

Pharmacokinetics

Second Edition
Revised and Expanded

Milo Gibaldi
Donald Perrier

Pharmacokinetics

DRUGS AND THE PHARMACEUTICAL SCIENCES

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Milo Gibaldi

University of Washington
School of Pharmacy
Seattle, Washington

Donald Perrier

School of Pharmacy
University of Arizona
Tucson, Arizona

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healthcare

New York London

Informa Healthcare USA, Inc.
52 Vanderbilt Avenue
New York, NY 10017

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Preface

Pharmacokinetics is the study of the time course of drug absorption, distribution, metabolism, and excretion. It also concerns the relationship of these processes to the intensity and time course of pharmacologic (therapeutic and toxicologic) effects of drugs and chemicals. Pharmacokinetics is a quantitative study that requires a preexisting competence in mathematics at least through calculus. It is also a biologic study and can be very useful to the biomedical scientist.

At a fundamental level, pharmacokinetics is a tool to optimize the design of biological experiments with drugs and chemicals. All biologists would benefit from some knowledge of pharmacokinetics whenever they engage in data analysis. It has become increasingly important in the design and development of new drugs and in the reassessment of old drugs. Clinical applications of pharmacokinetics have resulted in improvements in drug utilization and direct benefits to patients.

There is consensus that the origin of pharmacokinetics can be traced to two papers entitled "Kinetics of distribution of substances administered to the body" written by Torsten Teorell and published in the *International Archives of Pharmacodynamics* in 1937. Since this unheralded beginning, the study of pharmacokinetics has matured rapidly; undoubtedly growth has been stimulated by major breakthroughs in analytical chemistry, which permit us to quantitatively detect minute concentrations of drugs and chemicals in exceedingly small volumes of biological fluids, in data processing, and by the brilliant insights of many scientists. Dost, Kruger-Theimer, Nelson, Wagner, Riegelman, and Levy are among those scientists and must be reserved a special place in the history of the development of pharmacokinetics.

Our goals in preparing this revision were similar to those that prompted us to undertake the initial effort. The need for revision was amply clear to us each time we looked at our files, bulging with research papers and commentaries on pharmacokinetic methods and

applications published since 1975. The buzz words today are clearance concepts, noncompartmental models, and physiologic pharmacokinetics. Again, we strived to present the material in an explicit and detailed manner. We continue to believe that *Pharmacokinetics* can be used in formal courses, for self-study, or for reference purposes.

We thank our colleagues for their work and publications, our staffs for their labors and support, and our families for their love and understanding.

Milo Gibaldi
Donald Perrier

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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:

$$K = k_e + k_m + k'_m + k_b + \dots \quad (1.1)$$

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

$$\frac{dX}{dt} = -KX \quad (1.2)$$

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

$$s\bar{X} - X_0 = -K\bar{X} \quad (1.3)$$

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

$$\bar{X} = \frac{X_0}{s + K} \quad (1.4)$$

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

$$X = X_0 e^{-Kt} \quad (1.5)$$

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

$$\ln X = \ln X_0 - Kt \quad (1.6)$$

Then, based on the relationship

$$2.303 \log a = \ln a \quad (1.7)$$

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

$$\log X = \log X_0 - \frac{Kt}{2.303} \quad (1.8)$$

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:

$$X = VC \quad (1.9)$$

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:

$$\log C = \log C_0 - \frac{Kt}{2.303} \quad (1.10)$$

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

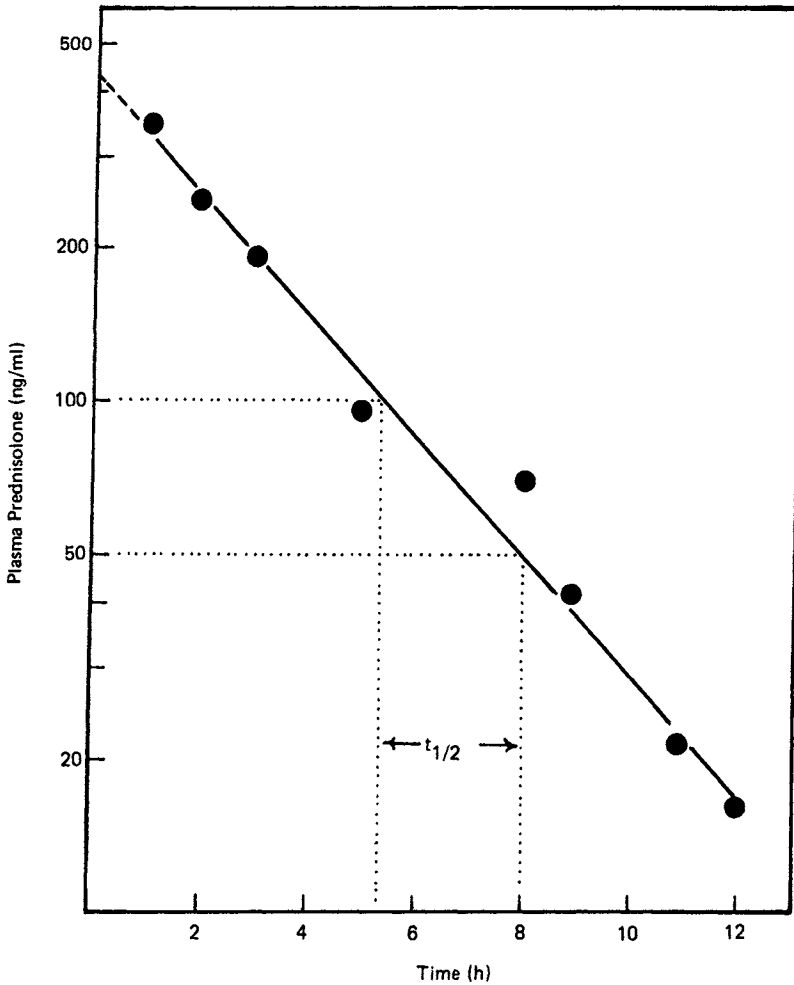


Fig. 1.1 Prednisolone concentration in plasma following an intravenous dose equivalent to 20 mg prednisone to a kidney transplant patient. The data show monoexponential decline that can be described by Eq. (1.10). C_0 = intravenous dose/ V ; slope = $-K/2.303$. (Data from Ref. 1.)

$$V = \frac{\text{intravenous dose}}{C_0} \quad (1.11)$$

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

$$K = \frac{0.693}{t_{1/2}} \quad (1.12)$$

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).

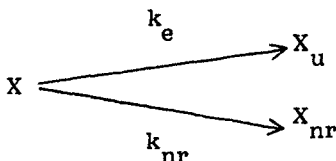
In principle, a plot of the logarithm of tissue drug concentration versus time should also be linear and give exactly the same slope as the plasma concentration-time curve. This is illustrated in Fig. 1.2.

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



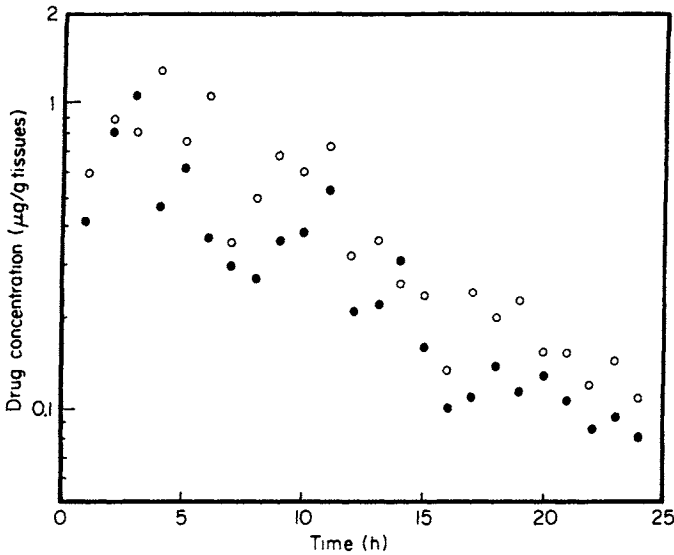


Fig. 1.2 Dipyridamole concentrations in serum (O) and heart tissue (●) after a single oral dose of the drug to guinea pigs. Drug concentrations in serum and heart decline in a parallel manner. (Data from Ref. 2.)

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

$$K = k_e + k_{nr} \quad (1.13)$$

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

$$\frac{dX_u}{dt} = k_e X \quad (1.14)$$

where X is the amount of drug in the body at time t . Substitution for X according to Eq. (1.5) yields

$$\frac{dX_u}{dt} = k_e X_0 e^{-Kt} \quad (1.15)$$

Therefore,

$$\log \frac{dX_u}{dt} = \log k_e X_0 - \frac{Kt}{2.303} \quad (1.16)$$

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

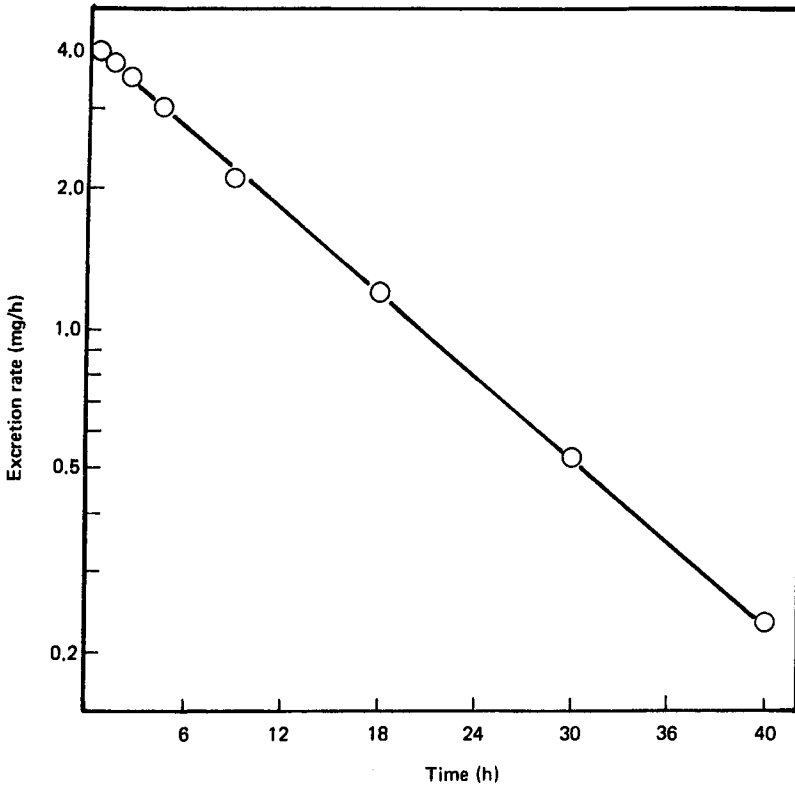


Fig. 1.3 Semilogarithmic plot of excretion rate versus time after intravenous administration of a drug. Data taken from Table 1.1. Each excretion rate is plotted at the midpoint of the urine collection interval. The data are described by Eq. (1.16). Slope = $-K/2.303$.

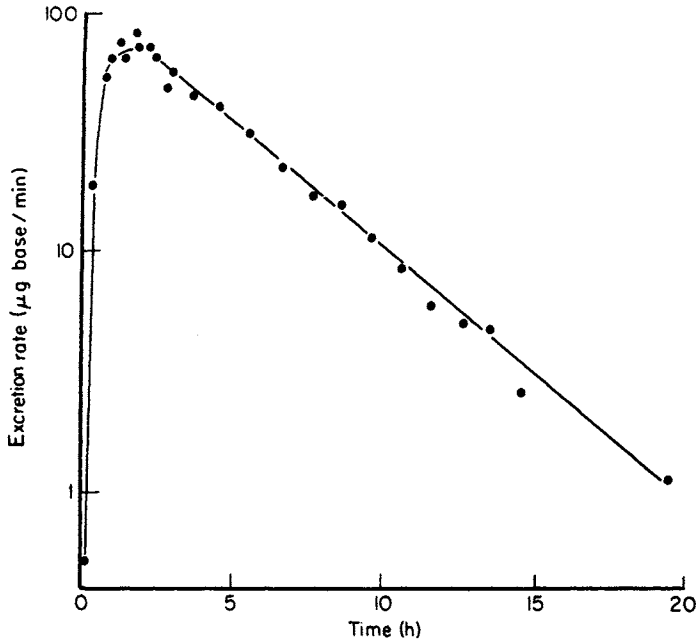


Fig. 1.4 Urinary excretion rate of norephedrine after oral administration of a single dose of the drug to a healthy adult subject. [From Ref. 4. © 1968 American Society for Pharmacology and Experimental Therapeutics, The Williams and Wilkins Company (agent).]

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

$$s\bar{X}_u = k_e \bar{X} \quad (1.17)$$

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

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

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

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

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

$$X_u^\infty = \frac{k_e X_0}{K} \quad (1.20)$$

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

$$X_u^\infty - X_u = X_u^\infty e^{-Kt} \quad (1.21)$$

which in logarithmic form is

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

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-

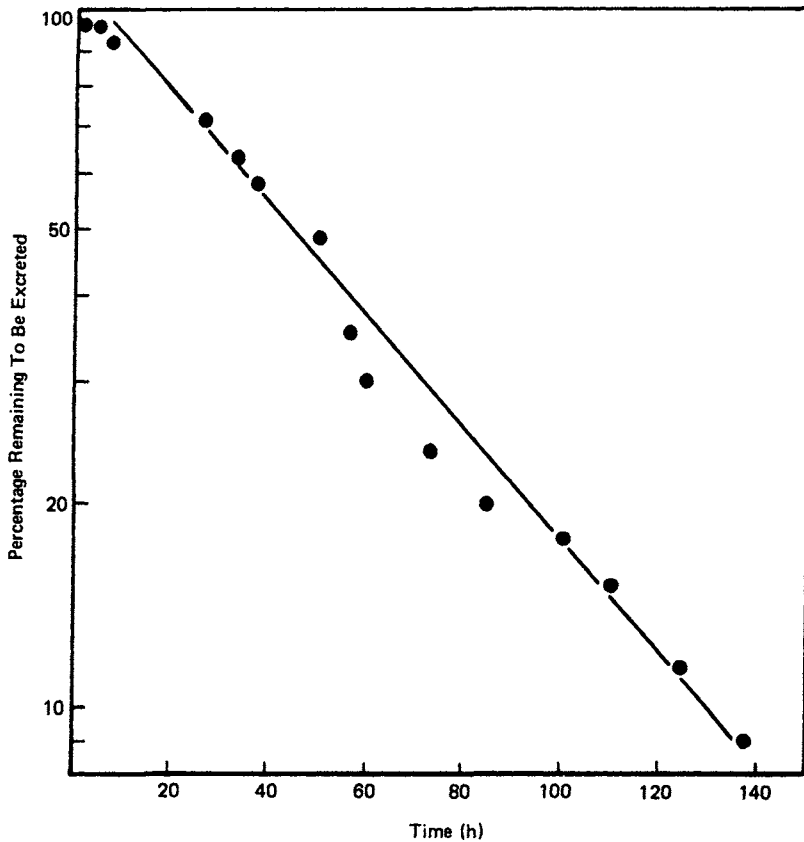


Fig. 1.5 Semilogarithmic plot of the average percentage unmetabolized drug remaining to be excreted versus time after oral administration of 250 mg of chlorpropamide to six healthy subjects. $t_{1/2} = 36$ h. (Data from Ref. 5.)

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

$$Cl_r = \frac{dX_u/dt}{C} \quad (1.23)$$

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

$$Cl_r = \frac{k_e X}{C} \quad (1.24)$$

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

$$Cl_r = k_e V \quad (1.25)$$

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

$$\frac{dX_u}{dt} = Cl_r C \quad (1.26)$$

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

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

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:

$$Cl_r = \frac{X_u^\infty}{\int_0^\infty C dt} = \frac{X_u^\infty}{AUC} \quad (1.28)$$

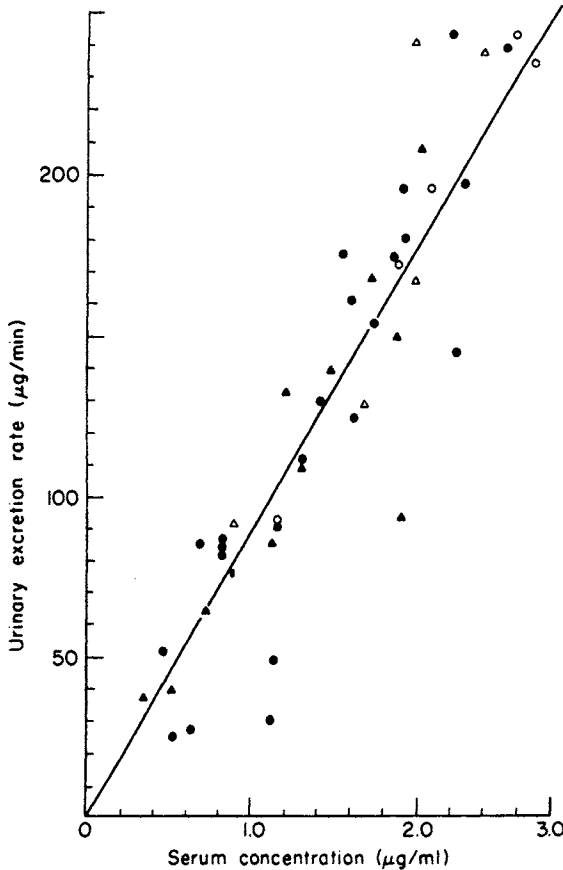


Fig. 1.6 Relationship between urinary excretion rates of tetracycline and serum concentrations of the drug determined at the midpoints of each urine collection interval after oral administration of a 250 mg dose to five healthy adults. Two different oral preparations (●, ▲) were given to each subject. 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.

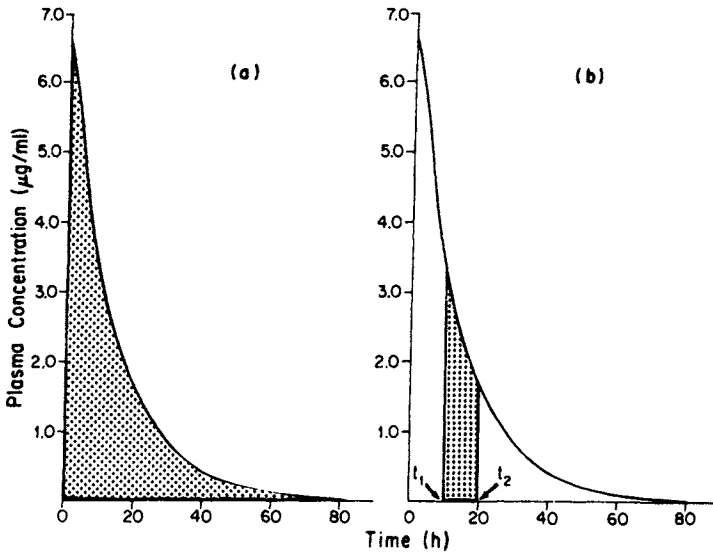


Fig. 1.7 Plots of drug concentration in plasma as a function of time after intravenous administration illustrating, by the shaded region, (a) $\int_0^{\infty} C dt$, the total area under the curve, AUC, and (b) $\int_{t_1}^{t_2} C dt$, the partial area under the curve from t_1 to t_2 .

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

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

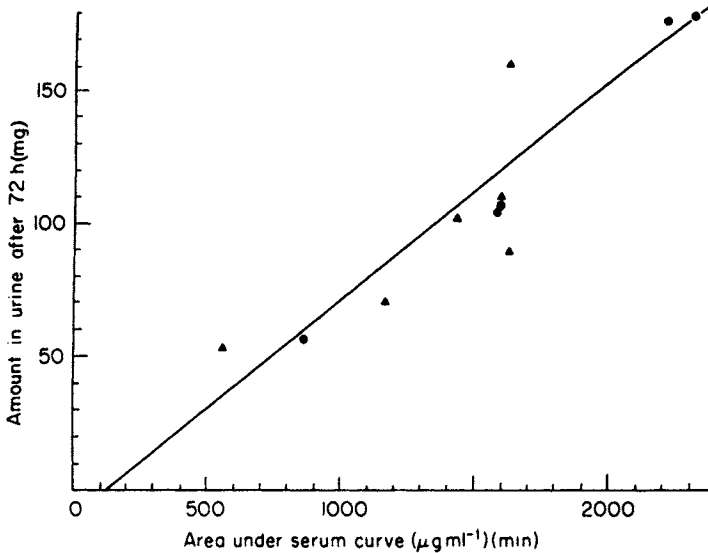


Fig. 1.8 Relationship between cumulative amount of tetracycline excreted after 72 h and the total area under the tetracycline concentration in serum versus time curve after oral administration of a 250 mg dose to five healthy adults. Two different oral preparations (●, ▲) were given to each subject. 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,

$$C = C_0 e^{-Kt} \quad (1.30)$$

Integration from time zero to time infinity yields

$$\text{AUC} = -\frac{C_0}{K} e^{-Kt} \Big|_0^{\infty} = \frac{C_0}{K} \quad (1.31)$$

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

$$V = \frac{X_u^\infty}{k_e \cdot AUC} \quad (1.32)$$

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

$$\frac{X_u^\infty}{k_e} = \frac{X_0}{K} \quad (1.33)$$

it follows that

$$Cl_s = VK = \frac{X_0}{AUC} \quad (1.34)$$

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):

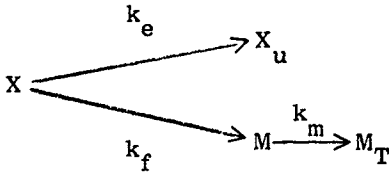
$$V = \frac{X_0}{K \cdot AUC} \quad (1.35)$$

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:

$$\frac{dM}{dt} = k_f X - k_m M \quad (1.36)$$

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

$$s\bar{M} = k_f \bar{X} - k_m \bar{M} \quad (1.37)$$

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

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

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

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

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

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

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about the authors . . .

MILO GIBALDI is Dean and Professor of Pharmaceutics at the School of Pharmacy, University of Washington, Seattle. He received the Ph.D. degree (1963) from Columbia University. Dr. Gibaldi is a member of the editorial boards of *Clinical Pharmacokinetics*, *Clinical Pharmacology and Therapeutics*, *Drug Metabolism Reviews*, *Journal of Pharmaceutical Sciences*, and *Journal of Pharmacokinetics and Biopharmaceutics*. He is the author of over 150 research papers in the fields of biopharmaceutics and pharmacokinetics. Dr. Gibaldi is also a consultant in the pharmaceutical industry and is a member of the G. D. Searle Science Advisory Board. He is a Fellow of the Academy of Pharmaceutical Sciences and the American Association for the Advancement of Science.

DONALD PERRIER is a professor at the School of Pharmacy at the University of Otago in New Zealand. He was formerly Associate Professor of Pharmaceutical Sciences at the College of Pharmacy, University of Arizona, Tucson. He received the Ph.D. degree (1973) from the State University of New York at Buffalo. Dr. Perrier is on the editorial board of *Drug Metabolism and Disposition* and is a Consulting Editor for *Clinical Pharmacy*. He is a member of the Drug Abuse Biomedical Research Review Committee of the National Institute of Drug Abuse, Academy of Pharmaceutical Sciences, American Pharmaceutical Association, and American Association of Colleges of Pharmacy.

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