Concept of a Volume of Distribution and Possible Errors in Evaluation of This Parameter

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To be pharmacokinetically correct, an estimate of the volume of distribution must establish a volume of a fictitious single compartment at a steady state of equilibrium and therefore independent of the role of metabolism and excretion. It has been shown previously that it is mathematically and physiologically more correct to conceive the body as exhibiting the properties of at least a two-compartmental rather than a single-compartmental model, which necessitates careful definition of the instant in time when the steady state (ss) of equilibrium exists. A mathematical relationship between the volume of distribution at steady state and those estimated by often used but incorrect methods is presented. Experimental data on acetylsalicylate, salicylate, griseofulvin, and several barbiturates are presented. The pharmacokinetic significance of these data is discussed.

THE VOLUME of distribution is not only an essential parameter in pharmacokinetic calculations, but is also a useful concept in physiology. However, examination of the literature in both fields clearly indicates a misunderstanding of the essential criteria which must be met when calculating this constant. Since the volume of distribution is a parameter of a particular model used to describe the distribution of a drug in the body, its physiological meaning is limited by the model. Nonetheless, it is a constant so that if the model is to be consistent its value must be independent of the method of measurement. In an earlier paper of this series (1), a detailed discussion was presented of the mathematical, physiological, and pharmacokinetic basis for representing the body as a mammillary model consisting of a central compartment with at least one peripheral compartment. Most of the presently published pharmacokinetic evaluations of drug absorption and elimination rates have been based on the supposition that the body need only be considered as a single compartment in assessing these constants. Little or no effort has been expended to evaluate the error involved in these measurements based on this presumption of a single-compartment model.

The purpose of this paper is to present some mathematical interrelationships of the various methods of calculation of the volume of distribution. A two-compartmental open-system model will be used to calculate the volume of distribution, Vd_{ss}, which exists at a steady state of equilibrium between these two compartments. The relationships between this Vd_{ss} and that obtained by various biased[1] methods of measurement will be derived. Data will be presented which allow one to predict the apparent Vd[2] obtained by one of the biased methods of calculating this constant and to assess its relative error.

Received April 14, 1967, from the Departments of Pharmacy and Pharmaceutical Chemistry, School of Pharmacy, University of California, San Francisco, CA 94122

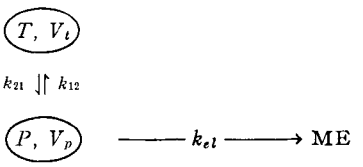
Accepted for publication August 29, 1967.

This research was supported in part by a research grant from the Research Committee, San Francisco Academic Senate, and from Glenbrook Laboratories.

Presented to the Basic Pharmaceutics Section, APhA Academy of Pharmaceutical Sciences, Las Vegas meeting, April 1967.

DISCUSSION

Definition of the Two-Compartmental Open-System Model—The two-compartmental open system model may be represented as follows:



where T = the amount of drug in the peripheral (tissue) compartment at any time, t,

P = the amount of the drug in the central compartment at time, t,

ME = the amount of the drug eliminated by all processes of metabolism and excretion, assumed to take place exclusively in the central compartment, up to time, t.

V_p, V_t = the volumes of central and tissue compartments, respectively.

Where

$$Vd_{ss} = V_t + V_p$$

and

k_{12}, k_{21} = first-order rate constants of distribution,

k_{ei} = the sum of the simultaneous processes of metabolism and excretion all assumed to be first order.

Widmark and Tandberg (2), Teorell (3), and Dominguez (4) recognized that from the kinetic point of view the so-called central compart-

[1] It will be shown subsequently that these estimates are biased in that they are dependent upon the elimination rate constant and distribution constants.

[2] We shall arbitrarily define Vd as the so-called constant value arrived at when estimated assuming the single-compartmental model applies. All other volumes of distribution, analyzed on the basis of the two-compartmental model, will be specified with a subscript referring to the method of their calculation.

ment includes, in addition to the plasma volume, that portion of the intercellular fluids and tissues which appear to spontaneously come into equilibrium with the blood. Riegelman *et al.* (1) pointed out that the peripheral compartment may well represent the muscle, skin, and a portion of the fat depot. However, both of these volumes are kinetic parameters of the model, varying with the partition and binding characteristics of the compounds, so that it serves no useful purpose in attempting to attach any physiological meaning to the values obtained. Such a two-compartmental open-system model, as defined in the distribution and elimination scheme illustrated above, results in the following bi-exponential equation:

$$C_p = Ae^{-\alpha t} + Be^{-\beta t} \qquad \text{(Eq. 1)}$$

where C_p = concentration of drug in plasma
α and β = hybrid rate constants dependent on all three specific rate constants of the model (see under *Appendix*).
$C_p^0 = A + B$
V_p = volume of central compartment

and

$$V_p = \text{dose}/C_p^0 \qquad \text{(Eq. 2)}$$

When sufficient time has passed such that the first term in the bi-exponential $Ae^{-\alpha}$ becomes vanishingly small, Eq. 1 reduces to a mono-exponential, which according to the single-compartmental model[3] becomes:

$$C_p = Be^{-\beta t} \qquad \text{(Eq. 3)}$$

Upon integration between zero and infinity, we arrive at the area under the curve, whereupon Eq. 1 becomes:

$$\text{area} = \int_0^\infty C_p dt = A/\alpha + B/\beta \qquad \text{(Eq. 4)}$$

and Eq. 3 becomes:

$$\text{area} = B/\beta \qquad \text{(Eq. 5)}$$

Essential Criteria in the Definition of a Volume of Distribution—Riggs (5) has presented an excellent analysis of the volume of distribution concept and some of the biased methods of calculating this parameter. He emphasizes that essential to its basic definition is the concept of an equilibrium state. The volume of distribution of a given compound in the whole body, with reference to its equilibrium concentration, $(C_p)_{eq.}$, in the plasma, is given by

$$Vd_{ss} = (Q_{tot.})_{eq.}/(C_p)_{eq.} \qquad \text{(Eq. 6)}$$

where $(Q_{tot.})_{eq.}$ = the quantity distributed throughout the entire system at equilibrium.

In the two-compartmental open-system model several difficulties in the evaluation of Vd_{ss} are immediately apparent. Simultaneous to the distribution of the drug into the second compartment is the consecutive loss by metabolism and excretion. This results in a steady state of equilibrium of the drug between the two compartments, central and peripheral, occurring at only one instant following an i.v. injection, *i.e.*, when the rate of change of drug in the peripheral compartment is zero ($dT/dt = 0$).

Riggs (5) has shown that the volume of distribution, Vd_{ss} can be estimated from the rate constants into and out of the central and peripheral compartments,

$$Vd_{ss} = \frac{k_{12} + k_{21}}{k_{21}} V_p \qquad \text{(Eq. 7)}$$

The necessity for this definition lies in the fact that it is impossible to sample the (fictitious) peripheral compartment and, therefore, the drug is conceived to be distributed in a volume referred to the concentration in the plasma at equilibrium (see Eq. 6).

Extrapolation Method—When the single-compartment concept is applied to the calculation of Vd, the mono-exponential portion of Eq. 1 is extrapolated to the y-intercept, and the result is:

$$B = \text{dose}/Vd \qquad \text{(Eq. 8)}$$

or

$$Vd = \text{dose}/B \qquad \text{(Eq. 9)}$$

However, by the two-compartmental model, the extrapolated value B is given by:

$$B = \frac{\text{dose}\ (k_{21} - \beta)}{V_p(\alpha - \beta)} \qquad \text{(Eq. 10)}$$

so that

$$Vd_{\text{extrap.}} = \text{dose}/B = V_p(\alpha - \beta)/(k_{21} - \beta) \qquad \text{(Eq. 11)}$$

It will be shown under the *Appendix* that Eq. 11 can be expressed in terms of the specific rate constants as follows:

$$Vd_{\text{extrap.}} = \frac{2\ V_p \cdot Z}{k_{21} - k_{12} - k_{el} + Z} \qquad \text{(Eq. 12)}$$

where $Z = [(k_{12} + k_{el} - k_{21})^2 + 4k_{12} \cdot k_{21}]^{1/2}$.

Area or Clearance Method—According to the single-compartment model, a second method of calculating Vd is by application of the area equation (Eq. 5) which upon substitution into Eq. 8 results in:

$$Vd = \text{dose}/\beta \cdot \text{area} \qquad \text{(Eq. 13)}$$

The same volume is obtained from urinary clearance studies as the following will show. If the processes of excretion and metabolism are presumed to obey first-order kinetics with constants k_e and k_m, respectively, and:

$$k_m + k_e = \beta \qquad \text{(Eq. 14)}$$

or

$$f \cdot \beta = k_e \qquad \text{(Eq. 15)}$$

where $f = k_e/(k_e + k_m)$.

The amount of the dose excreted intact from zero time until the drug is entirely eliminated is:

$$f \cdot \text{dose} = k_e \cdot Vd\ C_p dt \qquad \text{(Eq. 16)}$$

Substituting for k_e from Eq. 15, rearranging, and cancelling we arrive at Eq. 13.

With the two-compartmental model, the Vd_{area} can be estimated by the following equation, which is derived under *Appendix:*

$$Vd_{\text{area}} = Vd_{ss} + \frac{k_{el} - \beta}{k_{21}} V_p \qquad \text{(Eq. 17)}$$

[3] Many authors use the symbol K instead of β for the first-order rate constant of Eq. 3.

Zero-Order Infusion Method—Occasionally a drug is administered by constant infusion. If this is continued for a sufficient length of time, the drug becomes equilibrated in the body fluids.

Correcting for the drug eliminated during the infusion process, an estimate of the volume of distribution can be obtained. Since drug is lost by metabolism and excretion during the infusion process, the amount of drug remaining in the body ($D_{corr.}$) can be estimated by the ratio of the area under the blood curve from zero to the end of the infusion, divided by the total area, or:

$$Vd = \text{dose}/(C_p)_{eq.}\left[1 - \frac{\int_0^t C_p dt}{\int_0^\infty C_p dt}\right] = \text{dose}_{(corr.)}/C_{p_{eq.}} \quad \text{(Eq. 18)}$$

where $C_{p_{eq.}}$ = the plasma concentration at equilibrium.

This volume of distribution can be estimated from the two-compartmental model, resulting in

$$Vd_{inf.}^0 = Vd_{ss} + k_{el}/k_{21}\ (V_p) \quad \text{(Eq. 19)}$$

A comparison can now be made of the methods of estimation using the different proposed compartmental models. One cannot be satisfied simply by obtaining a constant value for the volume of distribution, since it is obvious that by insufficient sampling in the early period, the experimenter would miss the distributive phase and only obtain a monoexponential. Under this situation all the methods of estimation would arrive at the same incorrect value. What is important, however, is to attempt to describe the error which would be involved in these estimates, using data which result in well-defined bi-exponential equations.

EXPERIMENTAL PROCEDURE

The *N*-methylglucamine salt of acetylsalicylic acid (ASA) and of salicylic acid (SA) was prepared by mixing equimolar amounts of the base and acid. The solution was bacteriologically filtered and injected into the antecubital vein by rapid i.v. injection (over 5–10 sec.) or by constant infusion over a 1-hr. period with a Harvard infusion pump. Griseofulvin was formulated into a parenteral solution by dissolving the drug in sterilized polyethylene glycol 300. The solution was not injected directly into the test subject, but by diluting it into a rapidly flowing normal saline solution, which was being administered intravenously over a 3–6-min. period. The griseofulvin was also infused at a constant rate over a 2-hr. period of time. The exact details of preparation will be given in a subsequent paper where each system will be discussed at length.

RESULTS AND DISCUSSION

Table I lists the calculated and predicted values of the various volumes of distribution after an i.v. injection of ASA to three males. All three subjects showed large differences between the various estimates. However, the resultant predicted values of $Vd_{extrap.}$, Vd_{area}, and $Vd_{inf.}^0$ are in excellent agreement with the observed biased estimates. Stated another way, these biased estimates would result in a constant value for Vd_{ss}. It is immediately seen that the $Vd_{extrap.}$ always produces the largest error and in this instance has a value which is approximately twice that of Vd_{ss}. If the single-compartmental model is assumed, these estimates of Vd would be identical and equal to $Vd_{extrap.}$, *i.e.*,

$$Vd = D/B = D/\beta \text{ area} = D_{corr.}/C_{p_{eq.}} = Vd_{extrap.} \quad \text{(Eq. 20)}$$

and had insufficient data points been taken so as to miss the distribution phase, it therefore follows that the error will be as great as that of the $Vd_{extrap.}$ estimate.

Table II includes the data obtained after injection of various doses of SA into the same three test subjects. In this instance, the values obtained from the biased methods are almost identical with the Vd_{ss}. One might presume, therefore, that the single-compartmental model is adequate to represent the fate of this drug in the body. However, when ASA is administered intravenously as indicated in Table I, the rapid metabolic transformation of ASA to SA results in the accumulation of SA in the body. Analog computer simulation of these data was studied using the two-compartmental system for the

TABLE I—VOLUME OF DISTRIBUTION ESTIMATES AFTER i.v. INJECTION OF ASA IN MAN

Subject[a]	Biased Vd's: D/B	$D/\beta \cdot$ Area	$D_{(corr.)}/C_{p_{eq.}}$	V_p
1	19,700	13,800	...	6500
2	17,600	14,100	...	6900
3	21,000	13,900	15,700	5650
	Predicted Values: $Vd_{extrap.}$	Vd_{area}	$Vd_{inf.}^0$	Vd_{ss}
1	19,800	13,800	...	10,400
2	17,300	14,000	...	11,700
3	21,000	13,800	16,400	10,100

[a] The appropriate constants from which the calculations were made are listed below in running sequence for subjects *1–3*, respectively. Dose = 650, 650, 325, 1240 mg. (inf.); A = 67, 56, 42 mcg./ml.; α = 0.23, 0.314, 0.257 min.$^{-1}$; B = 33, 37, 15.5 mcg./ml.; β = 0.0495, 0.0506, 0.0478 min.$^{-1}$; area = 956, 920, 487 mcg./ml. × min.; k_{el} = 0.105, 0.110, 0.117 min.$^{-1}$; k_{12} = 0.067, 0.105, 0.0825 min.$^{-1}$; k_{21} = 0.109, 0.157, 0.104 min.$^{-1}$.

TABLE II—VOLUME OF DISTRIBUTION ESTIMATES[a] AFTER i.v. INJECTION OF SA IN MAN

Subject[b]	Biased Vd's: D/B	$D/\beta \cdot$ Area	V_p
1	10,400	10,200	5700
2	9,680	9,650	5900
3	8,800	8,700	5300
	Predicted Values: $Vd_{extrap.}$	Vd_{area}	Vd_{ss}
1	10,400	10,350	10,200
2	9,680	9,650	9,620
3	8,750	8,590	8,500

[a] These volume estimates are valid for the doses used since it is known that the metabolism and excretion characteristic of SA varies with dose. [b] The appropriate constants from which calculations were made are listed in a running sequence for subjects *1–3*, respectively. Dose = 508, 484, 508 mg.; A = 40, 32, 38 mcg./ml.; α = 0.140, 0.216, 0.173 min.$^{-1}$; B = 49, 50, 58 mcg./ml.; β = 0.0032, 0.0026, 0.0027 min.$^{-1}$; area = 15,500, 19,400, 21,600 mcg./ml. × min.; k_{el} = 0.0058, 0.0040, 0.0044 min.$^{-1}$; k_{12} = 0.061, 0.085, 0.064 min.$^{-1}$; k_{21} = 0.078, 0.133, 0.1055 min.$^{-1}$.

TABLE III—VOLUME OF DISTRIBUTION ESTIMATES AFTER i.v. INJECTION OF GRISEOFULVIN IN MAN

Subject[a]	Biased Vd's		
	D/B	$D/\beta \cdot$Area	V_p
1	129,000	120,000	62,000
2	138,000	117,800	56,000
3	145,000	118,000	60,000
	Predicted Values		
	$Vd_{extrap.}$	Vd_{area}	Vd_{ss}
1	129,000	120,100	112,000
2	142,000	118,600	104,000
3	146,000	121,700	103,000

[a] The appropriate constants from which the calculations were made are listed below in a running sequence for subjects *1–3*, respectively. Dose = 142.128, 90 mg.; A = 1.2, 1.35, 0.90 mcg./ml.; α = 0.60, 0.63, 0.41 hr.$^{-1}$; B = 1.1, 0.93, 0.62 mcg./ml.; β = 0.0445, 0.075, 0.063 hr.$^{-1}$; area = 26.0, 14.5, 12.1 mcg./ml. × hr.; k_{el} = 0.0850, 0.157, 0.126 hr.$^{-1}$; k_{12} = 0.25, 0.284, 0.145 hr.$^{-1}$; k_{21} = 0.31, 0.243, 0.200 hr.$^{-1}$.

ASA disposition and both the one-compartmental and the two-compartmental constants for the SA disposition. It was immediately apparent that for each subject, the single-compartmental disposition of SA did not fit the data and underestimated the values of the SA in the earlier time periods (6). In contrast, when both the ASA and SA were conceived to be distributing into two compartments, an excellent fit was obtained. This is once again a strong indication that the two-compartmental model is essential to the treatment of the disposition of SA as well as ASA, particularly if one wishes to estimate the absorption rate constants.

It might appear from the data on salicylates that the results obtained with ASA were unique to this compound due to its very fast metabolism and that drugs with slower elimination rates may be adequately analyzed for their volume of distribution by one of the biased methods. However, the data given in Table III for the i.v. studies on griseofulvin, in which the values of $0.693/\beta$ were from 9.5 to 17 hr., do not support this postulate. The biased estimates result in significant variation with the various methods of calculation on all three subjects. Further, the relatively large error in the biased estimates when compared with Vd_{ss} indicate that all three rate constants defining the distribution and elimination processes interact in affecting the biased estimates. A 2-hr. zero-order infusion was performed on one subject; however, this was not long enough to result in equilibration between the compartments (which would have required continuous infusion for at least 4 hr.).

In reviewing the four equations by which the volume of distribution can be estimated, it can be seen that the Vd_{ss} defined by Eq. 7 is the only one which is not influenced by the elimination processes. The $Vd_{inf.}{}^0$ is defined by Eq. 19 and includes k_{el}. This is equally true of $Vd_{extrap.}$ defined by Eq. 12, and Vd_{area} as defined by Eq. 17. Since the drug itself or a second drug may induce changes in the metabolic rate, it seems illogical to accept a definition of a volume of distribution which is dependent on metabolic changes. Indeed, the same can be said for the excretion rate, which can be affected by concomitant administration of other drugs.

The foregoing discussion leads to a number of important points. All the biased estimates $Vd_{extrap.}$, Vd_{area}, and $Vd_{inf.}{}^0$ will result in overestimation of the value of Vd_{ss} and will only approach this latter value when the elimination rate constant, k_{el}, becomes small in respect to k_{12} and k_{21}. This is readily seen by making k_{el} zero in each relevant equation. However, the $Vd_{extrap.}$ will always result in the biggest error. This can produce erroneous results and therefore misleading conclusions. An example is seen in the case of ASA and SA. From the $Vd_{extrap.}$ values, one might deduce that the volume of distribution of ASA was approximately twice that of SA. Comparison of their Vd_{ss} values, however, show them to be quite similar, which would seem more plausible as they have similar physical chemical properties.

In 1953 Brodie and co-workers administered pentobarbital and thiopentobarbital by rapid intravenous injection into test subjects (7). The data were taken from the excellent figures found in the reference and the constants of the bi-exponential equations were estimated by the usual procedures. The following were the results: thiopentobarbital (dose = 750 mg.)—$C_p = 10e^{-1.15t} + 2.6e^{-0.03t}$; V_p = 60,500 ml.; Vd_{ss} = 270,000 ml. Pentobarbital (dose = 1000 mg.)—$C_p = 8.5e^{-1.4t} + 7.6e^{-0.017t}$; V_p = 62,000 ml.; Vd_{ss} = 130,000 ml.

Many studies of thiopentobarbital have indicated that a more complex distribution model is required for an understanding of period of sleep induced by the drug relative to its distribution and metabolism (8, 9). It appears from the data of Brodie *et al.*, however, that not more than a two-compartmental model is necessary to fit the available data, and if one were attempting to estimate the true absorption rate of the drug or assess its true elimination rate constant, that this model may be adequate. It is interesting to note the similarity of the estimated volume of the central compartment for the two drugs, approximately 61,000 ml., and the large difference in the estimated volume of the tissue compartment(s)—68,000 ml. with pentobarbital and over 210,000 ml. with thiopentobarbital. These estimates are compatible with the suggestion that the latter drug enters the muscle, skin, and fat depots of the body to a higher degree than does pentobarbital. While these data have been obtained for only two compounds within a test series, these results appear to indicate that much more definitive information could be obtained from careful application of the two-compartmental model.

Most of the earlier pharmacokinetic studies have utilized one of the biased methods of analyzing for the volume of distribution. Dost and co-workers (10), Krueger-Thiemer (11), Gladtke (12), and other European workers (13) have utilized the extrapolation procedure to estimate the volume of distribution and in effect have assumed a single-compartmental model. The area or clearance method has been used by Wagner and co-workers (14), by Levy (15), and by many other American workers in our field. In many of these studies, the authors also estimated the metabolism and excretion rate constants, by assuming that the apparent elimination rate constant was equal to k_{el}, the true elimination rate constant. However, one can assess the error involved in making this assumption. If one presumes that sufficient blood samples are taken after an i.v. dose to define the so-called distribution phase, the area under the concentration-time curve, can be expressed in two alternative fashions, namely:

$$\text{area} = \int_0^\infty C_p dt = \text{dose}/Vd_{ss}\cdot\beta = \text{dose}/V_p\cdot k_{el} \qquad \text{(Eq. 21)}$$

Cancelling common terms, we arrive at the following:

$$\beta = V_p/Vd_{\text{area}}\cdot k_{el} \qquad \text{(Eq. 22)}$$

Therefore estimates of the metabolism and excretion rates, based on the fraction excreted intact, and presuming Eq. 14 applies, will be seriously in error. From examination of the volume ratios for the drug discussed above, it can be seen that the true elimination rate constants will be from twofold to fivefold larger than the apparent elimination rate constant, β. These discrepancies are due to the fact that β is a hybrid rate constant, for which we propose the alternative designation, *disposition* rate constant to indicate that it is dependent on the distribution rate constants k_{12} and k_{21}, as well as the elimination rate constant, k_{el}. It seems essential, therefore, that due caution be taken in making these estimates of metabolism and excretion rate constants, for mathematically according to the multicompartmental models, β can never exactly equal k_{el}.

There are some pharmacokinetic situations in which it is not important to define the volume of distribution in accordance with the two-compartmental model in order to correctly make the desired mathematical analysis of the data. It is to be noted that the denominators in Eq. 21—$Vd_{\text{area}}\cdot\beta$ or $V_p\cdot k_{el}$—must be equal and both represent the total clearance value for the drug from the body[4] by all processes of metabolism and excretion. The units of clearance are volume per unit time (ml./min.). Wagner proposed a method of estimating the mean equilibrium concentration, $\bar{C}_{p_{\text{eq.}}}$, of a drug in the blood given without interruption over a sufficient time period with a constant dosing interval of $\Delta t = t_2 - t_1$. This method in effect utilizes the relationship defined in Eq. 21, which includes these equivalent clearance terms. He assumed that a constant fraction of the administered dose (F) would be absorbed during each administration, and that at equilibrium the area under the concentration–time curve for the dosing interval would become equal to the total area under the curve from a single dose:

$$\text{area}\Big|_0^\infty = \text{area}\Big|_{t_1}^{t_2} = \frac{F\cdot D}{\text{clearance}} = C_{p_{\text{eq.}}}\cdot\Delta t \qquad \text{(Eq. 23)}$$

Since clearance is merely the ratio of the dose divided by the area (expressed in proper units), the calculation of $C_{p_{\text{eq.}}}$ becomes independent of the model. A valid estimate of the mean equilibrium concentration can be made from an analysis of a single dose as long as the other assumptions apply.

SUMMARY

A calculated volume of distribution is only one parameter of a model describing the fate of a drug in the body. However, calculations of that volume can lead to some evidence of the deficiencies of the single-compartmental model for the drug at hand. Nevertheless, even if the calculations of the V_d for the single-compartmental model result in a constant value, this in itself is not adequate information as to the validity of the model and additional tests must be met.

[4] The term body clearance is used in the analogous context to urinary clearance and represents the ml. of plasma cleared from the drug by all metabolic and excretion processes per unit time.

APPENDIX

Definition of $Vd_{\text{extrap.}}$ from the Two-Compartmental Model—On the basis of the two-compartmental open-system model as defined in this paper, the constants of the resultant bi-exponential equation can be defined as follows:

$$C_p = \frac{D(k_{21}-\alpha)}{V_p(\beta-\alpha)}e^{-\alpha t} + \frac{D}{V_p}\frac{(k_{21}-\beta)}{(\alpha-\beta)}e^{-\beta t} \qquad \text{(Eq. 1}a\text{)}$$

where

$$\alpha = (b + \sqrt{b^2 - 4c})/2$$

$$\beta = (b + \sqrt{b^2 - 4c})/2$$

and

$$b = k_{12} + k_{21} + k_{el}$$

$$c = k_{21}\cdot k_{el}$$

After sufficient time the first exponential term vanishes and back extrapolation of the linear portion of the semilog plot to the y-intercept yields:

$$B = \frac{D}{V_p}\frac{(k_{21}-\beta)}{(\alpha-\beta)} \qquad \text{(Eq. 2}a\text{)}$$

On rearrangement one has:

$$Vd_{\text{extrap.}} = \frac{D}{B} = \frac{V_p(\alpha-\beta)}{k_{21}-\beta} \qquad \text{(Eq. 3}a\text{)}$$

which is identical to Eq. 11 in the text. However, it can be shown that:

$$\alpha - \beta = (b^2 - 4c)^{1/2} \qquad \text{(Eq. 4}a\text{)}$$

$$= [(k_{12} + k_{el} - k_{21})^2 + 4k_{21}\cdot k_{12}]^{1/2} = Z$$

and

$$k_{21} - \beta = {}^1/_2[k_{21} - k_{12} - k_{el} + (Z)] \qquad \text{(Eq. 5}a\text{)}$$

substitution from Eqs. 4a and 5a into Eq. 3a results in:

$$Vd_{\text{extrap.}} = \frac{2V_p(Z)}{k_{21} - k_{12} - k_{el} + (Z)} \qquad \text{(Eq. 6}a\text{)}$$

which is represented as Eq. 12 in the text.

Definition of Vd_{area} from the Two-Compartmental Model—After sufficient time after the i.v. dose, the bi-exponential curve reduces to a mono-exponential. Expressed in terms of mass of the drug in accordance with the single-compartmental model we have:

$$dP/dt = -\beta P \qquad \text{(Eq. 7}a\text{)}$$

However, according to the two-compartmental model throughout the total curve the following equation applies:

$$dP/dt = k_{21}T - (k_{12} + k_{el})P \qquad \text{(Eq. 8}a\text{)}$$

Substituting for the differential, dP/dt for Eq. 7a and dividing by P we have:

$$\beta = k_{12} + k_{el} - k_{21}\frac{T}{P} \qquad \text{(Eq. 9}a\text{)}$$

or on rearrangement:

$$\frac{T}{P} = \frac{(k_{12} + k_{el} - \beta)}{k_{21}} \quad \text{(Eq. 10a)}$$

The volume of distribution, Vd_{area} can be expressed as:

$$Vd_{area} = \frac{T + P}{P/V_p} = (1 + T/P)\ V_p \quad \text{(Eq. 11a)}$$

Substituting for T/P from Eq. 10a, we have:

$$Vd_{area} = 1 + \left(\frac{k_{12} + k_{el} - \beta}{k_{21}}\right) V_p \quad \text{(Eq. 12a)}$$

$$= \left(\frac{k_{21} + k_{12}}{k_{21}}\right) V_p + \left(\frac{k_{el} - \beta}{k_{21}}\right) V_p$$

and finally

$$Vd_{area} = Vd_{ss} + \left(\frac{k_{el} - \beta}{k_{21}}\right) V_p \quad \text{(Eq. 13a)}$$

which is Eq. 17 in the text.

Definition of $Vd_{inf.}^0$ from the Two-Compartmental Model—After a constant zero-order infusion is maintained for a sufficient length of time, an equilibrium is established. Then the rate in and the rate out are such that a constant concentration of drug is achieved in the central compartment and a $Vd_{inf.}^0$ can be calculated as follows:

$$dP/dt = k_{21}T - k_{el})P = 0 \quad \text{(Eq. 14a)}$$

$$k_{21}T = (k_{12} + k_{el})\ P \quad \text{(Eq. 15a)}$$

$$T/P = \frac{k_{12} + k_{el}}{k_{21}} \quad \text{(Eq. 16a)}$$

From Eq. 7 in the text, we have:

$$Vd_{inf.}^0 = \frac{(Q_{tot.})}{(C_p)_{eq.}} = \frac{P + T}{P/V_p} \quad \text{(Eq. 17a)}$$

$$Vd_{inf.}^0 = (1 + T/P)\ V_p \quad \text{(Eq. 18a)}$$

Substituting for T/P from Eq. 16a, we have:

$$Vd_{inf.}^0 = 1 + \left(\frac{k_{12} + k_{el}}{k_{21}}\right) V_p \quad \text{(Eq. 19a)}$$

which can be simplified according to the definition of Vd_{ss}:

$$Vd_{inf.}^0 = Vd_{ss} + \left(\frac{k_{el}}{k_{21}}\right) V_p \quad \text{(Eq. 20a)}$$

The latter is represented as Eq. 19 in the text.

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Keyphrases

Volume of distribution
Acetylsalicylicacid–*n*-methylglucamine salt distribution
Salicylic acid–*n*-methylglucamine salt distribution
Griseofulvin distribution
Open-model system–two compartmental
Mathematical interrelation of calculation methods
Distribution volume—calculation errors
Distribution rate constant equations
Zero-order infusion method