1

One-Compartment Model

The most commonly employed approach to the pharmacokinetic characterization of a drug is to represent the body as a system of compartments, even though these compartments usually have no physiologic or anatomic reality, and to assume that the rate of transfer between compartments and the rate of drug elimination from compartments follow first-order or linear kinetics. The one-compartment model, the simplest model, depicts the body as a single, kinetically homogeneous unit. This model is particularly useful for the pharmacokinetic analysis of drugs that distribute relatively rapidly throughout the body. Almost invariably, the plasma or serum is the anatomical reference compartment for the one-compartment model, but we do not assume that the drug concentration in plasma is equal to the concentration of drug in other body fluids or in tissues, for this is rarely the case. Rather, we assume that the rate of change of drug concentration in plasma reflects quantitatively the change in drug concentrations throughout the body. In other words, if we see a 20% decrease in drug concentration in plasma over a certain period of time, we assume that the drug concentrations in kidney, liver, cerebrospinal fluid, and all other fluids and tissues also decrease by 20% during this time.

Drug elimination from the body can and often does occur by several pathways, including urinary and biliary excretion, excretion in expired air, and biotransformation in the liver or other fluids or tissues. Glomerular filtration in the kidneys is clearly a diffusional process, the rate of which can be characterized by first-order kinetics, but tubular secretion in the kidneys, biliary secretion, and biotransformation usually involves enzymatic (active) processes that are capacity limited. However, as demonstrated in subsequent sections of the text dealing with capacity-limited and nonlinear processes (Chap. 7), at low concentrations of drug (i.e., concentrations typically associated with therapeutic doses) the rate of these enzymatic processes can be approximated very well by first-order kinetics. Hence we find

that the elimination of most drugs in humans and animals following therapeutic or nontoxic doses can be characterized as an apparent first-order process (i.e., the rate of elimination of drug from the body at any time is proportional to the amount of drug in the body at that time). The proportionality constant relating the rate and amount is the first-order elimination rate constant. Its units are reciprocal time (i.e., min^{-1} or h^{-1}). The first-order elimination rate constant characterizing the overall elimination of a drug from a one-compartment model is usually written as K and usually represents the sum of two or more rate constants characterizing individual elimination processes:

$$K = k_e + k_m + k'_m + k_b + \cdots \tag{1.1}$$

where k_e and k_b are apparent first-order elimination rate constants for renal and biliary excretion, respectively, and k_m and k'_m are apparent first-order rate constants for two different biotransformation (metabolism) processes. These constants are usually referred to as apparent first-order rate constants to convey the fact that the kinetics only approximate first-order.

INTRAVENOUS INJECTION

Drug Concentrations in the Plasma

Following rapid intravenous injection of a drug that distributes in the body according to a one-compartment model and is eliminated by apparent first-order kinetics, the rate of loss of drug from the body is given by

$$\frac{dX}{dt} = -KX \tag{1.2}$$

where X is the amount of drug in the body at time t after injection. K, as defined above, is the apparent first-order elimination rate constant for the drug. The negative sign indicates that drug is being lost from the body.

To describe the time course of the amount of drug in the body after injection, Eq. (1.2) must be integrated. The method of Laplace transforms in Appendix A will be employed. The transform of (1.2) is

$$s\bar{X} - X_0 = -K\bar{X} \tag{1.3}$$

where X_0 is the amount injected (i.e., the dose) and s is the Laplace operator. Rearrangement of (1.3) yields

$$\bar{X} = \frac{X_0}{s + K} \tag{1.4}$$

which when solved using a table of Laplace transforms (Appendix A) gives

$$X = X_0 e^{-Kt} \tag{1.5}$$

where e represents the base of the natural logarithm. Taking the natural logarithm of both sides of (1.5) gives

$$\ln X = \ln X_0 - Kt \tag{1.6}$$

Then, based on the relationship

$$2.303 \log a = \ln a \tag{1.7}$$

Eq. (1.6) can be converted to common logarithms (base 10, log):

$$\log X = \log X_0 - \frac{Kt}{2.303} \tag{1.8}$$

The body is obviously not homogeneous even if plasma concentration and urinary excretion data can be described by representing the body as a one-compartment model. Drug concentrations in the liver, kidneys, heart, muscle, fat, and other tissues usually differ from one another as well as from the concentration in the plasma. If the relative binding of a drug to components of these tissues and fluids is essentially independent of drug concentration, the ratio of drug concentrations in the various tissues and fluids is constant. Consequently, there will exist a constant relationship between drug concentration in the plasma C and the amount of drug in the body:

$$X = VC \tag{1.9}$$

The proportionality constant V in this equation has the units of volume and is known as the apparent volume of distribution. Despite its name, this constant usually has no direct physiologic meaning and does not refer to a real volume. For example, the apparent volume of distribution of a drug in a 70 kg human can be several hundred liters.

The relationship between plasma concentration and the amount of drug in the body, as expressed by Eq. (1.9), enables the conversion of Eq. (1.8) from an amount-time to a concentration-time relationship:

$$\log C = \log C_0 - \frac{Kt}{2.303} \tag{1.10}$$

where C_0 is the drug concentration in plasma immediately after injection. Equation (1.10) indicates that a plot of log C versus t will be linear under the conditions stated (Fig. 1.1). C_0 may be obtained by extrapolation of the log C versus t plot to time zero. This intercept, C_0, may be used in the calculation of the apparent volume of distribution. Since X_0 equals the amount of drug injected intravenously (i.e., the intravenous dose), V may be estimated from the relationship

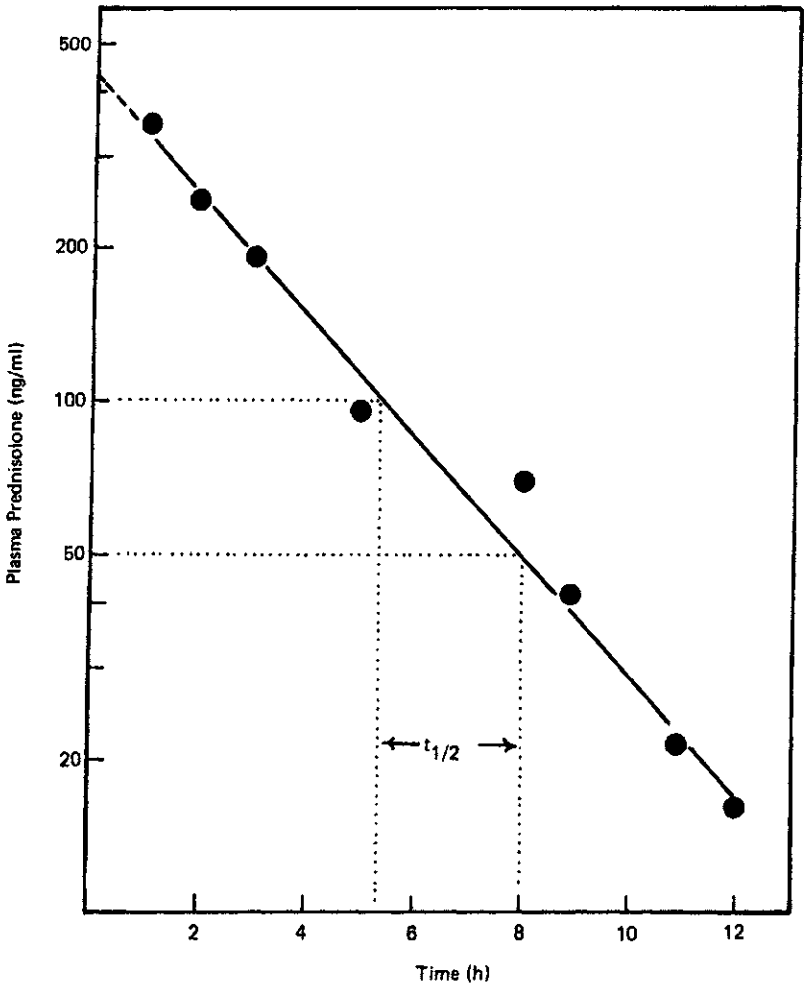


Fig. 1.1 Prednisolone concentration in plasma following an intravenous dose equivalent to 20 mg prednisone to a kidney transplant patient. The data show monoexponential decline that can be described by Eq. (1.10). C_0 = intravenous dose/V; slope = $-K/2.303$. (Data from Ref. 1.)

$$V = \frac{\text{intravenous dose}}{C_0} \tag{1.11}$$

Equation (1.11) is theoretically correct only for a one-compartment model where instantaneous distribution of drug between plasma and

tissues takes place. Since this is rarely true, a calculation based on Eq. (1.11) will almost always overestimate the apparent volume of distribution. Sometimes the error is trivial, but often the overestimate is substantial and the calculation may be misleading. More accurate and more general methods of estimating V will be discussed subsequently.

The slope of the line resulting from a plot of log C versus time is equal to $-K/2.303$ and K may be estimated directly from this slope. It is easier, however, to estimate K from the relationship

$$K = \frac{0.693}{t_{1/2}} \tag{1.12}$$

where $t_{1/2}$ is the biologic or elimination half-life of the drug. This parameter is readily determined from a semilogarithmic plot of plasma drug concentration (on logarithmic scale) versus time (on linear scale), as illustrated in Fig. 1.1. The time required for the drug concentration at any point on the straight line to decrease by one-half is the biologic half-life. An important characteristic of first-order processes is that the time required for a given concentration to decrease by a given percentage is independent of concentration. Equation (1.12) is easily derived by setting C equal to $C_0/2$ and t equal to $t_{1/2}$ in Eq. (1.10).

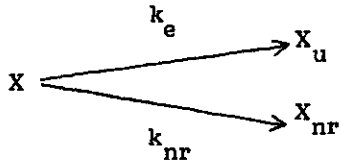
In principle, a plot of the logarithm of tissue drug concentration versus time should also be linear and give exactly the same slope as the plasma concentration-time curve. This is illustrated in Fig. 1.2.

Estimates of C_0, $t_{1/2}$, and K are often obtained from the best straight-line fit (by eye) to the log C versus time data. However, a more objective method is to convert all concentration values to logarithms, and then to determine the best-fitting line by the method of least squares, described in elementary textbooks of statistics [3]. Computer programs are available (see Appendix H) that do not require logarithmic conversions for nonlinear least-squares fitting of data.

Urinary Excretion Data

It is sometimes possible to determine the elimination kinetics of a drug from urinary excretion data. This requires that at least some of the drug be excreted unchanged. Consider a drug eliminated from the body partly by renal excretion and partly by nonrenal processes such as biotransformation and biliary excretion, as shown in Scheme 1,

Scheme 1



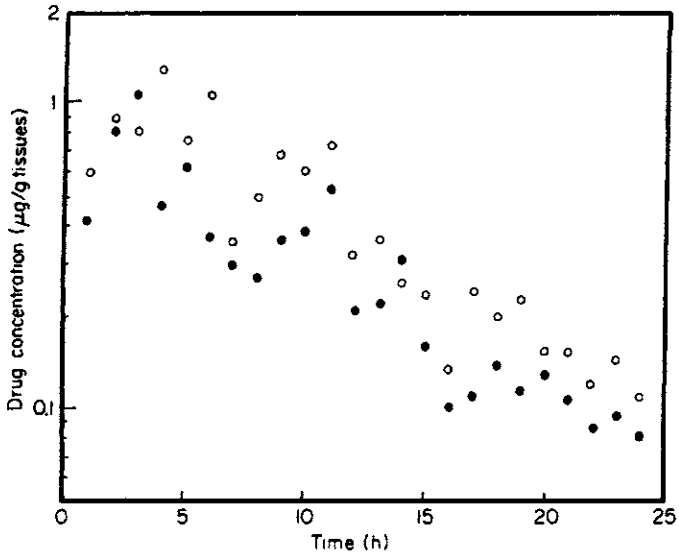


Fig. 1.2 Dipyridamole concentrations in serum (O) and heart tissue (●) after a single oral dose of the drug to guinea pigs. Drug concentrations in serum and heart decline in a parallel manner. (Data from Ref. 2.)

where X_u and X_{nr} are the cumulative amounts of drug eliminated unchanged in the urine and eliminated by all nonrenal pathways, respectively. The elimination rate constant K is the sum of the individual rate constants that characterize the parallel elimination processes. Thus

$$K = k_e + k_{nr} \tag{1.13}$$

where k_e is the apparent first-order rate constant for renal excretion and k_{nr} is the sum of all other apparent first-order rate constants for drug elimination by nonrenal pathways. Since in first-order kinetics, the rate of appearance of intact drug in the urine is proportional to the amount of drug in the body, the excretion rate of unchanged drug, dX_u/dt, can be defined as

$$\frac{dX_u}{dt} = k_e X \tag{1.14}$$

where X is the amount of drug in the body at time t.

Substitution for X according to Eq. (1.5) yields

$$\frac{dX_u}{dt} = k_e X_0 e^{-Kt} \tag{1.15}$$

Therefore,

$$\log \frac{dX_u}{dt} = \log k_e X_0 - \frac{Kt}{2.303} \tag{1.16}$$

Equation (1.16) states that a semilogarithmic plot of excretion rate of unmetabolized drug versus time is linear, with a slope of $-K/2.303$. This slope is the same as that obtained from a semilogarithmic plot of drug concentration in plasma versus time. Thus the elimination rate constant of a drug can be obtained from either plasma concentration or urinary excretion data. It must be emphasized that the slope of the log excretion rate versus time plot is related to the elimination rate constant K, not to the excretion rate constant k_e.

Urinary excretion rates are estimated by collecting all urine for a fixed period of time, determining the concentration of drug in the urine, multiplying the concentration by the volume of urine collected to determine the amount excreted, and dividing the amount excreted by the collection time. These experimentally determined excretion rates are obviously not instantaneous rates (i.e., dX_u/dt) but are average rates over a finite time period (i.e., $\Delta X_u/\Delta t$). However, we often find that the average excretion rate closely approximates the

Table 1.1 Calculation of Excretion Rate Versus Time Data for Estimating Half-Life

t (h)	X_u (mg)	Δt	ΔX_u	$\Delta X_u/\Delta t$ (mg/h)	t_m
0	0.0	1	4.0	4.0	0.5
1	4.0	1	3.8	3.8	1.5
2	7.8	1	3.5	3.5	2.5
3	11.3	3	9.1	3.0	4.5
6	20.4	6	13.5	2.2	9.0
12	33.9	12	14.7	1.2	18.0
24	48.6	12	6.4	0.53	30.0
36	55.0	12	2.8	0.23	42.0
48	57.8				

Note: The symbols are as follows: t, cumulative time after intravenous administration; X_u, cumulative amount of unmetabolized drug excreted in the urine; Δt, urine collection interval; ΔX_u, amount of drug excreted during each interval; $\Delta X_u/\Delta t$, experimentally determined excretion rate; t_m, midpoint of the collection interval.

instantaneous excretion rate at the midpoint of the urine collection period. The validity of this approximation depends on the collection period relative to the half-life of the drug. An individual collection period should not exceed one biologic half-life and, ideally, should be considerably less. These considerations are discussed in Appendix F. It is important to remember that urinary excretion rates must be plotted against the midpoints of the urine collection periods and not at the beginning or end of these periods (see Table 1.1 and Figs. 1.3 and 1.4).

Fluctuations in the rate of drug elimination are reflected to a high degree in excretion rate plots. At times the data are so scattered that an estimate of the half-life is difficult. To overcome this problem an

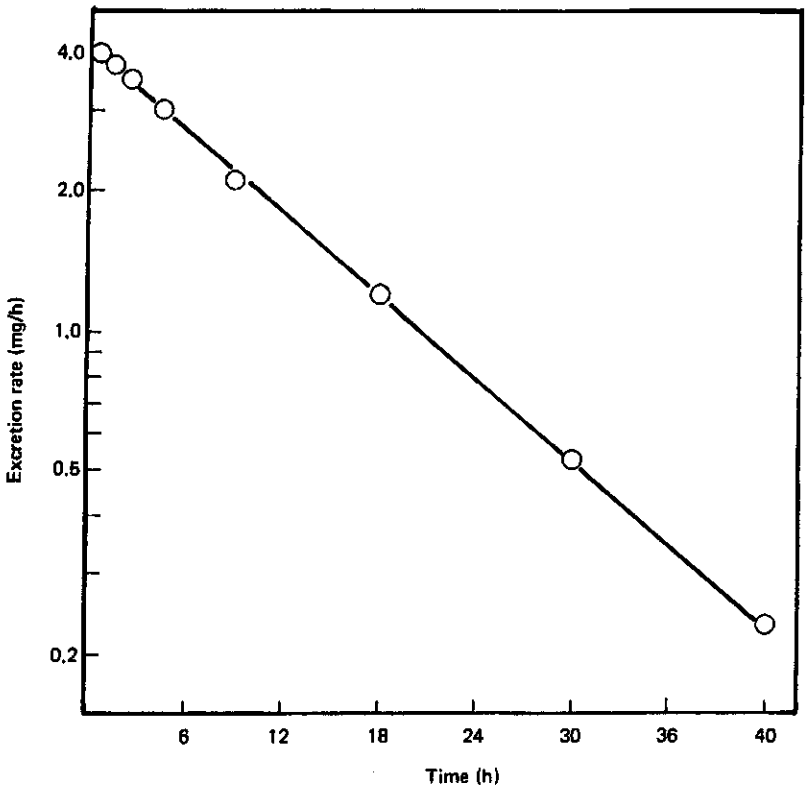


Fig. 1.3 Semilogarithmic plot of excretion rate versus time after intravenous administration of a drug. Data taken from Table 1.1. Each excretion rate is plotted at the midpoint of the urine collection interval. The data are described by Eq. (1.16). Slope = $-K/2.303$.

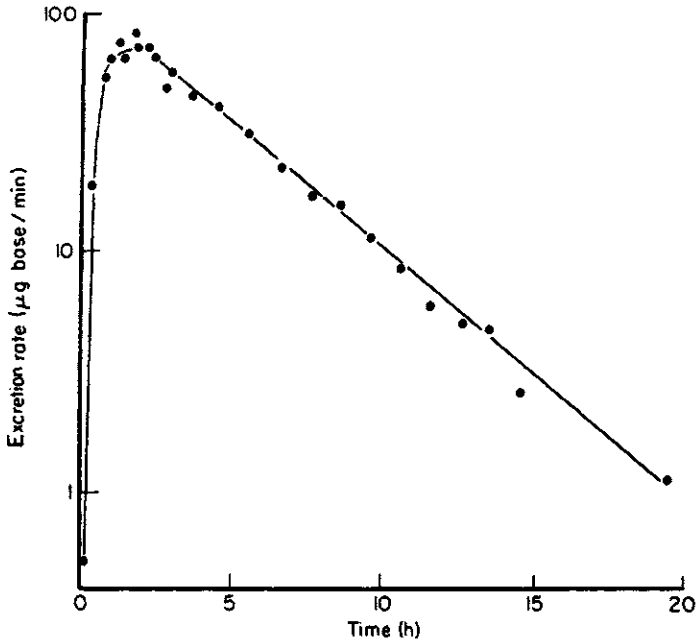


Fig. 1.4 Urinary excretion rate of norephedrine after oral administration of a single dose of the drug to a healthy adult subject. [From Ref. 4. © 1968 American Society for Pharmacology and Experimental Therapeutics, The Williams and Wilkins Company (agent).]

alternative approach, termed the sigma-minus method, is available. This method is considered less sensitive to fluctuations in drug elimination rate. The Laplace transform of Eq. (1.14) is

$$s\overline{X}_u = k_e\overline{X} \tag{1.17}$$

Substitution for $\overline{X}$ from Eq. (1.4) and rearrangement yields

$$\overline{X}_u = \frac{k_e X_0}{s(s + K)} \tag{1.18}$$

which when solved gives the following relationship between amount of drug in the urine and time:

$$X_u = \frac{k_e X_0}{K}(1 - e^{-Kt}) \tag{1.19}$$

where X_u is the cumulative amount of unchanged drug excreted to time t. The amount of unmetabolized drug ultimately eliminated in the urine, X_u^∞, can be determined by setting time in (1.19) equal to infinity; it is given by

$$X_u^\infty = \frac{k_e X_0}{K} \tag{1.20}$$

For a drug eliminated solely by renal excretion, $K = k_e$ and the amount ultimately excreted, X_u^∞, will be equal to the intravenous dose, X_0. In all cases the ratio of X_u^∞ to X_0 equals the ratio of k_e to K. This relationship is commonly employed to estimate k_e from urinary excretion data once the half-life of the drug is determined.

Substitution of X_u^∞ for $k_e X_0/K$ in (1.19) and rearrangement yields

$$X_u^\infty - X_u = X_u^\infty e^{-Kt} \tag{1.21}$$

which in logarithmic form is

$$\log (X_u^\infty - X_u) = \log X_u^\infty - \frac{Kt}{2.303} \tag{1.22}$$

The term $(X_u^\infty - X_u)$ is commonly called the *amount* of unchanged drug *remaining* to be *excreted*, or A.R.E. A plot of log A.R.E. versus time is linear (Fig. 1.5) with a slope equal to $-K/2.303$. Hence the elimination rate constant may be estimated from plots of log drug concentration in plasma versus time, log excretion rate versus time (the rate method), and log A.R.E. versus time (the sigma-minus method). To determine X_u^∞, total urine collection must be carried out until no unchanged drug can be detected in the urine. It is incorrect to plot log (dose $- X_u$) rather than log $(X_u^\infty - X_u)$ versus time.

When possible, total urine collection should be continued for a period of time equal to about seven half-lives of the drug to accurately estimate X_u^∞. This can be very difficult if the drug has a long half-life. The problem does not arise if the log excretion rate versus time plots are used since urine need be collected for only three or four half-lives to obtain an accurate estimate of the elimination rate constant. The rate method also obviates the need to collect all urine (i.e., urine samples may be lost or intentionally discarded to minimize the number of assays) since the determination of a single point on a rate plot simply requires the collection of two consecutive urine samples.

Renal Clearance

The kinetics of renal excretion of a drug may be characterized not only by a renal excretion rate constant k_e, but also by a renal clearance Cl_r. The concept of drug clearance is discussed in Chap. 8. At this point it suffices to state that the renal clearance of drug is equal to the volume of blood flowing through the kidneys per unit time from which all drug is extracted and excreted.

The renal clearance of a drug cannot exceed the renal blood flow. Clearance has units of flow (i.e., ml/min or liters/h). In pharmaco-

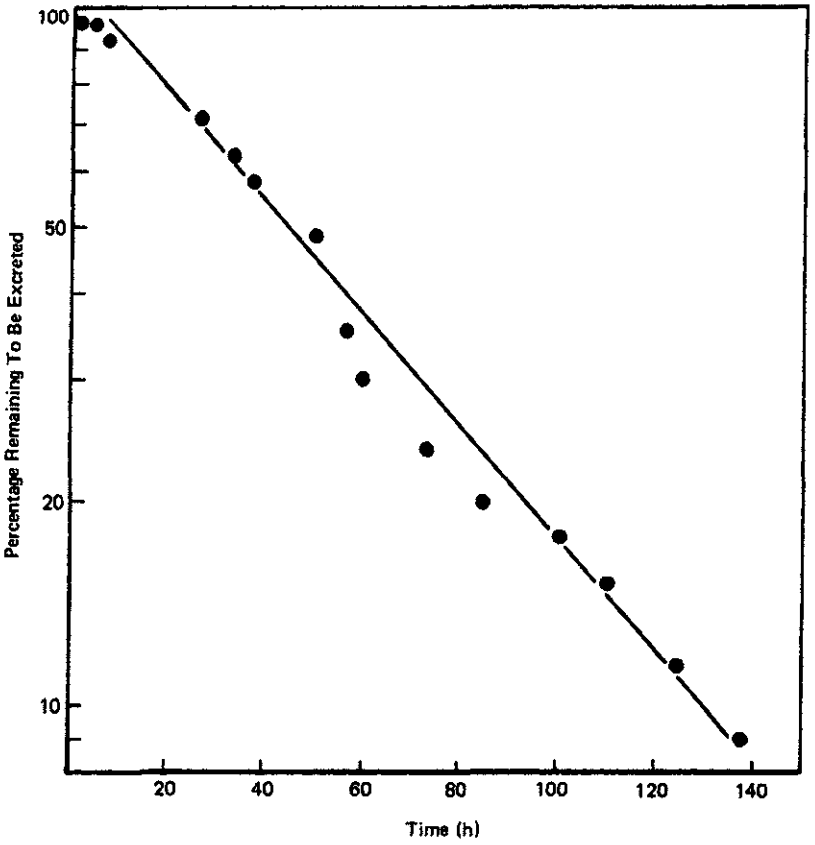


Fig. 1.5 Semilogarithmic plot of the average percentage unmetabolized drug remaining to be excreted versus time after oral administration of 250 mg of chlorpropamide to six healthy subjects. $t_{1/2}$ = 36 h. (Data from Ref. 5.)

kinetic terms renal clearance is simply the ratio of urinary excretion rate to drug concentration in the blood or plasma:

$$Cl_r = \frac{dX_u/dt}{C} \tag{1.23}$$

In practice, renal clearance is estimated by dividing the average urinary excretion rate, $\Delta X_u/\Delta t$, by the drug concentration in plasma at the time corresponding to the midpoint of the urine collection period.

Since excretion rate is the product of the urinary excretion rate constant and the amount of drug in the body [Eq. (1.14)], we can write

$$Cl_r = \frac{k_e X}{C} \tag{1.24}$$

Recognizing that X/C is simply the apparent volume of distribution [Eq. (1.9)], we can shown that renal clearance is the product of the urinary excretion rate constant and the apparent volume of distribution:

$$Cl_r = k_e V \tag{1.25}$$

All clearance terms can be expressed in terms of a rate constant and a volume.

An estimation of renal clearance by means of Eq. (1.23) may be misleading because like all rate processes in the body, renal excretion is subject to biologic variability. A more satisfactory approach is to plot urinary excretion rate versus drug concentration in plasma at the times corresponding to the midpoints of the urine collection periods (see Fig. 1.6). Since rearrangement of Eq. (1.23) yields

$$\frac{dX_u}{dt} = Cl_r C \tag{1.26}$$

the slope of an excretion rate-plasma concentration plot is equal to renal clearance.

A second method for calculating renal clearance requires simultaneous collection of plasma and urine. Integrating Eq. (1.26) from t_1 to t_2 yields

$$(X_u)_{t_1}^{t_2} = Cl_r \int_{t_1}^{t_2} C\, dt, \tag{1.27}$$

where $(X_u)_{t_1}^{t_2}$ is the amount of unmetabolized drug excreted in the urine during the time interval from t_1 to t_2 and $\int_{t_1}^{t_2} C\, dt$ is the area under the drug concentration in plasma versus time curve during the same time interval (see Fig. 1.7). Terms for area have units of concentration-time. A plot of $(X_u)_{t_1}^{t_2}$ versus $\int_{t_1}^{t_2} C\, dt$ yields a straight line with a slope equal to renal clearance.

Integration of Eq. (1.26) from time zero to time infinity, and rearrangement, gives an expression for the average renal clearance over the entire time course of drug in the body after a single dose:

$$Cl_r = \frac{X_u^{\infty}}{\int_0^{\infty} C\, dt} = \frac{X_u^{\infty}}{AUC} \tag{1.28}$$

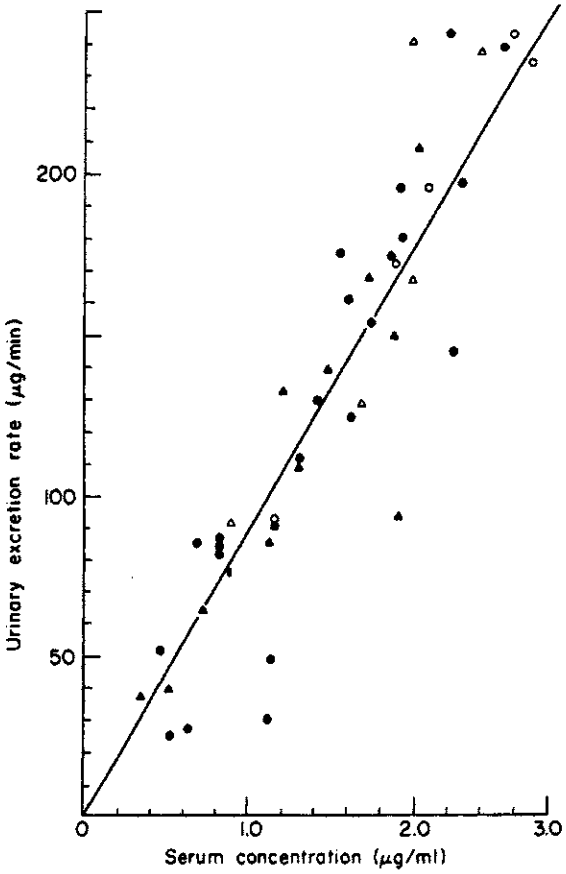


Fig. 1.6 Relationship between urinary excretion rates of tetracycline and serum concentrations of the drug determined at the midpoints of each urine collection interval after oral administration of a 250 mg dose to five healthy adults. Two different oral preparations (●, ▲) were given to each subject. The open symbols (○, △) denote the maximum excretion rate for each preparation. The data are described by Eq. (1.26); the slope of the line is equal to the average renal clearance of tetracycline in the group. (Data from Ref. 6.)

The term $\int_0^\infty C\,dt$ or AUC represents the total area under the drug concentration in plasma versus time curve plotted on rectilinear graph paper (see Fig. 1.7). This method has been used to estimate renal clearance (see Fig. 1.8) but is not ideal because it is difficult to collect urine for long periods to get an accurate estimate of X_u^∞, particularly for drugs with long half-lives.

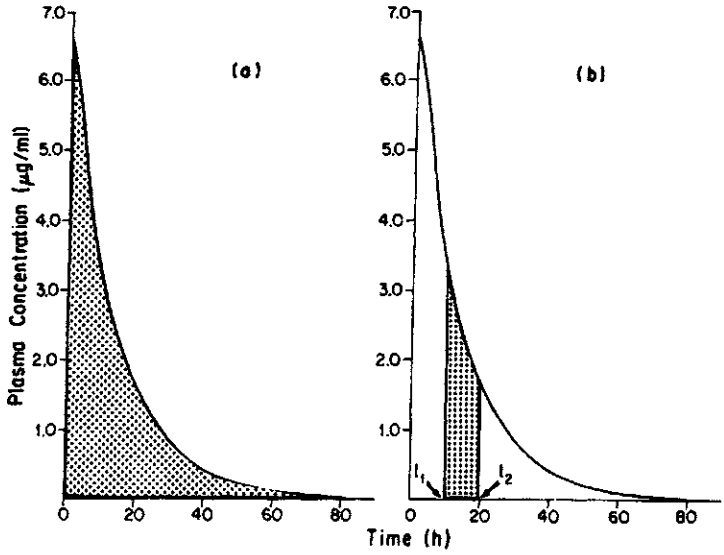


Fig. 1.7 Plots of drug concentration in plasma as a function of time after intravenous administration illustrating, by the shaded region, (a) $\int_0^\infty C\,dt$, the total area under the curve, AUC, and (b) $\int_{t_1}^{t_2} C\,dt$, the partial area under the curve from t_1 to t_2.

Use of Eqs. (1.27) and (1.28) for calculating renal clearance requires the measurement of areas under the drug concentration in plasma versus time curves. Several methods are available for determining the area under a curve. For each of these methods it is essential to obtain a sufficient number of blood samples to characterize adequately the curve or a portion thereof. A planimeter, which is an instrument for mechanically measuring the area of plane figures, is often used to measure the area under the curve (drawn on rectilinear graph paper). Another procedure, known as the cut and weigh method, is to cut out the area under the entire curve on rectilinear graph paper and to weigh it on an analytical balance. The weight thus obtained is converted to the proper units by dividing it by the weight of a unit area of the same paper. A third method to determine the area under the curve is to estimate it by means of the trapezoidal rule (see Appendix D). Other methods are described by Yeh and Kwan [7].

An exact mathematical method for determining the total area under the plasma concentration-time curve is to convert Eq. (1.10) to its exponential form and integrate over the time interval zero to infinity. Equation (1.10) expressed as natural logarithms is

$$\ln C = \ln C_0 - Kt \qquad (1.29)$$

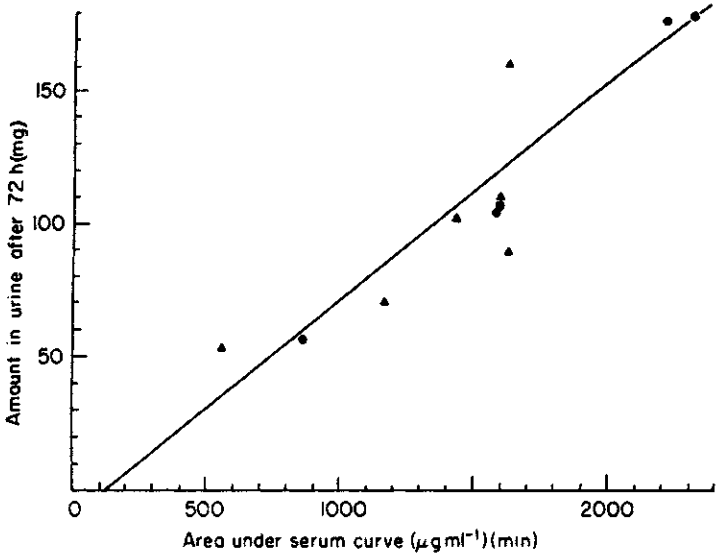


Fig. 1.8 Relationship between cumulative amount of tetracycline excreted after 72 h and the total area under the tetracycline concentration in serum versus time curve after oral administration of a 250 mg dose to five healthy adults. Two different oral preparations (●, ▲) were given to each subject. The data are described by Eq. (1.28); the slope of the line is equal to the average renal clearance of tetracycline in the group. (Data from Ref. 6.)

Therefore,

$$C = C_0 e^{-Kt} \tag{1.30}$$

Integration from time zero to time infinity yields

$$AUC = -\frac{C_0}{K} e^{-Kt} \Big|_0^{\infty} = \frac{C_0}{K} \tag{1.31}$$

Therefore, the total area under the plasma drug concentration-time curve is the plasma concentration at time zero, obtained by extrapolation, divided by the apparent first-order elimination rate constant of the drug. Since most drugs do not distribute instantaneously between plasma and tissues, Eq. (1.31) will usually underestimate the total area under the drug concentration in plasma versus time plot after intravenous administration. This error may be negligible or substantial, depending on the distribution and elimination characteristics of the drug.

Systemic Clearance

It has been shown that the product of the urinary excretion rate constant k_e and V is equal to renal clearance [Eq. (1.25)]. The product of the elimination rate constant K and V also yields a clearance term, which has alternatively been called plasma clearance, total body clearance, or systemic clearance. We will use the last-mentioned term and the designation Cl_s. It can be shown that the systemic clearance is given by the ratio of the intravenous dose to the total area under the drug concentration versus time curve. Since $Cl_r = k_e V$ [according to Eq. (1.25)], we can transform Eq. (1.28) to the expression

$$V = \frac{X_u^\infty}{k_e \cdot AUC} \tag{1.32}$$

Since we can show by rearranging Eq. (1.20) that

$$\frac{X_u^\infty}{k_e} = \frac{X_0}{K} \tag{1.33}$$

it follows that

$$Cl_s = VK = \frac{X_0}{AUC} \tag{1.34}$$

where X_0 is the intravenous dose.

Systemic clearance represents the sum of the clearances of all individual processes involved in the elimination of drug from the body. It is particularly useful for comparing data obtained using different compartmental models and for relating pharmacokinetic and physiologic processes. A comprehensive discussion of clearance is presented in Chap. 8.

Another particularly useful relationship, from which the apparent volume of distribution can be estimated, is obtained by rearranging Eq. (1.34):

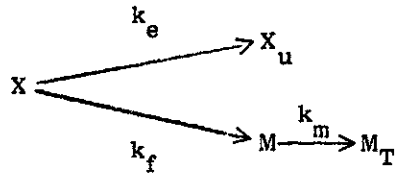
$$V = \frac{X_0}{K \cdot AUC} \tag{1.35}$$

This relationship is used very widely for calculating the apparent volume of distribution. The validity of Eq. (1.35) is not dependent on instantaneous distribution of drug between plasma and tissues, as is the case for Eq. (1.11). Accordingly, Eq. (1.35) can be applied in principle to many compartmental models. When applied to one-compartmental models, it is often called the area method for estimating apparent volume of distribution and V is sometimes written as V_{area}.

Metabolite Concentrations in the Plasma

Scheme 2 illustrates parallel routes of drug elimination; one is urinary, the kinetics of which have been discussed, and the other is metabolism.

Scheme 2



In this scheme X, X_u, and k_e are as defined previously, M is the amount of metabolite in the body, and M_T is the total amount of metabolite eliminated by renal and/or biliary pathways as well as by metabolism (i.e., where the primary metabolite M is further biotransformed). The constants k_f and k_m are the respective apparent first-order rate constants for metabolite formation and elimination. The time course of metabolite levels in the body is a function of the rates of formation and elimination of the metabolite:

$$\frac{dM}{dt} = k_f X - k_m M \tag{1.36}$$

The Laplace transform of this equation (see Appendix A) is

$$s\overline{M} = k_f\overline{X} - k_m\overline{M} \tag{1.37}$$

Solving for $\overline{M}$ and substituting for $\overline{X}$ from Eq. (1.4) yields

$$\overline{M} = \frac{k_f X_0}{(s + k_m)(s + K)} \tag{1.38}$$

which when solved for M, employing a table of Laplace transforms, gives

$$M = \frac{k_f X_0}{K - k_m}(e^{-k_m t} - e^{-Kt}) \tag{1.39}$$

This equation permits calculation of the amount of metabolite in the body at any time after intravenous injection of a dose X_0 of a drug. Dividing both sides of this equation by the apparent volume of distribution of the metabolite V_m yields

$$C_m = \frac{k_f X_0}{V_m(K - k_m)}(e^{-k_m t} - e^{-Kt}) \tag{1.40}$$

which describes the plasma concentration of metabolite C_m versus time curve following the intravenous administration of parent drug.

It is informative to consider two different cases, one in which k_m is greater than K and the other where K is greater than k_m. At one time the general assumption was that k_m was always greater than K since metabolites were considered to be more polar and hence more readily eliminated from the body than the parent drug. This assumption may be true when polar conjugates such as glucuronides and glycine conjugates are the major metabolites of a drug. However, the assumption is often not true when biotransformation results in acetylation or oxidation. If k_m is larger than K, then at some time after drug administration $e^{-k_m t}$ will approach zero, whereas e^{-Kt} still has a finite value resulting in Eq. (1.40) reducing to

$$C_m \simeq \frac{k_f X_0}{V_m(k_m - K)} e^{-Kt} \tag{1.41}$$

which when written in logarithmic form becomes

$$\log C_m \simeq \log \frac{k_f X_0}{V_m(k_m - K)} - \frac{Kt}{2.303} \tag{1.42}$$

Therefore, a plot of log plasma concentration of metabolite versus time will eventually become linear and parallel to the curve of log plasma concentration of unchanged drug versus time (i.e., both will have a slope of $-K/2.303$), as illustrated by Fig. 1.9. From a practical point of view, this will be obvious only when k_m is several times larger than K.

Conversely, if K is larger than k_m, metabolite concentration in the plasma will decline more slowly than the concentration of unchanged drug. In this instance the equation analogous to (1.42) is

$$\log C_m \simeq \log \frac{k_f X_0}{V_m(K - k_m)} - \frac{k_m t}{2.303} \tag{1.43}$$

The terminal slope of a plot of the logarithm of metabolite concentration versus time is $-k_m/2.303$ (Fig. 1.10). Again the linear segment will be obvious only when K is several times larger than k_m. In either instance (i.e., when $k_m > K$ or when $K > k_m$), the closer K and k_m are, the more difficult it is to delineate a linear segment of the curve. It is important to point out that by simply following metabolite concentration in the plasma as a function of time and obtaining a linear portion of a curve, one does not know whether the slope yields k_m or K. To resolve this dilemma, either the apparent first-order elimination rate constant of the drug, K, must be known, or in some limited circumstances the metabolite can be administered as such and its elimination

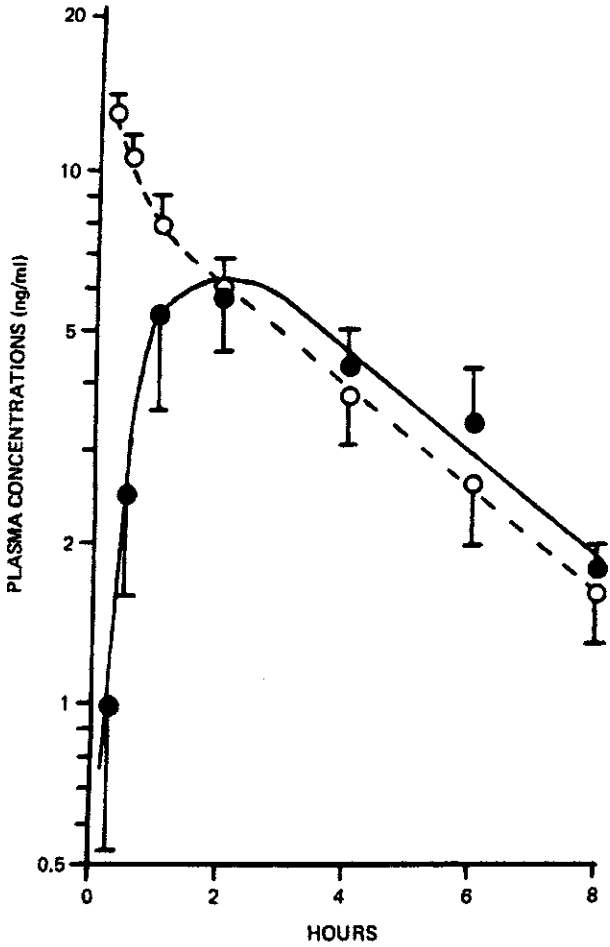


Fig. 1.9 Plasma concentrations of propranolol (○) and propranolol glucuronide (●) after a 0.05 mg/kg intravenous dose of propranolol to five normal volunteers. After about 4 h the concentrations of parent drug and metabolite decline in parallel since the metabolite has a shorter half-life than propranolol. (From Ref. 8.)

rate constant determined. Regardless of which rate constant (K or k_m) is determined from the terminal linear segment of the curve, the other rate constant can be estimated by the method of residuals (see Appendix C for a discussion of this method).

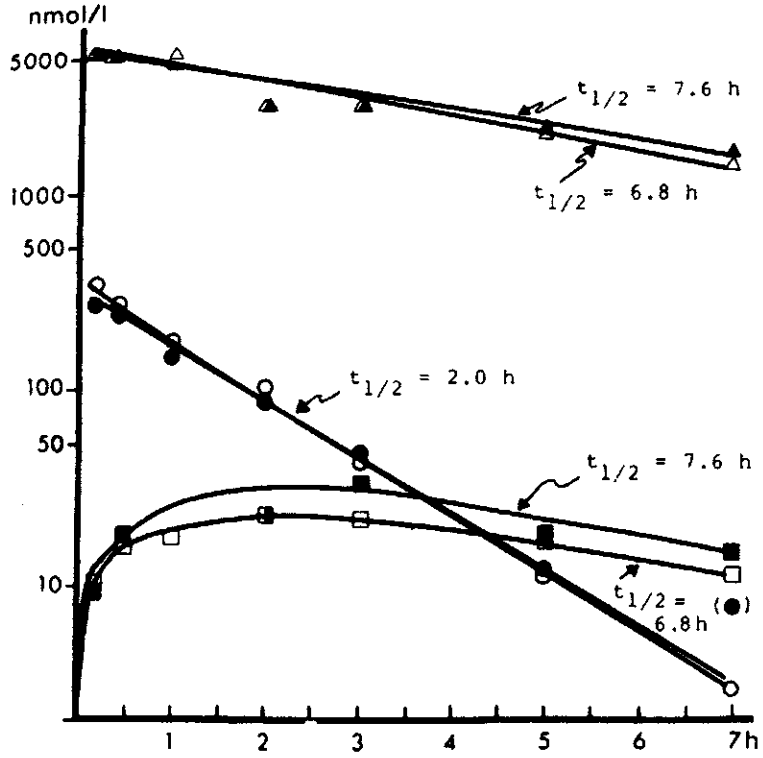
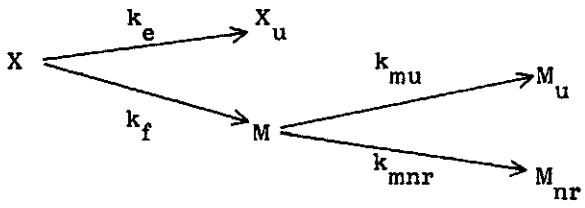


Fig. 1.10 Individual plasma concentrations of metoprolol (●,○), α-hydroxymetoprolol, a metabolite, formed after administration of metoprolol (■,□), and α-hydroxymetoprolol after administration of the metabolite per se (▲,△) in two dogs. The half-life of the metabolite is considerably longer than the half-life of the parent drug. (From Ref. 9. © 1979 Plenum Publishing Corp.)

Metabolite Excretion in the Urine

Urinary excretion data for a metabolite may be employed to determine the elimination kinetics of the parent drug and of the metabolite. According to Scheme 3

Scheme 3



the differential equation describing the appearance of metabolite in the urine is given by

$$\frac{dM_u}{dt} = k_{mu}M \tag{1.44}$$

where M_u is the amount of metabolite in the urine. M_{nr} is the amount of metabolite eliminated by all processes other than renal elimination. The constant k_{mu} is the apparent first-order rate constant for the excretion of metabolite in the urine, and k_{mnr} is the sum of all apparent first-order rate constants for the elimination of metabolite other than by renal excretion. The elimination rate constant of the metabolite k_m is the sum of these two rate constants (i.e., $k_m = k_{mu} + k_{mnr}$).

The Laplace transform of (1.44) is

$$s\bar{M}_u = k_{mu}\bar{M} \tag{1.45}$$

Substitution for $\bar{M}$ from (1.38) and solving for $\bar{M}_u$ yields

$$\bar{M}_u = \frac{k_{mu}k_fX_0}{s(s + k_m)(s + K)} \tag{1.46}$$

Solving for M_u employing a table of Laplace transforms results in the following relationship between metabolite levels in the urine and time:

$$M_u = k_{mu}k_fX_0\left[\frac{1}{k_mK} + \frac{e^{-k_mt}}{k_m(k_m - K)} - \frac{e^{-Kt}}{K(k_m - K)}\right] \tag{1.47}$$

Rearrangement of (1.47) yields

$$M_u = \frac{k_{mu}k_fX_0}{k_mK}\left[1 + \frac{1}{k_m - K}(Ke^{-k_mt} - k_me^{-Kt})\right] \tag{1.48}$$

At time $t = \infty$, M_u equals M_u^∞, the amount of metabolite in the urine at infinity, which is given by

$$M_u^\infty = \frac{k_{mu}k_fX_0}{k_mK} \tag{1.49}$$

Substituting M_u^∞ for the term $k_{mu}k_fX_0/k_mK$ in (1.48) and rearranging yields

$$M_u^\infty - M_u = \frac{M_u^\infty}{k_m - K}(k_me^{-Kt} - Ke^{-k_mt}) \tag{1.50}$$

A second biexponential relationship may be obtained by substituting in (1.44) the value of M from (1.39). This gives the rate expression

$$\frac{dM_u}{dt} = \frac{k_{mu} k_f X_0}{k_m - K}(e^{-Kt} - e^{-k_m t}) \qquad (1.51)$$

Assuming that k_m is greater than K, a plot of either log $(M_u^\infty - M_u)$ versus time or log (dM_u/dt) versus time will result in a biexponential curve (Fig. 1.11). The apparent first-order elimination rate constant K of the parent drug can be estimated from the slope of the terminal linear portion of each curve, which equals $-K/2.303$. Figure 1.12 shows the correlation between the half-life of antipyrine determined by following the decline of drug concentrations in plasma and that determined from a semilogarithmic plot of the urinary excretion rate

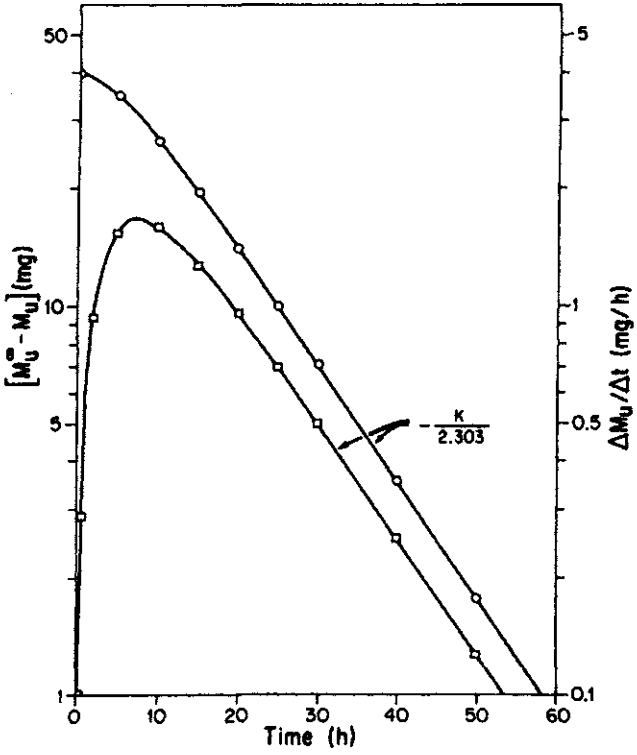


Fig. 1.11 Semilogarithmic plots of $[M_u^\infty - M_u]$ (O) and $\Delta M_u/\Delta t$ (□) versus time after intravenous administration of a drug. The data are described by Eqs. (1.50) and (1.51), respectively, for a situation where k_m is greater than K.

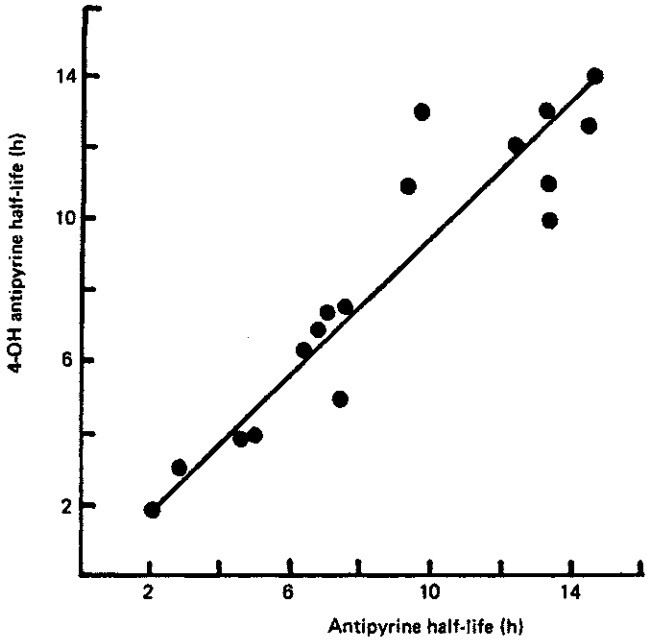


Fig. 1.12 Correlation between the half-life of antipyrine determined by following the decline of drug concentrations in plasma and that determined from a semilogarithmic plot of the urinary excretion rate of an antipyrine metabolite, 4-hydroxyantipyrine, versus time in individual patients. It is evident that the elimination rate constant of the metabolite, k_m, is significantly larger than the elimination rate constant of antipyrine, K. n = 17, r = 0.89, P < 0.001. (From Ref. 10.)

of an antipyrine metabolite, 4-hydroxyantipyrine, versus time in individual patients. Application of the method of residuals (see Appendix C) in both instances will enable estimation of k_m, the apparent first-order elimination rate constant of the metabolite. If, however, K is larger than k_m, k_m can be determined from the slopes of the terminal linear phases of these plots and K can be determined from the slopes of the residual lines. Without prior knowledge of either K or k_m, one cannot tell whether the slope of the terminal linear segment of the urinary excretion-time plots yields K or k_m.

With regard to the use of (1.50) and (1.51) for evaluating the elimination kinetics of a drug and its metabolite, the same factors must be considered as discussed for the analogous equations (1.15) and (1.21) for urinary excretion of parent drug. As with (1.15), experimentally determined urinary excretion rates of metabolite in (1.51) are not

instantaneous rates but average rates over a finite period of time (see Appendix F). With respect to (1.50), the determination of M_u^∞ requires urine collection to be carried out until no further metabolite can be detected in the urine. This may present difficulties if the parent drug or metabolite has a long half-life.

Determination of Metabolite-Associated Rate Constants

Scheme 3 suggests that three rate constants are of interest in characterizing the time course of metabolite in the body: the formation rate constant k_f, the overall rate constant for elimination of metabolite k_m (i.e., the sum of k_{mu} and k_{mnr}), and the rate constant for renal excretion of metabolite k_{mu}. The formation rate constant is usually estimated by determining the total amount of metabolite ultimately excreted in the urine. Equation (1.49) can be rearranged to give

$$k_f = \frac{k_m K M_u^\infty}{k_{mu} X_0} \tag{1.52}$$

If the metabolite is eliminated solely by renal excretion (i.e., $k_m = k_{mu}$), then

$$k_f = \frac{K M_u^\infty}{X_0} \tag{1.53}$$

Hence the ratio of total amount of metabolite ultimately excreted in the urine to the intravenous dose, times the rate constant for elimination of parent drug, is equal to the formation rate constant if the metabolite is subject to neither further metabolism nor nonrenal elimination in the body.

Kaplan et al. [11] have proposed a more general method for estimating k_f. This method is often limited to animal studies, for it requires the administration of the metabolite. To determine k_f in Scheme 3, one must give the parent drug intravenously and determine its elimination rate constant K, as well as the area under the metabolite concentration in plasma versus time curve resulting from this administration. Then one must administer intravenously a dose of metabolite that is equimolar to the dose of drug and again determine the area under the metabolite concentration versus time curve. The estimate of k_f is given by the relationship

$$k_f = \frac{K[\int_0^\infty C_m \, dt]_X}{\int_0^\infty C_m \, dt} \tag{1.54}$$

where $[\int_0^\infty C_m\,dt]_X$ and $\int_0^\infty C_m\,dt$ represent the total areas under the metabolite concentration-time curves after administration of the drug and metabolite, respectively.

Several relationships have been described for the determination of the rate constant for overall elimination of metabolite from the body, k_m [see Eqs. (1.40), (1.50), and (1.51)]. The rate constant may be estimated from either the slopes of the linear portions of the appropriate semilogarithmic plots or the residual curves derived from such plots (see Appendix C). Other methods have been proposed for estimating k_m [12] but seem to offer no particular advantage.

No general method appears to be available for estimating the rate constant for renal excretion of metabolite, k_{mu}, other than to administer the metabolite intravenously and carry out the appropriate measurements. This is usually not possible in humans. On the other hand, the renal clearance of the metabolite Cl_{rm} is relatively easily determined after administering the parent drug by determining metabolite concentrations in plasma and urine and applying equations analogous to Eqs. (1.23), (1.27), or (1.28); for example,

$$Cl_{rm} = \frac{dM_u/dt}{C_m} \tag{1.55}$$

or

$$Cl_{rm} = \frac{M_u^\infty}{[\int_0^\infty C_m\,dt]_X} \tag{1.56}$$

Interpretation of Total Radioactivity Data

Many studies in laboratory animals and some studies in humans involve the administration of radiolabeled drug. Often, the results of such studies are expressed in terms of total radioactivity in plasma. Sometimes, drug studies are initiated before a specific assay is available and the results are reported in terms of the concentration of apparent drug in plasma. In either case, great care must be exercised in attempting to carry out a pharmacokinetic analysis of such data. The concentration of total radioactivity or apparent drug in plasma, C_T, must be viewed as the sum of the concentrations of parent drug, C, and all metabolites that are detected by the assay method, C_{MT}. The time course of unmetabolized drug after intravenous administration is given by

$$C = \frac{X_0}{V}e^{-Kt} \tag{1.57}$$

Equation (1.40) describes the time course of a single metabolite in the plasma after intravenous administration of parent drug. This equation applies to each primary metabolite arising from the administered drug. Consequently, the plasma concentrations of all primary metabolites can be expressed by

$$C_{MT} = \sum_{i=1}^{n} \frac{(k_f)_i X_0}{(V_m)_i[K - (k_m)_i]} (e^{-(k_m)_i t} - e^{-Kt}) \qquad (1.58)$$

Combining Eqs. (1.57) and (1.58) and rearranging terms, we can show that

$$C_T = X_0 \left\{ \sum_{i=1}^{n} \frac{(k_f)_i e^{-(k_m)_i t}}{(V_m)_i[K - (k_m)_i]} + \left[\frac{1}{V} - \sum_{i=1}^{n} \frac{(k_f)_i}{(V_m)_i[K - (k_m)_i]} \right] e^{-Kt} \right\} \qquad (1.59)$$

where $(k_f)_i$, $(V_m)_i$, and $(k_m)_i$ are the apparent first-order formation rate constant, the apparent volume of distribution, and the apparent first-order elimination rate constant, respectively, for each of the n primary metabolites, V is the apparent volume of parent drug, K is the apparent first-order rate constant for drug elimination, and X_0 is the intravenous dose of drug.

If the individual rate constant for elimination of every primary metabolite is greater than the elimination rate constant of administered drug [i.e., $(k_m)_i > K$], a semilogarithmic plot of total radioactivity or apparent drug concentration in plasma versus time will yield a biexponential curve and the slope of the terminal segment is equal to $-K/2.303$. The same applies to plots of urinary excretion rates of total radioactivity versus time [i.e., log $d(X_T)_u/dt$ versus t] and to sigma-minus plots for total radioactivity (i.e., log $[(X_T)_u^\infty - (X_T)_u]$ versus t.

Hence under special circumstances which can be neither predicted nor assumed, one may find that the half-life of elimination of total radioactivity is equal to the elimination half-life of parent drug. Since one is not certain of the chemical species being measured by counting total radioactivity, no other pharmacokinetic parameter, including apparent volume of distribution, can be calculated. Perhaps the most useful pharmacokinetic information that may be derived unambiguously from studies based on total radioactivity is that the drug administered must have a biologic half-life equal to or less than the apparent half-life of elimination of total radioactivity.

INTRAVENOUS INFUSION

Drug Concentration in the Plasma

If a drug is administered intravenously at a constant rate, the following differential equation may be written for the change in amount of drug in the body with time:

$$\frac{dX}{dt} = k_0 - KX \tag{1.60}$$

where k_0 is the rate of drug infusion, expressed in amount per unit time. The Laplace transform of (1.60) is

$$s\overline{X} = \frac{k_0}{s} - K\overline{X} \tag{1.61}$$

Rearrangement yields

$$\overline{X} = \frac{k_0}{s(s + K)} \tag{1.62}$$

Solving (1.62), employing a table of Laplace transforms, gives the following relationship between the amount of drug in the body and time:

$$X = \frac{k_0}{K}(1 - e^{-Kt}) \tag{1.63}$$

which can be written in concentration terms:

$$C = \frac{k_0}{VK}(1 - e^{-Kt}) \tag{1.64}$$

During continuous constant rate intravenous infusion drug concentrantions in plasma increase according to Eq. (1.64) but eventually approach a constant value (i.e., as $t \to \infty$, $e^{-Kt} \to 0$ and $C \to k_0/VK$). This constant drug concentration or plateau is sometimes called infusion equilibrium but is actually a steady-state situation since at this concentration the elimination rate equals the infusion rate and $dC/dt = 0$. The steady-state concentration in plasma C_{ss} is given by

$$C_{ss} = \frac{k_0}{VK} \tag{1.65}$$

After infusing a drug for a period of time equal to four biologic half-lives, drug concentrations in plasma are within 10% of steady state. Infusion for a period of time equal to seven half-lives results in concentrations within 1% of steady state. Drug concentration in plasma at steady state is directly proportional to the infusion rate and inversely proportional to the systemic clearance (i.e., the product of

V and K) of the drug. The systemic clearance of a drug is readily calculated from the ratio of infusion rate to steady-state drug concentration in plasma:

$$Cl_s = VK = \frac{k_0}{C_{ss}} \tag{1.66}$$

The elimination rate constant and half-life of a drug may also be calculated from data collected during infusion to steady state. Substitution for k_0/VK in Eq. (1.64) according to Eq. (1.65) yields

$$C = C_{ss}(1 - e^{-Kt}) \tag{1.67}$$

Upon rearrangement it can be shown that

$$\frac{C_{ss} - C}{C_{ss}} = e^{-Kt} \tag{1.68}$$

Therefore,

$$\log \frac{C_{ss} - C}{C_{ss}} = -\frac{Kt}{2.303} \tag{1.69}$$

A semilogarithmic plot of $(C_{ss} - C)/C_{ss}$ versus time yields a straight line with a slope of $-K/2.303$. The elimination rate constant may be estimated directly from the slope. The half-life may be estimated either directly from the semilogarithmic plot or from K by rearranging Eq. (1.12),

$$t_{1/2} = \frac{0.693}{K} \tag{1.70}$$

The elimination rate constant may also be determined using the declining drug concentration in plasma versus time data collected after stopping the infusion. The differential equation describing these data is simply

$$\frac{dC}{dt} = -KC \tag{1.71}$$

The Laplace transform of Eq. (1.71) is given by

$$s\overline{C} - C_{max} = -K\overline{C} \tag{1.72}$$

where C_{max} is the drug concentration in plasma when the infusion was terminated, (i.e., the initial condition for the postinfusion period).

On rearranging Eq. (1.72), we obtain

$$\overline{C} = \frac{C_{max}}{s + K} \tag{1.73}$$

Solving Eq. (1.73) for C using a table of Laplace transforms gives

$$C = C_{max}e^{-Kt'} \tag{1.74}$$

or, in logarithmic form,

$$\log C = \log C_{max} - \frac{Kt'}{2.303} \tag{1.75}$$

where t' is the time after stopping the infusion. The time during which infusion took place is generally designated as T. If the infusion has been carried out for a sufficiently long period such that T > seven biologic half-lives, $C_{max} = C_{ss} = k_0/VK$. If the infusion were terminated before reaching steady state, $C_{max} = k_0(1 - e^{-KT})/VK$. Depending on the infusion time, Eq. (1.75) may be transformed to either

$$\log C = \log \frac{k_0}{VK} - \frac{Kt'}{2.303} \tag{1.76}$$

or

$$\log C = \log \frac{k_0}{VK}(1 - e^{-KT}) - \frac{Kt'}{2.303} \tag{1.77}$$

In either case a semilogarithmic plot of postinfusion drug concentration in plasma versus time t' will yield a straight line with a slope equal to $-K/2.303$. The time course of drug concentrations in plasma during and after constant rate intravenous infusions is shown in Fig. 1.13.

Data obtained from infusion studies are also useful for estimating the apparent volume of distribution of a drug. For example, we can show on rearranging Eq. (1.65) that

$$V = \frac{k_0}{C_{ss}K} \tag{1.78}$$

Alternatively, if the infusion is terminated before attaining steady state, then

$$V = \frac{k_0(1 - e^{-KT})}{C_{max}K} \tag{1.79}$$

where C_{max} is the drug concentration in plasma when the infusion was stopped and T is the infusion time. The validity of Eq. (1.79) requires the assumption of a one-compartment model, but Eq. (1.78) is a general relationship that applies to many situations.

If drug concentration versus time data are obtained during as well as after constant rate intravenous infusion, one can calculate systemic clearance Cl_s and apparent volume of distribution V from the

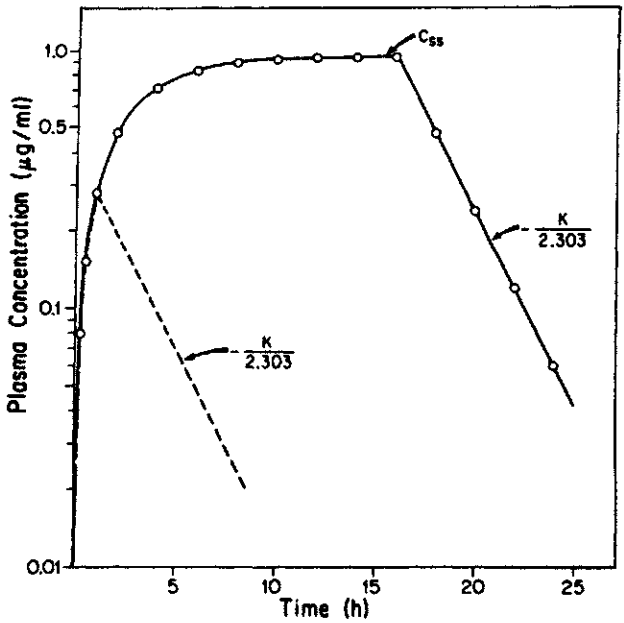


Fig. 1.13 Drug concentrations (log scale) in plasma during and after constant rate intravenous infusion to steady state. The dashed line denotes the decline of drug concentration in plasma after an infusion period shorter than the time required to reach steady state.

total area under the concentration versus time curve. The area under the up-curve is obtained by integrating Eq. (1.64) from t = 0 to t = T. The area under the down-curve is obtained by integrating Eq. (1.74) from t' = 0 to t' = ∞. Combining these areas and simplifying terms yields

$$AUC = \frac{k_0 T}{VK} \tag{1.80}$$

Therefore,

$$Cl_s = VK = \frac{k_0 T}{AUC} \tag{1.81}$$

and

$$V = \frac{k_0 T}{K \cdot AUC} \tag{1.82}$$

where T is the infusion time. Equations (1.81) and (1.82) apply irrespective of infusion time and do not require attainment of steady state. Both are general expressions that may be used for many pharmacokinetic models.

Simultaneous Rapid Intravenous Injection and Intravenous Infusion

Since the time required to reach steady state will be very long for a drug with a long half-life, it is often desirable in such cases to administer an intravenous loading dose just before starting the intravenous infusion. The loading dose should be large enough to yield the desired steady-state drug concentration in plasma, C_{ss}, immediately upon injection. The infusion rate should be fast enough to maintain this concentration. If we know the drug concentration we wish to maintain, the appropriate infusion rate is given by rearrangement of Eq. (1.65) (i.e., $k_0 = C_{ss}VK$). Recalling that V is the proportionality constant relating drug concentration in plasma to total amount of drug in the body, one concludes for a one-compartment model that the loading dose X_0 equals $C_{ss}V$. Using this dosage regimen, we can show that the amount of drug in the body is constant until the infusion is stopped.

The equation describing the time course of the amount of drug in the body following simultaneous intravenous injection of a loading dose and initiation of a constant rate intravenous infusion is the sum of the two equations describing each process [i.e., Eqs. (1.5) and (1.63)]. Therefore,

$$X = X_0 e^{-Kt} + \frac{k_0}{K}(1 - e^{-Kt}) \tag{1.83}$$

Substituting $C_{ss}V$ for X_0 and $C_{ss}VK$ for k_0 and rearranging terms yields

$$X = C_{ss}V \tag{1.84}$$

Hence the amount of drug in the body is constant throughout the time course of drug administration.

Urinary Excretion Data

Drug elimination kinetics may also be evaluated from urinary excretion data obtained during constant rate intravenous infusion. The differential equation for the rate of appearance of unmetabolized drug in the urine during infusion is the same as that describing urinary excretion of drug following an intravenous bolus injection [i.e., $dX_u/dt = k_e X$; Eq. (1.14)]. The Laplace transform of this expression is $s\bar{X}_u = k_e\bar{X}$ [Eq. (1.17)]. Substituting for $\bar{X}$ according to Eq. (1.62) and rearranging terms yields

$$\bar{X}_u = \frac{k_e k_0}{s^2(s + K)} \tag{1.85}$$

Solving for X_u (see Appendix A) gives the following relationship between the cumulative amount of drug in the urine and time:

$$X_u = \frac{k_e k_0}{K} t - \frac{k_e k_0}{K^2}(1 - e^{-Kt}) \tag{1.86}$$

When the drug has been infused for a sufficient period so as to approach steady state in the plasma, the term e^{-Kt} approaches zero and Eq. (1.86) reduces to

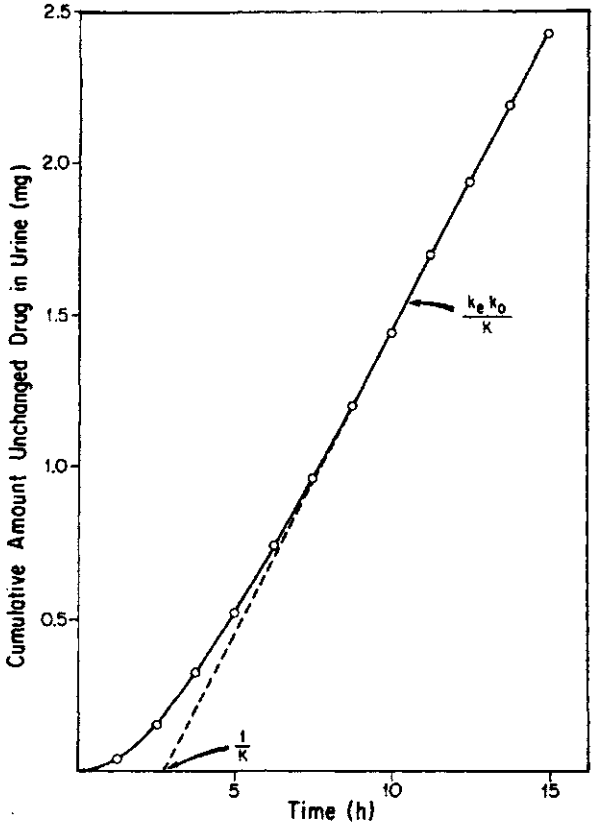


Fig. 1.14 Cumulative amount of unmetabolized drug excreted in the urine as a function of time during constant rate intravenous infusion. The data are described by Eq. (1.86).

$$X_u = \frac{k_e k_0}{K} t - \frac{k_e k_0}{K^2} \tag{1.87}$$

Accordingly, a plot of the cumulative amount of excreted drug versus time is curvilinear initially but eventually becomes linear (see Fig. 1.14). The slope of the linear region is $k_e k_0/K$. Extrapolation of the linear segment of the curve to the time axis yields an intercept equal to $1/K$, since according to Eq. (1.87), $t = 1/K$ when $X_u = 0$. In principle, a plot of cumulative amount of drug excreted during infusion to steady state versus time permits us to estimate both the overall elimination rate constant and the excretion rate constant of a drug.

FIRST-ORDER ABSORPTION

Drug Concentrations in the Plasma

A very large number of plasma concentration-time curves obtained after extravascular (e.g., oral, intramuscular, rectal, etc.) administration of drugs can be described by a one-compartment model with first-order absorption and elimination, despite the fact that first-order absorption is often difficult to rationalize rigorously based on theoretical principles. The equations describing this type of model are analogous to those developed for metabolite concentrations in the plasma and urine. For a drug that enters the body by an apparent first-order absorption process, is eliminated by a first-order process, and distributes in the body according to a one-compartment model, the following differential equation applies:

$$\frac{dX}{dt} = k_a X_a - KX \tag{1.88}$$

where X and K are as defined previously, k_a is the apparent first-order absorption rate constant, and X_a is the amount of drug at the absorption site. The Laplace transform of (1.88) is

$$s\bar{X} = k_a \bar{X}_a - K\bar{X} \tag{1.89}$$

The rate of loss of drug from the absorption site is

$$\frac{dX_a}{dt} = -k_a X_a \tag{1.90}$$

The Laplace transform of which is

$$s\bar{X}_a - FX_0 = -k_a \bar{X}_a \tag{1.91}$$

where F is the fraction of the administered dose X_0 that is absorbed following extravascular administration. Solving (1.91) for $\bar{X}_a$, substituting this value for $\bar{X}_a$ in (1.89), and solving for $\bar{X}$ yields

$$\bar{X} = \frac{k_a F X_0}{(s + K)(s + k_a)} \tag{1.92}$$

By employing a table of Laplace transforms, the following biexponential relationship between the amount of drug in the body and time results:

$$X = \frac{k_a F X_0}{k_a - K}(e^{-Kt} - e^{-k_a t}) \tag{1.93}$$

which in concentration terms is

$$C = \frac{k_a F X_0}{V(k_a - K)}(e^{-Kt} - e^{-k_a t}) \tag{1.94}$$

A survey of the literature indicates that for most drugs administered extravascularly in conventional dosage forms, the absorption rate constant is significantly larger than the elimination rate constant. As a result, at some time after administration the term $e^{-k_a t}$ approaches zero, whereas the term e^{-Kt} is finite, and (1.94) reduces to

$$C = \frac{k_a F X_0}{V(k_a - K)} e^{-Kt} \tag{1.95}$$

This equation describes the postabsorptive phase (i.e., the time when absorption no longer occurs) of a plasma concentration-time curve. Equation (1.95) written in common logarithms is

$$\log C = \log \frac{k_a F X_0}{V(k_a - K)} - \frac{Kt}{2.303} \tag{1.96}$$

A plot of the logarithm of drug concentration in plasma versus time yields a biexponential curve, the terminal portion of which is linear and described by (1.96) (Fig. 1.15). Therefore, an estimate of the elimination rate constant can be obtained from the slope of this terminal linear segment, which is equal to $-K/2.303$. The absorption rate constant may be calculated by the method of residuals (see Appendix C). This graphical approach for estimating k_a and K is useful only if the two rate constants are substantially different. In our experience the method works best if $k_a/K \geq 3$. If this is not the case, the rate constants are best estimated by fitting the concentration-time data to Eq. (1.94) with the aid of a nonlinear least-squares regression program and a digital computer (see Appendix H).

Some drugs are absorbed very slowly, usually because of limited solubility in the fluids at the site of administration—or by design. Other drugs are eliminated from the body very rapidly. In either case absorption may be relatively slow compared to elimination and the ab-

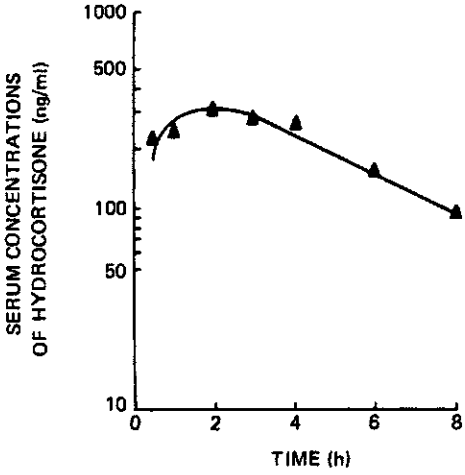


Fig. 1.15 Hydrocortisone concentrations in serum after rectal administration of a retention enema to a healthy subject. The data are described by Eq. (1.94) for the situation where k_a is greater than K. (From Ref. 13, subject 6.)

sorption rate constant may be smaller than the elimination rate constant. This situation is observed often after the administration of drugs in sustained-release dosage forms. In such cases the time course of drug concentration in plasma is described by Eq. (1.94), but the slope of the linear segment of the semilogarithmic plot of concentration versus time is equal to $-k_a/2.303$ rather than $-K/2.303$ and the elimination rate constant must be determined by the method of residuals (see Appendix C). This circumstance is frequently called the flip-flop phenomenon. The determination of whether the linear segment of a semilogarithmic plot of drug concentration in plasma versus time after extravascular administration is related to the elimination rate constant or to the absorption rate constant must be based on an independent estimation of the elimination rate constant either after intravenous administration of the drug or, in some circumstances, after administration of a dosage form from which the drug is more rapidly absorbed (e.g., a solution).

The time course of concentration in plasma of certain drugs suggests a time lag between oral administration and the apparent onset of absorption. This lag may be the result of delayed release of drugs from the dosage form or of a combination of negligible absorption from the stomach and slow gastric emptying. One usually concludes the existence of a time lag if the intersection of the extrapolations of the terminal exponential phase and residual line occurs at a time greater

than zero. If there is no lag time, both extrapolations intersect the log concentration axis at the same point. When a lag is evident, the appropriate equation to describe the time course of drug concentrations in plasma is

$$C = \frac{k_a F X_0}{V(k_a - K)} [e^{-K(t-t_0)} - e^{-k_a(t-t_0)}] \quad (1.97)$$

where t_0 is the lag time.

Drug concentration in plasma versus time data after oral administration can provide estimates of the apparent absorption and elimination rate constants of a drug but usually cannot provide unambiguous estimates of systemic clearance or apparent volume or distribution. Integration of Eq. (1.94) from time zero to time infinity yields

$$AUC = \frac{k_a F X_0}{V(k_a - K)} \left(\frac{1}{K} - \frac{1}{k_a}\right) \quad (1.98)$$

where $k_a F X_0 / V(k_a - K)$ is the intersection of the extrapolation of the terminal exponential phase on the log concentration axis (assuming no lag time). Rearrangement of Eq. (1.98) yields

$$AUC = \frac{F X_0}{VK} \quad (1.99)$$

It follows that the systemic clearance is given by

$$Cl_s = VK = \frac{F X_0}{AUC} \quad (1.100)$$

and the apparent volume of distribution by

$$V = \frac{F X_0}{K \cdot AUC} \quad (1.101)$$

where FX_0 is the amount of drug absorbed or more precisely the amount of drug reaching the systemic circulation. Cl_s and V can be estimated only by assuming absorption to be complete (i.e., by assuming that $F = 1$). If this is not the case, the ratio of administered dose to AUC is not Cl_s but Cl_s/F and the ratio of administered dose to the product of K and AUC is not V but V/F.

Some literature reports have incorrectly estimated V after oral administration by extrapolating the terminal linear phase of the log concentration versus time plot to the log concentration axis and by assuming that the intercept is equal to the administered dose divided by the apparent volume of distribution. As cited above, this intercept is equal to $k_a F X_0 / V(k_a - K)$ rather than to X_0/V.

Determination of C_{max} and t_{max}

Mathematical relationships can be developed to estimate the time at which a peak plasma concentration of drug should be observed and the maximum plasma concentration at this time following first-order input into the body. Expanding Eq. (1.94) yields

$$C = \frac{k_a F X_0}{V(k_a - K)} e^{-Kt} - \frac{k_a F X_0}{V(k_a - K)} e^{-k_a t} \tag{1.102}$$

which when differentiated with respect to time gives

$$\frac{dC}{dt} = \frac{k_a^2 F X_0}{V(k_a - K)} e^{-k_a t} - \frac{k_a K F X_0}{V(k_a - K)} e^{-Kt} \tag{1.103}$$

When the plasma concentration reaches a maximum (C_{max}) at time t_{max}, $dC/dt = 0$. Therefore,

$$\frac{k_a^2 F X_0}{V(k_a - K)} e^{-k_a t_{max}} = \frac{k_a K F X_0}{V(k_a - K)} e^{-K t_{max}} \tag{1.104}$$

which reduces to

$$\frac{k_a}{K} = \frac{e^{-K t_{max}}}{e^{-k_a t_{max}}} \tag{1.105}$$

Taking the logarithm of both sides of Eq. (1.105) and solving for t_{max} yields

$$t_{max} = \frac{2.303}{k_a - K} \log \frac{k_a}{K} \tag{1.106}$$

For a given drug, as the absorption rate constant increases, the time required for the maximum plasma concentration to be reached decreases.

The maximum plasma concentration is described by substituting t_{max} for t in Eq. (1.94):

$$C_{max} = \frac{k_a F X_0}{V(k_a - K)} (e^{-K t_{max}} - e^{-k_a t_{max}}) \tag{1.107}$$

However, a simpler expression can be obtained. From (1.105) it can be shown that

$$e^{-k_a t_{max}} = \frac{K}{k_a} e^{-Kt_{max}} \tag{1.108}$$

Substituting for $e^{-k_a t_{max}}$, according to (1.108), in (1.107) yields

$$C_{max} = \frac{k_a FX_0}{V(k_a - K)} \frac{k_a - K}{k_a} e^{-Kt_{max}} \tag{1.109}$$

which is readily simplified to

$$C_{max} = \frac{FX_0}{V} e^{-Kt_{max}} \tag{1.110}$$

The values of C_{max} and t_{max} under the special circumstance when $k_a = K$ is of mathematical interest and will be considered briefly. Under these conditions, Eq. (1.92) can be written as

$$\overline{X} = \frac{KFX_0}{(s + K)^2} \tag{1.111}$$

Hence

$$X = KFX_0 te^{-Kt} \tag{1.112}$$

$$C = \frac{KFX_0 te^{-Kt}}{V} \tag{1.113}$$

and

$$\log C = \log \frac{KFX_0 t}{V} - \frac{Kt}{2.303} \tag{1.114}$$

Equation (1.114) indicates that when $k_a = K$, a semilogarithmic plot of C versus t will contain no linear segments.

Differentiating Eq. (1.113) with respect to time yields

$$\frac{dC}{dt} = \frac{KFX_0}{V} e^{-Kt} - \frac{K^2 FX_0}{V} te^{-Kt} \tag{1.115}$$

At t_{max}, $C = C_{max}$ and $dC/dt = 0$. Therefore,

$$\frac{KFX_0}{V} e^{-Kt_{max}} = \frac{K^2 FX_0}{V} t_{max} e^{-Kt_{max}} \tag{1.116}$$

which simplifies to

$$t_{max} = \frac{1}{K} \tag{1.117}$$

Substituting t_{max} for t in Eq. (1.113) according to (1.117) gives

$$C_{max} = \frac{KFX_0}{V} \frac{1}{K} e^{-K(1/K)} \tag{1.118}$$

which simplifies to

$$C_{max} = \frac{FX_0}{V} e^{-1} = \frac{0.37FX_0}{V} \tag{1.119}$$

Urinary Excretion Data

Pharmacokinetic evaluation of urinary excretion data obtained after extravascular administration involves relationships similar to those described for evaluating such data after intravenous bolus injection. Substituting for X in Eq. (1.14) according to (1.93) yields

$$\frac{dX_u}{dt} = \frac{k_e k_a FX_0}{k_a - K} (e^{-Kt} - e^{-k_a t}) \tag{1.120}$$

The Laplace transform of Eq. (1.14) is $s\bar{X}_u = k_e\bar{X}$ [Eq. (1.17)]. Substituting for $\bar{X}$ according to Eq. (1.92) gives

$$\bar{X}_u = \frac{k_e k_a FX_0}{s(s + K)(s + k_a)} \tag{1.121}$$

which, when solved for X_u, yields

$$X_u = \frac{k_e k_a FX_0}{K} \left[\frac{1}{k_a} + \frac{e^{-Kt}}{K - k_a} - \frac{Ke^{-k_a t}}{k_a(K - k_a)} \right] \tag{1.122}$$

Equation (1.122) describes the time course of the cumulative amount of intact drug in the urine. At time infinity, (1.122) reduces to

$$X_u^\infty = \frac{k_e FX_0}{K} \tag{1.123}$$

Substitution of X_u^∞ for $k_e FX_0/K$ in (1.122) and rearrangement yields

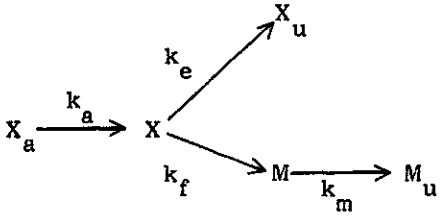
$$X_u^\infty - X_u = \frac{X_u^\infty}{k_a - K} (k_a e^{-Kt} - Ke^{-k_a t}) \tag{1.124}$$

Therefore, a plot of log (dX_u/dt) versus time or log $(X_u^\infty - X_u)$ versus time, according to Eq. (1.120) or (1.124), respectively, will result in a biexponential curve. If k_a is larger than K, the slope of the terminal linear segment of the curve will yield an estimate of the first-order elimination rate constant of parent drug. However, if the opposite is true (i.e., $K > k_a$), the constant obtained from the slope will be the absorption rate constant. If urine samples are obtained soon enough following drug administration, an estimate of k_a (when $k_a > K$) or K (when $K > k_a$) may be obtained by the method of residuals (see Appendix C). However, collection of a sufficient number of urine samples during the absorption phase to enable a pharmacokinetic analysis of this phase is often difficult unless the drug is absorbed slowly.

Metabolite Concentrations in Plasma and Urine

Metabolite concentrations in plasma and urine following oral or intramuscular drug administration may be used under certain conditions to obtain an estimate of the apparent first-order elimination rate constant of a drug. As illustrated in Scheme 4,

Scheme 4



three steps are involved in the appearance of the metabolite in the urine: absorption of the drug, conversion of the drug to a metabolite, and elimination of the metabolite. Considering the principles developed in analyzing metabolite concentrations in the plasma and urine following intravenous injection, it is apparent that the time course of metabolite in the plasma or urine following first-order absorption would be described by a triexponential equation (i.e., a third exponential term is required for the absorption step). Assuming that both k_a and k_m are significantly larger than K, a plot of log C_m, log (dM_u/dt), or log $(M_u^\infty - M_u)$ versus time yields a triexponential curve which at some time becomes linear. An estimate of K may be made from the slope of this terminal linear segment, which is equal to $-K/2.303$.

APPARENT ZERO-ORDER ABSORPTION

The gastrointestinal absorption of drugs is complex and involves several rate processes, including dissolution, absorption from dif-

ferent sites, and gastric emptying, that occur both simultaneously and sequentially. Despite this complexity the rate of appearance of drug in the systemic circulation after oral administration can usually be described by simple first-order kinetics.

Although the assumption of first-order absorption in pharmacokinetics is almost axiomatic, there are several exceptions. Under certain conditions, it has been found that the absorption of certain drugs may be better described by assuming zero-order (constant rate) rather than first-order kinetics (see Fig. 1.16).

The equation describing drug concentration in plasma under these conditions is derived in Appendix B and is given by

$$C = \frac{k_0(e^{KT} - 1)e^{-Kt}}{VK} \tag{1.125}$$

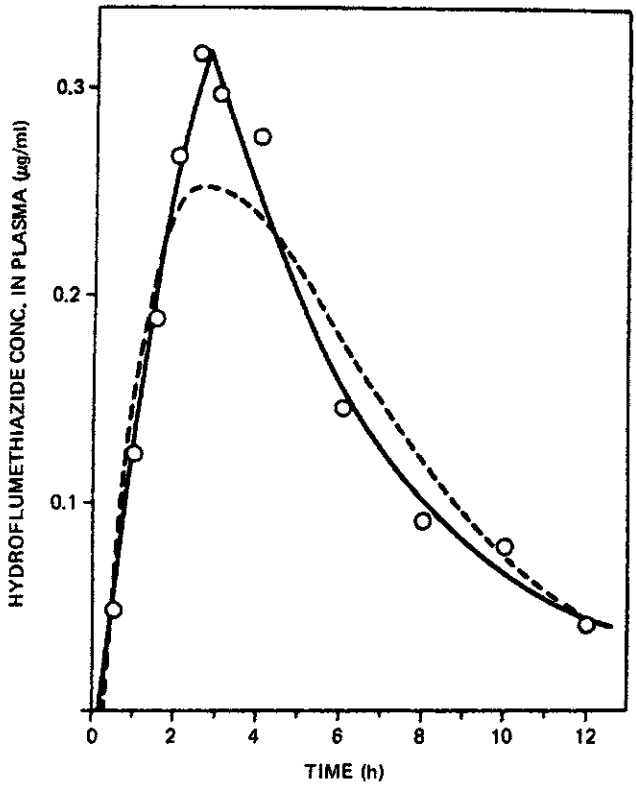


Fig. 1.16 Average hydroflumethiazide concentrations in plasma after a single 100 mg oral dose to 12 healthy subjects. The solid line represents the best fit of the data assuming zero-order abosrption [Eq. (1.125)], and the dashed line represents the best fit assuming first-order absorption [Eq. (1.94)]. (From Ref. 16).

where k_0 is the apparent zero-order absorption rate constant and t is time after drug administration. During absorption, T = t. After absorption apparently ceases, T is a constant corresponding to the absorption time. In the postabsorption phase t = T + t', where t' is the time from the start of the postabsorption phase. Equation (1.125) describes the entire time course of drug concentration in plasma and applies equally to drug concentrations in plasma during and after constant rate intravenous infusion. During the absorption phase $C = k_0(1 - e^{-Kt})/VK$, which is the same as Eq. (1.64) since T = t. The maximum drug concentration in plasma occurs at the end of the absorption phase when t = T. Thus $C_{max} = k_0(1 - e^{-KT})/VK$. During the postabsorption period drug concentrations decline according to Eq. (1.74) since $(e^{KT} - 1)e^{-K(T+t')} = (1 - e^{-KT})e^{-Kt'}$.

The pharmacokinetic parameters required to describe the time course of drug concentrations in plasma (i.e., k_0/V, K, and T) are best estimated by fitting the concentration-time data to Eq. (1.125) with the aid of a nonlinear least-squares regression program and a digital computer (see Appendix H).

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