SCIENTIFIC COMMENTARY

Linear Pharmacokinetic Equations Allowing Direct Calculation of Many Needed Pharmacokinetic Parameters from the Coefficients and Exponents of Polyexponential Equations Which Have Been Fitted to the Data

John G. Wagner[1,2]

It is shown that if the numerical values of the coefficients and exponents of the polyexponential equation describing the whole blood (plasma or serum) concentration after administration of a drug by bolus intravenous injection, or during or after termination of a constant-rate intravenous infusion, are known, then many needed pharmacokinetic parameters may be obtained directly. Parameters readily calculated by simple arithmetic are as follows: plasma or serum clearance, Cl_p; volume of plasma compartment, V_p; volume of distribution at steady state, V_{dss}; V_{darea} or V_β, extrapolated volume of distribution, V_{dext}; half-life of elimination, $t_{1/2}$; amount metabolized and/or excreted to time t, (A_e); amount in the body at time t, A_b; amount in the plasma (reference) compartment at time t, A_p; and amount in other compartments at time t, A_o. Simulations have shown that the equations yield the correct answers for an n-compartment mammillary model with central compartment elimination only, when rate constants, dose, and a value of V_p have been assigned. Since whole blood (plasma or serum) concentration–time data always lead to ambiguities as to which specific model is involved, the equations are most appropriate.

INTRODUCTION

In a linear pharmacokinetic system, plasma concentrations following bolus intravenous injection, $C_p^{i.v.}$, will be described by a polyexponential

equation as in equation 1. Expanded forms of equation 1, corresponding to one, two, and three exponential terms are shown as equations 2–4, respectively.

$$C_p^{\text{i.v.}} = \sum C_i e^{-\lambda_i t} \tag{1}$$

$$C_p^{\text{i.v.}} = C_1 e^{-\lambda_1 t} \tag{2}$$

$$C_p^{\text{i.v.}} = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} \tag{3}$$

$$C_p^{\text{i.v.}} = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} + C_3 e^{-\lambda_3 t} \tag{4}$$

In equations 1–4, C_i (C_1, C_2, C_3) are the coefficients, λ_i (λ_1, λ_2, λ_3) are the exponents, and t is time.

The numerical values of the C_i's and λ_i's of equation 1 obtained from a given set of data depend on (a) the *specific* linear pharmacokinetic model (including exactly how many exit rate constants there are and where they exit from the one or more compartments), (b) the numerical values of the rate constants (k_{ij}'s and k_{io}'s), (c) the dose, D, of the drug, and (d) the volume of the plasma (reference) compartment, V_p.

In another article (1), it is shown that one and sometimes two terms of the polyexponential equation describing the plasma concentration after either intravenous or oral administration can readily vanish a few minutes after administration. This fact, coupled with the more complicated, nonclassical linear models discussed in that article, indicates that most of the time we cannot even determine which *class* of model we are dealing with. Also, there is no *a priori* reason to assume that all subjects or patients in a panel should have the same model for a drug.

When only whole blood (plasma or serum) concentration–time data and/or urinary excretion data are available, there is really no rigorous method to determine whether elimination occurs only from the central (reference) compartment or from one or more of the peripheral compartments or both. Thus when evaluating such data the pharmacokineticist is presented with a dilemma. We have really not confronted this problem adequately to date. It has become customary in pharmacokinetics to assume *one specific model* for a given drug administered to a panel of subjects or patients, then to "force this specific model" on all sets of data, and to derive various kinetic parameters. There are three two-compartment open models, all of which give an equation of the form of equation 3 after bolus intravenous injection. There are 21 three-compartment open models, all of which give an equation of the form of equation 4 after bolus intravenous injection. We do not have the methods available to determine from the C_i's and λ_i's of equation 1 which class of models or which specific model applies to a given set of data in either of these situations. In fact, relative to the

disposition model, unless special sampling procedures are used to detect peripheral metabolism or excretion, we have no recourse but to assume that all elimination processes occur only from the central compartment.

Three proposals are being made in this article. These are as follows:

1. Assume (unless there is strong evidence to the contrary) that the general model which applies is an n-compartment mammillary model with elimination only from the central (reference) compartment as shown in Scheme I. The methods given for calculation of all pharmacokinetic parameters in this article apply to this general model. (See the discussion section for further details.)

2. Obtain a nonlinear least-squares fit of each set of data to the general equation 1, *but use the number of terms required for each set.* Don't "force" all data sets in a group to either a biexponential or a triexponential equation. Reevaluation of many sets of literature data has revealed that data from some members of a panel require only one exponential term, others require two exponential terms, and others require three exponential terms; such results will be reported in a subsequent article.

3. Calculate values of the pharmacokinetic parameters, such as V_p, V_{dss}, V_{darea}, V_{dext}, Cl_p, and $t_{1/2}$ (see next section) directly from the coefficients and exponents of the fitted polyexponential equation. It is best to express the dose in mg/kg if the concentration data are in
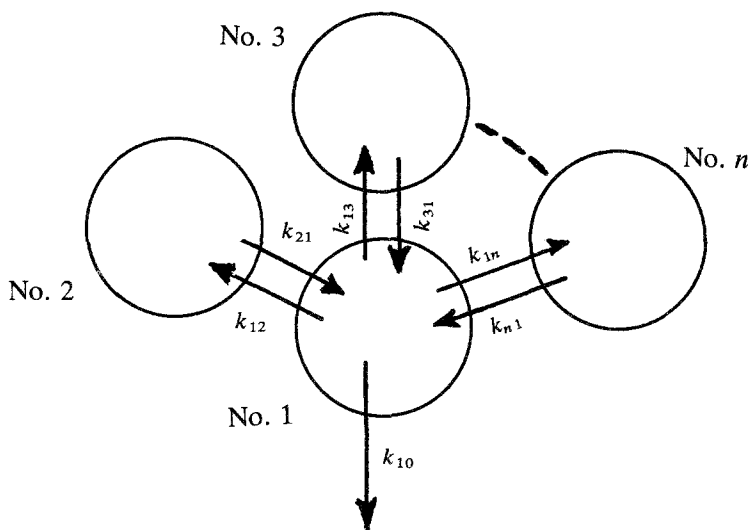
Scheme I. The n-compartment open mammillary model on which the equations are based.

μg/ml, and in μg/kg if the concentration data are in ng/ml, so that the volumes will have dimensions of liters/kg; such values usually have smaller coefficients of variation than values in liters obtained from the same data.

THEORETICAL

Symbolism

A_b is the amount of drug in the "body" (i.e., all compartments) at time t.

$(A_b)_\beta$ is the amount of drug in the "body" (all compartments) at time t in the terminal log-linear phase (i.e., only $C_1 e^{-\lambda_1 t}$ is still contributing).

A_b^{ss} is the amount of drug in the "body" (all compartments) at time t at steady state.

$\overline{A_b^{ss}}$ is the average amount of drug in the "body" (all compartments) at steady state.

A_e is the amount of drug which has been eliminated (metabolized and/or excreted) from the "body" in time t.

A_p is the amount of drug in the plasma (reference) compartment at time t.

$A_o = A_b - A_p$ is the amount of drug in compartments other than the plasma or reference compartment at time t.

AUC is the area under the plasma concentration–time curve (subscripts give limits).

B_i $(i = 1, 2, \ldots, n)$ is the coefficient of the ith exponential term of the polyexponential equation describing the plasma concentration following oral administration (i.e., analogous to equation 1 except that B_i replaces C_i).

C_i $(i = 1, 2, \ldots, n)$ is the coefficient of the ith exponential term of the polyexponential equation describing the plasma concentration following bolus intravenous administration.

Cl_p is the plasma clearance (dimension of volume/time).

C_p is the plasma concentration (i.e., concentration in the reference compartment with volume V_p) at time t. $C^{i.v.}$ refers to bolus intravenous administration and $C_p^{p.o.}$ refers to oral administration.

C_p^{ss} is the plasma concentration at time t at steady state.

$\overline{C_p^{ss}}$ is the average plasma concentration at steady state.

D is the dose of drug administered. For a constant-rate infusion $D = k_0 T$. $D_{p.o.}$ refers to oral administration and $D_{i.v.}$ refers to bolus intravenous administration.

D_L is the loading dose.

D_M is the maintenance dose.

E_{ij} is the exit rate constant for the ith compartment and equals the sum of all first-order rate constants whose arrowheads point away from the ith compartment.

F is the bioavailability factor concerned with incomplete absorption of the dose.

F^* is the bioavailability factor concerned with the so-called first-pass effect. This is defined by equation 28 when $F = 1$. For a given model, F^* is a combination of rate constants and $F^* \leq 1$.

f is the fraction of the drug which is free in the whole body.

k_{ij} is a first-order "microscopic rate constant" for transfer of drug from the ith to the jth compartment.

k_{io} is a first-order "microscopic rate constant" for transfer of drug from the ith compartment to outside "the body" or elimination rate constant of the ith compartment.

k_0 is the constant intravenous infusion rate (dimensions of mass/time).

λ_i is the exponent multiplying t in the exponential terms. Usually each λ_i will be an eigenvalue which is the absolute value of one of the roots when the determinant is set equal to zero; in this case, the λ_i is a function of all or many of the k_{ij}'s and k_{io}'s of the model. In some cases, the λ_i is equal to one of the k_{ij}'s. Note that λ_1 is the smallest λ_i (classically symbolized by β), λ_2 is the second smallest λ_i, etc.; i.e., the order of λ_i's with respect to magnitude is the same as that obtained by stripping the data. Note that λ_i refers to bolus intravenous administration or constant infusion and $\lambda_i^{\text{p.o.}}$ refers to oral administration.

Q_i ($i = 1$ or 2) are infusion rates (see equations 31 and 32 and text nearby).

S_i ($i = 1, \ldots, 5$) are particular sums defined by equations 5–9.

$\Sigma = \sum\limits_{i=1}^{n}$.

σ is the fraction of the drug which is free (not protein bound) in plasma.

$t_{1/2}$ is the apparent elimination half-life of the drug.

T is the duration of a constant-rate intravenous infusion (dimension of time).

τ is the uniform dosage interval (dimension of time).

t_0 is a lag time sometimes introduced into a polyexponential equation for $C_p^{\text{p.o.}}$ for oral administration (dimensions of time).

$t_{\text{ss}}^{\text{max}}$ is the time of the maximum plasma concentration after oral dosing at steady state.

V_β or $V_{d\,\text{area}}$ is defined by equations 6 and 13.

$V_{d\text{ss}}$ is the volume of distribution at steady state (based on the model of Scheme I).

$V_{d\text{ss}}C_p^{\text{ss}}$ is the amount of drug in the body at time t at steady state.

$V_{d\text{ss}}\bar{C}_p^{\text{ss}}$ is the average amount of drug in the body at steady state.

V_p is the volume of the plasma (reference) compartment.

X_i is the coefficient of the ith exponential term of the polyexponential equation giving the plasma concentration during constant-rate intravenous infusion.

Y_i is the coefficient of the ith exponential term of the polyexponential equation giving the plasma concentration after a constant rate infusion has ceased.

Equations

Equations for Bolus Intravenous Injection[3]

The plasma concentration is described by equation 1.

Let

$$S_1 = \sum C_i \tag{5}$$

$$S_2 = \sum C_i/\lambda_i \tag{6}$$

$$S_3 = \sum C_i/\lambda_i^2 \tag{7}$$

$$S_4 = \sum \frac{C_i}{\lambda_i} e^{-\lambda_i t} \tag{8}$$

$$S_5 = \sum \frac{C_i}{\lambda_i}(1 - e^{-\lambda_i t}) \tag{9}$$

Then the plasma clearance, Cl_p, is defined by equation 10.

$$\text{Cl}_p = D_{\text{i.v.}}/S_2 = D_{\text{i.v.}}/\text{AUC}_{0\to\infty} \tag{10}$$

The volume of the plasma compartment, V_p, is given by equation 11.

$$V_p = D_{\text{i.v.}}/S_1 \tag{11}$$

The volume of distribution at steady state, $V_{d\text{ss}}$, is given by equation 12.

$$V_{d\text{ss}} = D_{\text{i.v.}}S_3/(S_2)^2 \tag{12}$$

$V_{d\text{area}}$ or V_β is given by equation 13.

$$V_{d\text{area}} = D_{\text{i.v.}}/\lambda_1 S_2 = D/\lambda_1(\text{AUC}_{0\to\infty}) \tag{13}$$

[3]See Appendix for some derivations.

The extrapolated volume of distribution, $V_{d\text{ext}}$, is given by equation 14.

$$V_{d\text{ext}} = D/C_1 \tag{14}$$

The elimination half-life, $t_{1/2}$, is given by equation 15.

$$t_{1/2} = 0.693/\lambda_1 \tag{15}$$

The amount which has been metabolized and/or excreted to time t, A_e, is given by equation 16.

$$A_e = D_{\text{i.v.}} S_5/S_2 = D(\text{AUC}_{0 \to t})/(\text{AUC}_{0 \to \infty}) \tag{16}$$

It should be emphasized that equation 16 is mathematically correct only when elimination occurs solely from the central compartment. The amount of drug in the body at time t, A_b, is given by equation 17 (1).

$$A_b = D_{\text{i.v.}} S_4/S_2 = (V_d)_t \cdot C_p = D(\text{AUC}_{t \to \infty})/(\text{AUC}_{0 \to \infty}) \tag{17}$$

The amount of drug in the plasma compartment at time t, A_p, is given by equation 18.

$$A_p = D_{\text{i.v.}} C_p^{\text{i.v.}}/S_1 = V_p C_p^{\text{i.v.}} \tag{18}$$

The amount of drug in other compartments than the plasma compartment at time t, A_o, is given by equation 19.

$$A_o = A_b - A_p \tag{19}$$

Equations 19, in effect, lumps n peripheral compartments into one peripheral compartment.

The time-dependent volume of distribution, $(V_d)_t$, is given by equation 20, originally derived by Niazi (2).

$$(V_d)_t = A_b/C_p = D_{\text{i.v.}} S_4/C_p^{\text{i.v.}} S_2 = D(\text{AUC}_{t \to \infty})/C_p(\text{AUC}_{0 \to \infty}) \tag{20}$$

It should be noted that the order of magnitudes of the volumes is always

$$V_{d\text{ext}} > V_{d\text{area}} > V_{d\text{ss}} > V_p$$

It should also be noted that $(A_b)_\beta = V_{d\text{area}} \cdot C_p$, since $(V_d)_t = V_{d\text{area}}$ in the log-linear phase when all exponential terms, except $e^{-\lambda_1 t}$, essentially equal zero.

Relationship Between Bolus Intravenous and Infusion Equations

The relationships between the bolus intravenous and intravenous infusion equations are shown in Table I for expansions up to and including three exponential terms. During a constant-rate intravenous infusion ($t \gtrless T$) the

plasma concentration is described by equation 21, and after the infusion has ceased $(t \geq T)$ the plasma concentration is described by equation 22.

$$C_p = \sum X_i(1 - e^{-\lambda_i t}) = \sum \frac{C_i}{\lambda_i T}(1 - e^{-\lambda_i t}) \tag{21}$$

$$C_p = \sum Y_i\, e^{-\lambda_i t} = \sum C_i \left\{ \frac{e^{+\lambda_i T} - 1}{\lambda_i T} \right\} e^{-\lambda_i t} \tag{22}$$

By matching coefficients, we see that

$$X_i = C_i/\lambda_i T \tag{23}$$

$$Y_i = C_i \left\{ \frac{e^{+\lambda_i T} - 1}{\lambda_i T} \right\} \tag{24}$$

From equation 23 we see that $C_i = \lambda_i T X_i$, and from equation 24 we obtain equation 25.

$$C_i = \frac{\lambda_i T Y_i}{e^{+\lambda_i T} - 1} \tag{25}$$

Thus, if "during infusion" data are fitted to the X_i form of equation 21 and/or "postinfusion" data are fitted to the Y_i form of equation 22, one can readily obtain the coefficients, C_i, corresponding to bolus intravenous injection and then apply equations 5–20 to obtain the pharmacokinetic parameters. Corrections are needed with equation 25 even when infusions as short as 5 min are given and postinfusion data are evaluated.

Bioavailability

Equation 26 symbolizes the result obtained by fitting a set of $C_p^{p.o.}$, t data obtained following oral administration, if the system is linear.

$$C_p^{p.o.} = \sum B_i\, e^{-\lambda^{p.o.}(t - t_0)} = \sum B_i'\, e^{-\lambda^{p.o.} t} \tag{26}$$

where

$$B_i' = B_i\, e^{+\lambda^{p.o.} t_0} \tag{27}$$

Equations 26 and 27 include a lag time, t_0, which may be a positive value or zero. The program CSTRIP(3) automatically determines whether a lag time is needed to describe a given set of oral data. If $t_0 = 0$, then $B_i = B_i'$.

It should be noted that B_i' can replace C_i and $\lambda_i^{p.o.}$ can replace λ_i in equations 5 and 6. The result would give the sums $S_1^{p.o.}$ and $S_2^{p.o.}$, respectively. If the latter values are then used in equations 10 and 13, with substitution of $D_{p.o.}$ for $D_{i.v.}$, then Cl_p/FF^* and $V_{d\,area}/FF^*$, respectively, are calculated and not Cl_p and $V_{d\,area}$, respectively. It is very common in the

Table I. Relationships Between Bolus Intravenous and Infusion Equations

	One exponential term	Two exponential terms	Three exponential terms
Bolus intravenous	$C_p = C_1 e^{-\lambda_1 t}$	$C_p = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t}$	$C_p = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} + C_3 e^{-\lambda_3 t}$
During constant-rate infusion over T hr	$C_p = \dfrac{C_1}{\lambda_1 T}(1 - e^{-\lambda_1 t})$	$C_p = \dfrac{C_1}{\lambda_1 T}(1 - e^{-\lambda_1 t}) + \dfrac{C_2}{\lambda_2 T}(1 - e^{-\lambda_2 t})$	$C_p = \dfrac{C_1}{\lambda_1 T}(1 - e^{-\lambda_1 t}) + \dfrac{C_2}{\lambda_2 T}(1 - e^{-\lambda_2 t}) + \dfrac{C_3}{\lambda_3 T}(1 - e^{-\lambda_3 t})$
Postinfusion ($t \geq T$)	$C_p = C_1\left(\dfrac{e^{+\lambda_1 T} - 1}{\lambda_1 T}\right) e^{-\lambda_1 t}$	$C_p = C_1\left(\dfrac{e^{+\lambda_1 T} - 1}{\lambda_1 T}\right) e^{-\lambda_1 t} + C_2\left(\dfrac{e^{+\lambda_1 T} - 1}{\lambda_2 T}\right) e^{-\lambda_2 t}$	$C_p = C_1\left(\dfrac{e^{+\lambda_1 T} - 1}{\lambda_1 T}\right) e^{-\lambda_1 t} + C_2\left(\dfrac{e^{+\lambda_2 T} - 1}{\lambda_2 T}\right) e^{-\lambda_2 t} + C_3\left(\dfrac{e^{+\lambda_3 T} - 1}{\lambda_3 T}\right) e^{-\lambda_3 t}$

literature to ignore F^* completely and assume $F = 1$ for oral administration, then claim that the parameters estimated are Cl_p and $V_{d\,\text{area}}$. This technique just causes confusion.

By definition, the product FF^* is given by equation 28.

$$FF^* = \frac{D_{\text{i.v.}} \int_0^\infty C_p^{\text{p.o.}} \, dt}{D_{\text{p.o.}} \int_0^\infty C_p^{\text{i.v.}} \, dt} = \frac{D_{\text{i.v.}} \sum B_i'/\lambda_i^{\text{p.o.}}}{D_{\text{p.o.}} \sum C_i/\lambda_i} \tag{28}$$

Thus F^* is given by equation 28 when there is complete absorption of the oral dose ($F = 1$).

The value of F^* for a given model is obtained by substituting the appropriate expressions for $C_p^{\text{i.v.}}$ and $C_p^{\text{p.o.}}$ into equation 28, letting $D_{\text{i.v.}} = D_{\text{p.o.}}$ and $F = 1$, then performing the integrations and simplifying the resultant ratio, or by use of Laplace transforms to obtain expressions for the areas.

When real data sets have been fitted by the method of least squares and the numerical values of $D_{\text{i.v.}}, D_{\text{p.o.}}, B_i', \lambda_i$ are known, they may be substituted into the right-hand side of equation 28 and the value of FF^* calculated directly.

Drugs Bound to Plasma Protein and Tissues

If σ is the fraction of the drug which is free (not protein bound) in plasma, f is the fraction of the total drug in the body which is free, $(\lambda_1)_F$ is the intrinsic apparent elimination rate constant referenced to free drug, λ_1 is the apparent elimination rate constant obtained from C_p, t data, and the one-compartment open model with linear plasma protein binding and linear tissue binding applies, then

$$\lambda_1 = f(\lambda_1)_F \tag{29}$$

$$Cl_p = V_{d\text{ext}} \cdot \lambda_1 = V_{d\text{ext}} \cdot \sigma \cdot (\lambda_1)_F \tag{30}$$

For this particular one-compartment open model, $V_{d\,\text{area}} = V_{d\text{ext}}$ and both depend on both f and σ. This will be explained in a future publication by the author.

Safe and Rapid Attainment of Steady-State Plasma Concentrations

Once λ_1 and Cl_p are known for a linear system and a particular subject (or average parameter values are used), then steady-state plasma levels may be safely and rapidly attained by the method of Wagner (4). The steps are as follows:

1. Choose the desired steady-state plasma concentration, C_p^{ss}.
2. Choose the time T for the duration of the initial constant-rate intravenous infusion at the rate Q_1 (mass/time).

3. Calculate the final infusion rate Q_2 (mass/time) for $t \geqslant T$ with equation 31.

$$Q_2 = \text{Cl}_p \cdot C_p^{\text{ss}} \tag{31}$$

4. Calculate the initial infusion rate, Q_1, for $t \leqslant T$ with equation 32.

$$Q_1 = Q_2 / (1 - e^{-\lambda_1 T}) \tag{32}$$

Then, at zero time initiate the infusion at the rate Q_1. At time T, abruptly change the rate from Q_1 to Q_2. Steady state is reached in about an hour or less after the rate Q_2 is started. The amount of drug in the body at steady state, A_b^{ss}, is given by equation 33.

$$A_b^{\text{ss}} = V_{d\text{ss}} \cdot C_p^{\text{ss}} \tag{33}$$

Equations for Steady State After Oral Administration (5)

When steady-state equation corresponding to equation 26 is equation 34 when equal doses are given at equal time intervals, τ. In equation 34, t is the time after a dose given at steady state.

$$C_p^{\text{ss}} = \Sigma \left\{ \frac{B_i' e^{-\lambda_i^{\text{p.o.}} \cdot t}}{1 - e^{-\lambda_i^{\text{p.o.}} \cdot t}} \right\} \tag{34}$$

To find the time of the maximum steady-state plasma concentration, $t_{\text{ss}}^{\text{max}}$, one takes the derivative of equation 34 and sets it equal to zero, then solves the equation by use of logarithms if these are only one or two exponential terms, or, iteratively, if there are more than two exponential terms. This is indicated by equation 35.

$$\frac{dC_p^{\text{ss}}}{dt} = \Sigma \frac{-\lambda_i^{\text{p.o.}} \cdot B_i' e^{-\lambda_i^{\text{p.o.}} \cdot t_{\text{ss}}^{\text{max}}}}{1 - e^{-\lambda_i^{\text{p.o.}} \cdot \tau}} = 0 \tag{35}$$

Once $t_{\text{ss}}^{\text{max}}$ is known, then it may be substituted for t in equation 34 to yield the maximum plasma concentration at steady state, $C_{\text{ss}}^{\text{max}}$, indicated by equation 36.

$$C_{\text{ss}}^{\text{max}} = \Sigma \left\{ \frac{B_i' e^{-\lambda_i^{\text{p.o.}} \cdot t_{\text{ss}}^{\text{max}}}}{1 - e^{-\lambda_i^{\text{p.o.}} \cdot \tau}} \right\} \tag{36}$$

The minimum plasma concentration at steady state, $C_{\text{ss}}^{\text{min}}$, is obtained by substituting τ for t in equation 34, with the result shown as equation 37.

$$C_{\text{ss}}^{\text{min}} = \Sigma \left\{ \frac{B_i' e^{-\lambda_i^{\text{p.o.}} \cdot \tau}}{1 - e^{-\lambda_i^{\text{p.o.}} \cdot \tau}} \right\} \tag{37}$$

To attain steady state quickly on oral dosing, the ratio of the loading dose, D_L, to the maintenance dose, D_m, is given by equation 38 (5).

$$\frac{D_L}{D_m} = \frac{\int_0^\tau C_p^{ss}\, dt}{\int_0^\tau C_p\, dt} = \sum B_i'/\lambda_i^{p.o.} \bigg/ \sum \left[\frac{B_i'(1 - e^{-\lambda_i^{p.o.}\tau})}{\lambda_i^{p.o.}} \right] \tag{38}$$

Similar equations to 34–38 may be used for bolus intravenous injections given at intervals of τ hr, but B_i is replaced by C_i and $\lambda_i^{p.o.}$ is replaced by λ_i (i.e., one uses equation 1 in place of equation 26). When the intravenous route is used, then the average steady-state plasma concentration, $\overline{C_p^{ss}}$, is given by equation 39 (6).

$$\overline{C_p^{ss}} = D_m/(Cl_p \cdot \tau) \tag{39}$$

If one substitutes the maintenance dose, D_m, the clearance, Cl_p, and the dosage interval, τ, into the right-hand side of equation 39 for *oral administration*, the quantity estimated is $\overline{C_p^{ss}}/FF^*$ (since drug reaching the circulation is FF^*D_m and not D_m). However, if one had estimated an apparent plasma clearance, Cl_p/FF^*, from oral data and used it in place of Cl_p in equation 39, then $\overline{C_p^{ss}}$ would be estimated. There is much confusion in the literature about such calculations.

There is also some confusion in the literature as to what "clearances" mean. Various "clearances" were calculated for diphenhydramine from plasma concentrations measured both during and after a constant-rate intravenous infusion and after oral administration of similar (but known) doses of the drug given as an aqueous solution and in capsule form (7). Results obtained may be summarized as shown in Table II. It is obvious that F and F^* are confounded. We can obtain an estimate of F^* only if we assume $F_s = 1$ for the solution given orally.

EXPERIMENTAL

Example of Obtaining Coefficients of Bolus Intravenous Equations from Postinfusion Data

For the two-compartment open model with elimination only from the central compartment, let $k_{12} = 3$, $k_{21} = 2$, $k_{el} = 0.1$, $D_{i.v.} = 500{,}000$, $V_p = 5000$, $k_0 = 250{,}000$, and $T = 2$. For these constants, we find $\lambda_1 = 0.03952$ and $\lambda_2 = 5.0605$ (see Appendix). For bolus intravenous injection,

$$C_p = \frac{D_{i.v.}}{V_p(\lambda_2 - \lambda_1)} [(k_{21} - \lambda_1) e^{-\lambda_1 t} - (k_{21} - \lambda_2) e^{-\lambda_2 t}] \tag{40}$$

Table II. "Clearances" of Diphenhydramine

Subject	"Clearances" of diphenhydramine [liters/(kg × hr)]			Bioavailability factor[c]	
	From intravenous infusion data[a] Cl_p	From solution given orally[b] Cl_p/F_sF^*	From capsule given orally[b] Cl_p/F_cF^*	$F_sF^* = Cl_p/(Cl_p/F_sF^*)$	$F_c/F_s = (Cl_p/F_sF^*)/(Cl_p/F_cF^*)$
1	0.55	0.94	1.12	0.59	0.85
2	0.45	0.83	0.79	0.54	1.05

[a] Clearance estimated with equation 5.
[b] Apparent clearance estimated by fitting oral solution and oral capsule data to equation 23 and the using equation 5 but replacing C_i by B_i and λ_i by $\lambda_i^{p.o.}$.
[c] If one assumes $F_s = 1$, then $F_sF^* = F^*$ and $F_c/F_s = F_c$.

Substitution of the assigned values into equation 40 yields equation 41.

$$C_p = 39.0459\, e^{-0.03952t} + 60.9545\, e^{-5.0605t} \tag{41}$$

Hence $C_1 = 39.0459$ and $C_2 = 60.9454$.
    For postinfusion,

$$C_p = \frac{k_0(k_{21}-\lambda_1)(1-e^{+\lambda_1 T})}{-\lambda_1(\lambda_2-\lambda_1)V_p}\, e^{-\lambda_1 t} + \frac{k_0(k_{21}-\lambda_2)(1-e^{+\lambda_2 T})}{-\lambda_2(\lambda_1-\lambda_2)V_p}\, e^{-\lambda_2 t} \tag{42}$$

Substitution of the assigned values into equation 42 yields equation 43.

$$C_p = 40.6303e^{-0.03952t} + 149{,}712.2288e^{-5.0605t} \tag{43}$$

Hence

$$Y_1 = 40.6303 \qquad \text{and} \qquad Y_2 = 149{,}712.2288$$

Thus

$$C_1 = \frac{T\lambda_1 Y_1}{e^{+\lambda_1 T}-1} = \frac{(2)(0.03952)(40.6303)}{e^{+(0.03952)(2)}-1} = 39.0459 \tag{44}$$

and

$$C_2 = \frac{T\lambda_2 Y_2}{e^{+\lambda_2 T}-1} = \frac{(2)(5.0605)(149{,}712.2288)}{e^{+(5.0605)(2)}-1} = 60.9542 \tag{45}$$

The C_1 and C_2 values obtained with equations 44 and 45, respectively, are the same as those in the intravenous equation 41 within round-off error.

Examples Showing That Equation 12 Yields the Correct Value of V_{dss}

Example 1

Example 1 is of a two-compartment open model with elimination only from the central compartment.
    Let the constants be the same as in the above example, hence equation 41 holds.
    Substituting from equation 41 into equations 6, 7, and 12 gives equation 46.

$$V_{dss} = 500{,}000\left[\frac{39.0459}{(0.03952)^2} + \frac{60.9545}{(5.0605)^2}\right] \Big/ \left[\frac{39.0459}{0.03952} + \frac{60.9545}{5.0605}\right]^2$$
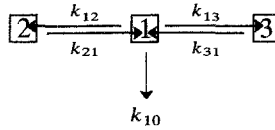
$$= 12{,}501 \tag{46}$$

For this model, V_{dss} is known to be given by equation 47.

$$V_{dss} = (1 + k_{12}/k_{21})V_p = (1 + 3/2)5000 = 12,500 \tag{47}$$

The difference of 1 in 12,500 is due only to round-off error in the C_i's and λ_1's.

Example 2

Example 2 is of a three-compartment open model with elimination only from the central compartment shown in Scheme II. The dose is put into compartment 1 at time zero.

Scheme II

By writing the differential equations for Scheme I, converting to Laplace transforms, and setting the determinant, Δ, equal to zero, one obtains equations 48–51,

$$\Delta = \begin{vmatrix} (S+E_1) & -k_{21} & -k_{31} \\ -k_{12} & (S+k_{21}) & 0 \\ -k_{13} & 0 & (S+k_{31}) \end{vmatrix} = S^3 + a_2 S^2 + a_1 S + a_0 = 0 \tag{48}$$

where

$$a_2 = E_1 + k_{21} + k_{31} \tag{49}$$

$$a_1 = E_1 k_{21} + E_1 k_{31} + k_{21} k_{31} - k_{12} k_{21} - k_{13} k_{31} \tag{50}$$

$$a_0 = E_1 k_{21} k_{31} - k_{12} k_{21} k_{31} - k_{13} k_{21} k_{31} \tag{51}$$

There are three negative roots (eigenvalues) of equations 48–51 and the absolute values of these roots are designated λ_1, λ_2, and λ_3. The relationships are

$$a_2 = \lambda_1 + \lambda_2 + \lambda_3 \tag{52}$$

$$a_1 = \lambda_1 \lambda_2 + \lambda_1 \lambda_3 + \lambda_2 \lambda_3 \tag{53}$$

$$a_0 = \lambda_1 \lambda_2 \lambda_3 \tag{54}$$

The Laplace transform of the amount of drug in compartment 1 at t, a_1, is given by equation 55.

$$a_1 = \frac{\begin{vmatrix} D & -k_{21} & -k_{21} \\ 0 & (S+k_{21}) & 0 \\ 0 & 0 & (S+k_{31}) \end{vmatrix}}{\Delta} = \frac{D(S+k_{21})(S+k_{31})}{(S+\lambda_1)(S+\lambda_2)(S+\lambda_3)} \quad (55)$$

Letting $C_p^{\text{i.v.}} = A_1/V_p$, and taking the antitransform of equation 55, gives

$$C_p^{\text{i.v.}} = \frac{D_{\text{i.v.}}}{V_p}\left[\frac{(k_{21}-\lambda_1)(k_{31}-\lambda_1)}{(\lambda_2-\lambda_1)(\lambda_3-\lambda_1)} e^{-\lambda_1 t} + \frac{(k_{21}-\lambda_2)(k_{31}-\lambda_3)}{(\lambda_1-\lambda_2)(\lambda_3-\lambda_2)} e^{-\lambda_2 t}\right.$$
$$\left. + \frac{(k_{21}-\lambda_3)(k_{31}-\lambda_3)}{(\lambda_1-\lambda_3)(\lambda_2-\lambda_3)} e^{-\lambda_3 t}\right] \quad (56)$$

For example, let $k_{12}=3$, $k_{21}=2$, $k_{13}=1$, $k_{31}=0.5$, $k_{10}=0.1$, $D_{\text{i.v.}}=500{,}000$, and $V_p = 5000$. Then

$$E_1 = 0.1 + 3 + 1 = 4.1 \quad (57)$$

$$a_2 = 4.1 + 2 + 0.5 = 6.6 \quad (58)$$

$$a_1 = (4.1)(2) + (4.1)(0.5) + (2)(0.5) - (3)(2) - (1)(0.5) = 4.75 \quad (59)$$

$$a_0 = (4.1)(2)(0.5) - (3)(2)(0.5) - (1)(2)(0.5) = 0.10 \quad (60)$$

Substituting from equations 58–60 into equation 48 gives

$$S^3 + 6.6S^2 + 4.75S + 0.10 = 0 \quad (61)$$

An electronic calculator cube root program gave the roots of equation 61 as -0.021705074, -0.796904816, and -5.7813901.
Hence $\lambda_1 = 0.021705074$, $\lambda_2 = 0.796904816$, and $\lambda_3 = 5.7813901$.
Substituting these values into equations 52–54 gave the appropriate values of $a_2 = 6.6$, $a_1 = 4.75$, and $a_0 = 0.10$.
Substitution of the values of D, V_p, k_{21}, k_{31}, λ_1, λ_2, and λ_3 into equation 56 and simplification gave the equation 62.

$$C_p^{\text{i.v.}} = 21.1921225\, e^{-0.021705074 t} + 9.2944971\, e^{-0.796904816 t}$$
$$+ 69.5633803\, e^{-5.78139015 t} \quad (62)$$

Substituting from equation 62 into equations 6, 7, and 12 gave equation 63.

$$V_{dss} = 500,000\left[\frac{21.1921225}{(0.021705074)^2} + \frac{9.2444971}{(0.796904816)^2} + \frac{69.5633803}{(5.7813901)^2}\right] \Bigg/$$
$$\left[\frac{21.1921225}{0.021705074} + \frac{9.2444971}{0.796909816} + \frac{69.5633803}{5.7813901}\right]^2$$

$$= 22,500 \tag{63}$$

For the particular three-compartment open model shown in Scheme II it is known that V_{dss} is given by equation 64.

$$V_{dss} = (1 + k_{12}/k_{21} + k_{13}/k_{31})V_p = (1 + 3/2 + 1/0.5)5000 = 22,500 \tag{64}$$

Hence the new equation yields the correct value of V_{dss} for the model shown in Scheme II. In general, for any of the three-compartment open models, where elimination may be from any compartment, V_{dss} is given by equation 65.

$$V_{dss} = \frac{A_b^{\overline{ss}}}{C_p^{\overline{ss}}} = \frac{\int_0^T A_1^{ss} \, dt + \int_0^T A_2^{ss} \, dt + \int_0^T A_3^{ss} \, dt}{\int_0^T C_p^{ss} \, dt} \tag{65}$$

The value of V_{dss} given by equation 12 will exactly coincide with the value given by equation 65 only when the particular three-compartment open model shown in Scheme II is involved. However, since we usually cannot determine from which compartments elimination occurs, this is part of the pharmacokineticist's dilemma. Hence unless there are good reasons for the contrary, the author suggests that V_{dss} always be calculated by means of equation 12.

DISCUSSION

As discussed earlier (1, 5), there are many alternative models, all of which yield a two- or three-term exponential equation as illustrated by equations 3 and 4. It is getting to be common practice to measure some pharmacological response as a function of time and occasionally to conclude that the response is related to the amount of drug in compartment 1, compartment 2, or compartment 3. An alternative recommendation is to fit the data to the required number of exponential terms, then to determine if the response is approximately related to A_b (from equation 17) or A_o (from equations 17–19). This will tell one whether the site of action is in "the plasma compartment" or "some other part of the theoretical body" according to pharmacokinetic theory. However, the use of equations 17–19 will in

effect lump all peripheral compartments into one compartment. Whether this is a better alternative requires further study. It is important to know which compartment may relate to specific responses for specific drugs so that appropriate predictions and explanations may be made. To carry out such a determination accurately requires that plasma concentrations and responses be measured more than once shortly after intravenous administration as well as at later times. This is so since A_b is a maximum at time of injection and falls off whenever A_o is zero at time zero, rises to a maximum at some later time, and then falls off. Hence the distinction is made readily with data collected shortly after intravenous administration.

Another point concerns degrees of freedom and what should be reported. If a bolus intravenous dose is administered and the plasma concentrations are fitted to a three-term exponential equation (equation 4), then one can report only six items as indicated by equation 4, namely C_1, C_2, C_3, λ_1, λ_2, and λ_3.

Fitting the data to equation 4 is a model-independent process. However, one must realize that λ_i values must be widely separated (i.e., greater than two- to fivefold) for one to accept the validity of any computer fit. A six-parameter equation probably requires 18 or more data points properly spaced throughout the C_p,t curve. Assuming relatively accurate measurement, such data may yield a reasonable estimate of the parameters if the resultant λ_i values are sufficiently separated as noted above. Otherwise, the computer-derived exponentials must be considered as only our tentative, probably inaccurate estimate of the appropriate equation.

If the data set fits the above restrictions, one can apply the equations listed in this article. Most of the equations 5–20 are model independent. However, equations 16 and 19 are model dependent, as noted earlier when they were originally discussed. Hence for consistency from one author to another it is here proposed that all authors use the general model shown in Scheme I and the general equations for this general model given in this article.

Parameters

$t_{1/2}$

The plasma half-life, $t_{1/2}$, may be defined as the time required for the plasma concentration to fall to one-half its value after absorption has ceased and pseudo-steady-state distribution has been attained. The latter, for practical purposes, means that the amount of drug in each peripheral compartment is falling off essentially at the same first-order rate as the amount of drug in the central (reference) compartment. Hence $t_{1/2}$ is the apparent elimination half-life. It is defined by equation 15, and, in the

symbolism section, λ_1 is defined as the smallest of the λ_i values. If the "rules are obeyed" and *terminal* plasma concentrations are well fitted by the polyexponential equation, then this definition is satisfactory. It will be λ_1 which has the most influence of all the λ_i values in determining C_{ss}^{min} (see equation 37) and $\overline{C_p^{ss}}$ (see equations 39 and 10). The problem of not having a sensitive enough assay to "see" the correct value of λ_1, and the errors which ensue, has been discussed by Wagner (7). If C_p,t data have been correctly computer-fitted to the general polynomial equation, this parameter, as with all other coefficients and exponentials, is really model independent, and does not rely on the general model shown in Scheme I.

Half-lives estimated from the other eigenvalues or k_{ij}'s, such as $0.693/\lambda_2$ and $0.693/\lambda_3$, have frequently been termed "distribution half-lives." But there are problems with such interpretations. If eigenvalues are involved, then they are a function of all the rate constants in the system and not just the microscopic distribution rate constants. If the coefficients and exponents of the polyexponential equation which is the "best fit" of each set of data are reported by an author, there appears to be no need to report the corresponding half-lives, since they may be readily calculated from the λ_i values. The terminal $t_{1/2}$ (calculated from λ_1) is the lone exception, and the reason for this is that scientists are used to thinking in terms of an elimination half-life rather than in terms of an apparent first-order elimination rate constant.

V_{dext}

By the nature of its calculation (equation 14), V_{dext} is also model independent, and does not actually rely on the general model shown in Scheme I. However, one of the commonest errors made in the literature is to assume that after a bolus intravenous injection $Cl_p = V_{dext} \cdot \lambda_1$. This is true only when $V_{dext} \simeq V_{darea}$, as is the case with some drugs such as warfarin. The requirements for such a situation have been discussed by Albert *et al.* (8). When V_{dext} is appreciably larger than V_{darea}, then V_{dext} is of no use pharmacokinetically. When $V_{dext} \simeq V_{darea}$, then V_{dext} is useful, since the latter parameter is more readily estimated (requiring fewer plasma assays) than V_{darea}.

V_p

If each set of data from a panel of subjects or patients is fitted with *the appropriate number of exponential terms for each subject*, then V_p is also truly model independent, and does not rely on the general model shown in Scheme I. However, if one fits a given set of data to a biexponential equation when the data really require a triexponential equation, then the value of V_p estimated from the two equations will be different.

$V_{d\text{ss}}$

The $V_{d\text{ss}}$ value calculated with equation 12 applies only to the general model shown in Scheme I. However, because of the dilemma of not knowing from which compartments there are exit rate constants to "outside the body," use of equation 12 will at least make all authors homogeneous in their approach.

$V_{d\text{area}}$

Equation 13 is based on mass balance considerations and is truly model independent when viewed in that light. However, $(A_b)_\beta = V_{d\text{area}} \cdot C_p$ in the terminal log-linear phase only for the general model shown in Scheme I.

Cl_p

Equation 10 is based on mass balance considerations and is model independent when viewed in that light. However, Cl_p is equivalent to "total body clearance" only for the general model shown in Scheme I. If there were an exit rate constant, k_{20}, from compartment No. 2 of Scheme I, then total body clearance would be equal to $V_1 k_{10} + V_2 k_{20}$ and not equal to Cl_p, as calculated with equation 10. Many equate Cl_p with "total body clearance" without specifying under which conditions they are equivalent.

A_e, A_b, and A_o

Expressions A_e, A_b, and A_o calculated with equations 16, 17, and 19 are dependent on the general model shown in Scheme I.

Conclusion

Most pharmacokinetic articles on specific drugs report some or all of the parameters discussed above. The advantage of the equations in this article is that all of them may be calculated directly from the coefficients and exponents of the polyexponential equation without deriving any microscopic rate constants.

APPENDIX

Derivation for A_b After Bolus Intravenous Dose

$$A_b = D_{\text{i.v.}} - Cl_p \int_0^t C_p \, dt \tag{66}$$

Now,

$$\int_0^t C_p\, dt = \int_0^t \sum C_i\, e^{-\lambda_i t}\, dt' = \sum \frac{C_i}{\lambda_i}(1 - e^{-\lambda_i t}) \tag{67}$$

Substituting from equation 10 for Cl_p and for the integral from equation 67 into equation 66 gives

$$A_b = D_{\mathrm{i.v.}} - \left[D_{\mathrm{i.v.}} \sum \frac{C_i}{\lambda_i}(1 - e^{-\lambda_i t}) \Big/ \sum C_i/\lambda_i \right]$$

$$= D_{\mathrm{i.v.}}\left[1 - \sum \frac{C_i}{\lambda_i}(1 - e^{-\lambda_i t}) \Big/ \sum C_i/\lambda_i \right]$$

$$= D_{\mathrm{i.v.}}\left[\sum C_i/\lambda_i - \sum \frac{C_i}{\lambda_i} + \sum \frac{C_i}{\lambda_i} e^{-\lambda_i t} \Big/ \sum C_i/\lambda_i \right]$$

$$= D_{\mathrm{i.v.}} \sum \frac{C_i}{\lambda_i} e^{-\lambda_i t} \Big/ \sum C_i/\lambda_i = D_{\mathrm{i.v.}} \cdot S_4/S_2 \tag{68}$$

Derivation for V_{dss} After Bolus Intravenous Injection

$$A_b^{\overline{ss}} = \int_0^\tau A_b^{ss}\, dt \Big/ \tau = D \sum \int_0^\tau \frac{C_i}{\lambda_i(1 - e^{-\lambda_i \tau})} e^{-\lambda_i t}\, dt \Big/ \tau \sum C_i/\lambda_i \tag{69}$$

Omitting the sum sign temporarily, we find that

$$\int_0^\tau \frac{C_i}{\lambda_i(1 - e^{-\lambda_i \tau})} e^{-\lambda_i t}\, dt = \left| -\frac{C_i}{\lambda_i^2(1 - e^{-\lambda_i \tau})} e^{-\lambda_i t} \right|_0^\tau$$

$$= -\frac{C_i}{\lambda_i^2(1 - e^{-\lambda_i \tau})} e^{-\lambda_i \tau} - \left[-\frac{C_i}{\lambda_i^2(1 - e^{-\lambda_i \tau})} \right]$$

$$= \frac{C_i}{\lambda_i^2(1 - e^{-\lambda_i \tau})} [1 - e^{-\lambda_i \tau}] = C_i/\lambda_i^2 \tag{70}$$

Hence

$$A_b^{\overline{ss}} = \left[\frac{D_{\mathrm{i.v.}}}{\tau} \sum C_i/\lambda_i^2 \right] \Big/ \sum C_i/\lambda_i \tag{71}$$

Also,

$$C_p^{\overline{ss}} = \frac{\int_0^\tau C_p^{ss}\, dt}{\tau} = \frac{\int_0^\infty C_p\, dt}{\tau} = \frac{\sum C_i/\lambda_i}{\tau} \tag{72}$$

$$V_{dss} = \frac{A_b^{\overline{ss}}}{C_p^{\overline{ss}}} = \frac{\left[\dfrac{D_{\mathrm{i.v.}}}{\tau} \sum C_i/\lambda_i^2 \right] \Big/ \sum C_i/\lambda_i}{[\sum C_i/\lambda_i]/\tau} = \frac{D_{\mathrm{i.v.}} \sum C_i/\lambda_i^2}{[\sum C_i/\lambda_i]^2} = D_{\mathrm{i.v.}} \cdot S_3/(S_2)^2 \tag{73}$$

## Time-Dependent Volume of Distribution After Bolus Intravenous Dose (2)

$(V_d)t$ is obtained by making a ratio of the above expressions for A_b and C_p with the result below.

$$(V_d)t = \frac{A_b}{C_p} = D_{\text{i.v.}} \sum \frac{C_i}{\lambda_i} e^{-\lambda_i t} \Big/ \Big[\sum C_i e^{-\lambda_i t} \Big] \Big[\sum C_i/\lambda_i \Big] = D_{\text{i.v.}} \cdot S_4 / C_p^{\text{i.v.}} \cdot S_2 \quad (74)$$
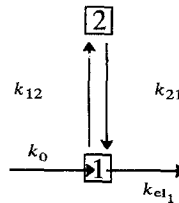
In the log-linear phase only λ_1 remains and $(V_d)_{t\beta}$ is given by equation 11.

Example Showing Relationship Between Coefficients for C_p,t Equations During Constant-Rate Infusion and After Bolus Intravenous Injection

Take as example the two-compartment open model.
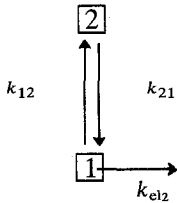
Scheme III. Bolus intravenous injection.   Scheme IV. During infusion.

After bolus intravenous injection, equation 40 applies, where

$$\lambda_1 + \lambda_2 = k_{12} + k_{21} + k_{\text{el}} \quad (75)$$

$$\lambda_1 \lambda_2 = k_{21} k_{\text{el}} \quad (76)$$

If we write equation 40 as equation 77,

$$C_p = C_1 e^{-\lambda_1 t} + C_2 e^{-\lambda_2 t} \quad (77)$$

then by matching coefficients, we find

$$C_1 = \frac{D(k_{21} - \lambda_1)}{V_p(\lambda_2 - \lambda_1)} \quad (78)$$

$$C_2 = \frac{-D(k_{21} - \alpha)}{V_p(\lambda_2 - \lambda_1)} \quad (79)$$

During a constant-rate intravenous infusion, equation 80 applies:

$$C_p = \frac{k_0(k_{21}-\lambda_1)(1-e^{+\lambda_1 t})}{-\lambda_1(\lambda_2-\lambda_1)V_p}\,e^{-\lambda_1 t} + \frac{k_0(k_{21}-\lambda_2)(1-e^{+\lambda_2 t})}{-\lambda_2(\lambda_1-\lambda_2)V_p}\,e^{-\lambda_2 t}$$

$$= \frac{k_0(k_{21}-\lambda_1)}{\lambda_1(\lambda_2-\lambda_1)V_p}\,(1-e^{-\lambda_1 t}) + \frac{k_0(k_{21}-\lambda_2)}{\lambda_2(\lambda_1-\lambda_2)V_p}\,(1-e^{-\lambda_2 t}) \qquad (80)$$

We may write equation 80 as equation 81.

$$C_p = X_1(1-e^{-\lambda_1 t}) + X_2(1-e^{-\lambda_2 t}) \qquad (81)$$

By matching coefficients of equations 80 and 81, we find

$$X_1 = \frac{k_0(k_{21}-\lambda_1)}{\lambda_1(\lambda_2-\lambda_1)V_p} \qquad (82)$$

$$X_2 = \frac{k_0(k_{21}-\lambda_2)}{\lambda_2(\lambda_1-\lambda_2)V_p} = -\frac{k_0(k_{21}-\lambda_1)}{\lambda_2(\lambda_2-\lambda_1)V_p} \qquad (83)$$

From the bolus intravenous equation 40 for the same model, we can see that

$$C_1 = \frac{D_{i.v.}(k_{21}-\lambda_1)}{(\lambda_2-\lambda_1)V_p} \qquad (84)$$

$$C_2 = \frac{-D_{i.v.}(k_{21}-\lambda_1)}{(\lambda_2-\lambda_1)V_p} \qquad (85)$$

Also,

$$k_0 = \frac{D_{i.v.}}{T} \qquad (86)$$

Utilizing equations 82, 84, and 86, we obtain equations 87–89.

$$\frac{X_1}{C_1} = \frac{D_{i.v.}(k_{21}-\lambda_1)}{\lambda_1 T(\lambda_2-\lambda_1)V_p} \cdot \frac{(\lambda_2-\lambda_1)V_p}{D_{i.v.}(k_{21}-\lambda_1)} = \frac{1}{\lambda_1 T} \qquad (87)$$

$$X_1 = C_1/\lambda_1 T \qquad (88)$$

$$C_1 = \lambda_1 T X_1 \qquad (89)$$

Utilizing equations 83, 85, and 86, we obtain equations 90–92.

$$\frac{X_2}{C_2} = \left[\frac{-D_{i.v.}(k_{21}-\lambda_1)}{\lambda_2 T(\lambda_2-\lambda_1)V_p}\right]\left[\frac{-(\lambda_2-\lambda_1)V_p}{D_{i.v.}(k_{21}-\lambda_1)}\right] = \frac{1}{\lambda_2 T} \qquad (90)$$

$$X_2 = C_2/\lambda_2 T \qquad (91)$$

$$C_2 = \lambda_2 T X_2 \qquad (92)$$

Hence we may write the infusion equations as shown in Table I and equation 21.

Post-intravenous-infusion equation 93 applies to Scheme IV.

$$C_p = \frac{k_0(k_{21}-\lambda_1)(1-e^{+\lambda_1 T})}{-\lambda_1(\lambda_2-\lambda_1)V_p}e^{-\lambda_1 t} + \frac{k_0(k_{21}-\lambda_2)(1-e^{+\lambda_2 T})}{-\lambda_2(\lambda_1-\lambda_2)V_p}e^{-\lambda_2 t}$$

$$= \frac{k_0(k_{21}-\lambda_1)(e^{+\lambda_1 T}-1)}{\lambda_1(\lambda_2-\lambda_1)V_p}e^{-\lambda_1 t} + \frac{k_0(k_{21}-\lambda_2)(e^{+\lambda_2 T}-1)}{\lambda_2(\lambda_1-\lambda_2)V_p}e^{-\lambda_2 t} \quad (93)$$

We may write equation 93 as equation 94.

$$C_p = Y_1 e^{-\lambda_1 t} + Y_2 e^{-\lambda_2 t} \quad (94)$$

By matching coefficients in equations 93 and 94, we find

$$Y_1 = \frac{k_0(k_{21}-\lambda_1)(e^{+\lambda_1 T}-1)}{\lambda_1(\lambda_2-\lambda_1)V_p} \quad (95)$$

$$Y_2 = \frac{k_0(k_{21}-\lambda_2)(e^{+\lambda_2 T}-1)}{\lambda_2(\lambda_1-\lambda_2)V_p} = -\frac{k_0(k_{21}-\lambda_2)(e^{+\lambda_2 t}-1)}{\lambda_2(\lambda_2-\lambda_1)V_p} \quad (96)$$

Utilizing equations 84, 86, and 95, we obtain equations 97–99.

$$\frac{Y_1}{C_1} = \frac{D_{i.v.}(k_{21}-\lambda_1)(e^{+\lambda_1 T}-1)}{\lambda_1 T(\lambda_2-\lambda_1)V_p} \cdot \frac{(\lambda_2-\lambda_1)V_p}{D_{i.v.}(k_{21}-\lambda_1)} = \frac{e^{+\lambda_1 T}-1}{\lambda_1 T} \quad (97)$$

$$Y_1 = C_1\left\{\frac{e^{+\lambda_1 T}-1}{\lambda_1 T}\right\} \quad (98)$$

$$C_1 = \frac{\lambda_1 T Y_1}{e^{+\lambda_1 T}-1} \quad (99)$$

Utilizing equations 83, 86, and 96, we obtain equations 100–102.

$$\frac{Y_2}{C_2} = \left[\frac{-D_{i.v.}(k_{21}-\lambda_2)(e^{+\lambda_2 T}-1)}{\lambda_2 T(\lambda_2-\lambda_1)V_p}\right]\left[\frac{-(\lambda_2-\lambda_1)V_p}{D_{i.v.}(k_{21}-\lambda_2)}\right] = \frac{e^{+\lambda_2 T}-1}{\lambda_2 T}$$

$$\quad (100)$$

$$Y_2 = C_2\left\{\frac{e^{+\lambda_2 T}-1}{\lambda_2 T}\right\} \quad (101)$$

$$C_2 = \frac{\lambda_2 T Y_2}{e^{+\lambda_2 T}-1} \quad (102)$$

Hence we may write the infusion equations as shown in Table I and equation 22.

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