5

Apparent Volume of Distribution

The proportionality constant relating drug concentration in blood or plasma to the amount of drug in the body has been termed the apparent volume of distribution. There has been considerable confusion concerning the estimation and meaning of the apparent volume of distribution of a drug. A principal cause of this confusion is the fact that there is no obvious relationship between the apparent and real volume of distribution of a drug.

The real distribution volume of a drug is related to body water and cannot exceed total body water (i.e., about 58% of body weight in the normal adult human). Body water may be divided into at least three distinct compartments: the vascular fluid or blood, the extracellular fluid, and the intracellular fluid. In humans, extracellular fluid is about one-third of total body water and includes the plasma, which is about 4% of body weight. Blood volume, which includes the intracellular fluid of the erythrocytes and other formed elements, is about twice the plasma volume.

Some high molecular weight substances, such as Evans blue or indocyanine green, are essentially confined to the circulating plasma after intravenous administration and can be used to estimate plasma volume (or blood volume if the hematocrit is determined). Certain ions, such as chloride or bromide, rapidly distribute throughout the extracellular fluid but do not easily cross cell membranes, so they may be used to estimate extracellular water. The volume of total body water may be estimated by means of heavy water or certain lipid-soluble substances, such as antipyrine, which distribute rapidly throughout the total body water.

The apparent volume of distribution of each of these tracers approximates its true volume of distribution because binding to plasma proteins and tissues is negligible. For most substances this is not the case. Most drugs are significantly bound in either the vascular or extravascular space, or both. Drugs that are predominantly bound to plasma proteins have apparent volumes of distribution that are

smaller than their real volumes of distribution, whereas drugs that are predominantly bound to extravascular tissues have apparent volumes of distribution that are larger than their real distribution space. For different drugs, volumes of distribution may range from about 0.04 to more than 20 liters/kg.

RELATIONSHIP BETWEEN VOLUME OF DISTRIBUTION, DRUG BINDING AND ELIMINATION, AND ANATOMIC VOLUME

A quantitative expression relating apparent volume of distribution, real distribution space, and binding may be developed using the model shown in Fig. 5.1. The model consists of two physiologic spaces, the vascular or blood space and the extravascular or tissue space. Linear binding occurs in both spaces and the concentration of free drug is the same throughout the total body water. After administration of drug into the vascular space by intravenous bolus injection, distribution is assumed to be instantaneous. Elimination occurs in a first-

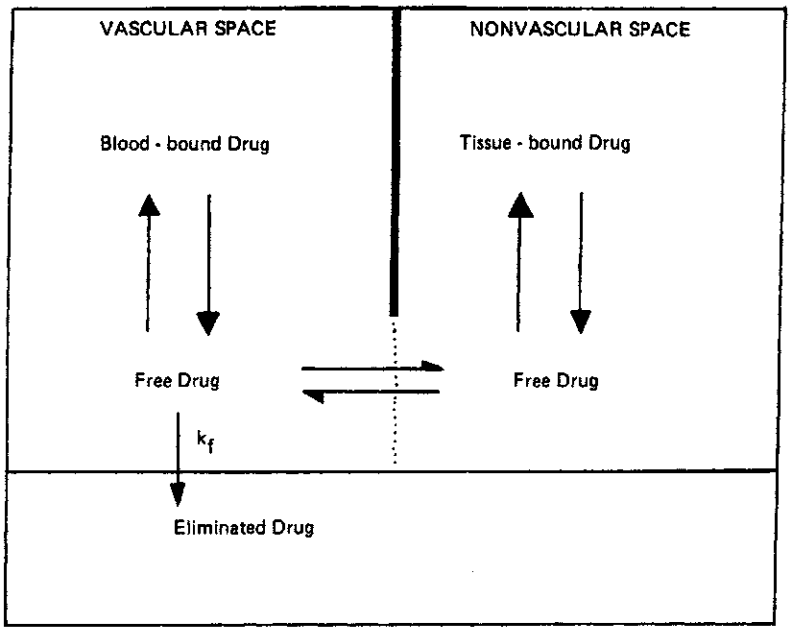

Fig. 5.1 One-compartment pharmacokinetic model with two linear binding sites. Initially, a bolus dose of drug is introduced in the vascular space; binding and distribution is assumed to be instantaneous. The rate of drug elimination is given by the product of k_f and free drug concentration.

order fashion at a rate proportional to the free drug concentration. The model is, in one sense, a one-compartment system in that drug distribution between the two physiologic spaces is assumed to be instantaneous. However, in another sense, the model is a two-compartment system since vascular binding sites (such as plasma proteins) and tissue binding sites are restricted to separate spaces.

In the case of linear binding in the vascular space (blood),

$$C_{Bb} = bC_f \tag{5.1}$$

and

$$A_{Bb} = bV_B C_f = bA_{Bf} \tag{5.2}$$

where C_{Bb} is the concentration of drug bound in the blood at time t; b is a proportionality constant relating free (unbound) drug concentration C_f to bound drug concentration in the blood; A_{Bb} and A_{Bf} are the amounts of drug bound and free, respectively, in the blood at time t; and V_B is blood volume.

Since the free drug concentration at any time is the same throughout the system, it follows that the amount of free drug in the blood is given by

$$A_{Bf} = \frac{V_B}{V_f} A_f \tag{5.3}$$

where V_f is the volume of distribution of free (unbound) drug and is equal to the sum of V_B and V_T (where V_T is the volume of the tissue or extravascular space), and A_f is the amount of free drug in the body at time t. It follows that

$$A_{Bb} = b \frac{V_B}{V_f} A_f \tag{5.4}$$

In the case of linear binding in the extravascular space,

$$C_{Tb} = BC_f \tag{5.5}$$

and

$$A_{Tb} = BV_T C_f = BA_{Tf} \tag{5.6}$$

where C_{Tb} is the concentration of drug bound in the extravascular space at time t; B is a proportionality constant relating free drug concentration to bound drug concentration in the extravascular space; A_{Tb} and A_{Tf} are the amounts of drug bound and free, respectively, in the extravascular space at time t; and V_T is the volume of the extravascular space. Since the free drug concentration at any time is the same in both spaces, it follows that

$$A_{Tf} = \frac{V_T}{V_f} A_f \tag{5.7}$$

and

$$A_{Tb} = B \frac{V_T}{V_f} A_f \tag{5.8}$$

At any time after administration, the entire dose D can be accounted for by the sum of the amounts bound in the vascular and extravascular space, the amount of free drug in the body, and the amount eliminated:

$$D = A_f + A_{Bb} + A_{Tb} + k_f \int_0^t A_f \, dt \tag{5.9}$$

where k_f is the first-order elimination rate constant and the term $k_f \int_0^t A_f \, dt$ represents the amount eliminated up to time t. Differentiation of Eq. (5.9) with respect to time yields

$$\frac{dA_f}{dt} + \frac{dA_{Bb}}{dt} + \frac{dA_{Tb}}{dt} + k_f A_f = 0 \tag{5.10}$$

By differentiating Eqs. (5.4) and (5.8), we obtain

$$\frac{dA_{Bb}}{dt} = b \frac{V_B}{V_f} \frac{dA_f}{dt} \tag{5.11}$$

and

$$\frac{dA_{Tb}}{dt} = B \frac{V_T}{V_f} \frac{dA_f}{dt} \tag{5.12}$$

Therefore, Eq. (5.10) may be transformed to

$$\frac{dA_f}{dt}\left(1 + b \frac{V_B}{V_f} + B \frac{V_T}{V_f}\right) + k_f A_f = 0 \tag{5.13}$$

Rearrangement yields

$$\frac{-dA_f}{dt}\left(1 + b \frac{V_B}{V_f} + B \frac{V_T}{V_f}\right) = k_f A_f \tag{5.14}$$

Since $A_f = V_f C_f$, it follows that

$$\frac{-dC_f}{dt} = \frac{k_f}{1 + b(V_B/V_f) + B(V_B/V_f)} C_f = \beta C_f \tag{5.15}$$

where β is the apparent elimination rate constant and is given by

$$\beta = \frac{k_f}{1 + b(V_B/V_f) + B(V_T/V_f)} \tag{5.16}$$

If we define a new term, f, as the fraction of the total amount of drug in the body which is free, then

$$f = \frac{A_f}{A_f + A_{Bb} + A_{Tb}} = \frac{1}{1 + (A_{Bb}/A_f) + (A_{Tb}/A_f)} \tag{5.17}$$

Rearranging Eq. (5.4) gives a term for A_{Bb}/A_f and rearranging Eq. (5.8) gives a term for A_{Tb}/A_f. Substituting these terms in Eq. (5.17) yields

$$f = \frac{1}{1 + b(V_B/V_f) + B(V_T/V_f)} \tag{5.18}$$

Substituting this expression in Eq. (5.16) gives

$$\beta = fk_f \tag{5.19}$$

It is evident that the apparent elimination rate constant β is the product of the instrinsic elimination rate constant for free drug k_f and the fraction of the total amount of drug in the body that is free, f. Ordinarily, we cannot measure f in humans and it is very difficult to measure in animals. On the other hand, we can determine the fraction free in the vascular space (i.e., the fraction unbound in blood) by relatively simple binding experiments. This parameter, f_B, is defined as

$$f_B = \frac{C_f}{C_f + C_{Bb}} = \frac{V_B C_f}{V_B C_f + V_B C_{Bb}} = \frac{A_{Bf}}{A_{Bf} + A_{Bb}} \tag{5.20}$$

Comparison of Eqs. (5.17) and (5.20) suggests that the relationship between f and f_B is complex and nonlinear. It follows that β will not be a linear function of f_B.

Integration of Eq. (5.15) yields

$$C_f = C_f^\circ e^{-\beta t} \tag{5.21}$$

where C_f° is the concentration of free drug at time zero (i.e., immediately after injection).

The total drug concentration in the blood C_B is given by

$$C_B = C_f + C_{Bb} = C_f + bC_f = (1 + b)C_f \tag{5.22}$$

It follows that

$$C_B = C_B^\circ e^{-\beta t} \tag{5.23}$$

The initial condition at time zero for the model is given by the equation

$$A_f^\circ + A_{Tb}^\circ + A_{Bb}^\circ = D \tag{5.24}$$

The ratio of A_B° to dose D is

$$\frac{A_B^\circ}{D} = \frac{V_B C_B^\circ}{D} = \frac{A_{Bf}^\circ + A_{Bb}^\circ}{A_f^\circ + A_{Tb}^\circ + A_{Bb}^\circ} \tag{5.25}$$

Therefore,

$$C_B^\circ = \frac{A_{Bf}^\circ + A_{Bb}^\circ}{A_f^\circ + A_{Tb}^\circ + A_{Bb}^\circ} \frac{D}{V_B} \tag{5.26}$$

Equations (5.17) and (5.20) apply equally at the initial condition and at any time t. Therefore, the ratio of f to f_B is given by

$$\frac{f}{f_B} = \frac{A_{Bf}^\circ + A_{Bb}^\circ}{A_f^\circ + A_{Bb}^\circ + A_{Tb}^\circ} \frac{A_f^\circ}{A_{Bf}^\circ} \tag{5.27}$$

Since A_f°/A_{Bf}° is equal to V_f/V_B, according to Eq. (5.3), it follows that on rearrangement of Eq. (5.27), we obtain

$$\frac{A_{Bf}^\circ + A_{Bb}^\circ}{A_f^\circ + A_{Bb}^\circ + A_{Tb}^\circ} = \frac{V_B}{V_f} \frac{f}{f_B} \tag{5.28}$$

Substituting Eq. (5.28) into Eq. (5.26) yields

$$C_B^\circ = \frac{f}{f_B} \frac{D}{V_B} \frac{V_B}{V_f} = \frac{f}{f_B} \frac{D}{V_f} \tag{5.29}$$

The systemic (blood) clearance of a drug, Cl_s, is calculated from the ratio of the dose to the total area under the blood concentration-time curve:

$$Cl_s = \frac{D}{\int_0^\infty C_B \, dt} \tag{5.30}$$

Integration of Eq. (5.23) from t = 0 to t = ∞, followed by substitution for C_B° from Eq. (5.29) and for β from Eq. (5.19), gives

$$\int_0^\infty C_B \, dt = \frac{C_B^\circ}{\beta} = \frac{D}{f_B V_f k_f} \tag{5.31}$$

Substituting this term in Eq. (5.30) yields

$$Cl_s = f_B(V_f k_f) \tag{5.32}$$

where $V_f k_f$ is the intrinsic clearance. Thus we see the classic relationship between systemic clearance and the fraction of drug free in the blood, which was first described by Levy and Yacobi [1].

By definition, systemic clearance is the product of the apparent volume of distribution and the apparent elimination rate constant:

$$Cl_s = V\beta \tag{5.33}$$

Therefore,

$$V = \frac{Cl_s}{\beta} \tag{5.34}$$

Substituting for Cl_s from Eq. (5.32) and for β from Eq. (5.19) gives

$$V = \frac{f_B}{f} V_f \tag{5.35}$$

Equation (5.35) indicates that in the absence of drug binding (i.e., $f = f_B = 1$), $V = V_f$. This is the case for antipyrine; the apparent volume of distribution of antipyrine closely approximates total body water.

From Eqs. (5.17) and (5.20) it can be shown that

$$\frac{f_B}{f} = \frac{A_{Bf}}{A_{Bf} + A_{Bb}} \frac{A_f + A_{Bb} + A_{Tb}}{A_f} \tag{5.36}$$

Since in all cases an amount term is the product of a concentration term and a volume term,

$$\frac{f_B}{f} = \frac{V_B C_f}{V_B C_f + V_B C_{Bb}} \frac{V_f C_f + V_B C_{Bb} + V_T C_{Tb}}{V_f C_f} \tag{5.37}$$

which simplifies to

$$\frac{f_B}{f} = \frac{V_f C_f + V_B C_{Bb} + V_T C_{Tb}}{C_f + C_{Bb}} \frac{1}{V_f} \tag{5.38}$$

Therefore,

$$\frac{f_B}{f} V_f = \frac{V_f C_f + V_B C_{Bb} + V_T C_{Tb}}{C_f + C_{Bb}} \tag{5.39}$$

Substituting Eq. (5.39) in Eq. (5.35) and rearranging terms yields

$$V(C_f + C_{Bb}) = V_f C_f + V_B C_{Bb} + V_T C_{Tb} \tag{5.40}$$

Dividing each term in Eq. (5.40) by C_f gives

$$\frac{V(C_f + C_{Bb})}{C_f} = V_f + \frac{V_B C_{Bb}}{C_f} + \frac{V_T C_{Tb}}{C_f} \tag{5.41}$$

It is helpful to define a new term f_T (i.e., the fraction free in the extravascular space), which is, by analogy to f_B [see Eq. (5.20)], given by

$$f_T = \frac{C_f}{C_f + C_{Tb}} \tag{5.42}$$

By rearranging terms in Eqs. (5.20) and (5.42), we can show that

$$\frac{C_{Bb}}{C_f} = \frac{1 - f_B}{f_B} \tag{5.43}$$

and

$$\frac{C_{Tb}}{C_f} = \frac{1 - f_T}{f_T} \tag{5.44}$$

Substituting Eqs. (5.20), (5.43), and (5.44) into Eq. (5.41) yields

$$\frac{V}{f_B} = V_f + \frac{1 - f_B}{f_B} V_B + \frac{1 - f_T}{f_T} V_T \tag{5.45}$$

Recognizing that V_f is simply the sum of V_B and V_T, and multiplying each term in Eq. (5.45) by f_B gives the following expression:

$$V = f_B(V_B + V_T) + (1 - f_B)V_B + f_B \frac{1 - f_T}{f_T} V_T \tag{5.46}$$

Expanding each term yields

$$V = f_B V_B + f_B V_T + V_B - f_B V_B + \frac{f_B - f_B f_T}{f_T} V_T \tag{5.47}$$

which simplifies to

$$V = V_B + \frac{f_B}{f_T} V_T \tag{5.48}$$

Experimentally, drug binding is determined, by one of several methods, in plasma or serum rather than in blood. Hence one determines f_p, the fraction of drug unbound (free) in the plasma, rather than f_B. However, f_p values can be easily converted to f_B values by multiplying f_p by the ratio of drug concentrations in plasma and in whole blood [i.e., $f_B = f_p(C_p/C_B)$].

In the event that no information is available concerning the partitioning of drug between plasma and red blood cells, an alternative expression for calculating apparent volume of distribution is as follows:

$$V' = V_p + V_T' \frac{f_p}{f_T'} \tag{5.49}$$

In Eq. (5.49), V' is the apparent volume of distribution relating the total amount of drug in the body to the total drug concentration in plasma, V_p is plasma volume, and V_T' is the volume of the extravascular space plus the erythrocyte volume. Drug binding to erythrocytes contributes to f_T'.

The derivation outlined above resulting in Eq. (5.48) or (5.49) was first presented by Gibaldi and McNamara [2] and leads to a relationship identical to that proposed by Wilkinson and Shand [3] based on the work of Gillette [4]. This relationship is conceptually very useful. It is evident that ordinarily, the smallest apparent volume of distribution of a drug is blood volume. This value is approached when there is extensive binding in the vascular space (i.e., $f_B \to 0$) and little binding in the extravascular space (i.e., $f_T \to 1$). A highly polar drug, restricted to the vascular space because of molecular weight considerations, may have an apparent volume of distribution equal to plasma volume. Lipid-soluble drugs such as dicumarol that are highly bound to plasma proteins but less bound to tissues (i.e., $f_B/f_T < 1$) have apparent volumes of distribution that are between the values of blood volume and the volume of total body water. Many basic drugs, including amphetamine, are preferentially bound to extravascular tissues (i.e., $f_B/f_T > 1$) and have apparent volumes of distribution that exceed the volume of total body water. Drugs that are negligibly bound (i.e., $f_B = f_T = 1$) have apparent volumes of distribution that approximate the volume of total body water in the cases of lipid-soluble compounds (e.g., antipyrine) or the volume of the extracellular space in the case of poorly lipid soluble compounds.

Equation (5.48) predicts a linear relationship between apparent volume of distribution V and fraction free in the blood f_B when the fraction free in the extravascular space is constant. Thus if certain perturbations such as disease state, concomitant drug therapy, or genetic factors affect plasma protein binding of a drug but have no effect on tissue binding, a plot of V versus f_B will be linear with a positive slope and an intercept equal to V_B (see Fig. 5.2). If the perturbation produces a parallel but smaller effect on tissue binding, an apparently linear plot may result, but the value of the intercept will be greater than V_B. If the effects on plasma protein and tissue binding are quantitatively similar, V is independent of f_B. Both of these cases are also shown in Fig. 5.2. Perturbations that principally

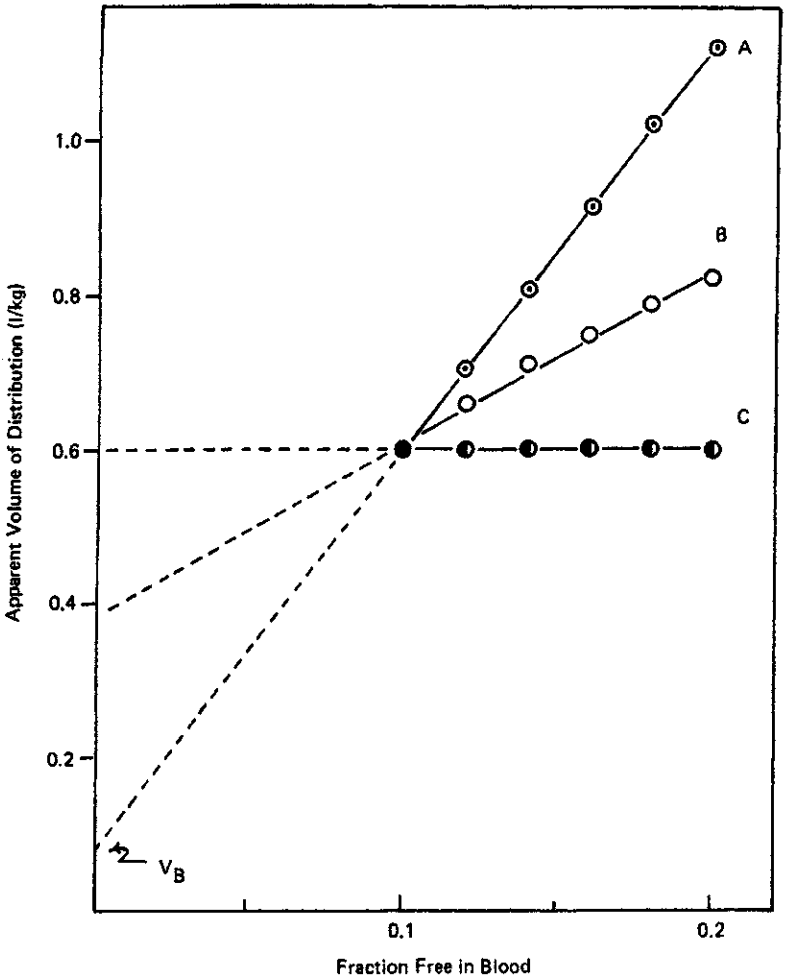

Fig. 5.2 Apparent volume of distribution as a function of free fraction of drug in blood, f_B. Blood volume is equal to 75 ml/kg. Total body water is equal to 600 ml/kg. Case A: f_B varies from 0.1 to 0.2, f_T is constant at 0.1. Case B: f_B varies from 0.1 to 0.2, f_T varies from 0.1 to 0.14 such that $f_T = 0.4\, f_B + 0.06$. Case C: Both f_B and f_T vary from 0.1 to 0.2 such that f_B/f_T is constant. (Data from Ref. 2.)

affect plasma protein binding will produce an increase in V, whereas those that principally affect tissue binding will result in a decrease in V. An example of the latter situation is found with digoxin in patients with renal disease [5].

TISSUE BINDING

Although the fraction free in the extravascular space, f_T, cannot be determined directly in humans, it may be possible, under certain circumstances, to estimate it indirectly by using a rearranged form of Eq. (5.48):

$$f_T = \frac{f_B V_T}{V - V_B} \tag{5.50}$$

By determining V and f_B experimentally and by using appropriate estimates of V_B and V_T, we can readily calculate f_T. Therefore, we can assess whether a perturbation that affects plasma protein binding also affects tissue binding. Using this approach it has been found that uremia and nephrosis, both of which significantly decrease the plasma protein binding of phenytoin in humans, have no effect on the apparent tissue binding of the drug. On the other hand, apparently genetically related differences in plasma protein binding of warfarin in individual rats are paralleled by differences in tissue binding [6].

Clarification of the role of tissue (extravascular) binding in drug disposition and drug effects requires further investigation, but it is clear that the systemic clearance of a drug is independent of tissue binding [see Eq. (5.32)]. On the other hand, tissue binding appears to be a principal determinant of the apparent elimination rate constant β or half-life of a drug.

By rearrangement of Eq. (5.33), we can show that

$$\beta = \frac{Cl_s}{V} \tag{5.51}$$

Substituting for Cl_s according to Eq. (5.32), and for V according to Eq. (5.48), yields

$$\beta = \frac{f_B V_f k_f}{V_B + (f_B/f_T)V_T} \tag{5.52}$$

If we assume a situation where drug binding to erythrocytes is negligible, and define apparent volume of distribution in terms of drug concentration in plasma rather than blood, we may rewrite Eq. (5.52) as

$$\beta = \frac{f_p V_f k_f}{V_p + (f_p/f_T)V'_T} \tag{5.53}$$

Since plasma volume is only about 40 ml/kg, it follows that for drugs with an apparent volume of distribution greater than 400 ml/kg, $V - V_p \simeq V \simeq V'_T(f_p/f_T)$ and

$$\beta \simeq \frac{f_p V_f k_f}{(f_p/f_T)V'_T} = \frac{f_T V_f k_f}{V'_T} \tag{5.54}$$

As we have noted, the product of V_f and k_f is usually designated as intrinsic clearance or Cl_I and reflects the intrinsic ability of the eliminating organ(s) (e.g., the liver or kidneys or both) to clear the drug from the blood. Therefore,

$$\beta \simeq \frac{f_T Cl_I}{V_T} \tag{5.55}$$

and

$$t_{1/2} \simeq \frac{0.693 V_T}{f_T Cl_I} \tag{5.56}$$

Equation (5.56) shows that, for many drugs, half-life is a function of the body's intrinsic ability to eliminate the drug and of the degree of binding of the drug in the extravascular space, and that half-life is independent of plasma protein binding. Although Eq. (5.56) applies rigorously only to drugs with apparent volumes of distribution exceeding 400 ml/kg, it has been shown for drugs with apparent volumes ranging from 100 to 400 ml/kg that, under the conditions stated half-life is largely dependent on tissue binding and less dependent on plasma protein binding [7]. The half-lives of drugs with apparent volumes of distribution of less than 100 ml/kg are highly dependent on plasma protein binding.

It should be recognized that f_T is a hybrid constant and reflects the weighted average of drug binding to different organs and tissues in the extravascular space. As noted by Gillette [4], Eq. (5.48) is more appropriately expressed as

$$V = V_B + \frac{f_B \sum_{i=1}^{n} (C_T)_i (V_T)_i}{C_f} \tag{5.57}$$

where C_f is the concentration of free (unbound) drug at steady state, $(C_T)_i$ is the total (bound and unbound) drug concentration in a given tissue or organ at steady state, and $(V_T)_i$ is the anatomic volume of the given organ or tissue. Since C_f/f_B is equal to total drug concentration in blood C_B, it follows that

$$V = V_B + \sum_{i=1}^{n} R_i (V_T)_i \tag{5.58}$$

where R_i is the partition coefficient or distribution ratio of drug between tissue and blood [i.e., $R_i = (C_T)_i/C_B$].

The fraction bound in the extravascular space, f_T, largely reflects the binding of drug to organs and tissues that contain large fractions of the total amount of drug in the body. An assessment of f_T by pharmacokinetic means [see Eq. (5.50)] to detect the effect of a perturbation on tissue binding may fail to reveal even substantial changes in drug binding to tissues or organs that contribute little to the overall apparent volume of the extravascular space.

ESTIMATION OF APPARENT VOLUMES OF DISTRIBUTION

In principal, one can calculate the apparent volume of distribution of drug in laboratory animals or in humans, on necropsy, by determining the distribution ratio between blood and each of the principal organs and tissues that account for the total amount of drug in the body, estimating the anatomic volume of each and using Eq. (5.58). This has been carried out for lidocaine in the monkey [8] but is a formidable task. Thus many other, considerably simpler, methods have been devised to estimate the apparent volume of distribution of a drug in the intact organism. All methods require that the drug be given intravenously so that the amount reaching the systemic circulation will be equivalent to the administered dose and be known.

For the model described in Fig. 5.1, it can be shown that drug concentrations in the vascular space (blood or plasma) decline exponentially with time (see Fig. 1.1). Extrapolation of such data to zero time on the drug concentration axis provides an estimate of the initial drug concentration C_0 immediately after intravenous bolus injection but before any drug has been eliminated. It follows that

$$V = \frac{\text{dose}}{C_0} \tag{5.59}$$

The volume term calculated by this equation is often called $V_{extrapolated}$. This equation must never be applied to data obtained after oral or intramuscular administration, even if complete absorption or availability can be assumed.

In practice, however, few drugs show simple monoexponential decline immediately after injection; that is, our assumption regarding instantaneous distribution throughout the body space seems rarely to be true. In most cases, it appears that a finite time is required for a drug to distribute throughout the body space, and most plots of log drug concentration versus time after intravenous bolus injection must be described by multiexponential equations (suggestive of a multicompartment system) rather than monoexponential equations (indicative of one-compartment systems). Under these conditions extrapolation of the linear portion of the log concentration versus time plot to the concentration axis yields a value which is less than the concentration of drug in the blood immediately after injection. Furthermore, calculation of V according to Eq. (5.59) by assuming that the extrapolated

value is equal to C_0 will result in an overestimate of the apparent volume of distribution. Therefore, we may use Eq. (5.59) only when the deviation of the log concentration versus time plot from a monoexponential expression is negligible.

A more general, and therefore more useful, approach for estimating V is to use the well-developed relationship between the total area under the drug concentration versus time curve, AUC, and the intravenous dose:

$$\text{AUC} = \frac{\text{dose}}{VK} \tag{5.60}$$

or

$$\text{AUC} = \frac{\text{dose}}{V\beta} = \frac{\text{dose}}{V\lambda_n} \tag{5.61}$$

where K is the first-order elimination rate constant (one-compartment model) and β or λ_n is the terminal slope (times 2.303) of the curve described by plotting log concentrations versus time for a drug in a linear multicompartment system. Upon rearrangement we obtain

$$V = \frac{\text{dose}}{K \cdot \text{AUC}} \tag{5.62}$$

and

$$V = \frac{\text{dose}}{\beta \cdot \text{AUC}} = \frac{\text{dose}}{\lambda_n \cdot \text{AUC}} \tag{5.63}$$

The volume term described by Eq. (5.62) is sometimes called V_{area}, whereas that described by Eq. (5.63) has been termed V_{area} or V_β. The terminology V_β arises from the fact that this volume term relates drug concentration in plasma or blood to the total amount of drug in the body during the terminal exponential phase (log-linear or β phase) of a log drug concentration in blood or plasma-time curve for any multicompartment model where elimination occurs from the central compartment [9]. Equation (5.62) or (5.63) may be applied to data obtained after oral administration of a drug *only* when complete absorption *and* complete systemic availability (i.e., no first-pass or gut metabolism) can be assumed.

An estimate of apparent volume of distribution that is equivalent to V_{area} or V_β may also be obtained from blood- or plasma-level data obtained after constant rate intravenous infusion for a sufficiently long period to attain steady state. The drug concentration in plasma or blood under these conditions, C_{ss}, is given by

$$C_{ss} = \frac{k_0}{Cl_s} \tag{5.64}$$

where k_0 is the zero-order infusion rate constant and Cl_s is systemic clearance. For a one-compartment model, $Cl_s = VK$, and for a multicompartment model, $Cl_s = V\beta$. Hence

$$V = \frac{k_0}{KC_{ss}} \tag{5.65}$$

or

$$V = \frac{k_0}{\beta C_{ss}} \tag{5.66}$$

If a one-compartment model can be assumed, an estimate of apparent volume of distribution may be obtained from data collected before steady state during constant rate intravenous infusion. Under these conditions

$$C = \frac{k_0}{VK}(1 - e^{-Kt}) \tag{5.67}$$

where t is infusion time. V may be calculated from the slope of a plot of C versus $1 - e^{-Kt}$, which is equal to k_0/VK. The infusion rate k_0 is known and the rate constant K may be estimated from data collected after stopping the infusion. The volume term calculated by means of Eq. (5.65) or (5.66) has sometimes been termed $V_{infusion}$ (V_{inf}) or $V_{infusion\ equilibrium}$ ($V_{inf\ eq}$) but is, in fact, equivalent to V_{area} or V_β.

If the body may be viewed as a single compartment with respect to the distribution and elimination kinetics of a drug, the volume terms introduced above (i.e., $V_{extrapolated}$, V_{area}, $V_{inf\ eq}$) and the physiologically based apparent volume of distribution defined by Eq. (5.48) or (5.58) are equivalent. This physiologically based volume is equivalent to the apparent volume of distribution at steady state, V_{ss}.

In those situations where the body may not be viewed as a single compartment and where there is a finite time required for distribution to take place so that a multicompartment model is required to describe the kinetics of the drug, the volume terms are not equivalent. Under these circumstances, one finds that $V_{extrapolated} > V_{area}$ or $V_\beta = V_{inf\ eq} > V_{ss}$. Moreover, yet another volume term, V_c or V_1, the volume of the central compartment, is often used to describe multicompartment models. By definition, $V_{ss} > V_c$. The only useful volume terms for multicompartment systems are V_β, V_c, and V_{ss}.

The β-phase apparent volume of distribution, V_β, may be calculated for any linear multicompartment model by determining the total area under the drug concentration in plasma or blood versus time curve, AUC, after a single intravenous administration and the slope of the long-linear or β phase and by applying Eq. (5.61). It can also be shown that $V_\beta = k_{10}V_c/\beta$, where k_{10} is the apparent elimination

rate constant of drug from the central compartment. The product of V_β and β or V_c and k_{10} is systemic clearance.

The principal shortcoming of this apparent volume of distribution term as an index of drug distribution is that V_β may reflect the degree of equilibration of a drug under dynamic conditions rather than its apparent distribution volume. This is more easily appreciated when one recognizes that V_β is a function of the elimination kinetics of a drug [10]. An increase in the intrinsic elimination rate constant will cause an increase in V_β, whereas a decrease in elimination will cause a decrease in V_β. Hence a change in the V_β of a drug may not reflect a change in the actual distribution space or in the degree of binding but may signify merely a change in the degree of equilibration between central and peripheral compartments secondary to a change in elimination kinetics. For a multicompartment system with drug elimination occurring from the central compartment, characterized by the rate constant k_{10}, the limits of V_β are ∞ as $k_{10} \to \infty$, and V_{ss} as $k_{10} \to 0$.

Drug concentration C in a linear multicompartment model as a function of time after intravenous injection can always be described by an equation of the form

$$C = \sum_{i=1}^{n} C_i e^{-\lambda_i t} \tag{5.68}$$

where C_i is the coefficient of the ith exponential term of the polyexponential equation and λ_i is the exponent multiplying time t in the exponential terms. Note that λ_1 is the largest λ_i (usually symbolized by α in a two-compartment model), λ_2 is the second largest, and so on. The term λ_n (or β) is used to denote the smallest value of λ_i. Under these conditions the apparent volume of the central compartment is given by

$$V_c = \frac{\text{intravenous dose}}{\Sigma C_i} \tag{5.69}$$

For a two-compartment open model, V_c = intravenous dose/(A + B). This volume term may be useful for estimating peak concentrations in plasma or blood for drugs that distribute relatively slowly in the body and are absorbed relatively rapidly after oral or intramuscular administration. Drugs with relatively small V_c/V_{ss} ratios may show unusually large peak-to-trough concentration ratios over a dosing interval even when administered relatively frequently.

The most useful volume term to describe the apparent distribution space in a multicompartment system is V_{ss}. As its name implies, V_{ss} relates the amount of drug in the body to the drug concentration in the plasma or blood at steady state, during repetitive dosing, or during constant rate infusion. V_{ss} is independent of drug elimination, and its relationship to anatomical space and drug binding has been described by Eqs. (5.48) to (5.50).

Equations to define and estimate V_{ss} have been developed in Chap. 2. A useful expression for calculating V_{ss} after rapid intravenous administration of a drug whose disposition is described by Eq. (5.68) is [11]

$$V_{ss} = \frac{D \sum_{i=1}^{n} C_i/\lambda_i^2}{\left(\sum_{i=1}^{n} C_i/\lambda_i\right)^2} = \frac{D \sum_{i=1}^{n} C_i/\lambda_i^2}{(AUC)^2} \tag{5.70}$$

Equation (5.70) is a general relationship that applies to any linear multicompartment model in which elimination occurs from the central compartment. For a two-compartment open model we may write Eq. (5.70) as

$$V_{ss} = \frac{D[(A/\alpha^2) + (B/\beta^2)]}{[(A/\alpha) + (B/\beta)]^2} \tag{5.71}$$

Thus calculation of V_{ss} simply requires curve-fitting of drug concentration-time data after intravenous bolus injection, to estimate C_i and λ_i values, and application of Eq. (5.70).

Although (5.70) is a rather general expression, it does require the implicit elaboration of a compartment model. A still more general, model-independent approach for estimating V_{ss} has been proposed [12,13]. It can be shown that the term $\sum_{i=1}^{n} C_i/\lambda_i^2$ [see the numerator of Eq. (5.70)] is, in fact, equal to the area under the first moment of the drug concentration in blood or plasma curve, AUMC, that is, the area under the curve of the product of time t and drug concentration C from time zero to infinity. In other words,

$$V_{ss} = \frac{D[(\int_0^\infty tC\ dt]}{[\int_0^\infty C\ dt]^2} = \frac{D[AUMC]}{[AUC]^2} \tag{5.72}$$

The principal assumptions required for developing Eq. (5.72) are that the system is linear and that drug elimination takes place from the measured site (i.e., the plasma, blood, or central compartment).

This method does not not require the assumption of a compartment model, nor does it require a curve-fitting procedure. To calculate V_{ss}, one must merely determine the total areas under the drug concentration versus time curve and under the first moment versus time curve (see Fig. 5.3) using the trapezoidal rule (see Appendix D) or some other convenient method.

Since many drugs are administered by a constant rate intravenous infusion over a short period of time rather than by a rapid intravenous injection, the following variant of Eq. (5.72) [14] is often useful:

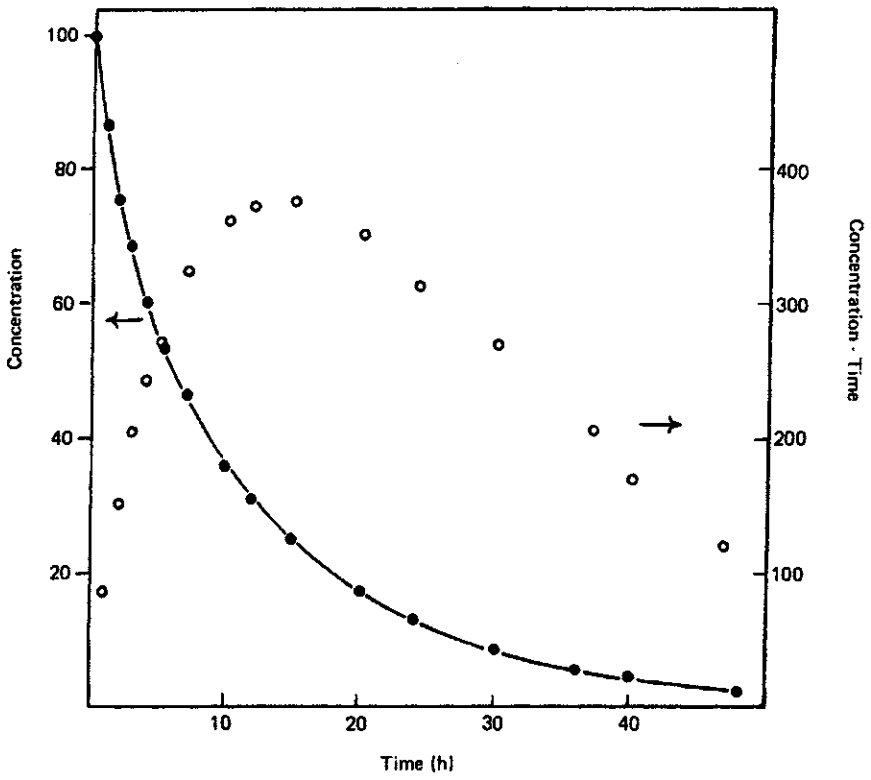

Fig. 5.3 Plots of concentration versus time (●) and of the product of concentration and time versus time (○) after intravenous bolus injection of a drug. The total area under the concentration versus time curve is AUC; the total area under the concentration-time versus time curve is AUMC.

$$V_{ss} = \frac{k_0 T \cdot AUMC}{(AUC)^2} - \frac{T(k_0 T)}{2 \cdot AUC} \qquad (5.73)$$

where k_0 is the infusion rate, T the infusion time, and k_0T the administered dose.

For many drugs V_β [see Eq. (5.63)] provides a close approximation of V_{ss}. However, in at least two situations, V_β significantly overestimates V_{ss}. One case is that of drugs that are rapidly cleared from the central compartment with short half-lives. For example, it has been calculated for benzypenicillin in humans that V_β = 26 liters, whereas V_{ss} = 15 liters [10]. A second case occurs where most of the dose of a drug is eliminated relatively rapidly but a small fraction

of the dose persists and gives rise to unusually long half lives. In such cases the area under the extrapolated line from the β phase to the drug concentration axis represent a relatively small fraction of the total area under the drug concentration versus time curve (see Fig. 2.9, curve Y). Based on data in the literature [15], it may be calculated that for gentamicin in humans, V_β = 202 liters, whereas V_{ss} = 33 liters. The latter value is a much more realistic and more useful estimate of the apparent distribution space of gentamicin.

In 1976, Niazi [16] suggested that the change in apparent distribution volume manifested by a drug in a multicompartment system as a function of time after intravenous administration might be a useful parameter for characterizing distribution kinetics (see Fig. 5.4). Immediately after injection the drug occupies a space we have termed V_c, the volume of the central compartment. V_c may also be thought of as a proportionality constant relating drug concentration in plasma or blood to the amount of drug in the body at t = 0 (i.e., the intravenous dose). The apparent volume or proportionality constant relating concentration and amount increases with time until it reaches a limiting value which we have termed V_β. We have noted that V_β is actually a proportionality constant relating drug concentration in plasma or blood to amount of drug in the body during the β phase and that $V_\beta > V_c$. The time-dependent volume of distribution V_t may be

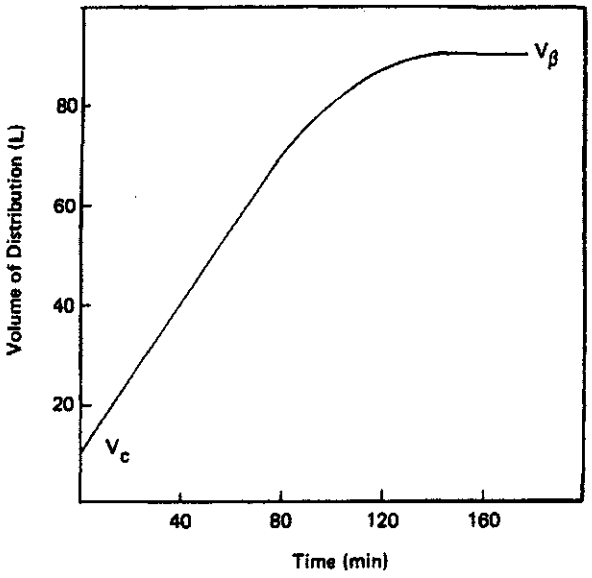

Fig. 5.4 Apparent volume of distribution of trichloromonofluoromethane as a function of time following intravenous administration in the dog. (Data from Ref. 16.)

defined as the ratio of the amount of drug in body at any time to the drug concentration in plasma or blood at that time and will vary in value from V_c to V_β. Since in a multicompartment model where the drug is eliminated only from the central compartment, the amount of drug remaining in the body as a function of time can be expressed in terms of fractional areas [17]. It can be shown that [16]

$$V_t = \frac{D \cdot AUC_{t \to \infty}}{C_t \cdot AUC_{0 \to \infty}} \tag{5.74}$$

where D is the intravenous dose, C_t is the drug concentration at time t, and the AUC terms refer to either partial or total areas under the concentration-time plot. Comparative plots of V_t versus time for different individuals or different species receiving the same drug might be helpful in characterizing rates of distribution.

The idea of time-dependent changes in apparent volume of distribution is also useful for systems showing nonlinear plasma protein binding or tissue binding. Such changes may be quantified for one-compartment models but are difficult to describe quantitatively for multicompartment models. In principle, it can be shown that V decreases with time when nonlinear plasma protein binding occurs, whereas V increases with time when only nonlinear extravascular tissue binding occurs [18].

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