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Applied Biopharmaceutics & Pharmacokinetics > Chapter 3. One-Compartment Open Model: Intravenous Bolus Administration >

## ONE-COMPARTMENT OPEN MODEL: INTRAVENOUS BOLUS ADMINISTRATION: INTRODUCTION

The most common and most desirable route of drug administration is orally—by mouth—using tablets, capsules, or oral solutions. In developing pharmacokinetic models to describe and predict drug disposition kinetically, the model must account for both the route of administration and the kinetic behavior of the drug in the body.

The *one-compartment open model* offers the simplest way to describe the process of drug distribution and elimination in the body. This model assumes that the drug can enter or leave the body (ie, the model is "open"), and the body acts like a single, uniform compartment. The simplest route of drug administration from a modeling perspective is a rapid intravenous injection (IV bolus). The simplest kinetic model that describes drug disposition in the body is to consider that the drug is injected all at once into a box, or compartment, and that the drug distributes instantaneously and homogeneously throughout the compartment. Drug elimination also occurs from the compartment immediately after injection.

Of course, this model is a simplistic view of drug disposition in the body, which in reality is infinitely more complex than a single compartment. In the body, when a drug is given in the form of an IV bolus, the entire dose of drug enters the bloodstream immediately, and the drug absorption process is considered to be instantaneous. In most cases, the drug distributes via the circulatory system to potentially all the tissues in the body. Uptake of drugs by various tissue organs will occur at varying rates, depending on the blood flow to the tissue, the lipophilicity of the drug, the molecular weight of the drug, and the binding affinity of the drug for the tissue mass. Most drugs are eliminated from the body either through the kidney and/or by being metabolized in the liver. Because of rapid drug equilibration between the blood and tissue, drug elimination occurs as if the dose is all dissolved in a tank of uniform fluid (a single compartment) from which the drug is eliminated. The volume in which the drug is distributed is termed the *apparent volume of distribution*,  $V_D$ . The apparent volume of distribution assumes that the drug is uniformly distributed in the body. The  $V_D$  is determined from the preinjected amount of the dose in the syringe and the plasma drug concentration resulting immediately after the dose is injected.

The apparent volume of distribution is a parameter of the one-compartment model and governs the plasma concentration of the drug after a given dose. A second pharmacokinetic parameter is the *elimination rate constant*,  $k$ , which governs the rate at which the drug concentration in the body declines over time. The one-compartment model that describes the distribution and elimination after an IV bolus dose is given in .

Figure 3-1.



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Pharmacokinetic model for a drug administered by rapid intravenous injection.  $D_B$  = drug in body;  $V_D$  = apparent volume of distribution;  $k$  = elimination rate constant.

The one-compartment open model does not predict actual drug levels in the tissues. However, the model assumes that changes in the plasma levels of a drug will result in proportional changes in tissue drug levels, since their kinetic profile is consistent with inclusion within the vascular compartment and the various drug concentrations within the compartment are in equilibrium. The *drug in the body*,  $D_B$ , cannot be measured directly; however, accessible body fluids (such as blood) can be sampled to determine drug concentrations.

## ELIMINATION RATE CONSTANT

The rate of elimination for most drugs from a tissue or from the body is a first-order process, in which the rate of elimination is dependent on the amount or concentration of drug present. The elimination rate constant,  $k$ , is a first-order elimination rate constant with units of  $\text{time}^{-1}$  (eg,  $\text{hr}^{-1}$  or  $1/\text{hr}$ ). Generally, the parent or active drug is measured in the vascular compartment. Total removal or elimination of the parent drug from this compartment is effected by metabolism (biotransformation) and excretion. The elimination rate constant represents the sum of each of these processes:

$$k = k_m + k_e \quad (3.1)$$

where  $k_m$  = first-order rate process of metabolism and  $k_e$  = first-order rate process of excretion. There may be several routes

of elimination of drug by metabolism or excretion. In such a case, each of these processes has its own first-order rate constant.

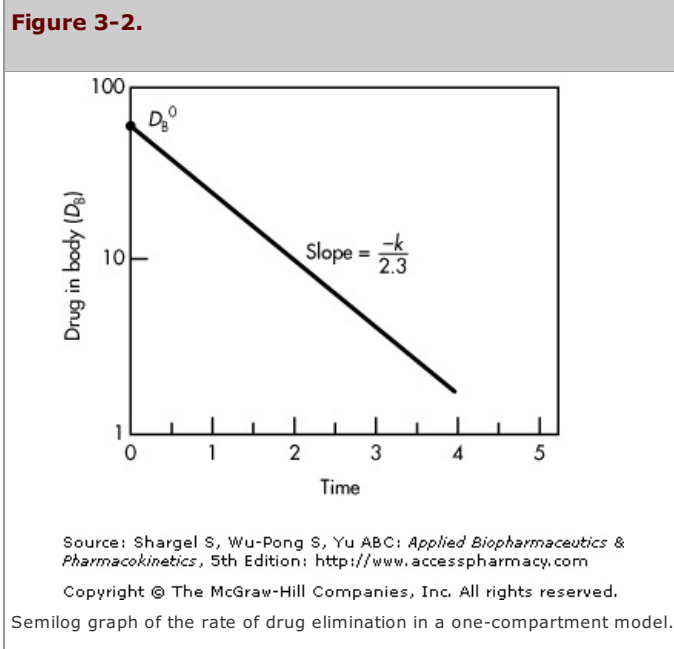
A rate expression for is

$$\frac{dD_B}{dt} = -kD_B \quad (3.2)$$

This expression shows that the rate of elimination of drug in the body is a first-order process, depending on the overall elimination rate constant,  $k$ , and the amount of drug in the body,  $D_B$ , remaining at any given time,  $t$ . Integration of Equation 3.2 gives the following expression:

$$\log D_B = \frac{-kt}{2.3} + \log D_B^0 \quad (3.3)$$

where  $D_B$  = drug in the body at time  $t$  and  $D_B^0$  = drug in the body at  $t = 0$ . When  $\log D_B$  is plotted against  $t$  for this equation, a straight line is obtained (). In practice, instead of transforming values of  $D_B$  to their corresponding logarithms, each value of  $D_B$  is placed at logarithmic intervals on semilog paper.



Equation 3.3 can also be expressed as

$$D_B = D_B^0 e^{-kt} \quad (3.4)$$

## APPARENT VOLUME OF DISTRIBUTION

In general, drug equilibrates rapidly in the body. When plasma or any other biologic compartment is sampled and analyzed for drug content, the results are usually reported in units of concentration instead of amount. Each individual tissue in the body may contain a different concentration of drug due to differences in drug affinity for that tissue. Therefore, the amount of drug in a given location can be related to its concentration by a proportionality constant that reflects the volume of fluid the drug is dissolved in. The *volume of distribution* represents a volume that must be considered in estimating the amount of drug in the body from the concentration of drug found in the sampling compartment. The volume of distribution is also the apparent volume ( $V_D$ ) in which the drug is dissolved (Eq. 3.5). Because the value of the volume of distribution does not have a true physiologic meaning in terms of an anatomic space, the term *apparent* volume of distribution is used.

The amount of drug in the body is not determined directly. Instead, a blood sample is removed at periodic intervals and analyzed for its concentration of drug. The  $V_D$  relates the concentration of drug in plasma ( $C_p$ ) and the amount of drug in the body ( $D_B$ ), as in the following equation:

$$D_B = V_D C_p \quad (3.5)$$

By substituting Equation 3.5 into Equation 3.3, a similar expression based on drug concentration in plasma is obtained for the first-order decline of drug plasma levels:

$$\log C_p = \frac{-kt}{2.3} + \log C_p^0 \quad (3.6)$$

where  $C_p$  = concentration of drug in plasma at time  $t$  and  $C_p^0$  = concentration of drug in plasma at  $t = 0$ . Equation 3.6 can also be expressed as

$$C_p = C_p^0 e^{-kt} \quad (3.7)$$

The relationship between apparent volume, drug concentration, and total amount of drug may be better understood by the following example.

### Example

Exactly 1 g of a drug is dissolved in an unknown volume of water. Upon assay, the concentration of this solution is 1 mg/mL. What is the original volume of this solution?

The original volume of the solution may be obtained by the following proportion, remembering that 1 g = 1000 mg:

$$\frac{1000 \text{ mg}}{x \text{ mL}} = \frac{1 \text{ mg}}{\text{mL}} \quad x = 1000 \text{ mL}$$

Therefore, the original volume was 1000 mL or 1 L.

If, in the above example, the volume of the solution is known to be 1 L, and the concentration of the solution is 1 mg/mL, then, to calculate the total amount of drug present,

$$\frac{x \text{ mg}}{1000 \text{ mL}} = \frac{1 \text{ mg}}{\text{mL}} \quad x = 1000 \text{ mg}$$

Therefore, the total amount of drug in the solution is 1000 mg, or 1 g.

From the preceding example, if the volume of solution in which the drug is dissolved and the drug concentration of the solution are known, then the total amount of drug present in the solution may be calculated. This relationship between drug concentration, volume in which the drug is dissolved, and total amount of drug present is given in the following equation:

$$V_D = \frac{\text{Dose}}{C_p^0} = \frac{D_B^0}{C_p^0} \quad (3.8)$$

where  $D$  = total amount of drug,  $V$  = total volume, and  $C$  = drug concentration. From Equation 3.8, which is similar to Equation 3.5, if any two parameters are known, then the third term may be calculated.

The body may be considered as a constant-volume system or compartment. Therefore, the apparent volume of distribution for any given drug is generally a constant. If both the concentration of drug in the plasma and the apparent volume of distribution for the drug are known, then the total amount of drug in the body (at the time in which the plasma sample was obtained) may be calculated from Equation 3.5.

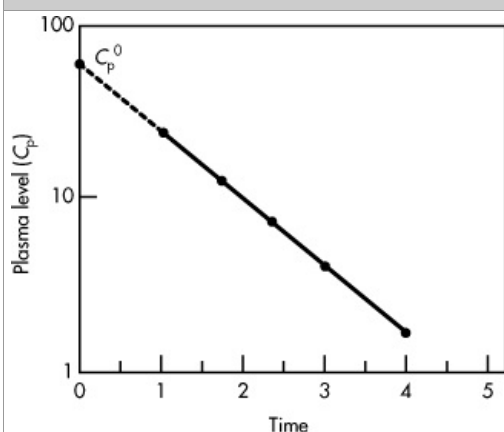
### Calculation of Volume of Distribution

In a one-compartment model (IV administration), the  $V_D$  is calculated with the following equation:

$$V_D = \frac{\text{Dose}}{C_p^0} = \frac{D_B^0}{C_p^0} \quad (3.9)$$

When  $C_p^0$  is determined by extrapolation, it represents the instantaneous drug concentration (concentration of drug at  $t = 0$ ) after drug equilibration in the body ( $\cdot$ ). The dose of drug given by IV bolus (rapid IV injection) represents the amount of drug in the body,  $D_B^0$ , at  $t = 0$ . Because both  $D_B^0$  and  $C_p^0$  are known at  $t = 0$ , then the apparent volume of distribution,  $V_D$ , may be calculated from Equation 3.9.

**Figure 3-3.**



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Semilog graph giving the value of  $C_p^0$  by extrapolation.

From Equation 3.2 (repeated here), the rate of drug elimination is

$$\frac{dD_B}{dt} = -kD_B$$

By substitution of Equation 3.5,  $D_B = V_D C_p$ , into Equation 3.2, the following expression is obtained:

$$\frac{dD_B}{dt} = -kV_D C_p \quad (3.10)$$

Rearrangement of Equation 3.10 gives

$$dD_B = -kV_D C_p dt \quad (3.11)$$

As both  $k$  and  $V_D$  are constants, Equation 3.10 may be integrated as follows:

$$\int_0^{D_0} dD_B = -kV_D \int_0^{\infty} C_p dt \quad (3.12)$$

Equation 3.12 shows that a small change in time ( $dt$ ) results in a small change in the amount of drug in the body,  $D_B$ .

The integral  $\int_0^{\infty} C_p dt$  represents the  $AUC_{0-\infty}$ , which is the summation of the area under the curve from  $t = 0$  to  $t = \infty$ . Thus, the apparent  $V_D$  may also be calculated from knowledge of the dose, elimination rate constant, and the area under the curve (AUC) from  $t = 0$  to  $t = \infty$ . The  $AUC_{0-\infty}$  is usually estimated by the trapezoidal rule (see ). After integration, Equation 3.12 becomes

$$D_0 = kV_D [AUC]_0^{\infty}$$

which upon rearrangement yields the following equation:

$$V_D = \frac{D_0}{k[AUC]_0^{\infty}} \quad (3.13)$$

The calculation of the apparent  $V_D$  by means of Equation 3.13 is a *model-independent* method, because no pharmacokinetic model is considered and the AUC is determined directly by the trapezoidal rule.

### Significance of the Apparent Volume of Distribution

The apparent volume of distribution is not a true physiologic volume. Most drugs have an apparent volume of distribution smaller than, or equal to, the body mass. For some drugs, the volume of distribution may be several times the body mass. Equation 3.9 shows that the apparent  $V_D$  is dependent on  $C_p^0$ . For a given dose, a very small  $C_p^0$  may occur in the body due to concentration of the drug in peripheral tissues and organs. For this dose, the small  $C_p^0$  will result in a large  $V_D$ .

Drugs with a large apparent  $V_D$  are more concentrated in extravascular tissues and less concentrated intravascularly. If a drug is highly bound to plasma proteins or remains in the vascular region, then  $C_p^0$  will be higher, resulting in a smaller apparent  $V_D$ . Consequently, binding of a drug to peripheral tissues or to plasma proteins will significantly affect  $V_D$ .

The apparent  $V_D$  is a volume term that can be expressed as a simple volume or in terms of percent of body weight. In expressing the apparent  $V_D$  in terms of percent body weight, a 1-L volume is assumed to be equal to the weight of 1 kg. For example, if the  $V_D$  is 3500 mL for a subject weighing 70 kg, the  $V_D$  expressed as percent of body weight is

$$\frac{3.5 \text{ kg}}{70 \text{ kg}} \times 100 = 5\% \text{ of body weight}$$

If  $V_D$  is a very large number—ie, >100% of body weight—then it may be assumed that the drug is concentrated in certain tissue compartments. Thus, the apparent  $V_D$  is a useful parameter in considering the relative amounts of drug in the vascular and in the extravascular tissues.

Pharmacologists often attempt to conceptualize the apparent  $V_D$  as a true physiologic or anatomic fluid compartment. By expressing the  $V_D$  in terms of percent of body weight, values for the  $V_D$  may be found that appear to correspond to true anatomic volumes ( ). However, it may be only fortuitous that the value for the apparent  $V_D$  of a drug has the same value as a real anatomic volume. If a drug is to be considered to be distributed in a true physiologic volume, then an investigation is needed to test this hypothesis.

**Table 3.1 Fluid in the Body**

Water Compartment	Percent of Body Weight	Percent of Total Body Water
Plasma	4.5	7.5

Total extracellular water	27.0	45.0
Total intracellular water	33.0	55.0
Total body water	60.0	100.0

Given the apparent  $V_D$  for a particular drug, the total amount of drug in the body at any time after administration of the drug may be determined by the measurement of the drug concentration in the plasma (Eq. 3.5). Because the magnitude of the apparent  $V_D$  is a useful indicator for the amount of drug outside the sampling compartment (usually the blood), the larger the apparent  $V_D$ , the greater the amount of drug in the extravascular tissues.

For each drug, the apparent  $V_D$  is a constant. In certain pathologic cases, the apparent  $V_D$  for the drug may be altered if the distribution of the drug is changed. For example, in edematous conditions, the total body water and total extracellular water increase; this is reflected in a larger apparent  $V_D$  value for a drug that is highly water soluble. Similarly, changes in total body weight and lean body mass (which normally occur with age) may also affect the apparent  $V_D$ .

## CLEARANCE

*Clearance* is a measure of drug elimination from the body without identifying the mechanism or process. Clearance is also discussed in subsequent chapters. Clearance (*drug clearance, systemic clearance, total body clearance,  $Cl_T$* ) considers the entire body as a drug-eliminating system from which many elimination processes may occur.

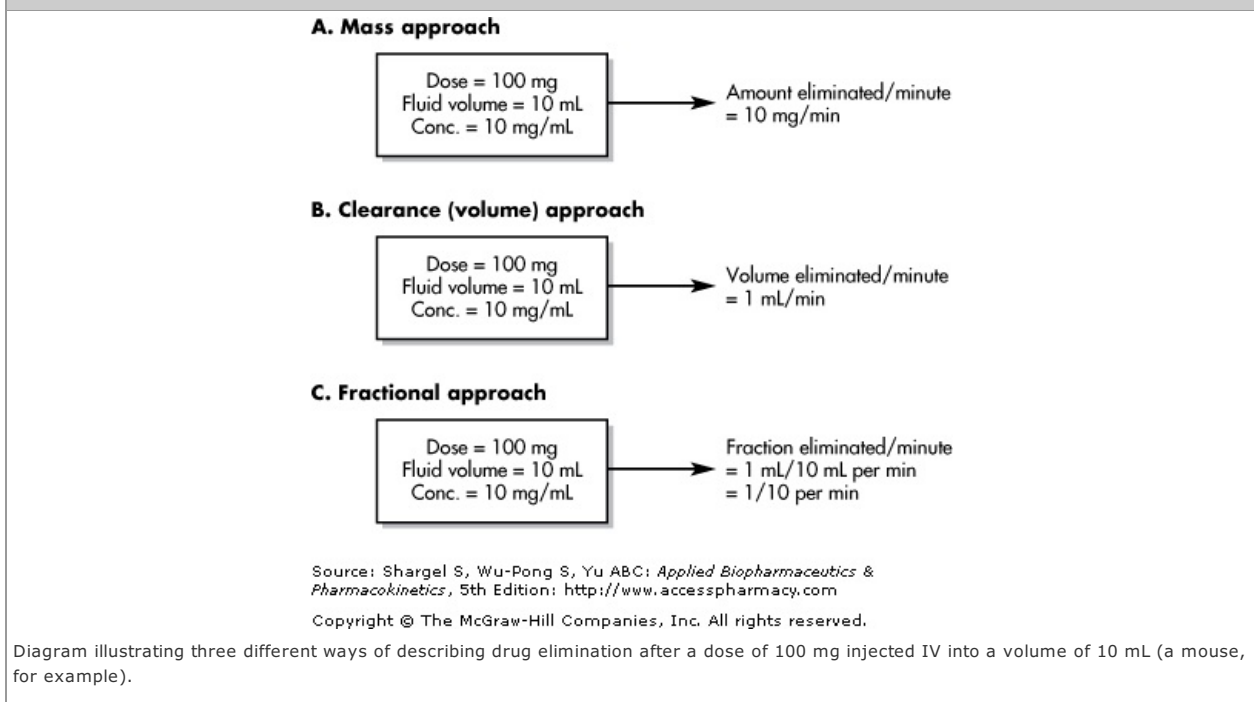
### Drug Clearance in the One-Compartment Model

The body is considered as a system of organs perfused by plasma and body fluids. Drug elimination from the body is an ongoing process due to both metabolism (biotransformation) and drug excretion through the kidney and other routes. The mechanisms of drug elimination are complex, but collectively drug elimination from the body may be quantitated using the concept of drug clearance. Drug clearance refers to the volume of plasma fluid that is cleared of drug per unit time. Clearance may also be considered as the fraction of drug removed per unit time multiplied by the  $V_D$ . The rate of drug elimination may be expressed in several ways, each of which essentially describes the same process, but with different levels of insight and application in pharmacokinetics.

### DRUG ELIMINATION EXPRESSED AS AMOUNT PER TIME UNIT

The expression of drug elimination from the body in terms of mass per unit time (eg, mg/min, or mg/hr) is simple, absolute, and unambiguous. For a zero-order elimination process, expressing the rate of drug elimination as mass per unit time is convenient because the rate is constant ( $\dot{}$ ). In contrast, the rate of drug elimination for a first-order elimination process is not constant and changes with respect to the drug concentration in the body. For a first-order elimination, drug clearance expressed as volume per unit time (eg, L/hr or mL/min) is convenient because it is a constant.

**Figure 3-4.**



### DRUG ELIMINATION EXPRESSED AS VOLUME PER TIME UNIT

The concept of expressing a rate in terms of volume per unit time is common in pharmacy. For example, a patient may be dosed at the rate of 2 teaspoonsful (10 mL) of a liquid medicine (10 mg/mL) daily, or alternatively, a dose (weight) of 100 mg of the drug daily.

Clearance is a concept that expresses "the rate of drug removal" in terms of volume of drug solution removed per unit time (at whatever drug concentration in the body prevailing at that time) (). In contrast to a solution in a bottle, the drug concentration in the body will gradually decline by a first-order process such that the mass of drug removed over time is not constant. The plasma volume in the healthy state is relatively constant because water lost through the kidney is rapidly replaced with fluid absorbed from the gastrointestinal tract.

Since a constant volume of plasma (about 120 mL/min in humans) is filtered through the glomeruli of the kidneys, the rate of drug removal is dependent on the plasma drug concentration at all times. This observation is based on a first-order process governing drug elimination. For many drugs, the rate of drug elimination is dependent on the plasma drug concentration, multiplied by a constant factor ( $dC/dt = kC$ ). When the plasma drug concentration is high, the rate of drug removal is high, and vice versa.

Clearance (volume of fluid removed of drug) for a first-order process is constant regardless of the drug concentration because clearance is expressed in volume per unit time rather than drug amount per unit time. Mathematically, the rate of drug elimination is similar to Equation 3.10:

$$\frac{dD_B}{dt} = -kC_p V_D \quad (3.2a)$$

Dividing this expression on both sides by  $C_p$  yields Equation 3.14:

$$\frac{dD_B/dt}{C_p} = \frac{-kC_p V_D}{C_p} \quad (3.14)$$

$$\frac{dD_B/dt}{C_p} = -kV_D = -Cl \quad (3.15)$$

where  $dD_B/dt$  is the rate of drug elimination from the body (mg/hr),  $C_p$  is the plasma drug concentration (mg/L),  $k$  is a first-order rate constant ( $\text{hr}^{-1}$  or 1/hr), and  $V_D$  is the apparent volume of distribution (L).  $Cl$  is clearance and has the units L/hr in this example. In the example in ,  $Cl$  is in mL/min.

Clearance,  $Cl$ , is expressed as volume/time. Equation 3.15 shows that clearance is a constant because  $V_D$  and  $k$  are both constants.  $D_B$  is the amount of drug in the body, and  $dD_B/dt$  is the rate of change (of amount) of drug in the body with respect to time. The negative sign refers to the drug exiting from the body.

## DRUG ELIMINATION EXPRESSED AS FRACTION ELIMINATED PER TIME UNIT

Consider a compartment volume, containing  $V_D$  liters. If  $Cl$  is expressed in liters per minute (L/min), then the fraction of drug cleared per minute in the body is equal to  $Cl/V_D$ .

Expressing drug elimination as the fraction of total drug eliminated is applicable regardless of whether one is dealing with an amount or a volume (). This approach is most flexible and convenient because of its dimensionless nature. Thus, it is valid to express drug elimination as a fraction (eg, one-tenth of the amount of drug in the body is eliminated or one-tenth of the drug volume is eliminated). Pharmacokineticists have incorporated this concept into the first-order equation (ie,  $k$ ) that describes drug elimination from the one-compartment model. Indeed, the universal nature of many processes forms the basis of the first-order equation of drug elimination (eg, a fraction of the total drug molecules in the body will perfuse the glomeruli, a fraction of the filtered drug molecules will be reabsorbed at the renal tubules, and a fraction of the filtered drug molecules will be excreted from the body giving an overall first-order drug elimination rate constant,  $k$ ). The rate of drug elimination is the product of  $k$  and the drug concentration (Eq. 3.2a). The first-order equation of drug elimination can be also based on probability and a consideration of the statistical moment theory ().

## CLEARANCE AND VOLUME OF DISTRIBUTION RATIO, $Cl/V_D$

### Example

Consider that 100 mg of drug is dissolved in 10 mL of fluid and 10 mg of drug is removed in the first minute. The drug elimination process could be described as:

- Number of mg of drug eliminated per minute (mg/min)
- Number of mL of fluid cleared of drug per minute
- Fraction of drug eliminated per minute

The relationship of the three drug elimination processes is illustrated in . Note that in , the fraction  $Cl/V_D$  is dependent on both the volume of distribution and the rate of drug clearance from the body. This clearance concept forms the basis of classical pharmacokinetics and is later extended to flow models in pharmacokinetic modeling. If the drug concentration is  $C_p$ , the rate of drug elimination (in terms of rate of change in concentration,  $dC_p/dt$ ) is:

$$\frac{dC_p}{dt} = -(Cl/V_D) \times C_p \quad (3.16)$$

For a first-order process,

$$\frac{dC_p}{dt} = -kC_p = \text{rate of drug administration} \quad (3.17)$$

Equating the two expressions yields:

$$kC_p = Cl/V_D \times C_p \quad (3.18)$$

$$k = \frac{Cl}{V_D} \quad (3.19)$$

Thus, a first-order rate constant is the fractional constant  $Cl/V_D$ . Some pharmacokineticists regard drug clearance and the volume of distribution as independent parameters that are necessary to describe the time course of drug elimination. Equation 3.19 is a rearrangement of Equation 3.15 given earlier.

### One-Compartment Model Equation in Terms of $Cl$ and $V_D$

Equation 3.20 may be rewritten in terms of clearance and volume of distribution by substituting  $Cl/V_D$  for  $k$ . The clearance concept may also be applied a biologic system in physiologic modeling without the need of a theoretical compartment.

$$C_p = C_p^0 e^{-kt} \quad (3.20)$$

$$C_p = D_0/V_D e^{-(Cl/V_D)t} \quad (3.21)$$

Equation 3.21 is applied directly in clinical pharmacy to determine clearance and volume of distribution in patients. When only one sample is available, ie,  $C_p$  is known at one sample time point,  $t$  after a given dose, the equation cannot be determined unambiguously because two unknown parameters must be solved, ie,  $Cl$  and  $V_D$ . In practice, the mean values for  $Cl$  and  $V_D$  of a drug are obtained from the population values (derived from a large population of subjects or patients) in the literature. The values of  $Cl$  and  $V_D$  for the patient are adjusted using a computer program. Ultimately, a new pair of  $Cl$  and  $V_D$  values that better fit the observed plasma drug concentration is found. The process is repeated through iterations until the "best" parameters are obtained. Since many mathematical techniques (algorithms) are available for iteration, different results may be obtained using different iterative programs. An objective test to determine the accuracy of the estimated clearance and  $V_D$  values is to monitor how accurately those parameters will predict the plasma level of the drug after a new dose is given to the patient. In subsequent chapters, mean predictive error will be discussed and calculated in order to determine the performance of various drug monitoring methods in practice.

The ratio of  $Cl/V_D$  may be calculated regardless of compartment model type using minimal plasma samples. Clinical pharmacists have applied many variations of this approach to therapeutic drug monitoring and drug dosage adjustments in patients.

### PRACTICAL FOCUS

The most accurate kinetic method to determine the volume of distribution and the distribution kinetic of a drug in a patient is to give the drug by a single IV bolus dose. An IV bolus dose avoids many variables such as delayed, irregular, and/or incomplete absorption compared to other routes of administration.

The IV single dose Equation 3.22 may be modified to calculate the elimination rate constant or half-life of a drug in a patient when two plasma samples and their time of collection are known:

$$\ln C_p = \ln C_p^0 - kt \quad (3.22)$$

If the first plasma sample is taken at  $t_1$  instead of at zero and corresponds to plasma drug concentration, then  $C_2$  is the concentration at time  $t_2$  and  $t$  is set to  $(t_2 - t_1)$ .

$$C_2 = C_1 e^{-k(t_2 - t_1)}$$

$$\ln C_2 = \ln C_1 - k(t_2 - t_1) \quad (3.23)$$

Rearranging:

$$\ln C_2 - \ln C_1 = -k(t_2 - t_1)$$

$$k = \frac{\ln C_1 - \ln C_2}{(t_2 - t_1)} \quad (3.24)$$

$$t_{1/2} = \frac{0.693(t_2 - t_1)}{\ln C_1 - \ln C_2} \quad (3.25)$$

where

$t_1$  = time of first sample collection

$C_1$  = plasma drug concentration at  $t_1$

$t_2$  = time of second sample collection

$C_2$  = plasma drug concentration at  $t_2$

In a clinical practice, several drug doses may have been given to the patient and the prior dosing times may not be accurately known. If the pharmacist judges that the drug in the body is in a declining phase (ie, absorption is completed), this equation may be used to determine the half-life of the drug in the patient by taking two plasma samples far apart and recording the times of sampling.

### Clearance from Drug-Eliminating Tissues

Clearance may be applied to any organ that is involved in drug elimination from the body. As long as first-order elimination processes are involved, clearance represents the sum of the clearances for each drug-eliminating organ as shown in Equation 3.26:

$$Cl_T = Cl_R + Cl_{NR} \quad (3.26)$$

where  $Cl_R$  is renal clearance or drug clearance through the kidney, and  $Cl_{NR}$  is nonrenal clearance through other organs. Generally, clearance is considered as the sum of renal,  $Cl_R$ , and nonrenal drug clearance,  $Cl_{NR}$ .  $Cl_{NR}$  is assumed to be due primarily to hepatic clearance ( $Cl_H$ ) in the absence of other significant drug clearances, such as elimination through the lung or the bile, as shown in Equation 3.27:

$$Cl_T = Cl_R + Cl_H \quad (3.27)$$

Drug clearance considers that the drug in the body is uniformly dissolved in a volume of fluid (apparent volume of distribution,  $V_D$ ) from which drug concentrations can be measured easily. Typically, plasma fluid concentration is measured and drug clearance is then calculated as the fixed volume of plasma fluid (containing the drug) cleared of drug per unit of time. The units for clearance are volume/time (eg, mL/min, L/hr).

Alternatively,  $Cl_T$  may be defined as the rate of drug elimination divided by the plasma drug concentration. Thus, clearance is expressed in terms of the volume of plasma containing drug that is eliminated per unit time. This clearance definition is equivalent to the previous definition and provides a practical way to calculate clearance based on plasma drug concentration data.

$$Cl_T = \frac{\text{elimination rate}}{\text{plasma concentration } (C_p)} \quad (3.28)$$

$$Cl_T = \frac{(dD_E/dt)}{C_p} = (\mu\text{g}/\text{min})/(\mu\text{g}/\text{mL}) = \text{mL}/\text{min} \quad (3.29)$$

where  $D_E$  is the amount of drug eliminated and  $dD_E/dt$  is the rate of drug elimination.

Rearrangement of Equation 3.29 gives Equation 3.30:

$$\text{Drug elimination rate} = \frac{dD_E}{dt} = C_p Cl_T \quad (3.30)$$

Therefore  $Cl_T$  is a constant for a specific drug and represents the slope of the line obtained by plotting  $dD_E/dt$  versus  $C_p$ , as shown in Equation 3.30.

For drugs that follow first-order elimination, the rate of drug elimination is dependent on the amount of drug remaining in the body.

$$\frac{dD_E}{dt} = kD_B = kC_p V_D \quad (3.31)$$

Substituting the elimination rate in Equation 3.30 for  $kC_p V_D$  in Equation 3.31 and solving for  $Cl_T$  gives Equation 3.32:

$$Cl_T = \frac{kC_p V_D}{C_p} = kV_D \quad (3.32)$$

Equation 3.32 shows that clearance,  $Cl_T$ , is the product of  $V_D$  and  $k$ , both of which are constant. This Equation 3.32 is similar to Equation 3.19 shown earlier. As the plasma drug concentration decreases during elimination, the rate of drug elimination,  $dD_E/dt$ , will decrease accordingly, but clearance will remain constant. Clearance will be constant as long as the rate of drug elimination is a first-order process.

For some drugs, the elimination rate process is more complex and a noncompartment method may be used to calculate certain pharmacokinetic parameters such as clearance. In this case, clearance can be determined directly from the plasma drug concentration-versus-time curve by

$$Cl_T = \frac{D_0}{[AUC]_0^\infty} \quad (3.33)$$

where  $D_0$  is the dose and  $[AUC]_0^\infty = \int_0^\infty C_p dt$

Because  $[AUC]_0^\infty$  is calculated from the plasma drug concentration-versus-time curve from 0 to infinity ( $\infty$ ) using the trapezoidal

rule, no compartmental model is assumed. However, to extrapolate the data to infinity to obtain the residual  $[AUC]^\infty_0$  or  $(C_{p,t}/k)$ , first-order elimination is usually assumed. In this case, if the drug follows the kinetics of a one-compartment model, the  $Cl_T$  is numerically similar to the product of  $V_D$  and  $k$  obtained by fitting the data to a one-compartment model.

### CALCULATION OF K FROM URINARY EXCRETION DATA

The elimination rate constant  $k$  may be calculated from urinary excretion data. In this calculation the excretion rate of the drug is assumed to be first order. The term  $k_e$  is the renal excretion rate constant, and  $D_u$  is the amount of drug excreted in the urine.

$$\frac{dD_u}{dt} = k_e D_B \quad (3.34)$$

From Equation 3.34,  $D_B$  can be substituted for  $D_B^0 e^{-kt}$ :

$$\frac{dD_u}{dt} = k_e D_B^0 e^{-kt} \quad (3.35)$$

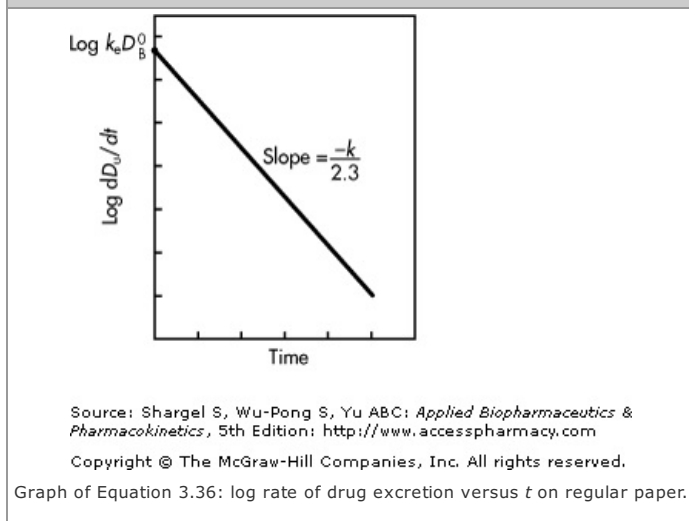
Taking the natural logarithm of both sides and then transforming to common logarithms, the following expression is obtained:

$$\log \frac{dD_u}{dt} = \frac{-kt}{2.3} + \log k_e D_B^0 \quad (3.36)$$

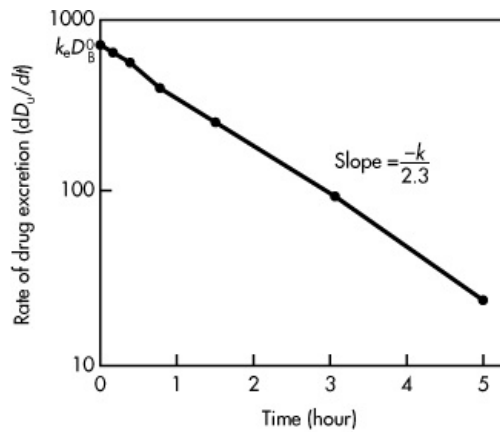
A straight line is obtained from this equation by plotting  $\log dD_u/dt$  vs time on regular paper or on semilog paper  $dD_u/dt$  against time ( and ). The slope of this curve is equal to  $-k/2.3$  and the y intercept is equal to  $k_e D_B^0$ . For rapid intravenous administration,  $D_B^0$  is equal to the dose  $D_0$ . Therefore, if  $D_B^0$  is known, the renal excretion rate constant ( $k_e$ ) can be obtained. Because both  $k_e$  and  $k$  can be determined by this method, the nonrenal rate constant ( $k_{nr}$ ) for any route of elimination other than renal excretion can be found as follows:

$$k - k_e = k_{nr} \quad (3.37)$$

**Figure 3-5.**



**Figure 3-6.**



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Semilog graph of rate of drug excretion versus time according to Equation 3.36 on semilog paper (intercept =  $k_e D_B^0$ ).

Substitution of  $k_m$  for  $k_{nr}$  in Equation 3.37 gives Equation 3.1. Because the major routes of elimination for most drugs are renal excretion and metabolism (biotransformation),  $k_{nr}$  is approximately equal to  $k_m$ .

$$k_{nr} = k_m \quad (3.38)$$

The drug urinary excretion rate ( $dD_u/dt$ ) cannot be determined experimentally for any given instant. Therefore, the average rate of urinary drug excretion,  $D_u/t$  is plotted against the average time,  $t^*$ , for the collection of the urine sample. In practice, urine is collected over a specified time interval, and the urine specimen is analyzed for drug. An average urinary excretion rate is then calculated for that collection period. The average value of  $dD_u/dt$  is plotted on a semilogarithmic scale against the time that corresponds to the midpoint (average time) of the collection period.

### Practice Problem

A single IV dose of an antibiotic was given to a 50-kg woman at a dose level of 20 mg/kg. Urine and blood samples were removed periodically and assayed for parent drug. The following data were obtained:

Time (hr)	$C_p$ ( $\mu\text{g/mL}$ )	$D_u$ (mg)
0.25	4.2	160
0.50	3.5	140
1.0	2.5	200
2.0	1.25	250
4.0	0.31	188
6.0	0.08	46

### Solution

Set up the following table:

Time (hr)	$D_u$ (mg)	$D_u/t$	mg/hr	$t^*$ (hr)
0.25	160	160/0.25	640	0.125
0.50	140	140/0.25	560	0.375
1.0	200	200/0.5	400	0.750
2.0	250	250/1	250	1.50
4.0	188	188/2	94	3.0
6.0	46	46/2	23	5.0

Here  $t^*$  = midpoint of collection period; and  $t$  = time interval for collection of urine sample.

Construct a graph on a semilogarithmic scale of  $D_u/t$  versus  $t^*$ . The slope of this line should equal  $-k/2.3$ . It is usually easier to determine the elimination  $t_{1/2}$  directly from the curve and then calculate  $k$  from

$$k = \frac{0.693}{t_{1/2}}$$

In this problem,  $t_{1/2} = 1.0$  hr and  $k = 0.693 \text{ hr}^{-1}$ . A similar graph of the  $C_p$  values versus  $t$  should yield a curve with a slope having the same value as that derived from the previous curve. Note that the slope of the log excretion rate constant is a function of elimination rate constant  $k$  and not of the urinary excretion rate constant  $k_e$  ().

An alternative method for the calculation of the elimination rate constant  $k$  from urinary excretion data is the *sigma-minus method*, or *the amount of drug remaining to be excreted method*. The sigma-minus method is sometimes preferred over the previous method because fluctuations in the rate of elimination are minimized.

The amount of unchanged drug in the urine can be expressed as a function of time through the following equation:

$$D_u = \frac{k_e D_0}{k} (1 - e^{-kt}) \quad (3.39)$$

where  $D_u$  is the cumulative amount of unchanged drug excreted in the urine.

The amount of unchanged drug that is ultimately excreted in the urine,  $D_u^\infty$ , can be determined by making time  $t$  equal to  $\infty$ .

Thus, the term  $e^{-kt}$  becomes negligible and the following expression is obtained:

$$D_u^\infty = \frac{k_e D_0}{k} \quad (3.40)$$

Substitution of  $D_u^\infty$  for  $k_e D_0/k$  in Equation 3.39 and rearrangement yields

$$D_u^\infty - D_u = D_u^\infty e^{-kt} \quad (3.41)$$

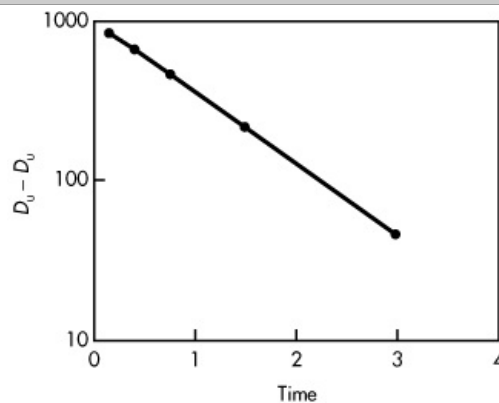
Equation 3.41 can be written in logarithmic form to obtain a linear equation:

$$\log (D_u^\infty - D_u) = \frac{-kt}{2.3} + \log D_u^\infty \quad (3.42)$$

Equation 3.42 describes the relationship for the amount of drug remaining to be excreted ( $D_u^\infty - D_u$ ) versus time.

A linear curve is obtained by graphing the logarithm scale of the amount of unchanged drug yet to be eliminated,  $\log (D_u^\infty - D_u)$  versus time. On semilog paper, the slope of this curve is  $-k/2.3$  and the y intercept is  $D_u^\infty$  ().

**Figure 3-7.**



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Sigma-minus method, or the amount of drug remaining to be excreted method, for the calculation of the elimination rate constant according to Equation 3.42.

### PRACTICE PROBLEM

Using the data in the preceding problem, determine the elimination rate constant.

#### Solution

Construct the following table:

Time (hr)	$D_u$ (mg)	Cumulative $D_u$	$D_u^\infty - D_u$
0.25	160	160	824
0.50	140	300	684

1.0	200	500	484
2.0	250	750	234
4.0	188	938	46
6.0	46	984	0

Plot  $\log (D^{\infty}_u - D_u)$  versus time. Use a semilogarithmic scale for  $(D^{\infty}_u - D_u)$ . Evaluate  $k$  and  $t_{1/2}$  from the slope.

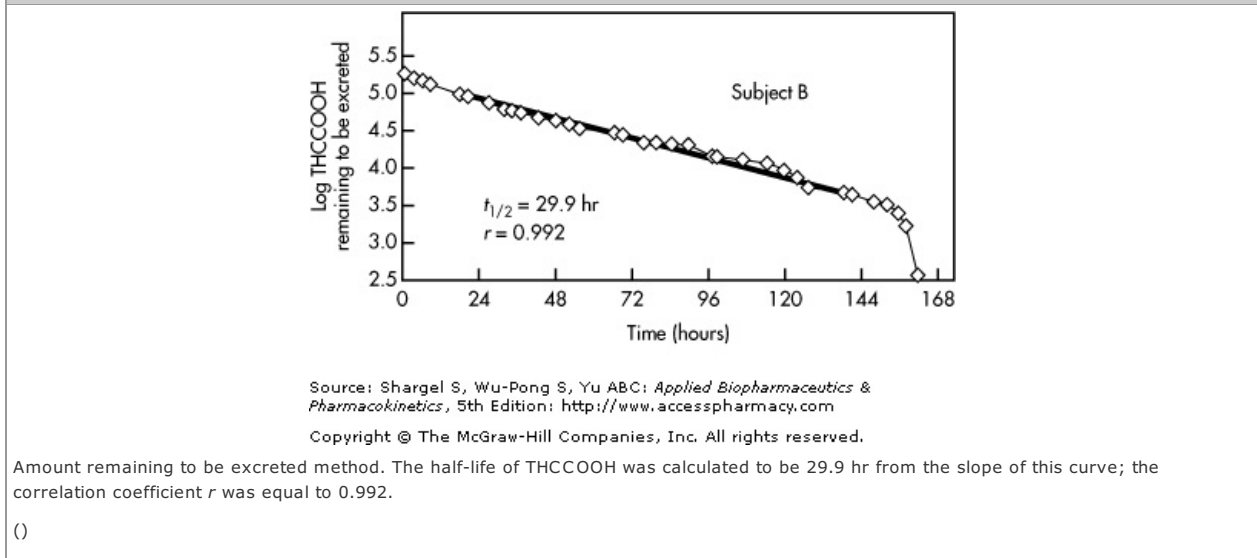
### Comparison of the Rate and the Sigma-Minus Methods

The rate method does not require knowledge of  $D^{\infty}_u$ , and the loss of one urine specimen does not invalidate the entire urinary drug excretion study. The sigma-minus method requires an accurate determination of  $D^{\infty}_u$ , which requires the collection of urine until urinary drug excretion is complete. A small error in the assessment of  $D^{\infty}_u$  introduces an error in terms of curvature of the plot, because each point is based on  $\log (D^{\infty}_u - D_u)$  versus time. Fluctuations in the rate of drug elimination and experimental errors including incomplete bladder emptying for a collection period cause appreciable departure from linearity using the rate method, whereas the accuracy of the sigma-minus method is less affected. The rate method is applicable to zero-order drug elimination process, while the sigma-minus method is not. Lastly, the renal drug excretion rate constant may be obtained from the rate method but not from the sigma-minus method.

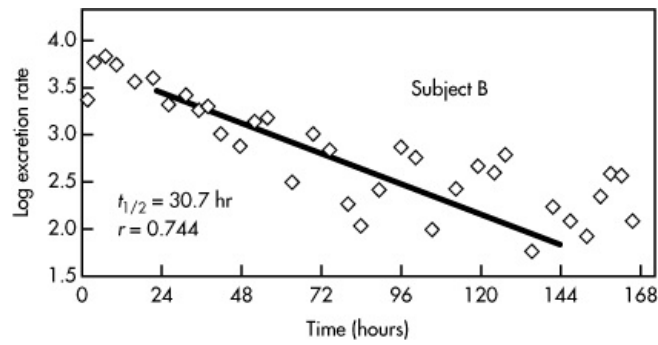
### CLINICAL APPLICATION

The sigma-minus method and the excretion rate method was applied to the urinary drug excretion in subjects following the smoking of a single marijuana cigarette (). The urinary excretion curves of 11-nor-carboxy 9-tetrahydrocannabinol (THCCOOH), a metabolite of marijuana, in one subject from 24 to 144 hours after smoking one marijuana cigarette are shown in and . A total of 199.7 mg of THCCOOH was excreted in the urine over 7 days, which represents 0.54% of the total 9-tetrahydrocannabinol available in the cigarette. Using either urinary drug excretion method, the elimination half-life was determined to be about 30 hours. However, the urinary drug excretion rate method data were more scattered (variable) and the correlation coefficient  $r$  was equal to 0.744 (), compared to the correlation coefficient  $r$  of 0.992 using the sigma-minus method ().

**Figure 3-8.**



**Figure 3-9.**



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Excretion rate method. The half-life of THCCOOH was calculated to be 30.7 hr from the slope of this curve; the correlation coefficient  $r$  was equal to 0.744.

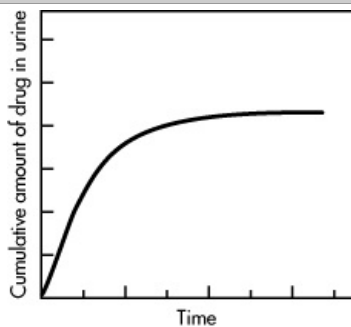
()

### Problems in Obtaining Valid Urinary Excretion Data

Certain factors can make it difficult to obtain valid urinary excretion data. Some of these factors are as follows:

1. A significant fraction of the unchanged drug must be excreted in the urine.
2. The assay technique must be specific for the unchanged drug and must not include interference due to drug metabolites that have similar chemical structures.
3. Frequent sampling is necessary for a good curve description.
4. Urine samples should be collected periodically until almost all of the drug is excreted. A graph of the cumulative drug excreted versus time will yield a curve that approaches an asymptote at "infinite" time (). In practice, approximately seven elimination half-lives are needed for 99% of the drug to be eliminated.
5. Variations in urinary pH and volume may cause significant variation in urinary excretion rates.
6. Subjects should be carefully instructed as to the necessity of giving a complete urine specimen (ie, completely emptying the bladder).

**Figure 3-10.**



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Graph showing the cumulative urinary excretion of drug as a function of time.

### FREQUENTLY ASKED QUESTIONS

1. What is the difference between a rate and a rate constant?
2. Why does  $k$  always have the unit 1/time (eg,  $\text{hr}^{-1}$ ), regardless of what concentration unit is plotted?
3. If a drug is distributed in the one-compartment model, does it mean that there is no drug in the tissue?
4. How is clearance related to the volume of distribution and  $k$ ?
5. If we use a physiologic model, are we dealing with actual volumes of blood and tissues? Why do we still use volumes of distribution that often are greater than the real physical volume?

### LEARNING QUESTIONS

1. A 70-kg volunteer is given an intravenous dose of an antibiotic, and serum drug concentrations were determined at 2 hours and 5 hours after administration. The drug concentrations were 1.2 and 0.3  $\mu\text{g}/\text{mL}$ , respectively. What is the biologic half-life for this drug, assuming first-order elimination kinetics?

2. A 50-kg woman was given a single IV dose of an antibacterial drug at a dose level of 6 mg/kg. Blood samples were taken at various time intervals. The concentration of the drug ( $C_p$ ) was determined in the plasma fraction of each blood sample and the following data were obtained:

$t$ (hr)	$C_p$ ( $\mu\text{g/mL}$ )
0.25	8.21
0.50	7.87
1.00	7.23
3.00	5.15
6.00	3.09
12.0	1.11
18.0	0.40

- What are the values for  $V_D$ ,  $k$ , and  $t_{1/2}$  for this drug?
  - This antibacterial agent is not effective at a plasma concentration of less than 2  $\mu\text{g/mL}$ . What is the duration of activity for this drug?
  - How long would it take for 99.9% of this drug to be eliminated?
  - If the dose of the antibiotic were doubled exactly, what would be the increase in duration of activity?
3. A new drug was given in a single intravenous dose of 200 mg to an 80-kg adult male patient. After 6 hours, the plasma drug concentration of drug was 1.5 mg/100 mL of plasma. Assuming that the apparent  $V_D$  is 10% of body weight, compute the total amount of drug in the body fluids after 6 hours. What is the half-life of this drug?
4. A new antibiotic drug was given in a single intravenous bolus of 4 mg/kg to five healthy male adults ranging in age from 23 to 38 years (average weight 75 kg). The pharmacokinetics of the plasma drug concentration–time curve for this drug fits a one-compartment model. The equation of the curve that best fits the data is

$$C_p = 78e^{-0.46t}$$

Determine the following (assume units of  $\mu\text{g/mL}$  for  $C_p$  and hr for  $t$ ):

- What is the  $t_{1/2}$ ?
  - What is the  $V_D$ ?
  - What is the plasma level of the drug after 4 hours?
  - How much drug is left in the body after 4 hours?
  - Predict what body water compartment this drug might occupy and explain why you made this prediction.
  - Assuming the drug is no longer effective when levels decline to less than 2  $\mu\text{g/mL}$ , when should you administer the next dose?
5. Define the term *apparent volume of distribution*. What criteria are necessary for the measurement of the apparent volume of distribution to be useful in pharmacokinetic calculations?
6. A drug has an elimination  $t_{1/2}$  of 6 hours and follows first-order kinetics. If a single 200-mg dose is given to an adult male patient (68 kg) by IV bolus injection, what percent of the dose is lost in 24 hours?
7. A rather intoxicated young man (75 kg, age 21) was admitted to a rehabilitation center. His blood alcohol content was found to be 210 mg%. Assuming the average elimination rate of alcohol is 10 mL of ethanol per hour, how long would it take for his blood alcohol concentration to decline to less than the legal blood alcohol concentration of 100 mg%? (*Hint*: Alcohol is eliminated by zero-order kinetics.) The specific gravity of alcohol is 0.8. The apparent volume of distribution for alcohol is 60% of body weight.
8. A single IV bolus injection containing 500 mg of cefamandole nafate (Mandol, Lilly) is given to an adult female patient (63 years, 55 kg) for a septicemic infection. The apparent volume of distribution is 0.1 L/kg and the elimination half-life is 0.75 hour. Assuming the drug is eliminated by first-order kinetics and may be described by a one-compartment model, calculate the following:
- The  $C_p^0$
  - The amount of drug in the body 4 hours after the dose is given
  - The time for the drug to decline to 0.5  $\mu\text{g/mL}$ , the minimum inhibitory concentration for streptococci
9. If the amount of drug in the body declines from 100% of the dose (IV bolus injection) to 25% of the dose in 8 hours, what is the elimination half-life for this drug? (Assume first-order kinetics.)
10. A drug has an elimination half-life of 8 hours and follows first-order elimination kinetics. If a single 600-mg dose is given to an

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adult female patient (62 kg) by rapid IV injection, what percent of the dose is eliminated (lost) in 24 hours assuming the apparent  $V_D$  is 400 mL/kg? What is the expected plasma drug concentration ( $C_p$ ) at 24 hours postdose?

**11.** For drugs that follow the kinetics of a one-compartment open model, must the tissues and plasma have the same drug concentration? Why?

**12.** An adult male patient (age 35 years, weight 72 kg) with a urinary tract infection was given a single intravenous bolus of an antibiotic (dose = 300 mg). The patient was instructed to empty his bladder prior to being medicated. After dose administration, the patient saved his urine specimens for drug analysis. The urine specimens were analyzed for both drug content and sterility (lack of bacteriuria). The drug assays gave the following results:

$t$ (hr)	Amount of Drug in Urine (mg)
0	0
4	100
8	26

a. Assuming first-order elimination, calculate the elimination half-life for the antibiotic in this patient.

b. What are the practical problems in obtaining valid urinary drug excretion data for the determination of the drug elimination half-life?

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