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Noncompartmental Determination of the Steady-State Volume of Distribution for Any Mode of Administration

Keyphrases □ Pharmacokinetics—noncompartmental determination of the steady-state volume of distribution for any mode of administration □ Volume of distribution—steady-state, noncompartmental determination for any mode of administration

To the Editor:

The analysis of concentration–time data by pharmacokinetic methods traditionally involves the use of compartmental models. The interpretation of this analysis, represented by a linear equation in the form of a sum of coefficient and exponential terms, provides useful insight into drug disposition. In recent years, however, there has been a move away from the traditional approach to an alternative method referred to as model-independent data analysis. There are reasons to recommend the latter approach; there is no need to ascribe the data to a specific model, and as a result it is not necessary to have a sophisticated computer and nonlinear regression programs available. The model-independent approach assumes only that all dispositional processes may be described by first-order kinetics with elimination occurring from the rapidly equilibrating or central compartment. This approach may also be termed an area analysis, since the useful parameters of clearance and volumes of distribution (V_{ss} and V_β or V_{area}) are based on determination of the total area under the plasma concentration–time curve (AUC) and total area under the first moment of the plasma concentration–time curve ($AUMC$). The areas generally are determined using the linear or logarithmic trapezoidal rule and extrapolation techniques. The elimination rate constant and half-life are determined from linear regression of the terminal (*i.e.*, post-absorption, post-distribution) concentration–time data.

Benet and Galeazzi (1) applied techniques of tracer kinetics, and used moment analysis (2, 3) to obtain the volume of distribution at steady state, V_{ss}, following an intravenous bolus injection. The purpose of this communication is to extend their analysis to permit calculation of V_{ss} for any mode of administration.

The mean transit time for a drug in the body, $\bar{t}_b$, is a function of the mean transit time for the response to the input (in), usually measured as plasma concentration, $\bar{t}_{b+in}$, and the mean transit time of the input, $\bar{t}_{in}$ (4):

$$\bar{t}_b = \bar{t}_{b+in} - \bar{t}_{in} \qquad \text{(Eq. 1)}$$

Mean transit or residence time for the response to the input, *i.e.*, plasma concentration, is given by:

$$\bar{t}_{b+in} = \int_0^\infty tC\,dt \Big/ \int_0^\infty C\,dt = AUMC/AUC \qquad \text{(Eq. 2)}$$

while the mean transit time for the input is given by (5):

$$\bar{t}_{in} = \int_0^\infty X\,dt/\text{dose} \qquad \text{(Eq. 3)}$$

where dose is the dose administered, and $\int_0^\infty X\,dt$ is the total area under the amount *versus* time curve for the input. For example, if a drug is administered as a zero-order infusion:

$$X = \text{dose} - k_0 t \qquad \text{(Eq. 4)}$$

In Eq. 4, X is the amount remaining to be infused at time t, and k_0 is the zero-order infusion rate. Administration by a first-order process (*e.g.*, extravascular administration) results in the following expression for X, the amount remaining to be administered:

$$X = F\,\text{dose}\,e^{-k_a t} \qquad \text{(Eq. 5)}$$

where k_a is an apparent first-order rate constant, and F is the fraction of the administered dose ultimately reaching the systemic circulation. Integration of Eqs. 4 and 5 yields:

$$\int_0^T X\,dt = k_0 T^2/2 \qquad \text{(Eq. 6)}$$

and

$$\int_0^\infty X\,dt = F\,\text{dose}/k_a \qquad \text{(Eq. 7)}$$

respectively. In Eq. 6, T is the duration of the infusion and is the upper limit of the integral, *i.e.*, T is equivalent to infinity.

Substitution for $\bar{t}_{b+in}$ and $\bar{t}_{in}$, according to Eqs. 2 and 3, respectively, in Eq. 1 gives the following expression for drug transit time in the body:

$$\bar{t}_b = AUMC/AUC - \int_0^\infty X\,dt/\text{dose} \qquad \text{(Eq. 8)}$$

Since V_{ss} is equal to the product of clearance (dose/AUC) and transit time (1), that is:

$$V_{ss} = \frac{\text{dose}}{AUC}\bar{t}_b \qquad \text{(Eq. 9)}$$

Equations 8 and 9 can be readily used to calculate V_{ss} following any mode of administration. Where there is a single mode of administration, Eqs. 8 and 9 can be readily solved for V_{ss}. For the case where drug is administered as a single bolus, $\int_0^\infty X\,dt = 0$,

$$V_{ss} = \frac{\text{dose}}{AUC}\bar{t}_b = \frac{\text{dose}}{AUC}\left(\frac{AUMC}{AUC}\right) = \text{dose}\,\frac{AUMC}{AUC^2} \qquad \text{(Eq. 10)}$$

This is the same equation as derived by Benet and Galeazzi

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Table I—Equations for $\int_0^\infty X\,dt$ and $\int_0^\infty X\,dt$/Dose for Various Modes of Drug Administration

Mode of Administration	$\int_0^\infty X\,dt$	$\int_0^\infty X\,dt$/dose
Intravenous bolus	0	0
Intravenous infusion	$k_0T^2/2$[a]	$T/2$
First-order input	F dose/k_a[b]	$1/k_a$
Simultaneous bolus plus infusion	$k_0t^2/2$	$k_0T^2/2(k_0T + \text{dose}_{iv})$[c]
Two consecutive infusions	$(k_0T^2/2)_1 + (k_0T^2/2)_2$[d]	$\frac{(k_0T^2/2)_1 + (k_0T^2/2)_2}{(k_0T)_1 + (k_0T)_2}$[c]

[a] See Eqs. 4 and 6. [b] See Eqs. 5 and 7. [c] See Eq. 13. [d] Subscript 1 refers to the first infusion, and subscript 2 refers to the second infusion.

(1). Substitution of $k_0T^2/2$ for $\int_0^\infty Xdt$ (see Eq. 6) in Eq. 8, and recognizing that k_0T equals dose, yields the following equation for V_{ss} for infusion data (6):

$$V_{ss} = \frac{\text{dose}}{AUC}\left(\frac{AUMC}{AUC} - \frac{T}{2}\right) = \text{dose}\,\frac{AUMC}{AUC^2} - \frac{T\ \text{dose}}{2\,AUC} \quad \text{(Eq. 11)}$$

If a case were to arise where input was first-order:

$$V_{ss} = \frac{F\ \text{dose}}{AUC}\left(\frac{AUMC}{AUC} - \frac{1}{k_a}\right) = F\ \text{dose}\,\frac{AUMC}{AUC^2} - \frac{F\ \text{dose}}{k_a\,AUC} \quad \text{(Eq. 12)}$$

If a value of F is not available, V_{ss}/F rather than V_{ss} would be calculated. As is apparent, information other than areas is required to determine V_{ss} where input is other than a bolus.

Administration of drug by multiple modes, for example, a simultaneous bolus plus an infusion, or consecutive infusions, may yield concentration–time data from which it may be desirable to estimate V_{ss}. Equation 9 in conjunction with a more general form of Eq. 8 may be used:

$$\bar{t}_b = \frac{AUMC}{AUC} - \frac{\sum \int_0^\infty X dt}{\sum \text{dose}} \quad \text{(Eq. 13)}$$

Table II—Calculation of V_{ss} for Various Modes of Administration[a]

Mode of Administration	AUC, (μg/ml) hr	$AUMC$, (μg/ml) hr^2	$\frac{AUMC}{AUC}$[b] hr	$\frac{\sum \int_0^\infty X\,dt}{\sum \text{dose}}$ hr	V_{ss}[c] L
IV bolus, 500 mg	1000.0[d]	25002.5[e]	25.0	0	25.0
IV infusion, 250 mg/hr over 2 hr	1000.0	26002.5[f]	26.0	1.0	25.0
First-order administration, 500 mg, $F = 1$, $k_a = 1.4\ \text{hr}^{-1}$	1000.0	25716.8[g]	25.7	0.7	25.0
Bolus plus infusion, 500 mg bolus plus 250 mg/hr over 2 hr	2000.0	51005.0[h]	25.5	0.5	25.0
Two consecutive infusions, 250 mg/hr over 2 hr followed by 41.67 mg/hr over 6 hr	1500.0	40003.7[i]	26.7	1.7	25.0

[a] Calculations based on equation, $C = A_1e^{-\lambda_1 t} + A_2e^{-\lambda_2 t}$, where $A_1 = 60.9545$ μg/ml, $\lambda_1 = 5.0605\ \text{hr}^{-1}$, $A_2 = 39.0459$ μg/ml and $\lambda_2 = 0.03952\ \text{hr}^{-1}$ following a 500-mg bolus dose. [b] See Table I. [c] See Eq. 13. [d] $AUC = \sum_{i=1}^{n} A_i/\lambda_i$. [e] $AUMC = \sum_{i=1}^{n} A_i/\lambda_i^2$. [f] $AUMC = \sum_{i=1}^{n} A_1/\lambda_i^2 + T\,AUC/2$. [g] $AUMC = N/k_a^2 + k_aA_1/\lambda_1^2(k_a - \lambda_1) + k_aA_2/\lambda_2^2(k_a - \lambda_2)$, where $N = k_a$ dose $(k_{21} - k_a)/V_c(\lambda_1 - k_a)(\lambda_2 - k_a)$. [h] Equals c plus d. [i] Use c for two different infusion rates, and add the resulting numbers. Note that only one-half the dose was given on the second infusion.

In Eq. 13, *AUMC* and *AUC* are the total areas under the resulting t C *versus* time and C *versus* time curves, and can be determined in the same manner as outlined for intravenous bolus data (1). The second term on the right hand side of Eq. 13 can be readily solved as the numerator is simply the sum of the $\int_0^\infty Xdt$ values for each mode of administration, and the denominator is the total dose administered by all modes of administration. Examples are illustrated in Table I.

The V_{ss} was determined for the various modes of administration outlined in Table I, utilizing the same data as employed by Benet and Galeazzi (1). All calculations were performed from explicit equations and are presented in Table II. Explicit equations were used to illustrate the validity of the relationships presented here. Estimation of the areas, *AUC* and *AUMC*, from time zero to the first point of the postabsorption and/or postdistribution phase with the linear or logarithmic trapezoidal rule, and from this latter point to time infinity using explicit equations (1) would yield values which vary from the theoretical values. Such variability is primarily due to inherent errors in the methods used to estimate the areas. However, the values obtained would be as reliable as those calculated using traditional methods of data analysis.

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Albumin Does Not Mediate the Removal of Taurocholate by the Rat Liver

Keyphrases □ Albumin—effect on removal of taurocholate from liver □ Taurocholate—removal from liver not mediated by albumin

To the Editor:

In a recent article by Forker and Luxon (1), the authors discuss what they refer to as a contradiction in liver extraction as a function of albumin concentration and taurocholate free concentration. The authors have failed to relate their experimental observations to a fundamental clearance concept (2):

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