Exposure and Response after a Single Dose
Kinetics Following an Intravenous Bolus Dose

OBJECTIVES

The reader will be able to:

• Define the meaning of the following terms: clearance, compartmental model, disposition kinetics, distribution phase, elimination half-life, elimination phase, elimination rate constant, extraction ratio, extravasation, first-order process, fraction excreted unchanged, fraction in plasma unbound, fractional rate of elimination, glomerular filtration rate, half-life, hepatic clearance, loglinear decline, mean residence time, monoexponential equation, renal clearance, terminal phase, tissue distribution half-life, volume of distribution.

• Estimate from plasma and urine data following an intravenous (i.v.) dose of a drug:
  • Total clearance, half-life, elimination rate constant, and volume of distribution.
  • Fraction excreted unchanged and renal clearance.
  • Calculate the concentration of drug in the plasma and the amount of drug in the body with time following an i.v. dose, given values for the pertinent pharmacokinetic parameters.

• Ascertain the relative contribution of the renal and hepatic routes to total elimination from their respective clearance values.

• Describe the impact of distribution kinetics on the interpretation of plasma concentration–time data following i.v. bolus administration.

• Determine the mean residence time of a drug when plasma concentration–time data after a single bolus dose are provided.

• Explain the statement, “Half-life and elimination rate constant depend upon clearance and volume of distribution, and not vice versa.”

Administering a drug intravascularly ensures that the entire dose enters the systemic circulation. By rapid injection, elevated concentrations of drug can be promptly achieved; by continuous infusion at a controlled rate, a constant concentration, and often response, can be maintained. With no other route of administration can plasma concentration be as promptly and efficiently controlled. Of the two intravascular routes, the i.v one is the most frequently employed. Intra-arterial administration, which has greater inherent manipulative dangers, is reserved for situations in which drug localization in a specific organ or tissue is desired. It is achieved by inputting drug into the artery directly supplying the target tissue.

The disposition characteristics of a drug are defined by analyzing the temporal changes of drug in plasma and urine following i.v. administration. How this informa-
tion is obtained following rapid injection of a drug, as well as how the underlying processes control the profile, form the basis of this chapter, Chapter 4, Membranes and Distribution, and Chapter 5, Elimination. These are followed by chapters dealing with the kinetic events following an extravascular dose and the physiologic processes governing drug absorption. The final chapter in this section of the book deals with the time course of drug response after administering a single dose. The concepts laid down in this section provide a foundation for making rational decisions in therapeutics, the subject of subsequent sections.

APPRECIATION OF KINETIC CONCEPTS

Toward the end of Chapter 2, we considered the impact that various shapes of the exposure-time profile following an oral dose may have on the clinical utility of a drug. Figures 3-1 and 3-2 provide a similar set of exposure–time profiles except that the drugs are now given as an i.v. bolus. Notice that following the same dose, the two drugs displayed in Fig. 3-1 have the same initial concentration but different slopes of decline, whereas those displayed in Fig. 3-2 have different initial concentrations but similar slopes of decline. The reasons for these differences are now explored.

Several methods are employed for graphically displaying plasma concentration–time data. One common method that has been mostly employed in the preceding chapters and shown on the left-hand side of Figs. 3-1 and 3-2 is to plot concentration against time on regular (Cartesian) graph paper. Depicted in this way, the plasma concentration is seen to fall in a curvilinear manner. Another method of display is a plot of the same data on semilogarithmic paper (right-hand graphs in Figs. 3-1 and 3-2). The time scale is the same as before, but now, the ordinate (concentration) scale is logarithmic. Notice now that all the profiles decline linearly and, being straight lines, make it easier in many ways to predict the concentration at any time. But why do we get a linear decline when plotting the data on a semilogarithmic scale (commonly referred to as a loglinear decline), and what determines the large differences seen in the profiles for the various drugs?

**FIGURE 3-1.** Drugs A (black line) and B (colored line) show the same initial (peak) exposure but have different half-lives and total exposure–time profiles (AUC). A. Regular (Cartesian) plot. B. Semilogarithmic plot. Doses of both drugs are the same.
VOLUME OF DISTRIBUTION AND CLEARANCE

To start answering these questions, consider the simple scheme depicted in Fig. 3-3. Here, drug is placed into a well-stirred reservoir, representing the body, whose contents are recycled by a pump through an extractor, which can be thought of as the liver or kidneys, that removes drug. The drug concentrations in the reservoir, $C$, and that coming out of the extractor, $C_{\text{out}}$, can be measured. The initial concentration in the reservoir, $C(0)$, depends on the amount introduced, Dose, and the volume of the container, $V$. Therefore,

$$C(0) = \frac{\text{Dose}}{V} \quad 3-1$$

Fluid passes through the extractor at a flow rate, $Q$. With the concentration of drug entering the extractor being the same as that in the reservoir, $C$, it follows that the rate of presentation to the extractor is then $Q \cdot C$. Of the drug entering the extractor, a fraction, $E$, is extracted (by elimination processes) never to return to the reservoir. The correspon-
The rate of elimination (or rate of extraction) is then:

$$\text{Rate of elimination} = \frac{Q \cdot (C - C_{\text{out}})}{Q \cdot C}$$

from which it follows that the extraction ratio, $$E$$, of the drug by the extractor is given by

$$E = \frac{\text{Rate of elimination}}{\text{Rate of presentation}} = \frac{Q \cdot (C - C_{\text{out}})}{Q \cdot C} = \frac{(C - C_{\text{out}})}{C}$$

Thus, we see that the extraction ratio can be determined experimentally by measuring the concentrations entering and leaving the extractor and by normalizing the difference by the entering concentration.

Conceptually, it is useful to relate the rate of elimination to the measured concentration entering the extractor, which is the same as that in the reservoir. This parameter is called clearance, CL. Therefore,

$$\text{Rate of elimination} = CL \cdot C$$

Note that the units of clearance are those of flow (e.g., mL/min or L/hr). This follows because rate of elimination is expressed in units of mass per unit time, such as µg/min or mg/hr, and concentration is expressed in units of mass per unit volume, such as µg/L or mg/L. An important relationship is also obtained by comparing the equalities in Eqs. 3-2 and 3-4, yielding

$$CL = \frac{Q \cdot E}{Q \cdot C}$$

This equation provides a physical interpretation of clearance. Namely, clearance is the volume of the fluid presented to the eliminating organ (extractor) that is effectively, completely cleared of drug per unit time. For example, if $$Q = 1$$ L/min and $$E = 0.5$$, then effectively 0.5 L of the fluid entering the extractor from the reservoir is completely cleared of drug each minute. Also, it is seen that even for a perfect extractor ($$E = 1$$) the clearance of drug is limited in its upper value to $$Q$$, the flow rate to the extractor. Under these circumstances, we say that the clearance of the drug is sensitive to flow rate, the limiting factor in delivering drug to the extractor.

Two very useful parameters in pharmacokinetics have now been introduced, volume of distribution (volume of the reservoir in this example) and clearance (the parameter relating rate of elimination to the concentration in the systemic circulation [reservoir]). The first parameter predicts the concentration for a given amount in the body (reservoir). The second provides an estimate of the rate of elimination at any concentration.

**FIRST-ORDER ELIMINATION**

The remaining question is: How quickly does drug decline from the reservoir? This is answered by considering the rate of elimination ($$CL \cdot C$$) relative to the amount present in the reservoir ($$A$$), a ratio commonly referred to as the fractional rate of elimination, $$k$$

$$k = \frac{\text{Rate of elimination}}{\text{Amount in the reservoir}} = \frac{CL \cdot C}{A} = \frac{CL \cdot C}{V \cdot C}$$

or

$$k = \frac{CL}{V}$$

This important relationship shows that $$k$$ depends on clearance and the volume of the reservoir, two independent parameters. Note also that the units of $$k$$ are reciprocal time. For example, if the clearance of the drug is 1 L/hr and the volume of the reservoir is 10 L, then $$k = 0.1$$ hr$$^{-1}$$ or, expressed as a percentage, 10% per hour. That is, 10% of that in the reservoir is eliminated each hour. When expressing $$k$$, it is helpful to choose time units so that the value of $$k$$ is much less than 1. For example, if instead of hours, we had
chosen days as the unit of time, then the value of clearance would be 24 L/day, and therefore \( k = 2.4 \text{ day}^{-1} \), implying that the fractional rate of elimination is 240% per day, a number which is clearly misleading.

To further appreciate the meaning of \( k \), consider the data in Table 3-1, which shows the loss of drug in the reservoir with time, when \( k = 0.1 \text{ hr}^{-1} \). Starting with 100 mg, in 1 hr, 10% has been eliminated, so that 90 mg remains. In the next hour, 10% of 90 mg, or 9 mg, is eliminated, leaving 81 mg remaining at 2 hrs, and so on. Although this method illustrates the application of \( k \) in determining the time course of drug elimination, and hence drug remaining in the body, it is rather laborious and has some error associated with it. A simpler and more accurate way of calculating these values at any time is used (see “Fraction of Dose Remaining” later in this chapter).

Considering further the rate of elimination, there are two ways of determining it experimentally. One method mentioned previously is to measure the rates entering and leaving the organ. The other method is to determine the rate of loss of drug from the reservoir, since the only reason for the loss from the system is elimination in the extrator. Hence, by reference to Eq. 3-6

\[
\text{Rate of elimination} = -\frac{dA}{dt} = k \cdot A \tag{3-8}
\]

where \(-dA\) is the small amount of drug lost (hence the negative sign) from the reservoir during a small interval of time \( dt \). Processes, such as those represented by Eq. 3-8, in which the rate of the process is directly proportional to the amount present, are known as first-order processes, in that the rate varies in direct proportion with the amount there raised to the power of one \((A^1 = A)\). For this reason, the parameter \( k \) is frequently called the first-order elimination rate constant. Then, substituting \( A = V \cdot C \) on both sides of Eq. 3-8, and dividing by \( V \) gives

\[
-\frac{dC}{dt} = k \cdot C \tag{3-9}
\]

which, on integration, yields

\[
C = C(0) \cdot e^{-k \cdot t} \tag{3-10}
\]

where \( e \) is the natural base with a value of 2.71828... Equation 3-10 is known as a mono-exponential equation, in that it involves a single exponential term. Examination of this equation shows that it has the right properties. At time zero, \( e^{-k \cdot t} = e^0 = 1 \), so that \( C = C(0) \) and, as time approaches infinity, \( e^{-k \cdot t} \) approaches zero and so therefore does

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**TABLE 3-1** Amount Remaining in the Reservoir over a 5-Hr Period after Introduction of a 100-mg Dose of a Drug with an Elimination Rate Constant of 0.1 hr⁻¹

<table>
<thead>
<tr>
<th>Time Interval (h)</th>
<th>Amount Lost during Interval (mg)</th>
<th>Amount Remaining in Reservoir at the End of the Interval (mg)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>—</td>
<td>100</td>
</tr>
<tr>
<td>0–1</td>
<td>10</td>
<td>90.0</td>
</tr>
<tr>
<td>1–2</td>
<td>9</td>
<td>81.0</td>
</tr>
<tr>
<td>2–3</td>
<td>8.1</td>
<td>72.9</td>
</tr>
<tr>
<td>3–4</td>
<td>7.3</td>
<td>65.6</td>
</tr>
<tr>
<td>4–5</td>
<td>6.56</td>
<td>59.04</td>
</tr>
</tbody>
</table>

²If the time unit of \( k \) had been made smaller than hours the amount lost, and hence remaining in the reservoir, with time would be slightly different because in this calculation the assumption is made that the loss occurs at the initial rate throughout the interval, when in reality it falls exponentially. In the limiting case, the fraction remaining at time \( t \) is \( e^{-k \cdot t} \) (Eq. 3-17), which in the above example is 60.63% at 5 hr.
concentration. Equation 10 describes the curvilinear plots in Figs. 3-1 and 3-2. To see why such curves become linear when concentration is plotted on a logarithmic scale, take the logarithms of both sides of Eq. 3-10.

\[ \ln C = \ln C(0) - k \cdot t \]  

where \( \ln \) is the natural logarithm. Thus, we see from Eq. 3-11 that \( \ln C \) is a linear function of time with a slope of \( -k \), as indeed observed in Figs. 3-1 and 3-2. Moreover, the slope of the line determines how fast the concentration declines, which in turn is governed by \( V \) and \( CL \), independent parameters. The larger the elimination rate constant \( k \) the more rapid is drug elimination.

**HALF-LIFE**

Commonly, the kinetics of drugs is characterized by a half-life \( (t_{1/2}) \), the time for the concentration (and amount in the reservoir) to fall by one half, rather than by an elimination rate constant. These two parameters are of course interrelated. This is seen from Eq. 3-10. In one half-life, \( C(0) / 2 = C(0) \cdot e^{-k \cdot t_{1/2}} \) or

\[ e^{-k \cdot t_{1/2}} = 0.5 \]

which, on inverting and taking logarithms on both sides, gives

\[ t_{1/2} = \frac{\ln 2}{k} \]

Further, given that \( \ln 2 = 0.693 \),

\[ t_{1/2} = \frac{0.693}{k} \]

or, on substituting \( k \) by \( CL/V \), leads to another important relationship, namely,

\[ t_{1/2} = \frac{0.693 \cdot V}{CL} \]

From Eq. 3-16, it should be evident that half-life is controlled by \( V \) and \( CL \), and not vice versa.

To appreciate the application of Eq. 3-16, consider creatinine, a product of muscle catabolism and used as a measure of renal function. For a typical 70-kg, 60-year-old patient, creatinine has a clearance of 4.5 L/hr (75 mL/min) and is evenly distributed throughout the 42 L of total body water. As expected by calculation using Eq. 3-16, its half-life is 6.5 hr. Inulin, a polysaccharide also used to assess renal function, has the same clearance as creatinine in such a patient, but a half-life of only 2.5 hr. This is a consequence of inulin being restricted to the 16 L of extracellular body water (i.e., its “reservoir” size is smaller than that of creatinine).

**FRACTION OF DOSE REMAINING**

Another view of the kinetics of drug elimination may be gained by examining how the fraction of the dose remaining in the reservoir \( (A/Dose) \) varies with time. By reference to Eq. 3-10 and multiplying both sides by \( V \)

\[ \text{Fraction of dose remaining} = \frac{A}{Dose} = e^{-k \cdot t} \]

Sometimes, it is useful to express time relative to half-life. The benefit in doing so is seen by letting \( n \) be the number of half-lives elapsed after a bolus dose \( (n = t/t_{1/2}) \). Then, as \( k = 0.693 / t_{1/2} \), one obtains

\[ \text{Fraction of dose remaining} = e^{-0.693n} \]
Since $e^{-0.693} = 1/2$, it follows that

$$\text{Fraction of dose remaining} = \left(\frac{1}{2}\right)^n$$

Thus, one half or 50% of the dose remains after 1 half-life, and one fourth ($\frac{1}{2}\times\frac{1}{2}$) or 25% remains after 2 half-lives, and so on. Satisfy yourself that by 4 half-lives, only 6.25% of the dose remains to be eliminated. You might also prove to yourself that 10% remains at 3.32 half-lives.

If one uses 99% lost (1% remaining) as a point when the drug is considered to have been for all practical purposes eliminated, then 6.64 half-lives is the time. For a drug with a 9-min half-life, this is close to 60 min, whereas for a drug with a 9-day half-life, the corresponding time is 2 months.

**CLEARANCE, AREA, AND VOLUME OF DISTRIBUTION**

We are now in a position to fully explain the different curves seen in Figs. 3-1 and 3-2, which were simulated applying the simple scheme in Fig. 3-3. Drugs A and B in Fig. 3-1A have the same initial (peak) concentration following administration of the same dose. Therefore, they must have the same volume of distribution, $V$, which follows from Eq. 3-1. However, Drug A has a shorter half-life, and hence a larger value of $k$, from which we conclude that, since $k = CL/V$, it must have a higher clearance. The lower total exposure (area under the curve $[AUC]$) seen with Drug A follows from its higher clearance. This is seen from Eq. 3-4, repeated here,

$$\text{Rate of elimination} = CL \cdot C$$

By rearranging this equation, it can be seen that during a small interval of time $dt$

$$\text{Amount eliminated in interval } dt = CL \cdot C \cdot dt$$

where the product $C \cdot dt$ is the corresponding small area under the concentration–time curve within the time interval $dt$. For example, if the clearance of a drug is 0.1 L/min and the $AUC$ between 60 and 61 min is 0.1 mg-min/L, then the amount of drug eliminated in that minute is 0.01 mg. The total amount of drug eventually eliminated, which for an i.v. bolus equals the dose administered, is assessed by adding up or integrating the amounts eliminated in each time interval, from time zero to time infinity, and therefore,

$$\text{Dose} = CL \cdot AUC$$

or, rearranging,

$$CL = \frac{\text{Dose}}{AUC}$$

where $AUC$ is the total exposure. Thus, returning to the drugs depicted in Fig. 3-1, since the clearance of Drug A is higher, its $AUC$ must be lower than that of Drug B for a given dose. Several additional points are worth noting. First, because clearance, calculated using Eq. 3-22, relates to total elimination of all drug from the body, irrespective of how eliminated, it is sometimes called total clearance. Second, in practice, once $AUC$ is known, clearance is readily calculated. Indeed, if this is the only parameter of interest, there is no need to know either the half-life or volume of distribution to calculate clearance. Third, Eq. 3-22 is independent of the shape of the concentration–time profile. The critical factor is to obtain a good estimate of $AUC$ (see Appendix A, Assessment of $AUC$). Lastly, it follows from Eqs. 3-7 and 3-22 that volume of distribution is given by

$$V = \frac{CL}{k} = \frac{\text{Dose}}{AUC \cdot k}$$

That is, once clearance and $k$ (or half-life) are known, $V$ can be calculated.

Now consider the two drugs, C and D, in Fig. 3-2 in which, once again, the same dose of drug was administered. From the regular plot, it is apparent that as the initial
concentration of Drug C is higher, it has a smaller $V$. And, as the total exposure ($AUC$) of Drug C is the greater, it has the lower clearance. However, from the semilogarithmic plot, it is apparent that, as the slopes of the two lines are parallel, they must have the same value of the elimination rate constant, $k$ (Eq. 3-11), and hence the same value of half-life (Eq. 3-15). These equalities can only arise because the ratio $CL/V$ is the same for both drugs. The lesson is clear. The important determinants of the kinetics of a drug following an i.v. bolus dose are clearance and volume of distribution. These parameters determine the resultant kinetic process, reflected by the secondary parameters, $k$ and $t_{1/2}$.

**MEAN RESIDENCE TIME**

Another view of the events occurring following drug administration is to consider how long molecules stay in the body, their *residence times*, before being eliminated. Molecules eliminated soon after administration have short residence times, whereas those eliminated later have longer ones. The average time molecules stay in body is known as the *mean residence time*, $MRT$. The $MRT$ can be calculated in the following manner.

A measure of the number of molecules in the body is the amount there; the number and the amount are directly related to each other by Avogadro number, which for all compounds is the same, $6.022 \times 10^{23}$ molecules per mole of compound. On giving a bolus dose, initially all the molecules are in the body, the dose; thereafter the number of molecules, and hence the amount, falls. The $MRT$ is therefore obtained by simply summing, or integrating, the number of residing molecules over all times and dividing by the total number of molecules, the dose. Thus,

$$MRT = \frac{\int_0^\infty A \cdot dt}{Dose}$$

3-24

So, returning to the reservoir model, the amount in the body with time is $Dose \cdot e^{-k \cdot t}$ (Eq. 3-17), which on substitution into Eq. 3-24 and integration yields

$$MRT = \frac{1}{k}$$

3-25

Thus, we see that $MRT$ is simply the reciprocal of the elimination rate constant. For example, when $k = 0.1 \ hr^{-1}$, $MRT = 10 \ hr$. That is, when the fractional elimination rate of a compound is 0.1 per hour, on average drug molecules stay in the body for 10 hr. $MRT$ is further explored in Chapter 19, Distribution Kinetics.

**A CASE STUDY**

In reality, the body is more complex than depicted in the simple reservoir model. The body comprises many different types of tissues and organs. The eliminating organs, such as the liver and kidneys, are much more complex than a simple extractor. To gain a better appreciation regarding how drugs are handled by the body, consider the data in Fig. 3-4 showing the decline in the mean plasma concentration of midazolam displayed in both regular and semilogarithmic plots, following an 8.55-mg i.v. bolus dose of midazolam hydrochloride (equivalent to 7.5-mg midazolam base) of this hypnotic sedative and anxiolytic drug in a group of subjects with an average weight of 79 kg. We would obviously have preferred to consider each individual separately, but as is commonly the case, mean data are usually provided in published literature. However, for our purpose, let us assume that the data are those of an individual.

As expected, the decline in concentration displayed on the regular plot (Fig. 3-4A) is curvilinear. However, contrary to the expectation of the simple reservoir model, the decline in the semilogarithmic plot (Fig. 3-4B) is clearly biphasic, rather than monoexponential, with the concentration falling very rapidly for about 1 hr. Thereafter, the decline is slower and linear. The early phase is commonly called the *distribution phase* and the latter, the *terminal* or *elimination phase*. 
DISTRIBUTION PHASE

The distribution phase is called such because distribution into tissues primarily determines the early rapid decline in plasma concentration. For midazolam, distribution is rapid and occurs significantly even by the time of the first measurement in Fig. 3-4, 5 min. This must be so because the amount of midazolam in plasma at this time is only 0.61 mg. This value is calculated by multiplying the highest plasma concentration, 180 µg/L (0.18 mg/L), by the physical volume of plasma expected in an average 79-kg adult, 3.4 L (the standard value is 0.043 L/kg). The majority, 6.9 mg or 92% of the total 7.5-mg dose of midazolam base, must have already left the plasma and been distributed into other tissues, which together with plasma comprise the initial dilution space. Among these tissues are the liver and the kidneys, which also eliminate drug from the body. However, although some drug is eliminated during the early moments, the fraction of the administered dose eliminated during the distribution phase is less than 50% for midazolam and much less so for many other drugs. This statement is based on exposure considerations and is discussed more fully later in this chapter. Nonetheless, because both distribution and elimination are occurring simultaneously, it is appropriate to apply the term disposition kinetics when characterizing the entire plasma concentration–time profile following an i.v. bolus dose.

TERMINAL PHASE

During the distribution phase, changes in the concentration of drug in plasma reflect primarily movement of drug within, rather than loss from, the body. However, with time, distribution equilibrium of drug in tissue with that in plasma is established in more and more tissues, and eventually changes in plasma concentration reflect a proportional
change in the concentrations of drug in all other tissues and, hence, in the amount of drug in the body. During this proportionality phase, the body acts kinetically as a single container or compartment, much like in the reservoir model. Because decline of the plasma concentration is now associated solely with elimination of drug from the body, this phase is often called the **elimination phase**, and parameters associated with it, such as $k$ and $t_{1/2}$, are often called the **elimination rate constant** and **elimination half-life**.

**Elimination Half-Life**
The elimination half-life is the time over which the plasma concentration, as well as the amount of the drug in the body, falls by one half. The half-life of midazolam determined by the time to fall, for example, from 20 to 10 μg/L, is 3.8 hr (Fig. 3-4B). This is the same time that it takes for the concentration to fall from 10 to 5 μg/L, or by half anywhere along the terminal decline. In other words, the elimination half-life of midazolam is independent of the amount of drug in the body. It follows, therefore, that less drug is eliminated in each succeeding half-life. Initially, there are 7.5 mg of midazolam in the body. After 1 half-life (3.8 hr), assuming that distribution equilibrium was virtually spontaneous throughout this period, 3.75 mg remains in the body. After 2 half-lives (7.6 hr), 1.88 mg remains, and after 3 half-lives (11.4 hr), 0.94 mg remains. In practice, the drug may be regarded as having been eliminated (99%) by 6.64 half-lives (25 hr, or approximately 1 day).

Once the half-life is known, the elimination rate constant, $k$, and the mean residence time in the body, $MRT$, can be readily calculated from Eqs. 3-15 and 3-25. These are 0.182 hr$^{-1}$ and 5.5 hr, respectively. Midazolam clearly is removed relatively quickly from the body.

**Clearance**
This parameter is obtained by calculating total exposure, since $CL = \frac{Dose}{AUC}$. For midazolam total $AUC$ is 287 μg-hr/L (0.287 mg-hr/L), and so $CL = \frac{7.5}{0.287}$ mg/0.287 mg-hr/L, or 26 L/hr, or 43 mL/min. That is, 26 L of plasma are effectively cleared completely of drug each hour.

**Volume of Distribution**
The concentration in plasma achieved after distribution is complete is a function of dose, the extent of distribution of drug into tissues, and the amount eliminated while distributing. This extent of distribution can be determined by relating the concentration obtained with a known amount of drug in the body. This is analogous to the determination of the volume of the reservoir in Fig. 3-3 by dividing the amount of compound added to it by the resultant concentration, after thorough mixing. The volume measured is, in effect, a dilution space but, unlike the reservoir, this volume is not a physical space but rather an apparent one.

The apparent volume into which a drug distributes in the body at equilibrium is called the **(apparent) volume of distribution**. Plasma, rather than blood, is usually measured. Consequently, the volume of distribution, $V$, is the volume of plasma at the drug concentration, $C$, required to account for the entire amount of drug in the body, $A$.

$$V = \frac{A}{C}$$  \hspace{1cm} (3-26)

Volume of distribution is useful in estimating the dose required to achieve a given plasma concentration or, conversely, in estimating amount of drug in the body when the plasma concentration is known.

Calculation of volume of distribution requires that distribution equilibrium be achieved between drug in tissues and that in plasma. The amount of drug in the body is known immediately after an i.v. bolus; it is the dose administered. However, distribution equilibrium has not yet been achieved, so, unlike the reservoir model, we cannot use, with any confidence, the concentration obtained by extrapolating to zero time to obtain
an estimate of $V$. To overcome this problem, use is made of a previously derived important relationship $k = \frac{CL}{V}$, which on rearrangement gives

$$V = \frac{CL}{k}$$

or, since $k = 0.693/t_{1/2}$ and the reciprocal of 0.693 is 1.44,

$$V = 1.44 \cdot \frac{CL}{t_{1/2}}$$

So, although half-life is known, we need an estimate of clearance to estimate $V$. Substituting $CL = 26 \text{ L/hr}$ and $t_{1/2} = 3.8 \text{ hr}$ into Eq. 3-28 gives a value for the volume of distribution of midazolam of 142 L.

Volume of distribution is a direct measure of the extent of distribution. It rarely, however, corresponds to a real volume, such as for a 70-kg adult, plasma volume (3 L), extracellular water (16 L), or total body water (42 L). Drugs distribute to various tissues and fluids of the body. Furthermore, binding to tissue components may be so great that the volume of distribution is many times the total body size.

To appreciate the effect of tissue binding, consider the distribution of 100 mg of a drug in a 1-L system composed of water and 10 g of activated charcoal, onto which 99% of the drug is adsorbed. After the charcoal has settled, the concentration of drug in the aqueous phase is 1 mg/L; thus, 100 L of the aqueous phase, a volume 100-times greater than that of the entire system, is required to account for the entire amount in the system.

**CLEARANCE AND ELIMINATION**

Knowing clearance allows calculation of rate of elimination for any plasma concentration. Using Eq. 3-4, since $CL = 26 \text{ L/hr}$, the rate of elimination of midazolam from the body is 0.26 mg/hr at a plasma concentration of 0.01 mg/L (10 $\mu$g/L). One can also calculate the amount eliminated during any time interval, as illustrated in Fig. 3-5. Thus, it follows from Eq. 3-20 that multiplying the area between any two times, for example from time 0 to time $t$ [$AUC(0, t)$], by clearance gives the amount of drug that has been eliminated up to that time.

Alternatively, when the area is expressed as a fraction of the total $AUC$, one obtains the fraction of the dose eliminated. The fraction of the total area beyond a given time is a measure of the fraction of dose remaining to be eliminated. For example, in the case of midazolam, by 2 hr, the area is 48% of the total $AUC$, and hence 48% of the administered 7.5-mg dose, or 3.6 mg, has been eliminated from the body and 3.9 mg has yet to be eliminated.

**DISTRIBUTION AND ELIMINATION: COMPETING PROCESSES**

Previously, it was stated that relatively little midazolam is eliminated before attainment of distribution equilibrium. Or to be more precise, relatively little more has been eliminated than expected had distribution equilibrium occurred instantaneously. This conclusion is
based on the finding that the area under the concentration–time profile during the distribution phase (up to about 2 hr, see Fig. 3-4B) represents less than 50% of the total AUC, and hence less than 50% of the total amount eliminated. One would expect 30% to have been eliminated anyway during the 2-hr interval (2/3.8 of one half-life). This occurs because the speed of tissue distribution of this, and of many other drugs, is faster than that of the corresponding elimination process.

**FIGURE 3-6.** The events occurring within the body after a 100-mg i.v. bolus dose are the result of interplay between the kinetics of distribution and elimination. Distribution is depicted here as an exchange of drug between a central pool, comprising blood and rapidly equilibrating tissues, including the eliminating organs, liver and kidneys, and a pool containing the more slowly equilibrating tissues, such as muscle and fat. Because of distribution kinetics, a biexponential decline is seen in the semilogarithmic plot of drug in the central pool (and hence plasma). Two scenarios are considered. The first (left-hand set of panels, A) is one in which distribution is much faster than elimination, shown by large arrows for distribution and a small one for elimination. Distribution occurs so rapidly that little drug is lost before distribution equilibrium is achieved, when drug in the slowly equilibrating pool parallels that in the central pool, as is clearly evident in the semilogarithmic plot of events with time. Most drug elimination occurs during the terminal phase of the drug; this is seen in the linear plot of percent of dose eliminated with time. In the second scenario (right-hand set of panels, B), distribution (small arrows) is much slower than elimination (large arrow). Then, although, because of distribution kinetics, a biexponential decline from the central pool is still evident, most of the drug has been eliminated before distribution equilibration has been achieved. Then the phase associated with the majority of elimination is the first phase, and not the terminal exponential phase, which reflects redistribution from the slowly equilibrating tissues.
of elimination. These competing events, distribution and elimination, which determine the disposition kinetics of a drug, are shown schematically in Fig. 3-6. Here, the body is portrayed as a compartmental model, comprising two body pools, or compartments, with exchange of drug between them and with elimination from the first, often called central, pool. One can think of the blood, liver, kidneys, and other organs into which drug equilibrates rapidly as being part of this central pool where elimination and input of drug occurs, and the more slowly equilibrating tissues, such as muscle and fat, as being part of the other pool. The size of each arrow represents the speed of the process; the larger the arrow the faster the process. Two scenarios are depicted. The first, and most common, depicted in Fig. 3-6A, is one in which distribution is much faster than elimination. Displayed is a semilogarithmic plot of the fraction of an i.v. bolus dose within each of the pools, as well as the sum of the two (total fraction remaining in the body), as a function of time. Notice that, as with diazepam, a biphasic curve is seen and that little drug is eliminated from the body before distribution equilibrium is achieved; thereafter, during the terminal phase, drug in the two pools is in equilibrium, and the only reason for the subsequent decline is elimination from the body. The decline of drug in plasma then reflects changes in the amount of drug in the body.

Next consider the situation, albeit less common, depicted in Fig. 3-6B. Here, distribution of drug between the two pools is slow, and elimination from the central pool is rapid. Once again, a biphasic curve is seen. Also, during the terminal phase, at which time distribution equilibrium has been achieved between the two pools, the only reason for decline is again elimination of drug from the body and events in plasma reflect changes in the rest of the body. But there the similarity ends. Now, most of the drug has been eliminated from the body before distribution equilibrium is achieved, so there is little drug left to be eliminated during the terminal phase. An example of this latter situation is shown in Fig. 3-7 for the aminoglycoside antibiotic, gentamicin. This is a large polar compound

![Graph](image1)

**FIGURE 3-7.** Semilogarithmic (A) and linear (B) plots of the decline in the mean plasma concentration of gentamicin following an i.v. bolus dose of 1 mg/kg to a group of 10 healthy men. Notice that, although a biexponential decline is seen in the semilogarithmic plot with the terminal phase reached by 36 hr (indicated by the arrow), based on analysis of the linear plot, essentially all the area, and hence elimination, has occurred before reaching the terminal phase. This is a consequence of elimination occurring much faster than tissue distribution. (From: Adelman M, Evans E, Schentag JJ. Two-compartment comparison of gentamicin and tobramycin in normal volunteers. Antimicrob Agents Chemother 1982;22:800–804.)
that is rapidly cleared from the body via the kidneys, but which permeates very slowly into many cells of the body. Over 95% of an i.v. dose of this antibiotic is eliminated into the urine before distribution equilibrium has occurred. Hence, with respect to elimination, it is the first phase and not the terminal phase that predominates. In conclusion, assigning the terminal phase as the elimination phase of a drug is generally reasonable, and unless mentioned otherwise, is assumed to be the case for the rest of this book. However, keep in mind, there are always exceptions.

**PATHWAYS OF ELIMINATION**

Some drugs are totally excreted unchanged in urine. Others are extensively metabolized, usually within the liver. Knowing the relative proportions eliminated by each pathway is important as it helps to predict the sensitivity of clearance of a given drug in patients with diseases of these organs or who are concurrently receiving other drugs that affect these pathways, particularly metabolism. Of the two, renal excretion is much the easier to quantify, achieved by collecting unchanged drug in urine; there is no comparable method for determining the rate of hepatic metabolism.

**RENAI CLEARANCE**

Central to this analysis of urinary excretion is the concept of renal clearance. Analogous to total clearance, renal clearance ($CL_R$) is defined as the proportionality term between urinary excretion rate and plasma concentration:

$$\text{Rate of excretion} = CL_R \cdot C$$  \hspace{1cm} 3-29

with units of flow, usually mL/min or L/hr.

Practical problems arise, however, in estimating renal clearance. Urine is collected over a finite period (e.g., 4 hr, during which time the plasma concentration is changing continuously. Shortening the collection period reduces the change in plasma concentration but increases the uncertainty in the estimate of excretion rate owing to incomplete bladder emptying. This is especially true for urine collection intervals of less than 30 min. Lengthening the collection interval, to avoid the problem of incomplete emptying, requires a modified approach for the estimation of renal clearance. This approach is analogous to that taken with total clearance. By rearranging Eq. 3-29, during a very small interval of time, $dt$,

$$\text{Amount excreted} = CL_R \cdot C \cdot dt$$  \hspace{1cm} 3-30

where $C \cdot dt$ is the corresponding small area under the plasma drug concentration–time curve. The urine collection interval (denoted by $\Delta t$) is composed of many such very small increments of time, and the amount of drug excreted in a collection interval is the sum of the amounts excreted in each of these small increments of time, that is,

$$\text{Amount excreted in collection interval} = CL_R \cdot [\text{AUC within interval}]$$  \hspace{1cm} 3-31

The problem in calculating renal clearance therefore rests with estimating the AUC within the time interval of urine collection (see Appendix A). The average plasma drug concentration during the collection interval is given by $\text{(AUC within interval)}/\Delta t$. This average plasma concentration is neither the value at the beginning or at the end of the collection time but is the value at some intermediate point. When the plasma concentration changes linearly with time, the average concentration occurs at the midpoint of the collection interval. Because the plasma concentration of drug is in fact changing exponentially with time, the assumption of linear change is reasonable only when loss during the interval is small relative to the amount in the body. In practice, the interval should be less than an elimination half-life. This method of calculating renal clearance is useful when addressing questions of change in this parameter with time or urine pH (further examined in Chapter 5, *Elimination*).
Integrating Eq. 3-30 over all time intervals, from zero to infinity, one obtains the useful relationship

\[ \text{Renal clearance} = \frac{\text{Total amount excreted unchanged}}{\text{AUC}} \quad 3-32 \]

where \( \text{AUC} \) is the total area under the plasma drug concentration–time curve. To apply Eq. 3-32, care must be taken to ensure that all urine is collected and for a sufficient period of time to gain a good estimate of the total amount excreted unchanged. In practice, the period of time must be at least 6 elimination half-lives of the drug. Thus, if the half-life of a drug is in the order of a few hours, no practical difficulties exist in ensuring urine collections taken over an adequate period of time. Severe difficulties with compliance in urine collection occur, however, for drugs such as the antimalarial mefloquine, with a half-life of about 3 weeks, since all urine excreted over a period of at least 4 months must be collected. In this case, because of practical problems to ensure complete urine collection, renal clearance is usually determined over a shorter time interval, applying Eq. 3-31.

**RENAL EXCRETION AS A FRACTION OF TOTAL ELIMINATION**

The fraction excreted unchanged of an i.v. dose, \( fe \), is an important pharmacokinetic parameter. It is a quantitative measure of the contribution of renal excretion to overall drug elimination. Knowing \( fe \) aids in establishing appropriate modifications in the usual dosage regimen of a drug for patients with diminished renal function. Among drugs, the value of \( fe \) in patients with normal renal function lies between 0 and 1.0. When \( fe \) is low (\(<0.3\)), which is common for many highly lipophilic drugs that are extensively metabolized, excretion is a minor pathway of drug elimination. Occasionally, as in the case of gentamicin and the \( \beta \)-adrenergic blocking agent atenolol, used to lower blood pressure, renal excretion is virtually the sole route of elimination, in which case the value of \( fe \) approaches 1.0. By definition, the complement, \( 1 - fe \), is the fraction of the i.v. dose that is eliminated by other mechanisms, usually hepatic metabolism.

An estimate of \( fe \) is most readily obtained from cumulative urinary excretion data following i.v. administration, since by definition,

\[ fe = \frac{\text{Total amount excreted unchanged}}{\text{Dose}} \quad 3-33 \]

In practice, care should be taken to ensure all urine is collected and over a sufficient period of time to obtain a good estimate of total amount excreted unchanged.

Substituting Eq. 3-33 for \( fe \) and Eq. 3-21 for \( CL \) into Eq. 3-32 indicates that \( CLR \) can be estimated directly from the relationship

\[ CL_R = fe \cdot CL \quad 3-34 \]

Thus, \( fe \) may also be defined and estimated as the ratio of renal and total clearances. This approach is particularly useful in those situations in which total urine collection is not possible.

**ESTIMATION OF PHARMACOKINETIC PARAMETERS**

To appreciate how the pharmacokinetic parameters defining disposition are estimated, consider the plasma and urine data in Table 3-2 obtained following an i.v. bolus dose of 100 mg of a drug.

**PLASMA DATA ALONE**

From the table, the plasma concentration is seen to drop progressively with time, but only after the data are plotted semilogarithmically (Fig. 3-8), when a polyphasic decline is still seen, is there clear evidence of distribution kinetics. Initially, concentration falls rapidly until after about 2 hr, when distribution equilibrium has been achieved, after
which time it falls monoexponentially, the terminal phase. Only then can the elimination half-life and associated rate constant be readily determined. The half-life, taken as the time for the concentration to fall in half (e.g., from 1.2 to 0.6 mg/L or 0.6 to 0.3 mg/L), is 18 hr, so that \( k \) is 0.038 hr\(^{-1} \), and therefore the MRT is 26.3 hr. Clearance is determined by dividing dose (100 mg) by \( AUC \). The total \( AUC \), estimated using the trapezoidal rule (Appendix A, Assessment of \( AUC \)), is 41.48 mg-hr/L. Accordingly, clearance is 2.41 L/hr. Volume of distribution, estimated from \( CL/k \) (Eq. 3-23), is therefore 63.4 L. Lastly, for this drug one can be sure that little has been eliminated before distribution equilibrium is reached. This is readily seen by calculating the area above the line when the terminal slope in Fig. 3-8 is extrapolated back to zero time. This area comprises only 7% of the total \( AUC \). That is, only 7% of the dose has been eliminated during the attainment of distribution equilibrium above that expected from the terminal half-life.

**PLASMA AND URINE DATA**

The cumulative amount excreted unchanged up to 72 hr is 28.2 mg. During this period, 4 half-lives have elapsed, and based on half-life considerations (Eq. 3-19), 93.75% of the ultimate amount will have been excreted. Hence, a reasonable estimate of the total amount excreted unchanged \( (Ae) \) is 28.2/0.973 or 30 mg, so that the fraction of the dose excreted unchanged, \( fe \), is 30 mg/100 mg, or 0.30.

Both plasma and urine data are required to estimate renal clearance. This parameter can be obtained from the slope of a plot of the amount excreted within a collection interval against \( AUC \) within the same time interval (Fig. 3-9). The straight line implies that

<table>
<thead>
<tr>
<th>Observation</th>
<th>Plasma Data</th>
<th>Urine Data</th>
<th>Treatment of Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time (hr)</td>
<td>Concentration (mg/L)</td>
<td>Time interval of collection (hr)</td>
<td>Volume of urine (mL)</td>
</tr>
<tr>
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<td>0–12</td>
<td>907</td>
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<tr>
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<td>12–24</td>
<td>950</td>
</tr>
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<td>2.2</td>
<td>24–36</td>
<td>1232</td>
</tr>
<tr>
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<td>36–48</td>
<td>784</td>
</tr>
<tr>
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<td>1.8</td>
<td>48–72</td>
<td>1430</td>
</tr>
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<td>72</td>
<td></td>
</tr>
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</tr>
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</tr>
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<td></td>
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</tr>
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<td>60</td>
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</tr>
</tbody>
</table>

| TABLE 3-2 Plasma and Urine Data Obtained Following an Intravenous 100-mg Bolus Dose |
CHAPTER 3 | Kinetics Following an Intravenous Bolus Dose

3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0

10.0

0.1

FIGURE 3-8. Regular (A) and semilogarithmic (B) plots of the plasma concentration–time data given in Table 3-2.

10 15

20

AUC within the Urine Collection Interval (mg-hr/L)

FIGURE 3-9. The amount excreted is directly proportional to the AUC measured over the urine collection interval. Renal clearance is given by the slope of the line. (Data from Table 3-2.)
renal clearance is constant and independent of plasma concentration over the range covered. The slope of the line indicates that the renal clearance of this drug is 0.74 L/hr. Essentially the same value is obtained by multiplying total clearance (2.5 L/hr) by fe (0.30) (cf., Eq. 3-34).

A QUESTION OF PRECISION
Had you plotted the same data and calculated the pharmacokinetic parameters by visual inspection, you may have obtained answers that differ from those given. This is not unusual and will occur in many cases when you check your answers to the problems at the end of each chapter against those given in Appendix J. The reason lies in differences in where you draw your line through the data, after they have been plotted, and in rounding-off numbers. All measurements have errors associated with analytic methods, conditions of storage, and handling of samples prior to analysis, leading to some uncertainty in knowing the true curve.

Also, had the study just considered been repeated subsequently in the same individual, the estimated half-life may have been 16.5 or 19.1 hr instead of 18 hr. For almost all clinical situations, this degree of within individual variation is acceptable. To reflect the acceptable 5% to 10% variation, most answers here and throughout the remainder of the book are usually given to no more than two or three significant places.

In this chapter, many symbols have been defined, as it is the first time that they are used. These symbols are reused repeatedly throughout the book. To avoid continually redefining them in every chapter and to facilitate reference to them, the “Definitions of Symbols” appear in a table just before Chapter 1. Some infrequently used symbols that occur only within one chapter are defined there and may not be included in the table.

MEASUREMENT FLUID
Strictly speaking, when referring to concentration, one should use the terminology concentration of drug in plasma (or whole blood, or plasma water, as appropriate). For expediency, in much of this chapter and throughout the rest of the book, this phrase is often shortened to plasma (or blood) drug concentration. Indeed, this is sometimes even further shortened to plasma concentration (or blood concentration) in many contexts in which concentration of a drug is understood. Similarly, the phrase amount in body refers to the amount of drug in the body, unless otherwise stated.

USE OF COMPUTERS
Today, computers are used to analyze pharmacokinetic and pharmacodynamic data and make predictions. Implicit in the approach is the application of a model. Based on statistical criteria, the parameter values giving the best fit of the parameters of the appropriate equation or model to the experimental data are obtained. This approach not only provides the best estimate of the parameters but also one’s confidence in them. Furthermore, application of the same computer program to a set of data results in the same answers independent of the operator. This consistency cannot be achieved by fitting graphical data by eye. Moreover, unlike an exponential equation, there are many situations in pharmacokinetics and particularly pharmacodynamics that require equations that cannot be linearized. Obtaining a best fit by eye then becomes virtually impossible. This limitation does not arise using a computer. Nonetheless, a great deal is learned by displaying data graphically. One gains a feeling for the quality of the data and the equation or model that is most likely to describe them appropriately. Ultimately, the suitability of a model can be judged by how well predictions match observations at all times. Because of the great benefits to learning pharmacokinetics and pharmacodynamics gained by plotting data and interpreting graphical representations, this element is incorporated throughout the book and emphasized in study problems and simulation exercises.
CHANGE IN DOSE

An adjustment in dose is often necessary to achieve optimal drug therapy. The kinetic consequences of adjustment are made more readily when the values of the pharmacokinetic parameters of a drug do not vary with dose or with concentration. For example, the AUC is expected to double when the single i.v. dose of 50 mg is doubled to 100 mg, because clearance is unchanged. There are, however, many reasons for a change in a parameter value (e.g., CL, with dose). These are dealt with in Chapter 16, Nonlinearities. Throughout the majority of the book, however, pharmacokinetic parameters are assumed not to change with either dose or time.

KEY RELATIONSHIPS

\[ E = \frac{(C - C_{\text{ume}})}{C} \]

Rate of elimination = \( CL \cdot C \)

\[ CL = Q \cdot E \]

\[ k = \frac{CL}{V} \]

Rate of elimination = \( -\frac{dA}{dt} = k \cdot A \)

\[ C = C(0) \cdot e^{-k \cdot t} \]

\[ ln C = ln C(0) - k \cdot t \]

\[ t_{1/2} = \frac{0.693}{k} \]

\[ t_{1/2} = \frac{0.693 \cdot V}{CL} \]

Fraction of dose remaining = \( e^{-k \cdot t} = \left(\frac{1}{2}\right)^n \)

Dose = \( CL \cdot AUC \)

\[ V = \frac{A}{C} \]

\[ V = 1.44 \cdot CL \cdot t_{1/2} \]

\[ \text{MRT} = \frac{1}{k} \]

\[ fe = \frac{\text{Total drug excreted unchanged}}{\text{Dose}} \]

Renal clearance = \( fe \cdot CL \).
1. Define the following terms: clearance, compartmental model, disposition kinetics, elimination half-life, elimination rate constant, extraction ratio, first-order process, fraction excreted unchanged, fraction in plasma unbound, fractional rate of elimination, half-life, mean residence time, monoexponential equation, renal clearance, terminal phase, volume of distribution.

2. Given that the disposition kinetics of a drug is described by a one-compartment model, which of the following statements is (are) correct? The half-life of a drug following therapeutic doses in humans is 4 hr, therefore,
   a. The elimination rate constant of this drug is 0.173 hr$^{-1}$
   b. It takes 16 hr for 87.5% of an i.v. bolus dose to be eliminated.
   c. It takes twice as long to eliminate 37.5 mg following a 50 mg bolus dose as it does to eliminate 50 mg following a 100-mg dose.
   d. Complete urine collection up to 12 hr is needed to provide a good estimate of the ultimate amount of drug excreted unchanged.
   e. The fraction of the administered dose eliminated by a given time is independent of the size of the dose.

3. For a drug exhibiting one-compartment disposition kinetics, calculate the following:
   a. The fraction of an i.v. dose remaining in the body at 3 hr, when the half-life is 6 hr.
   b. The half-life of a drug, when 18% of the dose remains in the body 4 hr after an i.v. bolus dose.

4. The average values of clearance and volume of distribution of valproic acid, an antiepileptic drug, in the adult patient population are 0.5 L/hr and 9 L, respectively.
   a. Calculate the rate of elimination of valproic acid when the plasma concentration is 30 mg/L.
   b. Calculate the half-life of valproic acid.
   c. What is the amount of valproic acid in the body at distribution equilibrium when the plasma concentration is 60 mg/L?
   d. What is the expected plasma concentration 12 hr after an i.v. 700-mg dose of valproic acid (administered as the equivalent amount of the sodium salt)?

5. A drug that displays one-compartment disposition kinetics is administered as a 100-mg single bolus dose. Depicted in Fig. 3-10A is the plasma concentrations of drug observed initially (10 mg/L) and 10 hr later (2.5 mg/L). Depicted in Fig. 3-10B is the cumulative urinary excretion of unchanged drug at 48 hr (60 mg). Complete the figures by drawing continuous lines that depict the fall of drug concentration in plasma and the accumulation of drug in urine with time.

6. From 0 to 3 hr after a 50-mg i.v. bolus dose of drug, the $AUC$ is 5.1 mg-hr/L. The total $AUC$ is 22.4 mg-hr/L and the cumulative amount excreted unchanged, $Ae_{uc}$ is 11 mg.
   a. Determine the amount of drug remaining in the body at 3 hrs as a percent of the administered dose.
   b. Calculate total clearance.
c. Calculate the renal clearance of the drug.

d. What is the fraction of the dose that is eliminated by renal excretion?

7. When 100 mg of a drug was given as an i.v. bolus, the following plasma concentration–time relationship ($C$ in mg/L and $t$ in hours) was observed,

$$C = 7.14e^{-0.051t}$$

Calculate:

a. Volume of distribution.

b. Elimination half-life.

c. Total $AUC$.

d. Total clearance.

e. The plasma concentration 70 min after a 250-mg i.v. bolus dose.

8. A 10-mg dose of diazepam is injected intravenously into a patient with status epilepticus. The half-life and volume of distribution of the drug are 48 hr and 80 L, respectively, in the patient. Calculate your expectation for each of the following:

a. The elimination rate constant.

b. The plasma diazepam concentration 12 hr after giving the dose.

c. The fraction of the dose remaining in the body 48 hr after the dose is given.

d. The clearance of diazepam.

e. The initial rate of elimination when the entire dose is in the body.

f. The $AUC$.

g. The amount of drug in the body 1 week after giving the dose.

9. The data given in Table 3-3 are the plasma concentrations of cocaine as a function of time after i.v. administration of 33 mg cocaine hydrochloride to a subject. (Molecular weight of cocaine hydrochloride = 340 g/mol; molecular weight of cocaine = 303 g/mol.) (Adapted from Chow MJ, Ambre JJ, Ruo TI, et al. Kinetics of cocaine distribution, elimination, and chronotropic effects. Clin Pharmacol Ther 1985;38:318–324.)

a. Prepare a semilogarithmic plot of plasma concentration versus time. Graph paper is available online at the companion web site: http://thePoint.lww.com/Rowland4e. Regular Graph Paper, 2-Cycle Semilogarithmic Graph Paper, 3-Cycle Semilogarithmic Graph Paper, and Log-log Graph Paper are available. You may prefer to plot the data using Excel or some other software program.

b. Estimate the half-life.
c. Estimate the total $AUC$ of cocaine by integration of the exponential equation and by use of the trapezoidal rule (Appendix A, Assessment of $AUC$). Comment on any differences between these two estimates.

d. Calculate the clearance of cocaine.

e. Given that the body weight of the subject is 75 kg, calculate the volume of distribution of cocaine in L/kg.

ten. Figure 3-11 shows a semilogarithmic plot of the plasma concentration–time profile of theophylline following a 500-mg i.v. bolus dose in a 70-kg patient. Notice that the decline is biexponential, with the break in the curve at around 30 min. Theophylline is 40% bound in plasma and freely passes across membranes and distributes into all body water spaces. It is also extensively metabolized with only 10% of the dose excreted in the urine unchanged.

### TABLE 3-3

<table>
<thead>
<tr>
<th>Time (hr)</th>
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<tbody>
<tr>
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<td>17</td>
</tr>
<tr>
<td>3.0</td>
<td>10</td>
</tr>
</tbody>
</table>

a. The total area under the plasma-concentration time profile of theophylline is 125 mg-hr/L. Calculate the total clearance of theophylline.
b. Is it appropriate to call the initial decline phase up to about 30 min the distribution phase knowing that the $AUC$ of theophylline up to that time is 13.1 mg-hr/L?
c. The plasma concentration at the first sampling time of 5 min is 33 mg/L. What percent of the dose has left the plasma by then and to where does the drug primarily go?
d. Calculate the renal clearance of theophylline.
e. From the plot, estimate the half-life of theophylline.
f. Estimate the volume of distribution of theophylline.