DRUG THERAPY FOR THE ELDERLY

Edited by

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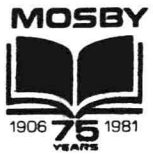

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Preface

The elderly constitute an increasing proportion of the world's population. Moreover, they often are afflicted with one or more chronic diseases for which multiple medications are administered. Drug clearance and homeostatic mechanisms are frequently diminished in elderly patients, resulting in more pronounced and longer-lasting drug effects. Adverse drug reactions and drug interactions occur more often, exposing these patients to risks of therapy that at times may be greater than the benefits the practitioner anticipates.

This book is written in an attempt to elucidate the influences of age and disease on drug absorption, distribution, elimination, and effects. It is our hope that by applying this information physicians will be able to employ medications more judiciously, improving therapeutic efficacy while minimizing adverse effects.

Kenneth A. Conrad
Rubin Bressler

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SECTION I

Basic concepts in drug disposition

1 Fundamental principles of pharmacokinetics

MICHAEL MAYERSOHN

During the last decade the medical literature has evidenced an increasing number of reports concerned with the application of pharmacokinetic principles to the evaluation and improvement of drug therapy. Considerable insight into drug disposition and factors influencing disposition may be obtained by properly designed experimentation and by data analysis according to those principles. A good example is attempts to quantitatively evaluate drug disposition in the elderly. Pharmacokinetic considerations in this group are discussed in a subsequent chapter. The aim of this chapter is to introduce several basic ideas of pharmacokinetics to provide a groundwork for the subsequent presentation. This discussion is presented at a level that has minimized mathematical treatment. The readers are referred to several reviews that further illustrate the clinical applications of pharmacokinetics[2,3,5] and to several more advanced treatments of the subject.[4,18]

THE CONCEPT OF BIOLOGIC MODELS

Scientists who deal with biologic systems for the purpose of quantitating one or several distinct processes being studied must in some manner contend with the complexity of that real system. This complexity exists whether one is examining an individual cell or organ or an entire animal body. We face such a problem when we attempt to describe the disposition of a drug in a whole animal. How can we rigorously quantitate the processes of drug disposition in such a complex system? A successful approach that has been used in resolving this problem rests on making a number of assumptions that considerably simplify the real system. Based upon these assumptions one constructs a "biologic model" that we conceive to be an analogue of the real system, albeit a much simplified construct. In the same way that a model airplane is an analogue of its mechanically complex counterpart, a biologic model reflects the complex real biologic system. These models are not replicates of the real system, however, for in that form they would not serve to simplify.

A useful biologic model must have at least two characteristics: it must be simple for the purposes of data analysis and it must reflect the behavior of the real system. The beauty of a theoretical

biologic model lies in its simplicity and therefore in the relative ease with which one can mathematically analyze the processes of interest—in this case drug disposition. Because of this simplicity one can derive explicit mathematical relationships that will enable the interpretation of experimental data. However, if the model is too simple because of the assumptions made in its development, then the model will not adequately reflect or explain the experimental data. The ultimate test for the usefulness of a model is the second characteristic cited above—how well the model reflects the data and how well it can predict the behavior of the real biologic system. The most appropriate model is the simplest one that explains the data and the behavior of the real system.

One approach that has been successfully used in pharmacokinetics conceives of the body as being made of a series of interconnected regions referred to as "compartments." These compartments are abstractions in that they may not refer to any specific organs or tissues in the body. The compartments represent regions of the body that behave in a similar way with respect to drug disposition. For example, tissues that are highly perfused by blood, such as those of the kidney, liver, and brain, may be considered one compartment because of the similarity of these tissues with respect to drug distribution. The complexity of a model with respect to the number of compartments depends on the distribution characteristics of the drug, the intensity and duration of the sampling of biologic fluids (e.g., blood), and the number of different fluids that may be sampled. The latter two factors may severely limit the complexity of a model. In theory one may describe a model with any number of compartments, but in practice one seldom needs to exceed a two- or three-compartment system; indeed one rarely has sufficient data to do so. The models most frequently encountered in pharmacokinetics are illustrated in Fig. 1-1. Also illustrated are hydrodynamic analogies and drug concentration-time profiles corresponding to each model. Each of these models assumes intravenous (IV)

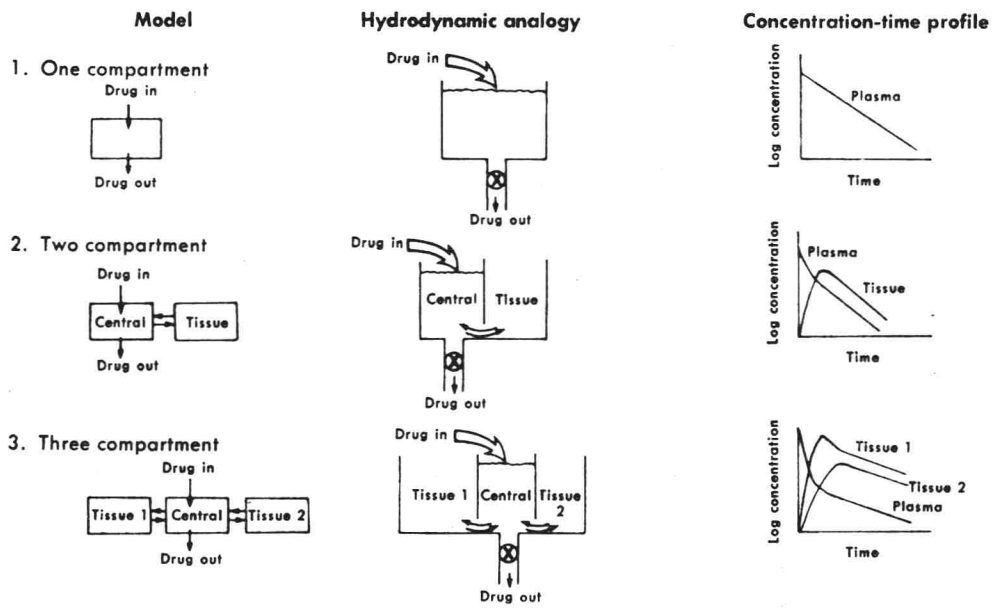

Fig. 1-1. Examples of three increasingly more complex compartmental biologic models and their corresponding hydrodynamic analogies and concentration-time profiles. These models are frequently used in pharmacokinetics to describe drug disposition.

drug administration, that drug loss takes place from only one compartment (central), and that other compartments are directly attached to the central region (i.e., mammillary models). The appropriate model is usually determined from a statistical analysis of drug plasma concentration-time data after IV administration. From the results of this analysis, one is able to predict concentrations in the other "tissue" compartments. The use of these biologic models will be illustrated in subsequent discussions.

VASCULAR (INTRAVENOUS) DRUG ADMINISTRATION

The most accurate approach to examine the disposition of a drug is to introduce the compound directly into the bloodstream by IV administration. In this way one is assured that the entire dose of the drug has been placed into the body. After sequential blood samples are taken and the concentration of unchanged drug in each sample is determined, a plot of concentration vs. time frequently has the appearance of the graph shown in Fig. 1-2. The slope of this line represents the rate of drug loss or decline from the body, and this rate of loss decreases with time (such a process is referred to as exponential loss). As a result the rate of loss of drug from the body at a given time is proportional to the concentration of drug in the body at that time. The rate of loss of drug (dC/dt) may be given by equation 1, in which C represents the concentration of drug in the body and t is time. The negative sign reflects the fact that drug is being lost or eliminated from the body. The proportionality sign has been replaced by a constant, K, in the equation

$$\text{Rate of loss} = \frac{dC}{dt} = -K \cdot C \qquad (1)$$

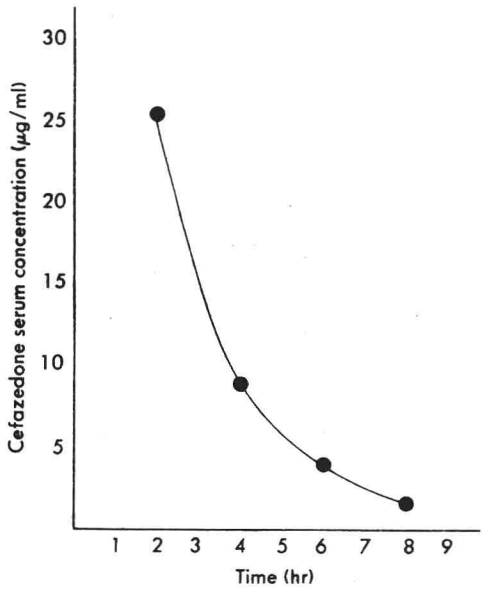

Fig. 1-2. Average cefazedone serum concentration as a function of time after IV administration of 1 gm dose to ten normal men. Data are plotted on regular (Cartesian coordinate) graph paper. Shape of curve indicates exponential drug elimination. (Data from Pabst, J., et al.: Arzneim.-Forschung **29**:437, 1979.)

Equation 1 is characteristic of a process referred to as first-order kinetics. The term simply refers to the fact that rate of loss depends directly on concentration of drug. The proportionality constant, K, is referred to as the *first-order elimination rate constant* (units, 1/time, or time^{-1}). Because we are more interested in the relationship between concentration of drug and time than the relationship between rate of loss and concentration, equation 1 must be integrated to obtain a more useful expression. The integrated form of equation 1 is

$$C = C^0 \cdot e^{-K \cdot t} \qquad (2)$$

In this equation e is the base of natural numbers and C^0 is the initial concentration of drug in the body at time 0. We noted that the curve in Fig. 1-2 is referred to as an exponential process; the reason for that is given by the relationship between C and time in equation 2. The concentration of drug in the body will decrease according to the exponent in that equation.

Because it is difficult to analyze the data as shown in Fig. 1-2, these data are usually plotted in such a way that a straight line relationship is obtained between C and time. This can be achieved by taking the logarithms of equation 2, and when this is done the following relationship is obtained:

$$\log C = \log C^0 - \frac{K \cdot t}{2.3} \qquad (3)$$

A graph of the data according to equation 3 may be obtained either by taking the logarithms of the C values and plotting as a function of time or, more usually, by plotting the values of C on semilogarithmic graph paper. The latter approach is preferred because it is more simple and less prone to calculation errors. Semilog paper does not convert values to logarithms but rather spaces the values on a logarithmic scale. Equation 3 is in the general form of a straight line equation (i.e., $Y = b + m \cdot x$, where b = intercept and m = slope). A semilog plot of C vs. time will result in a straight line with an intercept of C^0 and a slope equal to $-K/2.3$. The data of Fig. 1-2 are replotted on semilog graph paper in Fig. 1-3 according to the straight line equation (equation 3). The elimination rate constant, K, can be determined by calculating the slope and multiplying by 2.3. Any two points on this line will suffice for that calculation. However, a simpler way of calculating K involves introducing an important pharmacokinetic parameter, *elimination half-life* (T½), which is defined as the time required for a given value of plasma concentration to decline by 50%. This definition will be qualified later when drug distribution and absorption are discussed. It can be shown for a first-order kinetic process that T½ and K are inversely related.

$$T½ = \frac{0.693}{K} \qquad (4)$$

The value for T½ may be determined from a graph of data as shown in Fig. 1-3. The T½ has been calculated by determining the time required for the cefazedone plasma concentration to decline from 20 to 10 μg/ml. The vertical lines indicate that the T½ for cefazedone is approximately 1.5 hours (i.e., 3.9 − 2.4 hr). Any other convenient pair of points could be used (e.g., 10 to 5 or 5 to 2.5). If T½ is known, K may be calculated by equation 4 ($K = 0.693/1.5\ hr = 0.46\ hr^{-1}$). To get an appreciation for the meaning of K and T½, it is instructive to refer to the hydrodynamic analogy for the one-compartment model shown in Fig. 1-1. The outflow pipe connected to the body tank has a certain cross-sectional diameter the magnitude of which is proportional to the value of K. The larger this diameter, the larger the value of K and the more rapidly will the drug be eliminated from the body. If K is large, T½ is small, consistent with short drug residence in the body. T½ is an extremely useful parameter and it is characteristic of a given drug and a given patient. Table 1-1 lists the average T½ of several commonly used drugs in healthy adults.

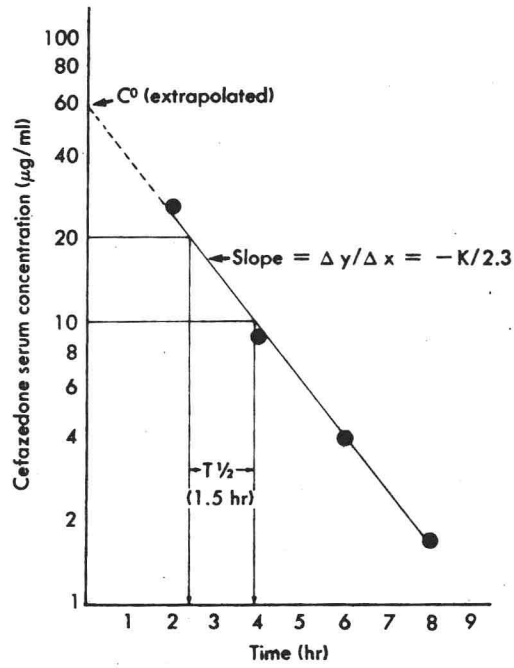

Fig. 1-3. Average cefazedone serum concentration as a function of time after IV administration. Graph is semilog plot of same data used in Fig. 1-2. Slope of line is −K/2.3 (K = first-order elimination rate constant). Straight line has been extended to y axis to give intercept equal to C^0 (extrapolated). Vertical lines indicate values used to determine elimination half-life (T½, 1.5 hours). (Data from Pabst, J., et al.: Arzneim.-Forschung **29**:437, 1979.)

Equation 4 indicates another important aspect of drug elimination by a first-order process—T½ is *independent of dose*. Therefore, if one were to give different doses of, for example, cefazedone, a series of lines would be obtained that are parallel to the one shown in Fig. 1-3. This behavior is frequently referred to as linear or *dose-independent pharmacokinetics*. Fortunately, the majority of

Table 1-1. Average elimination half-lives of some commonly used drugs in healthy adults

Drug	*T½ (hr)*
Diazepam	48
Digitoxin	150
Digoxin	36
Gentamicin	2
Lidocaine	2
Phenobarbital	90

drugs (with some notable exceptions) are eliminated by a first-order kinetic process. The disposition of such drugs is predictable, since with a change in dose the T½ will remain constant and there will be a proportional change in plasma concentrations.

The cefazedone data as illustrated in Figs. 1-2 and 1-3 are consistent with the one-compartment model (Fig. 1-1). This model assumes that once a drug gains access to the bloodstream it distributes instantaneously throughout the body, and because distribution is so rapid it cannot be measured. The ability to measure this distribution process results in the need to develop multicompartment models. In the one-compartment model, it is important to distinguish between kinetic and concentrational homogeneity. Although in this model all body regions are grouped into a single compartment, the concentrations of drug in, for example, the liver and blood may be very different even though these concentrations decline with the same overall T½. Therefore, these various body regions are kinetically homogenous, but the drug concentrations in these regions may not be the same.

If identical doses of several different drugs were to be given IV to one subject, the resulting plasma concentrations would likely be quite different. One reason for this difference is explained by a parameter referred to as the apparent *volume of distribution* (V_d). A drug will distribute throughout the body in an apparent volume the magnitude of which depends on certain physiologic characteristics and on certain characteristics of the drug molecule, for example, oil-water partition coefficient, molecular size, extent of ionization at body fluid pHs, preferential binding to body tissues or organs, plasma protein concentration, and blood flow. Since the characteristics cited will vary among different drugs, the apparent volume and therefore plasma concentrations will also be different. The volume of distribution serves primarily two functions. The volume is a proportionality constant between plasma concentration and the amount of drug in the body (i.e., plasma concentration $\cdot$ V_d = amount of drug in the body). As long as distribution is instantaneous (e.g., one-compartment model) the above relationship will hold true at any time after drug administration. The cefazedone data shown in Fig. 1-3 appear consistent with the assumption of instantaneous distribution, and therefore the straight line can be extrapolated to the y axis to obtain an estimate of the initial, time 0 serum concentration (i.e., C^0 or $C^0_{extrapolated}$). Although we will reexamine this assumption later, the value for V_d can be obtained by the relationship $V_d = X^0/C^0$, where X^0 is the IV dose (1000 mg). Since the extrapolated C^0 is approximately 60 μg/ml, V_d is approximately 16.7 L. This V_d has been obtained by using an extrapolated value for C^0, and it is properly referred to as $V_{d \cdot xtrp}$. It is important to recognize that V_d is being defined with plasma or blood serving as the reference region for concentration. This is done simply because blood is an easily accessible body fluid. The volume of distribution relative to a different body fluid or tissue will have a completely different value and meaning.

The second major function of V_d is to serve as an indication of the extent of drug distribution out of the vascular region. If a drug has a large V_d, this reflects the fact that the drug distributes extensively into body tissues other than the blood. Conversely, a small V_d will usually indicate that distribution out of the bloodstream is not extensive. For example, drugs that are extensively bound to plasma proteins frequently have a small V_d and relatively high plasma concentrations (e.g., warfarin). On the other hand, drugs that distribute extensively into adipose tissue will have a large V_d and relatively small plasma concentrations (e.g., thiopental). It is important to recognize that V_d is only an *apparent* volume and it will not necessarily represent a real physiologic or anatomic space. For example, digoxin has a V_d of about 70 L (10 L/kg) in normal adults. This obviously is not a real space but reflects the fact that digoxin is found in greater amounts in certain regions of

the body (e.g., skeletal muscle) as compared with blood. On the other hand, the aminoglycoside antibiotics have a V_d (approximately 0.24 L/kg) that, based on their known distribution characteristics, appears to correspond primarily to extracellular fluid volume.

At this point it is necessary to reexamine the correctness of an assumption made in the discussion of volume of distribution. The assumption made was that drug distribution was instantaneous after IV administration. If this is the case, then we are dealing with a one-compartment model, which is consistent with the cefazedone plasma concentration-time data illustrated in Fig. 1-3. It has become apparent, however, that this is a simplification that is not consistent with the actual distribution behavior of many drugs (i.e., distribution is not instantaneous). As a result, we frequently have to resort to the next more complex model, the two-compartment model (Fig. 1-1), to properly describe the plasma concentration-time profile. In this situation, the equation that describes the time course of plasma concentration after an IV dose is biexponential and is usually given as

$$C = Ae^{-\alpha t} + Be^{-\beta t} \qquad (5)$$

A and B are coefficients the values of which may be obtained from the y axis, and α and β are first-order rate constants. To appreciate the disposition of a drug that is described by a two-compartment model, refer to Fig. 1-1. Immediately after IV administration the entire dose of the drug is placed into the central compartment, which has a volume, V_c. The body regions that are grouped into this compartment are determined by the characteristics of the drug, but usually only those regions that are highly perfused by blood will be in this central region (e.g., liver, kidney, and brain). The plasma concentration at this time (time 0) will be a reflection of V_c. After the dose is administered, the drug begins to distribute to other body regions that are represented by the tissue (or peripheral) compartment in the model. During this distributive phase plasma concentrations decline relatively rapidly. Eventually a distribution equilibrium is attained, and when this happens drug concentrations in the central and tissue compartments decline in parallel. As mentioned previously, this is a kinetic rather than a concentrational homogeneity. At times after this equilibrium or in the postdistributive phase, plasma and tissue concentrations will be described by a straight line on semilog paper. The latter is a result of one exponent ($e^{-\alpha t}$) contributing little to the plasma concentration value, and thus at these times plasma concentrations are described by only one exponent ($e^{-\beta t}$).

The actual cefazedone plasma concentration-time data have been replotted in Fig. 1-4, but this graph includes all data points immediately after administration (Fig. 1-3 has points only after 2 hours). When all data are plotted, the line in Fig. 1-4 indicates that distribution is not instantaneous; the more correct model to describe disposition of this drug is the two-compartment model. One conclusion that can be reached when contrasting Figs. 1-3 and 1-4 is that if blood sampling is not intensive following drug administration (i.e., at times earlier than 2 hours), the wrong biologic model may be applied. The T½ can only be correctly determined from data on the straight line (in the postdistributive phase). The T½ is numerically equal to that determined in Fig. 1-3 (i.e., 1.5 hours). Frequently the first-order rate constant describing this straight line is referred to as β rather than K, and although β and K have different meanings they are numerically equal.

One error frequently made in analyzing data such as those shown in Fig. 1-4 is that of extrapolating the straight line back to the y axis (as was done in Fig. 1-3) to calculate a $V_{d \cdot xtrp}$. This volume term, which was calculated to be about 16.7 L, has no useful meaning. It would be correct and useful only if distribution were instantaneous (i.e., one-compartment model). However, $V_{d \cdot xtrp}$ will not serve one of the primary useful functions of a volume of distribution; that is, it will not relate plasma concentration to the amount of drug in the body. To avoid this problem another volume of distribution term must be employed. A correct and useful volume term, referred to either as $V_{d \cdot \beta}$ or $V_{d \cdot area}$, which is independent of the model required to describe drug disposition, is given by

$$V_{d \cdot \beta} = \frac{X_{IV}^0}{(AUC)_0^\infty \cdot \beta} \qquad (6)$$

$(AUC)_0^\infty$ represents the total area (i.e., from time 0 to infinity) under the plasma concentration-time

curve. This area may be determined by applying the trapezoidal rule or by computer fitting the data and using the values of the parameters in equation 5 (i.e., $[AUC]_0^\infty = A/\alpha + B/\beta$). This area represents the integration of the equation describing the plasma concentration-time curve (i.e., equation 5). If the cefazedone data are reevaluated according to equation 6 (where $X_{IV}^0 = 1000$ mg, $\beta = 0.46$ hr^{-1}, and $[AUC]_0^\infty$ can be determined to be 197 mg/L · hr), a value of 11.0 L is obtained for $V_{d \cdot \beta}$. This value is considerably smaller than the $V_{d \cdot xtrp}$ of 16.7 L. The error made in determining a volume by either $V_{d \cdot xtrp}$ or $V_{d \cdot \beta}$ will depend on the magnitude of drug distribution. If distribution is minimal the disposition of the drug may be approximated by a one-compartment model and there will be little difference between the two volume terms. On the other hand, if distribution is pronounced there will be a major difference between the two with $V_{d \cdot xtrp}$ being a large overestimate of $V_{d \cdot \beta}$. There is one restriction in the use of $V_{d \cdot \beta}$, namely, that it relates plasma concentration and amount of drug in the body only at times in the postdistributive phase. There is no useful volume term for this purpose during the distributive phase.

In addition to the information that may be obtained from plasma concentration-time data, the analysis of urinary excretion data will provide further knowledge about drug disposition. The routes of drug elimination can be established by assaying urine for unchanged drug and metabolites. Urine data may also be quantitated to obtain estimates of T½. One method to determine T½ is known as the excretion rate method. Complete urine collections are obtained at timed intervals after drug adminis-

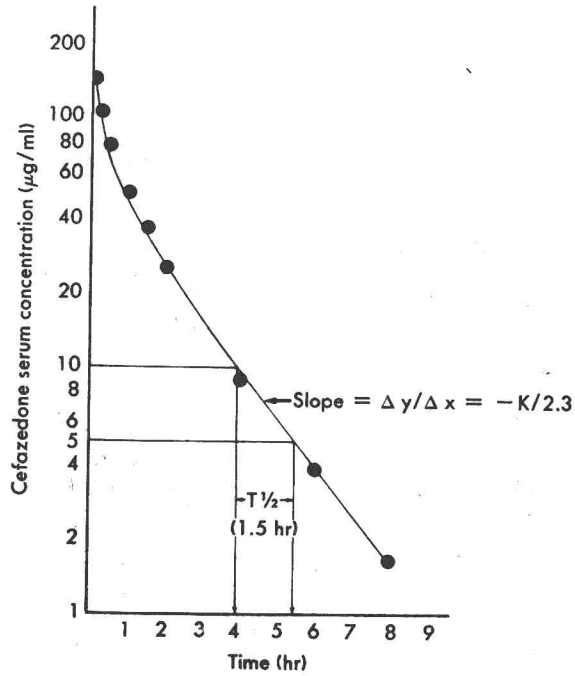

Fig. 1-4. Average cefazedone serum concentration as a function of time after IV administration. Same data as in Fig. 1-3 are replotted here, as are data obtained immediately after dose administration. Data indicate that drug distribution is not instantaneous and is consistent with a two-compartment model. T½ (1.5 hours) is same as that calculated in Fig. 1-3. (Data from Pabst, J., et al.: Arzneim.-Forschung 29:437, 1979.)

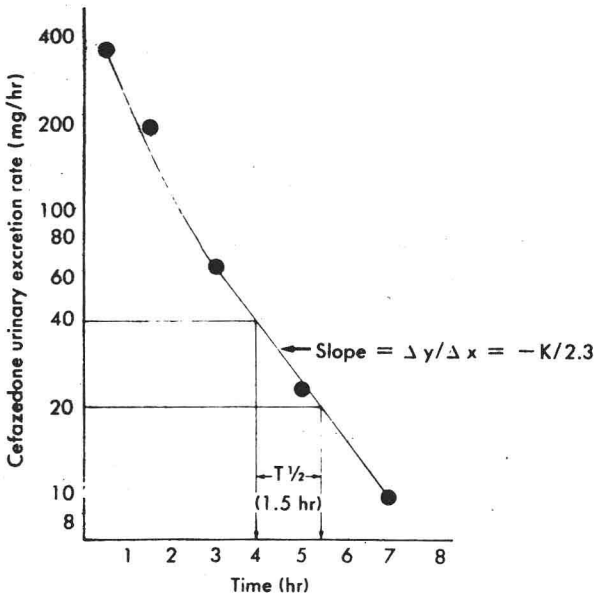

Fig. 1-5. Average cefazedone urinary excretion rate as a function of time after IV administration of 1 gm to ten normal men. Data are plotted on semilog paper. Determination of T½ (1.5 hours) is illustrated. (Data from Pabst, J., et al.: Arzneim.-Forschung **29:437**, 1979.)

tration and the urine is assayed for unchanged drug. By determining the amount of unchanged drug excreted in each of these collection intervals one can calculate an excretion rate (usually expressed as, for example, mg/hr). By plotting excretion rate as a function of time on semilog paper, a straight line is obtained from which T½ can be determined. This analysis is illustrated in Fig. 1-5 for the cefazedone data. Approximately 80% of the IV cefazedone dose is ultimately excreted unchanged in the urine. The latter value is determined after collecting total urine for a period of approximately six T½s (approximately 9 hours). The latter point is important because if the T½ were 24 hours, then urine must be collected for about 6 days to obtain an accurate estimate of the fraction of the dose ultimately excreted unchanged.

It would be useful to have a means of expressing the efficiency of an elimination process, for example, renal excretion or hepatic metabolism. Rate of elimination does not serve this purpose since, for a first-order process, rate constantly changes with time as plasma concentration decreases. The proportional rate of removal, K, may be useful for this purpose (as long as rate of loss and concentration are directly related); however, its value depends on the volume of the compartment from which loss occurs. In contrast the parameter *clearance* depends only on the efficiency of the removal process. The clearance of a compound by any given elimination process is defined as *the volume of the compartment from which the compound is completely removed (or cleared) per unit of time*. Clearance has units of flow (e.g., ml/min). Renal clearance has been used by physiologists to express the efficiency of urinary excretion and it is a useful parameter in evaluating the mechanism of excretion (i.e., glomerular filtration, active tubular secretion, or reabsorption). The idea of clearance may be applied to any eliminating organ (e.g., hepatic clearance or pulmonary clearance). In addition, one can determine the total body clearance (TBC), which represents the sum of each clearance term associated with drug removal from the body.