T is the volume of intracellular tissue water. Equation 9 can be simplified further to

$$V_D = 7 + 8f_u + 27 \left[\frac{f_u}{f_{uT}} \right] \quad (10)$$

This model has been extremely useful in predicting the magnitude of changes in the apparent volume of distribution due to alterations in (1) plasma protein binding, (2) tissue protein binding, and (3) the volume of extracellular and intracellular fluid. For example, if a drug distributes into extracellular fluid but not intracellular fluid, the apparent volume of distribution can be expressed as

$$V_D = 7 + 8f_u \quad (11)$$

and will vary between 7 and 15 L, depending upon the extent of plasma protein binding to albumin. For such a compound, with a relatively small volume of distribution, alterations in the plasma protein binding will not produce proportional changes in the apparent volume of distribution. Indeed, as reported by Williams et al,⁶ the free fraction of tolbutamide in plasma increases in patients with cirrhosis by 28%, from 0.068 to 0.087, yet the apparent volume of distribution increases less than 10%, from 0.15 to 0.164 L/kg. Conversely, drugs with a volume of distribution greater than total body water indicate drug distribution and binding to tissue proteins and other cellular components. Such compounds also may be bound highly to plasma proteins. With drugs having a large volume of distribution (>50–100 L), the contribution of plasma and extracellular water space can be ignored, and Equation 3 simplifies to

$$V_D = 27 \left[\frac{f_u}{f_{uT}} \right] \quad (12)$$

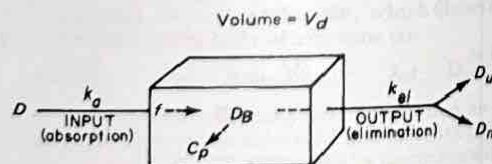


Figure 58-7. The open one-compartment pharmacokinetic model. The amount of the drug dose (D) that enters the body is D_B ; in the case of intravenous injection, this is the entire dose, whereas in the case of extravascular administration, some fraction of the dose (F) is absorbed with a rate constant of k_a . The compartment has an apparent volume of distribution (V_D) into which drug distributes instantaneously to achieve a concentration of C_p . Drug is eliminated from the compartment with a rate constant k_{el} . D_u is the amount excreted into urine, feces, bile, expired air, sweat, milk, etc; D_m is the amount of drug metabolized.

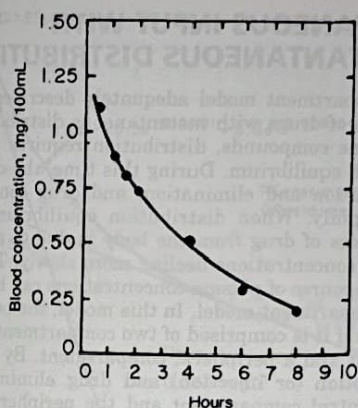


Figure 58-8. Elimination curve of average blood levels of theophylline in 11 human subjects after intravenous administration of 0.5 g aminophylline per 70 kg to each. (Data from Truitt EB Jr, et al. *J Pharmacol Exp Ther* 1950; 100:309.)

Changes in the plasma or plasma-free fraction will produce proportional changes in the apparent volume of distribution. For example, a twofold increase in the free fraction of drug in tissue, f_{uT} , will decrease the apparent volume of distribution by twofold. Less drug will be distributed to tissue, reflected by an increase in plasma concentrations. The volume necessary to account for the total amount of drug in the body will appear to have been decreased.

Once a drug is in the vascular system, it is transported by the blood to tissues where it can be eliminated from the circulation by distribution into tissue, metabolism by the tissue, or excretion from the tissue (see Fig 58-4). All of these processes lower the plasma concentration of drug. Each separate process may be described by a first-order rate constant, and the overall change in the plasma concentration is the net effect of all of these parallel, competing, first-order processes.

Intravenous injection of a drug that has nearly instantaneous distribution and first-order elimination can be described by an open one-compartment model (Fig 58-7). The body behaves as if it were a homogeneous compartment. In the one-compartment model, distribution is very rapid and can be considered instantaneous and is, therefore, ignored. After intravenous administration the plasma concentration declines exponentially according to

$$C = C_0 e^{-\lambda t} \quad (13)$$

where C_0 is the initial concentration and λ is the overall elimination rate constant. Such an exponential elimination of theophylline given intravenously, is shown in Figure 58-8.⁷ According to Equation 13, if the data of Figure 58-8 are plotted on semilog paper, a straight line should result, and such a plot is shown in Figure 58-9. Several derived data can be obtained from a plot of log concentration versus time. Extrapolation to zero time (ie, the y-intercept) gives an estimated theoretical concentration in plasma at time zero, from which the apparent volume of distribution (V_D) can be estimated by simply dividing the dose by C_0 . It is a theoretical concentration because neither the injection nor distribution are actually instantaneous.

The *half-life* of a drug is the time required to reduce the amount of drug in the body or the plasma concentration by 50%. For a first-order process, the half-life is constant and is independent of the starting value of the amount of drug in the body (or plasma concentration). The plasma half-life, $t_{1/2}$, can be determined directly from the graph or from the elimination rate constant, λ or k_{el} , by means of the relationship

$$t_{1/2} = \frac{0.693}{\lambda} = \frac{0.693}{k_{el}} \quad (14)$$

As shown, the half-life is related inversely to the elimination rate constant. When the elimination rate constant, k_{el} , is determined from the slope of the concentration versus time plot, one must keep in mind that the data need to be plotted on a semilog scale. From Figure 58-9, the k_{el} is determined to be 0.22 hr^{-1} . This is the instantaneous rate constant and indicates that 22% of the theophylline in the body is lost per hour. The rate constant for elimination (see Fig 58-7) is shown without reference to the route of elimination. It must be recognized that k_{el} represents the overall elimination by all competing, parallel pathways and is equal to the sum of the rate constants that define the various simultaneous (ie, parallel) contributory processes (eg, metabolism, renal excretion, or biliary secretion). Thus, the overall rate constant, $k_{el} = k_1 + k_2 + k_3 + \dots + k_N$, where $k_1 + k_2 + k_3 + \dots + k_N$ are the rate constants of the separate contributory processes.

Half-life is a clinically useful pharmacokinetic parameter in that it indicates when the next dose of a drug needs to be administered and is therefore helpful in designing an optimal dosing regimen. The half-life also is useful in determining

1. The fluctuation of plasma concentrations between doses;
2. The time required to reach steady-state equilibrium after beginning continuous drug administration; and
3. The persistence of drug in the system once drug administration has ceased.

Under some conditions, it is not possible to obtain plasma concentration data over sufficient time to obtain accurate estimates of the half-life for designing dosage regimens. The elimination rate constant, and hence the half-life, may be estimated from the excretion rate of unchanged drug. Because the first-order elimination rate constant is independent of the amount of drug in the body, the instantaneous excretion rate, dD_u/dt is directly proportional to the total amount of drug in the body.

$$\frac{dD_u}{dt} = k_e D_B \quad (15)$$

where D_B and D_u are the amount of drug in the body at time zero and the amount of drug excreted in the urine, respectively, and k_e is the urinary excretion rate constant. A plot of $\log dD_u/dt$ versus time yields a straight line with slope of $-k_e/2.3$. One also may estimate the half-life from urinary excretion data using the cumulative amount of drug excreted (sigma-minus) method. Using this approach

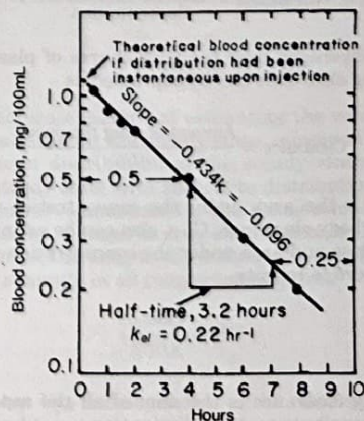


Figure 58-9. Semilog plot of the elimination curve in Figure 58-8. Note the log scale of the ordinate.

$$D_u = D_B \frac{k_u}{k_{el}} (1 - e^{-k_{el}t}) \quad (16)$$

k_u/k_{el} represents the fraction of the drug in the body that eventually is excreted in urine as unchanged drug and D_u^∞ represents the total amount of unchanged drug excreted in urine. A plot of the log of the amount of drug remaining to be excreted ($D_u^\infty - D_u$) versus time yields a slope equal to $-k_{el}/2.303$. This method requires collecting urine for at least 6 to 8 half-lives to achieve an accurate measure of D_u^∞ .

For a drug eliminated by first-order kinetics, the elimination rate constant, k_{el} , can be expressed as the fraction of the volume of distribution that is presented to an eliminating organ and cleared of drug per unit time (clearance) relative to the total volume of distribution, V_D . Thus, k_{el} represents the fractional removal rate of drug from the system, and the elimination rate constant can be expressed in terms of clearance and volume of distribution:

$$\frac{\text{Clearance}}{V_D} = \text{Elimination-rate constant } (k_{el}) \quad (17)$$

As written in Equation 17, the elimination rate constant (and hence, plasma half-life) is a dependent parameter that, by itself, is not always the most reliable indicator of drug removal from the body. Disease or altered physiology (eg, aging, pregnancy) can alter protein binding, thereby affecting the apparent volume of distribution, or alter organ function, thereby affecting clearance, but these changes may not be reflected by changes in the half-life. For example, the volume of distribution may be altered due to changes in tissue or plasma protein binding, independent of specific organ function (clearance). In this instance, the half-life of a drug may be changed, but clearance could remain constant. Although a useful parameter, one must always bear in mind that half-life is a dependent or derived parameter that does not reliably reflect irreversible removal of drug from the body. A more accurate way to express half-life (Equation 14) therefore is

$$t_{1/2} = 0.693 \frac{V_D}{CL} \quad (18)$$

Clearance is the most useful pharmacokinetic indicator of irreversible loss of drug from the body and refers to a volume of fluid from which drug appears to be removed in a given amount of time. Clearance also can be expressed as the quotient of overall rate of elimination of a drug relative to the drug concentration at a particular organ of elimination,

$$\text{Clearance} = \frac{\text{Rate of elimination}}{\text{Concentration}} \quad (19)$$

and, if time-averaged over the time course of plasma concentrations, drug clearance can be expressed as

$$\text{Clearance} = \frac{\text{Amount of drug removed}}{AUC} \quad (20)$$

where AUC is the area under the concentration-versus-time curve. Total body clearance, CL_T , also can be estimated as the quotient of dose and area under the concentration-versus-time curve from zero to infinity,

$$CL_T = \frac{\text{Dose}_{IV}}{AUC_0^\infty} \quad (21)$$

Total body clearance is the sum of all the separate clearances that contribute to drug elimination

$$CL_T = CL_{RENAL} + CL_{HEPATIC} + CL_{OTHER} \quad (22)$$

INSTANTANEOUS INPUT WITH NONINSTANTANEOUS DISTRIBUTION

The one-compartment model adequately describes the pharmacokinetics of drugs with instantaneous distribution. However, for some compounds, distribution requires some finite time to reach equilibrium. During this time, the drug undergoes distribution and elimination, and drug concentrations decrease rapidly. When distribution equilibrium is established, the loss of drug from the body is due to elimination, and plasma concentrations decline more slowly. This biexponential time-course of plasma concentrations can be described by a two-compartment model. In this model, the body appears to behave as if it is comprised of two compartments, a central compartment and a peripheral compartment. By convention, drug absorption (or injection) and drug elimination occur from the central compartment and the peripheral compartment is closed and communicates with the environment only through the central compartment (Fig 58-10). The movement of drug between compartments following rapid intravenous injection with elimination from the central compartment can be described by

$$\frac{dD_1}{dt} = k_{21}D_2 - k_{12}D_1 - k_{10}D_1$$

and

$$\frac{dD_2}{dt} = k_{12}D_1 - k_{21}D_2 \quad (23)$$

where D_2 is the amount of drug in the peripheral or tissue compartment, D_1 is the amount of drug in the central compartment, k_{21} and k_{12} are the apparent first-order intercompartmental distribution rate constants, and k_{10} or k_{el} is the apparent first-order elimination rate constant from Compartment 1.

After intravenous injection of a drug that obeys two-compartment pharmacokinetics, the plasma concentration de-

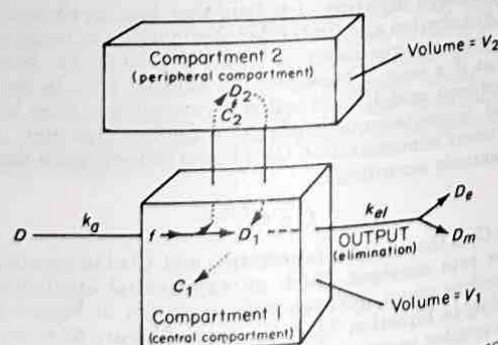


Figure 58-10. Diagram of open two-compartment pharmacokinetic model. The amount of dose that enters the body for an intravenous injection is the entire dose, and administration is instantaneous. The amount of dose absorbed from an extravascular dose is $F \cdot D$, where F is the fraction of dose absorbed with a rate constant, k_a . Some of the absorbed drug enters Compartment 2 with a first-order rate constant of k_{12} and is returned to Compartment 1 with a first-order rate constant of k_{21} . D_1 is the amount of drug in Compartment 1, and D_2 in Compartment 2; C_1 and C_2 are the respective concentrations in Compartments 1 and 2 ($C_1 = C_p$). Drug is eliminated from Compartment 1 with a first-order rate constant, k_{el} , which, however, is obscured by the lag in transfer of drug from Compartment 2 to Compartment 1. D_u is the amount excreted into urine, feces, expired air, sweat, milk, etc; D_m is the amount of drug metabolized. The relative volumes V_1 and V_2 may vary greatly, V_1 sometimes being the larger and other times the smaller.

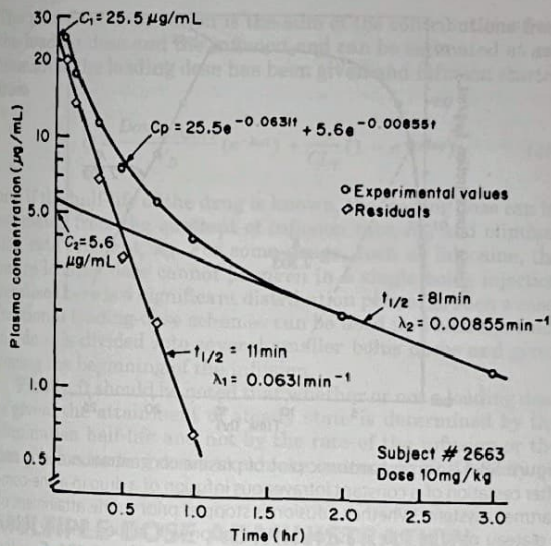


Figure 58-11. Resolution of the plasma concentration curve for pralidoxime into its distribution and elimination components after intravenous administration. Note that plasma concentration is plotted on a logarithmic scale. The time constant for the elimination phase is determined from the slope, $-0.434 \lambda_2$; it is a hybrid constant and λ_2 is not the same as k_{el} (see text). Likewise, the time constant for distribution, λ_1 , is obtained from the slope, $-0.434 \lambda_1$, of the distribution line; λ_1 is also a hybrid constant. (From Gibaldi M, Perrier D. *Pharmacokinetics*, 2nd ed. New York: Dekker, 1982.)

clines in a complex biexponential fashion. When plotted on semilog graph paper, the separate processes of distribution and elimination can be identified by the method of residuals (Fig 58-11).⁸ Figure 58-11 shows such a resolution of the biexponential decay into the two components of distribution and elimination. From the slopes and intercepts of the residuals, the plasma concentration, C , at any time, t , can be described as the sum of two exponentials, namely

$$C = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} \quad (24)$$

where

$$C_1 = \frac{\text{Dose}(\lambda_1 - k_{21})}{V_1(\lambda_1 - \lambda_2)} \quad (25)$$

and

$$C_2 = \frac{\text{Dose}(k_{21} - \lambda_2)}{V_1(\lambda_1 - \lambda_2)} \quad (26)$$

Distribution is more rapid than elimination, such that at some point, the first term in Equation 24, $C_1 e^{-\lambda_1 t}$ approaches zero and the biological half-life can be determined from the slope of the terminal phase

$$t_{1/2} = \frac{0.693}{\lambda_2} \quad (27)$$

C_1 , C_2 , λ_1 , and λ_2 are hybrid constants, representing the intercepts, C_1 , C_2 , and slopes, λ_1 , λ_2 , of the two exponential phases, which can be obtained by computer-fitting the biexponential data. The zero-time intercept and the volume of the central compartment, V_1 , and the actual pharmacokinetic parameters k_{12} , k_{21} , and k_{el} can be derived from the hybrid rate constants using the following relationships. At time $t = 0$

$$C_0 = C_1 + C_2; V_1 = \frac{\text{Dose}}{C_1 + C_2} \quad (28)$$

The hybrid rate constants, λ_1 and λ_2 , can be defined using the following two equations:

$$\lambda_1 \lambda_2 = k_{21} k_{el} \quad (29)$$

$$\lambda_1 + \lambda_2 = k_{12} + k_{21} + k_{el} \quad (30)$$

Thus

$$k_{el} = \frac{\lambda_1 \lambda_2}{k_{21}} \quad (31)$$

$$k_{21} = \frac{C_1 \lambda_2 + C_2 \lambda_1}{\lambda_1 - \lambda_2} \quad (32)$$

$$k_{12} = \lambda_1 + \lambda_2 - k_{21} - k_{el} \quad (33)$$

The reader is referred to Gibaldi and Perrier (see *Bibliography*) for a more in-depth derivation of these expressions. The slope of the final phase of biexponential disposition, λ_2 , can be related to the elimination-rate constant, k_{el} , by

$$\lambda_2 = f_C k_{el} \quad (34)$$

where f_C is the fraction of the drug that is in the central compartment after distribution equilibrium has been achieved. After distribution, the fraction of the drug in the central compartment is a constant.

$$f_C = \frac{k_{21} - \lambda_2}{k_{21} + k_{12} - \lambda_2} \quad (35)$$

The terminal disposition constant, λ_2 , reflects disposition from the entire body and is a function of distribution and elimination. The rate constant, k_{el} , represents only elimination from the theoretical central compartment.

The volume of distribution, V_D , can be determined in a two-compartment system; however, the estimation is complicated by the noninstantaneous nature of the distribution phase between the two compartments and results in the apparent volume of distribution being time-dependent. From Equation 18, it can be seen that the volume of distribution of the central compartment, V_1 , can be obtained following administration of an intravenous dose, D_{IV} , of drug from

$$V_1 = \frac{D_{IV}}{C_1 + C_2} \quad (36)$$

Clearance can be calculated from the product of k_{el} and V_1 , and the volume of the central compartment can be expressed as

$$V_1 = \frac{D_{IV}}{k_{10} \int_0^\infty C dt} \quad (37)$$

The most accurate method of estimating the volume of distribution is to estimate the steady-state volume of distribution. The volume of distribution at the steady state, V_{SS} , represents the steady state with respect to distribution of the drug from the central compartment to the tissue compartments and is not altered by changes in drug elimination or clearance. The total amount of the drug in the body at the steady state is the sum of the amounts in all compartments, thus

$$V_{SS} = V_1 + \frac{k_{12}}{k_{21}} V_1 \quad (38)$$

Notice that V_{SS} is independent of the elimination rate constant, k_{el} , and λ_2 .

The volume of distribution by area, V_B , is an alternate method of estimating the apparent volume of distribution and relies on

the assumption that the plasma and the amount of drug in the body decline in parallel during the postdistributive phase.

$$V_p = \frac{V_1 k_{el}}{\lambda_2} \quad (39)$$

The least accurate method of estimating the volume of distribution for a drug that follows biexponential elimination kinetics is by extrapolation, V_{EXTRAP} , because changes in distribution can alter the estimation of the hybrid intercept, C_2 .

$$V_{EXTRAP} = \frac{D_{IV}}{C_2} \quad (40)$$

Distribution to various tissues depends upon both blood flow to that tissue and the rate of uptake (effective partition coefficient) into a particular tissue and its cells. The overall pattern of drug distribution is governed by both tissue perfusion and diffusion of drug within tissues. Tissues with the highest blood flow, such as liver, kidney, and brain, equilibrate more rapidly than tissues that are perfused less well, such as skin and fat. Once in the tissue vasculature, drug distribution into tissue is controlled largely by diffusional barriers of cell membranes. Rowland and Tozer (see *Bibliography*) present a useful expression for the first-order rate constant for distribution of drug into tissue.

$$k_{TISSUE} = \frac{(Q/V_{TISSUE})}{k_{PARTITION}} \quad (41)$$

where $k_{PARTITION}$ is the equilibrium distribution ratio of tissue and venous drug concentration, Q is tissue blood flow, V_{TISSUE} is the tissue volume, and the quotient of Q and V_{TISSUE} is the tissue perfusion rate. The time to reach tissue equilibrium is the reciprocal of Equation 41. For a poorly perfused tissue such as fat, the $k_{PARTITION}$ may be quite high and the Q/V_{TISSUE} low, resulting in a long time to reach tissue equilibrium. Even for highly perfused tissues, such as the brain, the distribution of some drugs may be quite variable and will depend upon diffusion across cell membranes. In this case, distribution is said to be diffusion-rate-limited and will depend upon both the oil-to-water partition coefficient and the degree of ionization at physiological pH.

For most drugs, distribution usually occurs more rapidly than elimination, resulting in complete distribution before most of the drug has been eliminated. For some drugs, once injected, distribution is so rapid that the overall plasma-concentration time-course represents elimination (see Fig 58-7). Thus, both administration and distribution appear to be instantaneous, and the pharmacokinetics can be modeled by the simplest one-compartment model (see Fig 58-7). For such a drug, the volume of distribution can be calculated as the quotient of the intravenous dose and the extrapolated plasma concentration at time zero, C_0 .

CONTINUOUS INPUT

It is sometimes desirable to administer a drug continuously to maintain constant plasma concentration. This is often the case for drugs with very rapid elimination or for those that have a low therapeutic index. Continuous input commonly is thought of in terms of intravenous infusion; however, sustained-release oral dosage forms and delivery of drugs through the skin from patches also are examples of continuous input, and the pharmacokinetics of drug administration is similar for all systems with continuous input.

With constant intravenous infusion, the plasma concentration rises in a logarithmic fashion and eventually reaches a plateau (Fig 58-12).⁸ The time to reach the plateau or steady-state concentration is determined by the elimination rate constant. The rate of change of drug in the body (D_B) during a constant rate infusion (R_0) is the difference between the zero-order infusion rate and the first-order elimination rate.

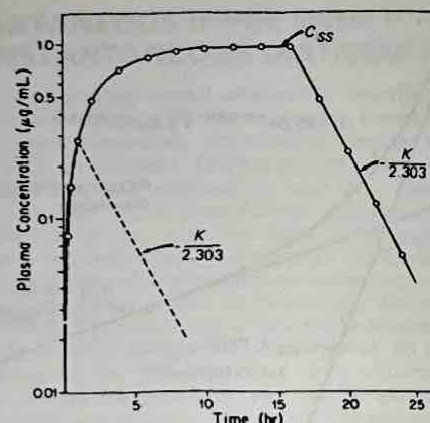


Figure 58-12. Semilogarithmic plot of plasma concentration during and after cessation of a constant intravenous infusion of a drug in a one-compartment system. Whether infusion is stopped prior to the attainment of a plateau or after, the plasma concentration will fall log-linearly with a slope of $-0.434k_{el}$. In the figure, K is k_{el} and $1/2.303 = 0.434$. C_{ss} is the steady-state concentration, C_p^{ss} . (From Gibaldi M, Perrier D. *Pharmacokinetics*, 2nd ed. New York: Dekker, 1982.)

$$\frac{dD_B}{dt} = R_0 - (k_{el} \cdot D_B) \quad (42)$$

The plasma concentration (C) at any time during the constant infusion is

$$C = \frac{R_0}{CL_T} (1 - e^{-k_{el} t_{inf}}) \quad (43)$$

where t_{inf} equals the time of the infusion. As the time of the infusion increases, the exponential expression approaches zero, and the concentration approaches steady state. At steady state, the rate of infusion is equal to the rate of elimination, and the simplified expression can be expressed as

$$C_{ss} = \frac{R_0}{CL_T} \quad (44)$$

The fraction of the steady state that is achieved in some time, t_{inf} , after the start of the infusion can be calculated as

$$\frac{C}{C_{ss}} = (1 - e^{-k_{el} t_{inf}}) \quad (45)$$

and can be expressed in terms of half-lives as

$$\frac{C}{C_{ss}} = (1 - 2^{-n}) \quad (46)$$

where n is the ratio of infusion time and half-life. For example, when the infusion time equals three half-lives ($n = 3$), the concentration is at 87.5% of the steady state, and when the infusion has lasted for four half-lives ($n = 4$), the concentration has achieved 93.75% of the steady state. Theoretically, one never reaches steady-state conditions because this is an exponential process; however, for clinical purposes one can assume, with little error, that steady-state concentrations are achieved within four to five half-lives.

If a drug has a relatively long half-life and the therapeutic situation demands rapid attainment of therapeutic plasma concentrations, it is sometimes desirable to give a loading dose at the beginning of the constant-rate infusion. The loading dose should approximate the amount of drug in the body at steady state. If the apparent volume of distribution and target concentration is known, the loading dose can be calculated simply as

$$\text{Dose}_{LOADING} = (\text{Target concentration})(V_D) \quad (47)$$

The plasma concentration is the sum of the contributions from the loading dose and the infusion and can be estimated at any time after the loading dose has been given and infusion started from

$$C = \frac{\text{Dose}_{\text{LOADING}}}{V_D} (e^{-k_{el}t}) + \frac{R_0}{CL_T} (1 - e^{-k_{el}t_{inf}}) \quad (48)$$

and if the half-life of the drug is known, the loading dose can be estimated from the quotient of infusion rate, R_0 , and elimination rate constant, k_{el} . For some drugs, such as lidocaine, the entire loading dose cannot be given in a single bolus injection because there is a significant distribution phase. In such a case, fractional loading-dose schemes can be used in which the loading dose is divided into several smaller bolus doses and given during the beginning of the infusion.

Finally, it should be noted that whether or not a loading dose is given, the attainment of steady state is determined by the elimination half-life and not by the rate of the infusion or the use of bolus loading doses to achieve concentrations rapidly.

MULTIPLE-DOSE ADMINISTRATION

Continuous administration of a drug is often impractical, and multiple-dose regimens are used to maintain the concentration of a drug within an acceptable range that minimizes the development of toxicity and avoids loss of efficacy. Usually, the dose of a drug is administered with a constant dose interval, referred to as τ . Some features of a multiple dosage scheme are shown in Figure 58-13. The drug is administered at a fixed dose and a fixed interval. Each successive dose is administered before the previous dose has been eliminated entirely, and thus drug accumulation occurs. As with the constant intravenous infusion, the time to reach a steady-state fluctuation depends upon the elimination half-life and not on the size of the dose or the dosing interval. In Figure 58-13, the dose, D , is administered at a dosing interval equal to the half-life. After the first dose is given, the amount of drug in the body is equal to that dose. When the next dose is given, the amount of drug in the body is

equal to $D + 0.5D$. At the end of each dose interval, the total amount of drug in the body is half of the postinjection peak and is the sum of the amount remaining from all of the previous doses. The maximum, $C_{\text{MAX,SS}}$, and minimum, $C_{\text{MIN,SS}}$, concentrations at steady state are described by

$$C_{\text{MAX,SS}} = \frac{\text{Dose}/V_D}{(1 - e^{-k_{el}\tau})} \quad (49)$$

and

$$C_{\text{MIN,SS}} = C_{\text{MAX,SS}} e^{-k_{el}\tau} \quad (50)$$

The concentration at the midpoint of a dosing interval at the steady state is a time-averaged concentration, C_{AV} , over the entire dosing interval and is described by

$$C_{\text{AV}} = \frac{D_{IV}}{V_D k_{el} \tau} = \frac{1.44 t_{1/2} D_{IV}}{\tau} \quad (51)$$

NONCOMPARTMENTAL ANALYSIS FOLLOWING INSTANTANEOUS INPUT

There are numerous disadvantages associated with viewing drug disposition from a compartmental perspective, not the least of which is the lack of physiological relevance of such models. Noncompartmental models have been developed and are generally the preferred method for assessing overall drug disposition, in part because parameters such as volume of distribution and clearance can be calculated directly from the data, without computer fitting. Moreover, parameters estimated by these methods generally are less sensitive to variability in the data. Noncompartmental methods characterize drug disposition using time- and concentration-averaged parameters and have been described by Jusko.⁹ This analysis also is known as nonparametric analysis and assumes that all processes are first-order and that the parameters of the model reflect steady-state behavior. A primary tool used in this methodology is that of statistical moments.¹⁰

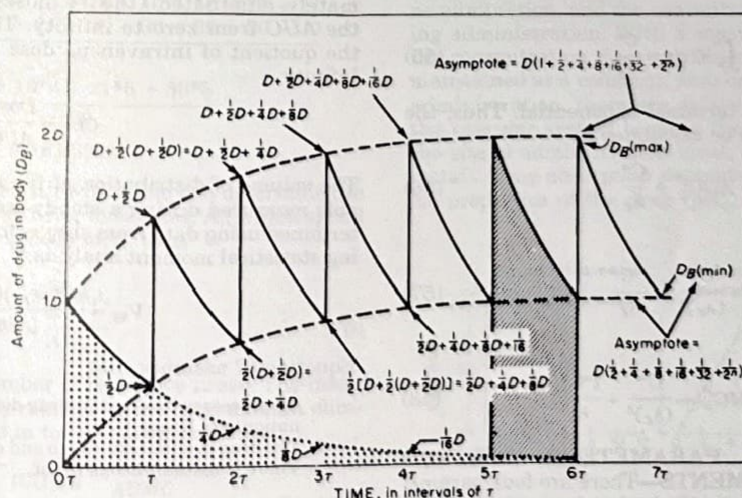


Figure 58-13. The accumulation of drug in the body during a regimen of multiple dosing. Dose, D , is administered intravenously at intervals, τ , equal to the half-life, $t_{1/2}$. Thus, after each dose, the amount in the body, D_B , has decreased to half the previous peak amount at the time each dose is administered. When the cumulated amount in the body after injection reaches $2D$, the body content will fluctuate from $2D$ to $1D$ during each dose interval thereafter. Approximately five half-lives are required before this leveling off (plateau) of the body content occurs. The stippled area is the area under the elimination curve of a single injection, if no second dose had been given. The cross-hatched area is the area under the curve during a single-dose interval at steady state. The two areas are equal.

STATISTICAL MOMENTS—The use of statistical moments in the analysis of the time-course of drug concentrations is especially useful because it frees the investigator from the use of such models as the compartmental, which often are derived empirically and do not represent physiological events.

The time-course of drug concentration in blood generally can be viewed as a statistical distribution curve and described in a similar manner as any other array of data. A moment is simply a mathematical description of a discrete distribution of data. In the field of statistics, for example, the sample size (n), mean, and variance are the zero (M_0), first (M_1) and second (M_2) moments, respectively, for an array of data. In physics, for example, weight, center of mass, and moment of inertia represent (M_0), (M_1), and (M_2), respectively.

In statistics, the mean of a population is estimated by the sample mean. Similarly, in pharmacokinetics one may calculate estimates of the true function that describes the drug concentration versus time using statistical moments. Assume the existence of a theoretical relationship for $C(t)$ as a function of time. The nonnormalized moments, S_r , where $r = 0, 1, 2, \dots, m^{\text{th}}$ moment, about the origin are calculated as

$$S_r = \int_0^\infty t^r C(t) dt \quad (r = 0, 1, 2, \dots, m) \quad (52)$$

Hence

$$S_0 = \int_0^\infty C(t) dt = AUC \quad (53)$$

$$S_1 = \int_0^\infty t C(t) dt = AUMC \quad (54)$$

where $AUMC$ is the area under the $C \cdot t$ versus time curve, whereas S_0 and S_1 are the zero and first nonnormalized moments, respectively. These two parameters, AUC and $AUMC$, are derived from the drug concentration versus time data and are used to calculate the pharmacokinetic parameters of interest.

The use of noncompartmental methods requires a means of determining the AUC . While several methods are available for such determinations, the simplest is the use of the trapezoidal rule.¹¹ This permits calculation of the AUC or the $AUMC$ from zero to the time of the last sample (t^n). However, it generally is necessary to determine the area from zero to infinity. If one assumes that there is log-linear decline from t^n to infinity, then

$$AUC_\infty^n = \int_0^\infty C dt = \frac{C^n}{\lambda_z} \quad (55)$$

where λ_z is the slope of the terminal exponential. Thus, the AUC from zero to infinity can be calculated as

$$AUC_0^\infty = AUC_0^n + \frac{C^n}{\lambda_z} \quad (56)$$

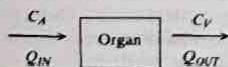
for the $AUMC$

$$AUMC_\infty^n = \frac{C^n}{(\lambda_z)^2} + \frac{t^n C^n}{\lambda_z} \quad (57)$$

and

$$AUMC_0^\infty = AUMC_\infty^n + \frac{C^n}{(\lambda_z)^2} + \frac{t^n C^n}{\lambda_z} \quad (58)$$

PHARMACOKINETIC PARAMETERS DERIVED FROM STATISTICAL MOMENTS—There are four parameters of primary interest that are derived using statistical moments, the most important of which is clearance. A conceptual consideration of clearance is provided by considering an organ through which blood containing a drug flows.



where Q_{IN} , Q_{OUT} , C_A , and C_V are the blood flow in and out and the concentration of the drug in arterial and venous blood, respectively. If $C_V < C_A$, the organ is capable of elimination and is referred to as a clearing organ, or an organ of elimination. The elimination of a drug can be described using mass balance considerations:

$$\text{Rate of the drug entering the organ} = QC_A \quad (59)$$

$$\text{Rate of the drug leaving the organ} = QC_V \quad (60)$$

Rate of elimination of the drug

$$= QC_A - QC_V = Q(C_A - C_V) \quad (61)$$

The ratio of the rate of drug elimination and the rate at which the drug enters the organ is defined as the extraction ratio, E .

$$E = \frac{\text{Rate of elimination}}{\text{Rate of entry}} = \frac{Q(C_A - C_V)}{QC_A} = \frac{(C_A - C_V)}{C_A} \quad (62)$$

The extraction ratio is a measure of the efficiency with which an organ eliminates a drug. From this parameter, the organ clearance of a drug can be described as

$$CL_T = QE = \frac{Q(C_A - C_V)}{C_A} \quad (63)$$

Recall that clearance is defined as the volume of blood from which all of the drug would appear to be removed per unit time. By analogy to the definition of organ clearance, one can define the total or systemic clearance as the ratio of overall elimination rate, dX/dt , to drug concentration in blood, C :

$$CL_T = \frac{dX/dt}{C} \quad (64)$$

Integrating from zero to infinity yields

$$CL_T = \frac{\int_0^\infty \frac{dX}{dt} dt}{\int_0^\infty C dt} \quad (65)$$

where the numerator is the total amount of the drug ultimately eliminated (the IV dose) and the denominator is the AUC from zero to infinity. Thus, the total clearance is the quotient of intravenous dose and the AUC from zero to infinity.

$$CL_T = \frac{\text{Dose}_{IV}}{AUC_0^\infty} \quad (66)$$

The volume of distribution at the steady-state, V_{ss} , most reliably measured during a steady-state infusion, now can be determined using data from single-dose experiments and employing statistical moment analysis.¹²

$$V_{ss} = \frac{(\text{Dose}_{IV})(AUMC)}{(AUC)^2} \quad (67)$$

Equation 67 assumes that

1. All processes involved in drug disposition (eg, distribution, elimination) are linear.
2. The drug is administered to and eliminated via the sampling site.
3. There is instantaneous input.

If the drug is administered via a short infusion, the volume of distribution at the steady state can be estimated from

$$V_{ss} = \frac{(R_0 T)(AUMC)}{(AUC)^2} - \frac{R_0 T^2}{2(AUC)} \quad (68)$$

where R_0 is the rate of infusion and T is the duration of the infusion.

Another important pharmacokinetic parameter that can be determined using statistical moment analysis is the *systemic availability*, F , which is a measure of the fraction of the administered dose that reaches the systemic circulation following oral administration. This parameter can be calculated as

$$F = \frac{AUC_{PO} Dose_{IV}}{AUC_{IV} Dose_{PO}} \quad (69)$$

where AUC_{PO} and $Dose_{PO}$ are the oral area under the concentration-versus-time curve and oral dose, respectively.

When administering a drug, the amount administered in terms of gross weight (eg, mg, g, or μ g) often is considered. It is, however, probably more appropriate to focus on *molecules* when considering pharmacokinetic and pharmacodynamic events. Even the administration of a relatively small dose of drug may represent a large number of molecules. Consider the administration of 1 mg of a drug with a molecular weight of 300 daltons. The number of molecules in this dose is approximately 2×10^{18} . Instantaneous administration of the entire dose will result in drug molecules spending various amounts of time in the body. After the intravenous injection of a drug, one can imagine that some of the drug molecules are eliminated immediately, whereas some of the molecules require a longer time to be eliminated, and some molecules even require a very long time to be eliminated. The time spent in the body, for a given molecule, is its residence time. The *mean residence time*, MRT , is the sum of all the residence times divided by the number of molecules. A conceptual understanding of this can be gained from the following example.

Assume a child receives 20 dimes for his birthday and immediately places them in his piggy bank. Over the next month, he periodically removes one or more dimes from the piggy bank to purchase candy. Specifically, 3 days after placing the coins in his bank, he removes 5 dimes, on day 10 he removes 4 dimes, on day 21 he removes 6 dimes, and on day 30 he removes 5 dimes. At the 30th day after placing the coins in his bank, all of the coins have been removed. Hence, the *elimination* of dimes from the bank is complete. The MRT of dimes in the piggy bank is simply the sum of the times that coins spend in the bank divided by the number of dimes placed in the bank:

$$MRT = \frac{3 + 3 + 3 + 3 + 3 + 10 + 10 + 10 + 10 + 21 + 21 + 21 + 21 + 21 + 30 + 30 + 30 + 30 + 30}{20}$$

$$MRT = \frac{3 \cdot 5 + 10 \cdot 4 + 21 \cdot 6 + 30 \cdot 5}{20}$$

$$MRT = 16.55 \text{ days}$$

This provides a relationship with which one can determine the MRT for any given number of drug molecules, A_i , which spend a given amount of time in the body of, t_i , thus

$$MRT = \frac{\sum_{i=1}^n A_i t_i}{A_{TOTAL}} \quad (70)$$

where n equals the total number of residence times. The mean rate of drug leaving the body relative to the total amount eliminated also can be expressed in terms of concentration.

$$MRT = \frac{\int_0^\infty t C(t) dt}{\int_0^\infty C(t) dt} = \frac{AUMC}{AUC} \quad (71)$$

Equation 71 is not a definition of MRT , rather it is the derived expression from which one can calculate MRT when clearance is constant. The mean residence time assumes instantaneous administration, and therefore, it is technically incorrect to calculate the mean residence time following an oral dose using the

quotient of $AUMC_{PO}$ and AUC_{PO} . When calculated in this manner, it often is stated that the MRT is a function of the route of administration. Actually, MRT is *independent* of the route of administration because the mean time that molecules reside in the body is not influenced by the route of administration.¹³ However, the interpretation of the ratio of $AUMC$ and AUC does change as a function of administration because this ratio only yields the MRT when the input is instantaneous.

A better way to express the route dependence of the $AUMC/AUC$ is to refer to this ratio as the *mean transit time*, MTT . The MTT is the average time required for drug molecules to leave a kinetic system after administration. Thus, because an IV bolus assumes instant input,

$$AUMC_{IV}/AUC_{IV} = MRT = MTT_{IV} \quad (72)$$

whereas

$$AUMC_{PO}/AUC_{PO} = MTT_{PO} = MTT_{IV} + MAT$$

$$= MRT + MAT \quad (73)$$

where MAT is the mean absorption time. Thus, for oral absorption, the $AUMC/AUC$ provides an MTT in the kinetic system that is composed of the gastrointestinal (GI) tract and the body. The MRT also can be calculated as the quotient of the V_{SS} and clearance. Finally, one can relate the MRT to the elimination half-life by considering the situation in which a drug displays monoexponential decline. The MRT can be written as

$$MRT = \frac{AUMC}{AUC} = \frac{C_0/\lambda^2}{C_0/\lambda} = \frac{1}{\lambda} \quad (74)$$

and represents the time required for 63.2% of an intravenous dose to be eliminated from the body.

ABSORPTION

If a drug is administered intravenously in a single, rapid injection, the process of absorption is bypassed. The time for this injection is typically so short compared with other pharmacokinetic processes that it is ignored. As previously described for a one-compartment model, peak plasma concentration and distribution equilibrium are achieved instantaneously. This is depicted in Figure 58-14A.¹⁴ In the model for the figure, there is no elimination, and the concentration remains constant following administration. With a constant intravenous infusion (B), the concentration rises rectilinearly so long as the infusion is maintained at a constant, zero-order rate. With other routes of administration, there are delays in the appearance of drug in the vascular system because the drug must be absorbed from the site of administration (oral, intramuscular, subcutaneous, rectal). Drug absorption depends upon both the physicochemical properties of the drug (pK_a , dosage form, partition coefficient,

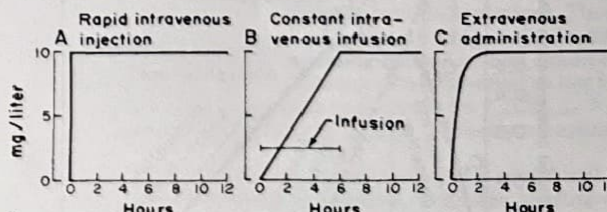


Figure 58-14. Time-concentration curves for injection (A), infusion (B), and extravenous (C) administration of drug in the one-compartment model. The volume of the compartment is 100 L ($V_d = 100$ L); the amount of drug administered in each instance is 1000 mg. Drug elimination has been set to zero, so that the time-concentration curve for each model of administration can be examined without the complication of simultaneous elimination. (Adapted from Bigger JT. *Am J Med* 1975; 58:479.)

cient) and the physiology of the site of absorption (surface area, blood flow). Most drugs are absorbed by simple diffusion, and the kinetics are first-order. Zero-order absorption occurs for some processes that are saturable and for sustained-release dosage forms. Absorption and elimination of a drug are a sequential process, and the rate of change of drug in the body is the difference between the rate of uptake (absorption) and rate of efflux (elimination). For a drug that is absorbed by a first-order process and eliminated by a first-order process, with instantaneous distribution, the rate of change of the amount of drug in the body can be expressed as

$$\frac{dD_B}{dt} = \text{RATE}_{IN} - \text{RATE}_{OUT} \quad (75)$$

For a drug that is absorbed from the GI tract, the rate of change of the amount of drug in the body is

$$\frac{dD_B}{dt} = Fk_a D_{GI} - kD_{BODY} \quad (76)$$

The time-course of absorption and elimination is shown in Figure 58-15.⁷ The plasma concentration at any time t is equal to

$$C = \frac{k_a D_0 F}{V_D(k_a - k_{el})} (e^{-k_{el}t} - e^{-k_a t}) \quad (77)$$

where F is the fraction of the dose, D_0 , that is absorbed from the GI tract and k_{el} and k_a are the first-order rate constants for elimination and absorption, respectively. The time to reach the maximum concentration, t_{MAX} , can be determined from

$$t_{MAX} = \frac{2.3 \log(k_a/k)}{k_a - k} \quad (78)$$

and this time substituted into Equation 77 will determine the maximum concentration, C_{MAX} . The rising phase of the plot (see Fig 58-15) is not log-linear because absorption and elimination are occurring simultaneously. At C_{MAX} , the absorption rate is equal to the elimination rate, and after absorption is complete, the plot declines in a log-linear manner. This log-linear line described by the elimination phase, when extrapolated to zero time, yields a theoretical zero-time concentration. The absorption rate constant, k_a , can be obtained from the difference between the empirical curve and the extrapolated line using the

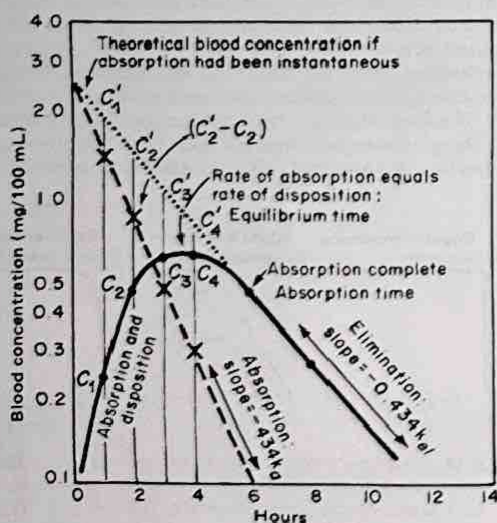


Figure 58-15. Kinetics of absorption and disposition of theophylline in a human subject after oral administration of 0.5 g of aminophylline per 70 kg. Blood concentration is plotted on a log scale. (Data from Truitt EB Jr, et al. *J Pharmacol Exp Ther* 1950; 100:309.)

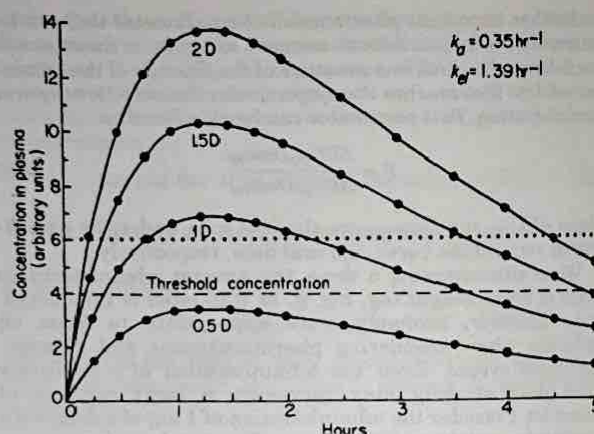


Figure 58-16. The effect of the size of the dose of a drug on the peak concentration, time of peak concentration, and duration of action. The data were calculated from a one-compartment model.

method of residuals. This is a commonly used technique in pharmacokinetics to separate a curve into its component parts and is often referred to as *feathering*, *stripping*, or *peeling* the curve. The reader is referred to Gibaldi and Perrier (see *Bibliography*) for a more comprehensive discussion with examples of the application of this technique.

That the peak concentration should vary with the dose is self-evident from Equations 77 and 78 and from Figure 58-16. The time of the peak concentration is the same for all doses. The time to peak concentration can be affected by both the absorption rate and the elimination rate. In Figure 58-17, the effect of altering the absorption rate on the time to peak concentration is shown. With faster absorption, the time to peak concentration occurs earlier and is higher than with slower absorption. Figure 58-18 shows the effect of altering the elimination rate constant on the t_{MAX} . With a rapid elimination rate (shorter half-life), the peak concentration occurs sooner and is lower than with slower elimination (longer half-life).

The maximum concentration at the steady state for an oral regimen is given by

$$C_{MAX,SS} = \frac{FDose}{V_D} \left(\frac{1}{1 - e^{-k\tau}} \right) e^{-k t_{PEAK}} \quad (79)$$

The minimum concentration at the steady state is

$$C_{MIN,SS} = \frac{k_a FD}{V(k_a - k)} \left(\frac{1}{1 - e^{-k\tau}} \right) e^{-k\tau} \quad (80)$$

To design multiple oral dosing regimens, the equations that describe the maximum and minimum concentrations at the steady state are somewhat unwieldy. In clinical practice, values for k_a are not always readily available, and in such instances the equations for the maximum and minimum concentrations at the steady state following intravenous administration will generally suffice as long as one recalls that because absorption is not instantaneous, the peak concentration and time to peak concentration will not occur immediately.

ORGAN-SPECIFIC CLEARANCE

The total clearance of a drug from the body almost always involves more than one organ of elimination. The anatomy of the human body is such that the clearance from the composite clearing organs occurs in parallel and is, therefore, additive. For example, if a drug is eliminated solely by hepatic and renal elimination, the total clearance, CL_T , of the drug is given as

$$CL_T = CL_H + CL_R \quad (81)$$

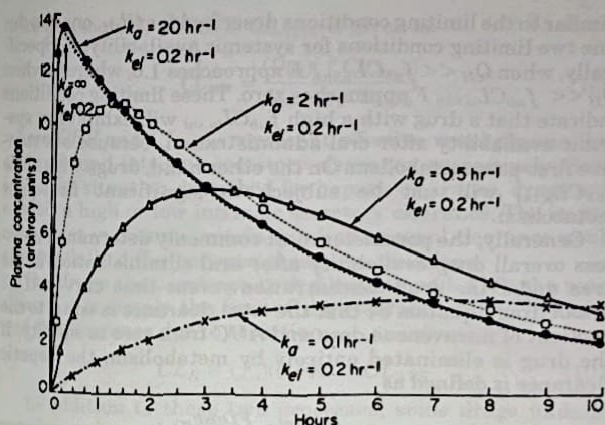


Figure 58-17. The effect of differences in the rate of absorption of drugs on the peak concentration, time of peak concentration, and sojourn in the body. The rate of elimination is the same for all curves. The dotted line ($k_a = \infty$) is approximately what the concentration curve would be, had the drug been given intravenously. The data were calculated from a one-compartment model.

where CL_H and CL_R are the hepatic and renal clearance, respectively. Measurement of the total amount of drug excreted unchanged in urine, D_U , after an intravenous dose, D_{IV} , allows the calculation of the fraction of the drug eliminated renally, F_r , where

$$F_r = \frac{D_U}{D_{IV}} \quad (82)$$

The renal clearance, CL_R , may be determined as the product of total clearance and the fraction of the drug eliminated by the kidney. If the liver is the only other eliminating organ, the hepatic clearance is given by

$$CL_H = CL_T - CL_R \rightarrow (1 - F_r)CL_T \quad (83)$$

One exception to the principle of the additivity of organ clearances is pulmonary drug elimination. This exception is because the lung is in circulatory series with the rest of the body organs such that 100% of cardiac output passes through the lungs. Few drugs exhibit significant elimination by the lungs so that this exception is rarely of concern in the overall assessment of drug elimination.

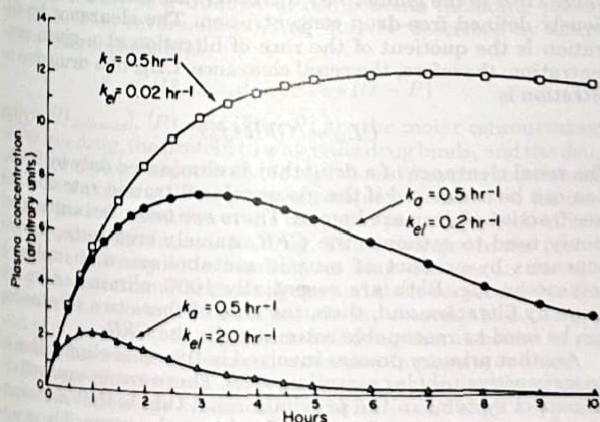


Figure 58-18. The effect of differences in the rate of elimination of drugs on the peak concentration, time of peak concentration, and sojourn in the body. The rate of absorption is the same for all curves. The data were calculated from a one-compartment model.

HEPATIC CLEARANCE—It was shown previously that the ratio of the rate of drug elimination and the rate at which drug enters the organ of elimination is defined as the extraction ratio, E , and is a measure of the efficiency with which an organ eliminates a given drug. One can define the organ clearance of a drug as the product of blood flow to the organ, Q , and the extraction ratio, and for hepatic clearance the equation becomes

$$CL_H = Q_H E \quad (84)$$

where Q_H is the hepatic blood flow. While an initial examination of this simplistic model for hepatic clearance would suggest that CL_H is directly proportional to Q_H , this conclusion is not correct because E varies inversely with Q_H . Specifically, as Q_H increases, E decreases. This observation indicates that a more complex model of hepatic clearance is necessary if quantitative and qualitative predictions of hepatic drug clearance are to be made. In particular, this parameter must be described in terms that are physiologically independent.

Numerous models have been proposed and tested to describe the hepatic clearance of drugs. While a discussion of the advantages and disadvantages of the various models proposed is beyond the scope of this chapter, the *venous equilibrium* model of hepatic clearance has shown substantial utility in the prediction of both pathophysiological and drug-induced changes in hepatic clearance. For a good discussion of the various models of hepatic clearance, see the review by Morgan and Smallwood.¹⁵ In the venous equilibrium model, the hepatic extraction is described by

$$E = \frac{f_{ub}CL_{u,int}}{Q_H + f_{ub}CL_{u,int}} \quad (85)$$

where f_{ub} and $CL_{u,int}$ are the unbound fraction in blood and the unbound intrinsic hepatic clearance, respectively. The unbound intrinsic clearance reflects the ability of the liver to remove drug from blood in the absence of other confounding factors, such as Q_H and f_{ub} . Since it has already been shown that hepatic clearance is the product of Q_H and E

$$CL_H = \frac{(Q_H)(f_{ub}CL_{u,int})}{Q_H + f_{ub}CL_{u,int}} \quad (86)$$

This model for hepatic clearance provides a powerful tool for predicting changes in drug clearance and, subsequently, steady-state drug concentrations, when certain limiting conditions are met. In particular

When $Q_H \gg f_{ub}CL_{u,int}$, CL_H

can be approximated by $f_{ub}CL_{u,int}$ (87)

When $Q_H \ll f_{ub}CL_{u,int}$, CL_H can be approximated by Q_H (88)

Compounds with a high $f_{ub}CL_{u,int}$ are said to exhibit perfusion rate-limited elimination; that is, their elimination rate will be rate-limited by hepatic blood flow. Compounds with a low $f_{ub}CL_{u,int}$ are said to be perfusion rate-independent. These limiting conditions allow us to place many drugs into classifications that exhibit similar pharmacokinetics. For example, agents with an $f_{ub}CL_{u,int} < 0.2$ L/min can be classified as low intrinsic clearance drugs, whereas those with an $f_{ub}CL_{u,int} > 5$ L/min are defined as exhibiting a high intrinsic clearance (Table 58-1).

The venous equilibrium model also serves as a useful tool in the assessment of the impact of changes in protein binding on hepatic clearance. Recall in Equation 87 that for a drug exhibiting a low intrinsic clearance, changes in protein binding will result in proportional changes in hepatic clearance. This type of drug is said to exhibit *restrictive clearance*; that is, only the free (or unbound) drug is available for clearance by the liver. High intrinsic clearance drugs, on the other hand, are said to exhibit *nonrestrictive clearance*.

These relationships provide important insight into the effect of changes in protein-binding on the steady-state concentration

Table 58-1. Examples of Drugs with Low and high Intrinsic Clearances That Are Eliminated Largely by Hepatic Metabolism

LOW $f_{ub}CL_{u,int}$ (<0.2 L/min)	HIGH $f_{ub}CL_{u,int}$ (>5.0 L/min)
Antipyrine	Chlorpromazine
Barbiturates	Encainide
Diazepam	Meperidine
Digitoxin	Metoprolol
Isoniazid	Organonitrates
Phenytoin	Propafenone
Theophylline	Propranolol
Tolbutamide	Tricyclic antidepressants
Warfarin	Verapamil

of drugs. Consider the case of a drug being administered as a constant-rate intravenous infusion. As described previously

$$C_{ss} = R_0/CL_T \rightarrow R_0/CL_H \quad (89)$$

for a drug solely eliminated by the liver. In the case of a drug with a low intrinsic clearance, Equation 89 can be simplified to

$$C_{ss} = R_0/(f_{ub}CL_{u,int}) \quad (90)$$

If f_{ub} were to be increased, for example, by displacement from protein-binding sites, the steady-state concentration would decrease. This may lead one to the conclusion that the infusion rate needs to be increased to maintain the original steady-state concentration. However, one needs to examine the effects of altered physiology on the free or unbound drug concentration, $C_{u,ss}$

$$C_{u,ss} = f_{ub}C_{ss} \rightarrow C_{ss} = C_{u,ss}/f_{ub} \quad (91)$$

substituting for C_{ss} in Equation 90 and solving for $C_{u,ss}$ yields

$$C_{u,ss} = R_0/CL_{u,int} \quad (92)$$

It can be seen that the steady-state concentration of unbound (active) drug is independent of changes in the free fraction, and no dosage adjustment would be necessary. This conclusion also is valid following the oral administration of a drug with a low intrinsic clearance.

In contrast, for a drug with a high intrinsic clearance, a change in f_{ub} will result in a proportional change in the steady-state unbound drug concentration during a constant-rate infusion.

An additional consideration, which must be accounted for with high intrinsic clearance drugs, is the impact of the first-pass effect. When a drug is absorbed from the stomach and small intestine, the venous blood from the sites of absorption enters into the portal venous flow. This results in all of the absorbed drug passing through the liver prior to entry into the systemic circulation. For drugs that exhibit a high intrinsic clearance, the consequence of presystemic hepatic metabolism is a substantial reduction in the systemic availability of the drug when administered orally. This phenomenon explains the marked discrepancy between an oral and an intravenous dose of a given drug required to achieve identical plasma concentrations. For example, the therapeutic dose of propranolol ranges between 1 and 6 mg intravenously, whereas the oral doses necessary to achieve therapeutic effect range from 40 to 200 mg.

The systemic availability, F , of a drug that is absorbed completely from the GI tract after oral administration is the fraction of the absorbed dose that escapes extraction and is given as

$$F = 1 - E \quad (93)$$

Rearranging Equation 85 and substituting for E in Equation 93 yields

$$F = \frac{Q_H}{Q_H + f_{ub}CL_{u,int}} \quad (94)$$

Similar to the limiting conditions described for CL_H , one can define two limiting conditions for systemic availability, F . Specifically, when $Q_H \ll f_{ub}CL_{u,int}$, F approaches zero, whereas when $Q_H \gg f_{ub}CL_{u,int}$, F approaches 1.0. These limiting conditions indicate that a drug with a high $f_{ub}CL_{u,int}$ will exhibit low systemic availability after oral administration, because of extensive first-pass metabolism. On the other hand, drugs with a low $f_{ub}CL_{u,int}$ will not be subject to significant first-pass metabolism.

Generally, the parameter most commonly determined to assess overall drug availability after oral administration is the area under the drug concentration-versus-time curve, AUC . Recall from Equation 67 that the total clearance is equal to the quotient of intravenous dose and AUC from zero to infinity. If the drug is eliminated entirely by metabolism, the hepatic clearance is defined as

$$CL_H = \frac{\text{Dose}_{IV}}{AUC_{IV}} = \frac{F\text{Dose}_{PO}}{AUC_{PO}} \quad (95)$$

Substituting Equation 86 for CL_H and Equation 94 for F yields

$$\frac{(Q_H)(f_{ub}CL_{u,int})}{Q_H + f_{ub}CL_{u,int}} = \left(\frac{\text{Dose}_{PO}}{AUC_{PO}} \right) \left(\frac{Q_H}{Q_H + f_{ub}CL_{u,int}} \right) \quad (96)$$

Simplifying,

$$f_{ub}CL_{u,int} = \text{Dose}_{PO}/AUC_{PO} \quad (97)$$

Thus, for a high intrinsic hepatic clearance drug, the AUC_{PO} is independent of Q_H . Additionally, the steady-state AUC for unbound drug is independent of the free fraction. For a more in-depth discussion of these concepts on hepatic clearance, see the paper by Wilkinson and Shand.¹⁶

RENAL CLEARANCE—Physiologists studied the renal clearance of endogenous and exogenous substances long before the use of clearance concepts became popular in pharmacokinetics. Indeed, the basis for the understanding of drug clearance in pharmacokinetics has its roots in the decades of work by renal physiologists. Moreover, there are significant differences in the complexity of processes involved in hepatic and renal handling of drugs. In the kidney, there are three primary processes (and one minor process) responsible for the renal elimination of drugs, namely filtration, secretion, and reabsorption (and metabolism), respectively. Each of the major processes are affected by common, yet unique, determinants.

The rate of filtration in the kidney for a drug is given as

$$\text{Rate of filtration} = (GFR)(C_u) \quad (98)$$

where GFR is the glomerular filtration rate and C_u is the previously defined free-drug concentration. The clearance by filtration is the quotient of the rate of filtration at a given concentration; therefore, the renal clearance, CL_R , of a drug due to filtration is

$$CL_R = (GFR)(f_u) \quad (99)$$

The renal clearance of a drug that is eliminated only by filtration can be estimated if the glomerular filtration rate and the free fraction of drug are known. There are two substances commonly used to estimate the GFR , namely creatinine, an endogenous by-product of muscle metabolism, and inulin, a polysaccharide. Both are essentially 100% eliminated in the urine by filtration and, thus, the CL_T of these two substances can be used as reasonable estimates for the GFR .

Another primary process involved in the renal elimination of drugs is active tubular secretion, ATS . There are several active-transport systems in the proximal renal tubule that are capable of excreting drugs from the blood into the urine. There appears to be a multiplicity of systems for the ATS of cations and anions. Whenever the renal clearance is greater than the product of the GFR and the free fraction, there must be net tubular secretion in addition to clearance by filtration. The renal clear-

ance due to *ATS*, which is CL_{ATS} , is given as

$$CL_{ATS} = \frac{(Q_{RP})(f_u CL_{u,s,int})}{Q_{RP} + f_u CL_{u,s,int}} \quad (100)$$

where Q_{RP} and $CL_{u,s,int}$ represent effective renal plasma flow and unbound intrinsic secretory clearance, respectively. Similar to the situation described for hepatic clearance, drugs may exhibit a high or low intrinsic secretory clearance. The impact of changes in plasma protein-binding on renal clearance would substantially differ between these two situations.

For drugs that undergo both filtration and *ATS*, the renal clearance is simply the sum of the clearance due to filtration and the clearance due to secretion

$$CL_R = (f_u)(GFR) + CL_{ATS} \quad (101)$$

In addition to these two processes, some drugs undergo tubular reabsorption, whereby some fraction of the drug excreted into the urine by filtration and secretion is reabsorbed into the body. Therefore, the full expression for renal clearance, taking into account all three processes, is given by

$$CL_R = (f_u)(GFR) + CL_{ATS} - F_{TR}((f_u)(GFR) + CL_{ATS})$$

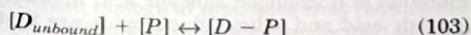
or $CL_R = (1 - F_{TR})((f_u)(GFR) + CL_{ATS}) \quad (102)$

where F_{TR} is the fraction undergoing tubular reabsorption.

These relationships provide the basis for determining the primary mechanisms involved in the renal handling of a given drug. Specifically, determination of the ratio of renal clearance and that of inulin provides a clinically useful means to determine the processes that are primarily responsible for renal excretion. If the ratio is equal to 1, the drug would appear to be filtered exclusively by the kidney. Both *ATS* and *TR* also could be occurring, but at equal rates (an unlikely occurrence). If the ratio of renal clearance to inulin clearance is greater than 1, it is clear that the drug is undergoing net tubular secretion as well as filtration. Similarly, if the ratio is less than 1, the drug must be undergoing net tubular reabsorption.

Assessment of the mechanisms for the renal excretion of specific drugs is important because different factors will alter CL_R . For example, if a drug undergoes net tubular secretion, other drugs secreted by the same transport processes may compete for secretory sites, resulting in an overall decrease in the renal excretion of the drug. Alternatively, if a drug undergoes tubular reabsorption and is a weak acid (eg, salicylate) or a weak base (eg, amphetamine), the renal clearance may be altered by manipulation of the urine pH or urine flow. See the review by Tucker¹⁷ for a description of the methods for calculation of CL_R .

PROTEIN-BINDING—Drugs circulating in the blood may bind reversibly to a number of components including plasma proteins. This reversible binding may be described by simple mass-law relationships.



where $[D_{unbound}]$, $[P]$, and $[D - P]$ are the molar concentrations of the free drug, the protein to which the drug binds, and the drug-protein complex, respectively. It is obvious from this relationship that the amount of drug-protein complex formed is a function both of the concentration of the drug and protein and the affinity between the protein and the drug. Thus, changes in the protein concentration may alter binding, as may changes in the total drug concentration. For most drugs and their respective binding proteins, the concentration of protein far exceeds the concentration of drug, such that the fraction of drug that is bound to protein is independent of drug concentration in plasma or blood.

Because plasma proteins often have a molecular size that restricts their passage across cell membranes and capillary walls, drugs that are bound to plasma proteins are restricted similarly. Thus, plasma protein-binding can have a marked effect on the distribution and elimination of drugs. It is a basic tenet of pharmacology that only the unbound (free) drug is pharmacologically active, because it is assumed that the unbound drug

is able to traverse biological membranes and reach the site of drug action. While there have been few direct tests of this hypothesis, those investigations that have been conducted support the assumption that the free drug is the principal pharmacologically active species.

There are several methods by which drug protein-binding may be described quantitatively, though the most frequent and useful is the free fraction, f_u . The f_u can be determined as

$$f_u = \frac{C_u}{C_u + C_B} = \frac{C_u}{C_T} \quad (104)$$

where C_u is the concentration of unbound or free drug, C_B is the concentration of drug bound to protein, and C_T is the concentration of total drug (bound plus free). Obviously, f_u can range from 0 to 1. This relationship provides a means by which free drug *in vivo* can be calculated if the total concentration and the free fraction are known.

$$C_u = (C_T)(f_u) \quad (105)$$

Recognizing changes in protein-binding is important because it may substantially alter the pharmacokinetics of a drug. The previous section described the impact of protein-binding on clearance, referenced to total drug concentration. Protein-binding changes also may result in alterations in other pharmacokinetic parameters. The volume of distribution at the steady state can be expressed as

$$V_{ss} = V_{blood} + V_{TW} \frac{f_u}{f_{uT}} \quad (106)$$

where V_{TW} is the volume of tissue water and f_{uT} is the free fraction of drug in tissue. From the relationship in Equation 106 (which is analogous to Equation 12, for drugs with a volume of distribution >50 L), it is clear that a decrease in protein-binding (ie, an increase in f_u) will result in an increase in the V_{ss} . The impact of changes in f_u on the half-life of a drug with a large volume of distribution can be assessed from Equation 18 and either Equations 87 or 88. The impact resulting from a change in protein-binding of a drug depends upon the magnitude of such binding alterations on both V_{ss} and CL_T .

The two major drug-binding proteins in plasma are albumin and α^1 -acid glycoprotein (AAG). Albumin is the major protein both in plasma and in the extracellular space outside of plasma and is present in concentrations ranging from 3.5 to 5.5 g/dL in normal, healthy individuals. Albumin is the primary binding protein for acidic drugs, such as salicylate, tolbutamide, or warfarin. Numerous diseases can result in marked reductions in the concentration of albumin, including nephrotic syndrome, severe burns, liver disease, malnutrition, and some chronic inflammatory conditions.¹⁸ Thus, disease is most likely to produce an increase in f_u for those drugs highly bound to albumin.

The substance AAG belongs to the family of *acute-phase reactants*, endogenous substances that are markedly increased in concentration secondary to some type of stress. While normal AAG concentrations range from 80 to 120 mg/dL, concentrations may increase above 300 mg/dL in patients experiencing major stress, such as surgery, trauma, or burns. More-moderate elevations of AAG have been observed in patients following a myocardial infarction or in inflammatory diseases such as Crohn's disease. The increase in AAG concentration results in a decrease in f_u , and AAG is the major binding protein for many basic, lipophilic drugs.

A major source of drug interactions is competition for protein-binding sites. Each albumin molecule contains at least four different drug-binding sites, two of which are the sites where most drugs that bind to albumin interact with the other molecule. If two drugs bind to the same site on a protein, they may compete with each other for binding. Thus, the addition of a drug to the existing therapeutic regimen of a patient may result in displacement of existing bound drug molecules from their protein-binding sites. However, as described in the *Hepatic Clearance* section of this chapter, these types of interactions rarely are clinically significant (ie, these interactions do

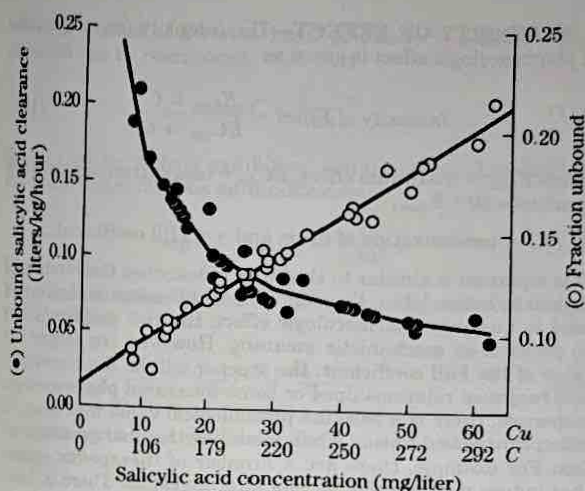


Figure 58-19. The clearance of unbound drug (●), determined under steady-state conditions, and the fraction unbound in plasma (○) vary inversely with each other as the salicylic acid concentration is increased. The corresponding total plasma salicylic acid concentrations are superimposed on the linear scale of the concentration of unbound drug, 1 mg/L = 7.2 micromolar. (Redrawn from Furst DE, Tozer TN, Melmon KL. *Clin Pharmacol Ther* 1979; 26:380.)

STEREOCHEMICAL CONSIDERATIONS

Chiral drugs constitute approximately 60% of the drugs that are currently commercially available. Most of these are marketed as racemic mixtures. These facts obviously indicate the importance of understanding the impact of stereochemistry on both pharmacokinetics and pharmacodynamics. While it has long been appreciated that optical isomers often differ in the potency of pharmacological or toxic effect, it is only recently that significant attention has been paid to the influence of chirality on pharmacokinetic processes involved in absorption, distribution, and elimination. This is primarily due to the previous lack of analytical methodology required to separate drug enantiomers. The recent development of reasonably inexpensive methods for the separation of stereoisomers has led to a more comprehensive assessment of the pharmacokinetics of drugs that are administered as racemic mixtures.

Enantiomers possess identical physical and chemical properties, despite significant differences in spatial configuration. Thus, biological processes that are passive in nature (and thereby depend only upon physical and chemical characteristics of the molecule) do not display selectivity for one isomer over another. In contrast, biological processes that require the interaction of a drug molecule with a macromolecule (such as protein-binding or metabolism) may exhibit stereoselectivity. This knowledge permits some generalizations about when pharmacokinetic processes may differ between enantiomers.

ABSORPTION—Since most drugs are absorbed by passive diffusion, most will not exhibit stereoselective alterations in absorption. Drugs that are absorbed by a carrier-mediated or active process may display such stereoselectivity. Indeed, demonstration of stereoselective absorption would be strong evidence that a drug is absorbed via a carrier-mediated process.

PROTEIN-BINDING—Drug association with plasma proteins requires interaction of a small molecule with a macromolecule, which depends upon the spatial configuration of both components. It should not be surprising, therefore, that plasma protein-binding has been found to exhibit stereoselectivity for some drugs, including disopyramide, ibuprofen, mexilitene, propranolol, and verapamil.

METABOLISM—Biotransformation requires the interaction of a drug with an enzyme, an interaction in which spatial arrangement is critical. Many drugs that undergo metabolism

exhibit stereoselective hepatic clearance. For example, the oral clearance of verapamil (a high intrinsic clearance drug) displays profound stereoselectivity such that the oral clearance ratio of the *R* to *S* isomers is approximately 4.

RENAL EXCRETION—Filtration in the kidney is a passive process; however, if a drug exhibits stereoselective protein-binding, one might anticipate that the drug enantiomers would exhibit differential filtration rates. Active tubular secretion, being an active process, also may demonstrate stereoselectivity for some drugs. Indeed, numerous drugs, including chloroquine, disopyramide, and terbutaline, have been found to be secreted stereoselectively by the kidney. While passive tubular reabsorption would not be expected to show stereoselective effects, active reabsorption may demonstrate these effects as has been shown for certain endogenous substances such as glucose and amino acids.

KINETICS OF PHARMACOLOGIC EFFECT

In addition to considering the relationship between drug concentration and time, proper design of therapeutic regimens often necessitates an understanding of the relationship between concentration and response. These two relationships can be combined to produce a time course of pharmacologic response, and this is referred to as pharmacodynamics. This area of investigation provides important quantitative information regarding the onset, duration, and intensity of pharmacologic effect often in relation to drug concentration. Full characterization of these elements can involve the development of pharmacokinetic-pharmacodynamic models. Modeling the kinetics of effect requires an understanding of the mechanism of pharmacologic action, of which there are many. These include receptor stimulation (eg, β_2 -adrenoceptor agonists), receptor antagonism (eg, H_1 -histamine receptor antagonists), transporter inhibition (probenecid, diuretics), enzyme inhibitors (eg, angiotensin converting enzyme), substrate replacement (eg, thyroxine, testosterone), non-receptor-mediated drug action (eg, chelation) and chemotherapy (eg, antibiotics).

Clinically useful information can often be derived from relatively simplistic models. The relationship between drug response and concentration is usually graded, that is, the rise in concentration results in a progressively increasing magnitude of effect (Fig 58-20). There is essentially always a ceiling, or maximum, to the intensity of effect, such that further increases in drug concentration will not result in additional increases in the intensity of pharmacologic response. In practice, plasma concentrations rarely, if ever, reach the maximum effect because toxicities often develop. Thus, only the linear portion of the concentration-effect curve may be observed. The placement of the curve along the x-axis may vary among compounds, resulting in differences in the potency the drugs. Moreover, the steepness of the curve (the rate at which the intensity of the effect changes as a function of concentration) will vary among drug responses. For some drugs, such as narcotic agonists, a small change in the drug concentration can result in marked changes in drug effect (see Fig 58-20).

There are certain agents that appear to exhibit an all-or-none response. Rather than the typical graded increase in effect as concentration increases, these compounds exhibit a threshold of response that once reached result in the detection in the response. While a given individual's response to the drug is identified by the presence or absence of the effect, the fraction of subjects in a sample population responding will increase as the concentration of drug is increased. A good example of this is seen in the conversion to normal sinus rhythm in patients with atrial fibrillation treated with an antiarrhythmic agent (Fig 58-21). In this instance, there is variation within the patient population in the concentration that must be achieved to convert a specific patient from atrial fibrillation to normal sinus rhythm. Thus, the higher the concentration achieved in a patient, the more likely they are to exhibit the pharmacologic effect.

not significantly alter the free-drug concentration). Hence, while protein-binding interactions are probably the most widely reported drug interaction, they rarely necessitate alterations in drug therapy (citation Benet and Hoerner, CPT).

DOSE- AND TIME-DEPENDENT PHARMACOKINETICS

Up to this point, the processes for drug absorption, distribution, metabolism, and elimination have been assumed to be characterized by first-order rate constants, and the general concepts and equations presented are applicable to a wide variety of drugs, with modification. Moreover, with any of the pharmacokinetic models (compartmental, noncompartmental, or physiological), a number of basic assumptions apply, in particular, the principle of superposition holds. In other words, measurements of the concentration of drug plasma, urinary excretion of unchanged drug, or amount of metabolite recovered in bile increase proportionally with increases in dose. When these measurements or other observations are corrected for dose, the values are identical or superimposable. Thus, the pharmacokinetic parameters V_D , CL_T , and F remain constant with respect to time and with dose or concentration.

But the processes controlling the disposition of drugs are biological and therefore involve processes that are mediated by specialized carriers or enzymes. Under some conditions, these processes can become saturated, and changes in dose may produce nonproportional changes (eg, in concentration, amount of metabolite(s) produced, etc.) Table 58-2 delineates some of the various causes of nonlinear pharmacokinetic behavior.

Nonlinearity is a term applied to all situations in which a semilogarithmic plot of plasma concentration versus time data cannot be resolved completely into log-linear components (ie, first-order processes). There are a wide variety of causes for nonlinearity, such as capacity-limited metabolism, capacity-limited absorption, saturable first-pass metabolism, changes in blood supply to the site of absorption and/or the organ of elimination, low or erratic dissolution or release rates from dosage forms, low solubility of the drug, or drug-induced changes in organ function or body temperature. Nonlinear drug disposition primarily has been determined by measuring the pharmacokinetics at several dosage levels. When a capacity-limited enzyme metabolism is the source of the nonlinearity, the Henri-Michaelis-Menten equation

$$\text{Velocity} = \frac{V_{\text{MAX}}C_{\text{SS}}}{K_M + C_{\text{SS}}} \quad (107)$$

can be applied to assess the velocity versus substrate (drug) concentration relationship. There are several techniques for the determination of the direct cause of nonlinearity in drug kinetics, including direct calculation of CL_T , CL_{ORAL} , F , V_{SS} , and V_1 . Most commonly, lack of superposition (disproportionate increase in AUC with increasing dose) is an indication of nonlinearity in the system.

PROTEIN-BINDING—When the amount of drug bound to plasma proteins approaches saturation, the percentage of the drug that is unbound may vary considerably with increasing dose. Under the conditions of saturation, for example, after a salicylate overdose, the f_u may vary considerably with the total amount of drug in the body and hence, certain pharmacokinetic parameters, such as apparent volume of distribution, will be influenced.

TIME-DEPENDENT KINETICS—Carbamazepine is a drug with low-to-intermediate intrinsic clearance, which also induces an increase in the activity of the biotransforming enzyme system by which it is metabolized. This increase will increase total clearance and decrease half-life. Because such autoinduction of metabolism does not occur until several dose-intervals of repetitive dosing, the pharmacokinetics vary with time and are called time-dependent. *Allosteric* (feedback)

Table 58-2. Examples of Mechanisms for Dose- and Time-Dependent Pharmacokinetics (Nonlinear Drug Disposition)

KINETIC PROCESS AND MECHANISM	EXAMPLES
Gastrointestinal absorption	
Saturable transport	Riboflavin, penicillins
Intestinal metabolism	Salicylamide
Biotransformation	
Saturable metabolism	Phenytoin, salicylate
Product inhibition	Phenytoin (rat)
Cosubstrate depletion	Acetaminophen
Plasma protein-binding	Prednisolone, disopyramide
Renal excretion	
Glomerular filtration/ protein-binding	Naproxen
Tubular secretion	p-Aminohippuric acid, mezlocillin
Tubular reabsorption	Riboflavin, cephalaprin
Biliary excretion	
Biliary secretion	Iodipamide, BSP
Enterohepatic cycling	Cimetidine, isotretinoin
Tissue distribution	
Plasma protein-binding	Prednisolone, ceftriaxone
Hepatic uptake	Indocyanine green, warfarin (rat)
CSF transport	Benzylpenicillins
Cellular uptake	Methicillin (rabbit)
Tissue-binding	Cyclosporine, dideoxyinosine (rat)

inhibition by accumulated metabolites of a drug, or an effect of a drug to impair its route of elimination, also will cause dose- and time-dependent changes in pharmacokinetics. Drugs that cause the depletion of some slowly replaceable intermediary factor, such as the depletion of norepinephrine by reserpine or the depletion of inorganic sulfate by acetaminophen, will manifest time-dependent effects.

DOSE-DEPENDENT KINETICS—When the elimination route is saturated by either capacity-limited metabolism or capacity-limited renal excretion, it is evident that the total clearance of a drug will decrease and the half-life will increase with increases in doses. Examples of important drugs that demonstrate dose-dependent kinetics are salicylic acid, phenylbutazone, probenecid, levodopa, phenytoin, heparin, and dicumarol. Ethanol obeys essentially zero-order elimination kinetics at blood concentrations above 0.02 to 0.04%, which is a fact of considerable social and legal importance.

Salicylic acid is one of the most interesting examples of dose-dependent kinetics from multiple sources. Salicylic acid is eliminated from the body by at least five, parallel, competing processes.¹⁹ Two of these are saturable processes for the formation of salicyluric acid (the glycine conjugate of salicylic acid) and salicylphenol glucuronide. The other three processes of elimination, excretion of unchanged salicylic acid in urine and formation of gentisic acid and salicyl glucuronide are first-order processes. The half-life of salicylic acid increases from about 3 hr to over 20 hr as the dose is increased upward from 300 mg to 10 g. At low doses, the half-life is about 3 hr, the apparent volume of distribution is approximately 9L, and a total clearance can be estimated to be 2 L/hr. The binding of salicylic acid to albumin also is capacity-limited (saturable), and saturation occurs even at therapeutic (low) doses of the drug. Therefore, as the amount of salicylic acid in the body increases, the $CL_{u, \text{int}}$ decreases, whereas the f_u increases. These two effects tend to oppose each other, such that the total clearance of salicylic acid remains relatively unchanged within the anti-inflammatory range of unbound concentrations (between 10 and 60 mg/L; Fig 58-19).²⁰ Finally, the renal excretion of salicylic acid ($pK_a = 3.5$) can be increased by increasing urinary pH, resulting in a decrease in renal tubular reabsorption (data not shown). The toxicological consequences of a salicylic acid overdose are well known, but it is not always appreciated that as the concentration of salicylic acid increases, the total amount of drug in the body increases out of proportion to the total plasma concentration.