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Pharmacokinetic Analysis of Blood Level Data interpreted by a Two-Compartment Model

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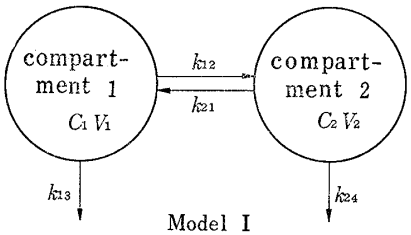
Although a two-compartment model represents an adequate model for a reasonably sophisticated description of the time course of many drugs in the body, the still simpler one-compartment model provides certain pharmacokinetic parameters which are useful, particularly in clinical application. A single-compartment approximation may be made under certain conditions by omitting blood level data in the period shortly after rapid intravenous administration. Pharmacokinetic calculations utilizing the parameters from this approximation were compared with those based on the true two-compartment model. Simple equations were developed to test the validity of the single-compartment approximation. Errors in the calculated values based on the single-compartment approximation were expressed in terms of the smaller exponent β and ratios ($m=A/B$ and $n=\alpha/\beta$) of the coefficients and the exponents from biexponential fitting to blood level data after rapid intravenous administration. It was shown that the single-compartment approximation may or may not be satisfactorily used for clinical purposes depending upon size of m and n or relative size of m and n. Using the formulas derived in this report and data from intravenous administration on a few patients, it is possible to determine for a particular drug whether the one-compartment model is an adequately approximate model for clinical purposes, or whether the two-compartment model is really necessary.

A semilogarithmic plot of blood level (C_1) *versus* time after intravenous administration of a drug is frequently shown by the following biexponential equation:

$$C_1 = Ae^{-\alpha t} + Be^{-\beta t} \tag{1}$$

This blood level-time relation may be interpreted in terms of a two-compartment model shown in Chart 1 to describe the rate process of distribution and elimination of the drug in the body.[2]



Model I

Chart 1. Schematic Representation of the Body as the Two-Compartment Model

C_1 and C_2 are the drug levels in the two compartments at time t after administration of a drug into compartment 1. V_1 and V_2 are the volumes of the two compartments. The rate constants k_{12} and k_{21} are the distribution rate constants, and k_{13} and k_{24} are the elimination rate constants from the two compartments. All the rate constants are assumed to be first-order.

On the other hand, in a one-compartment model the body is considered to exhibit the properties of a single compartment. If a drug is eliminated from this compartment by first-order biotransformation and excretion after intravenous administration, a semilogarithmic plot of blood level *versus* time yields one straight line, and the blood level may be described by a monoexponential equation. When a blood level-time curve has a significant curvature on a semilogarithmic plot during the early period after intravenous administration, the two-compartment model is probably an appropriate model. If the faster rate constant (α), however, is considerably larger than the slower rate constant (β) in Eq. 1, the first term of Eq. 1 will

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make only a very small contribution to C_1. When this term becomes negligible very rapidly with small values of time, Eq. 1 may be approximated by the following monoexponential equation:

$$C_1 = Be^{-\beta t} \quad (2)$$

In that case, the α phase, which is due primarily to the distribution of drug throughout the body, is completed very early, and the approximation based on Eq. 2 is valid over nearly all of the time course of the drug in the body. The one-compartment model is therefore actually an approximation used to describe the two-compartment model when $\alpha \gg \beta$.[3a)]

The model and its model parameters, chosen based upon the adequacy in describing the drug level data after rapid injection, are useful in pharmacokinetic calculations. For example, prediction of steady-state blood levels after multiple doses of a drug may be made by kinetic analysis of blood levels observed after single doses of the drug.[4,5)] Absorption rates of a drug into the general circulation may be evaluated by comparing kinetically blood levels after intravenous administration of the drug and extravascular administration of the drug in dosage forms.[6–10)] Visual and/or statistical examination of blood level data will indicate whether the curve is monoexponential or biexponential so that the appropriate model can be applied.[11)] In practice, blood level data measured at frequent intervals commencing shortly after rapid intravenous injection are necessary to decide whether the two-compartment model or the one-compartment model is more appropriate. This is sometimes difficult in routine clinical situation. For practical purposes, a monoexponential equation obtained from omitting blood level data in the period shortly after intravenous administration will probably be satisfactory under certain conditions for its application to pharmacokinetic calculations.

It is the purpose of this report to show that the contribution of the first exponential term of Eq. 1 to pharmacokinetic calculations may be expressed using relative magnitude (A/B and α/β) of the exponents and the coefficients of the two exponential terms of Eq. 1. The mathematical errors associated with pharmacokinetic calculations using Eq. 2 were represented in terms of the ratios A/B and α/β, and simple equations were developed to test the validity of the single-compartment approximation.

Calculation and Result

Individual Rate Constants Expressed Using Ratios of Exponents and Coefficients of Biexponential Equation——In the two-compartment model the body is simply assumed to be divided into two compartments, compartments 1 and 2, as depicted schematically in Chart 1. Compartment 1 can be assumed to be the plasma and other fluids or tissue between which a drug rapidly equilibrates, and is sometimes referred to as a central compartment. Compartment 2 is a compartment which has a significant barrier for the distribution of the drug from compartment 1, and is sometimes referred to as a peripheral compartment. C_1 and C_2 are the concentrations of the drug in the two compartments at any time t after administration, and the volumes of distribution for the two compartments are designated V_1 and V_2. Rate constants k_{12} and

3) J.G. Wagner, "Biopharmaceutics and Relevant Pharmacokinetics," 1st ed., Drug Intelligence Publications, Hamilton, Ill, 1971, *a*) p. 291; *b*) p. 254; *c*) p. 293.
4) J.G. Wagner, J.I. Northam, C.D. Alway, and O.S. Carpenter, *Nature*, **207**, 1301 (1965).
5) B. Alexanderson, *Europ. J. Clin. Pharmacol.*, **4**, 82 (1972).
6) "Guidelines for Biopharmaceutical Studies in Man," ed. by APhA Academy Sciences, Washington, D.C., 1972, p. 9.
7) J.C.K. Loo and S. Riegelman, *J. Pharm. Sci.*, **57**, 918 (1968).
8) S.A. Kaplan, M. Lewis, M.A. Schwartz, E. Postma, S. Cotler, C.W. Abruzzo, T.L. Lee, and R.E. Weinfeld, *J. Pharm. Sci.*, **59**, 1569 (1970).
9) H.E. Barber and G.R. Bourne, *Brit. J. Pharmacol.*, **41**, 513 (1971).
10) B.E. Cabana, L.E. Whillhite, and M.E. Bierwagen, *Antimicrob. Agents Chemother*., **1969**, 35.
11) H. Nogami, M. Hanano, S. Awazu, and H.H. Moon, *Chem. Pharm. Bull.* (Tokyo), **17**, 2097 (1969).

k_{21} are the distribution rate constants, and k_{13} and k_{24} are the elimination rate constants from the two compartments. All the rate constants are assumed to be first-order.

A graphical analysis technique is usually employed to separate Eq. 1 plotted on a semilogarithmic scale into two straight components, and gives slopes, which may be defined as $-\alpha/2.303$ and $-\beta/2.303$, and extrapolated intercepts of A and B at time zero.[12a] Ratios m and n of the parameters of the biexponential equation are defined by Eq. 3 and 4, respectively.

$$A = mB \tag{3}$$

$$\alpha = n\beta \tag{4}$$

Therefore,

$$A + B = B(m+1)$$

The sum $A+B$ is the concentration of drug in compartment 1 at time zero. The rate constants α and β are defined by Eq. 5 and 6 in the course of integration and solution of the differential equations for model I shown in Chart 1 after instantaneous administration of a drug into compartment 1 ($C_1=A+B$ and $C_2=0$ at $t=0$).[12b]

$$k_{12} + k_{21} + k_{13} + k_{24} = \alpha + \beta \tag{5}$$

$$k_{13}k_{21} + k_{13}k_{24} + k_{12}k_{24} = \alpha\beta \tag{6}$$

The simulated first-order rate constants (k_{12}, k_{21}, k_{13}, and k_{24}) for model I are related to A, B, α, and β as shown by Eq. 7 and 8, the first halves of which are derived in the Appendix. Furthermore, by substituting mB and $n\beta$ for A and α, respectively, the equations are shown as follows:

$$k_{21} + k_{24} = \frac{A\beta+B\alpha}{A+B} = \frac{m+n}{m+1}\beta \tag{7}$$

$$k_{12} + k_{13} = \frac{A\alpha+B\beta}{A+B} = \frac{mn+1}{m+1}\beta \tag{8}$$

Unless some additional relation between the individual rate constants in model I is given, the values of k_{12}, k_{21}, k_{13}, and k_{24} can not be calculated with A, B, α, and β. If a ratio of k_{12} to k_{21} is assumed to be Q, all the individual rate constants are expressed in terms of m, n, β, and Q by substituting $k_{21}Q$ for k_{12} in Eq. 6—8 and by solving the equations. The individual rate constants so obtained are shown in Table I. Once

Table I. Individual Rate Constants of the Two-Compartment Model Expressed in Terms of m, n, β, and Q

Model	k_{12}	k_{21}	k_{13}	k_{24}
I	$\frac{\sqrt{mQ}(n-1)}{m+1}\beta$	$\frac{\sqrt{m}(n-1)}{\sqrt{Q}(m+1)}\beta$	$\frac{mn+1-\sqrt{mQ}(n-1)}{m+1}\beta$	$\frac{\sqrt{Q}(m+n)-\sqrt{m}(n-1)}{\sqrt{Q}(m+1)}\beta$
II	$\frac{m(n-1)^2}{(m+1)(m+n)}\beta$	$\frac{m+n}{m+1}\beta$	$\frac{n(m+1)}{m+n}\beta$	
III	$\frac{mn+1}{m+1}\beta$	$\frac{m(n-1)^2}{(m+1)(mn+1)}\beta$		$\frac{n(m+1)}{mn+1}\beta$

Q is defined as a ratio of k_{12} to k_{21}.

a value for Q is arbitrarily chosen to determine all the rate constants in model I, the ratios of any two rate constants such as k_{13} to k_{24} and k_{12} to k_{13} will be fixed. Here, let R denotes a ratio of k_{13} to k_{24}. The relationship between the ratios Q and R can be derived by eliminating the individual rate constants (k_{12}, k_{21}, k_{13}, and k_{24}) from the five equations, Eq. 6—8, $k_{13}=Rk_{24}$, and $k_{12}=Qk_{21}$. The result is as follows:

12) D.S. Riggs, "The Mathematical Approach to Physiological Problems," Williams & Wilkins Co., Baltimore, Md., 1963, *a*) p. 146; *b*) p. 203.

$$\sqrt{\frac{m}{Q}}(n-1)(Q-R) + R(m+n) = mn + 1 \qquad (9)$$

As an example, the relationship between the ratios Q and R is given in Fig. 1 for $m=0.713$ and $n=11.6$ derived from the data after intravenous administration of sulfisoxazole in man.[13] The ratio Q is given by values between limits of approximately 1.07 to 0.53 against the ratio R between zero and infinity in the two-compartment model for sulfisoxazole. The ratio Q becomes equal to m, if unity is substituted for R in Eq. 9 (*i.e.* $k_{13}=k_{24}$). Furthermore, substitution of m for Q in the formulas representing k_{13} and k_{24} of model I (Table I) results in $k_{13}=k_{24}=\beta$.

The individual rate constants for models II and III, in which either elimination process can be neglected, is expressed in terms of m, n, and β (Table I). The individual rate constants shown in Table I were applied to kinetic analysis based on Models I—III.

Prediction of Drug Amount Remaining in the Body——The total amount of drug (M) present in the body for model I is given by the following equation,

$$M = D\left[\left(\frac{\beta-k_{13}}{\beta-\alpha}\right)e^{-\alpha t} + \left(\frac{\alpha-k_{13}}{\alpha-\beta}\right)e^{-\beta t}\right] \qquad (10)$$

which are derived in the Appendix. Here, the dose (D) is assumed to be put instantaneously into compartment 1. By using Eq. 4 and $k_{13}=[mn+1-\sqrt{mQ}(n-1)]\beta/(m+1)$, Eq. 10 may be rewritten in the following way:

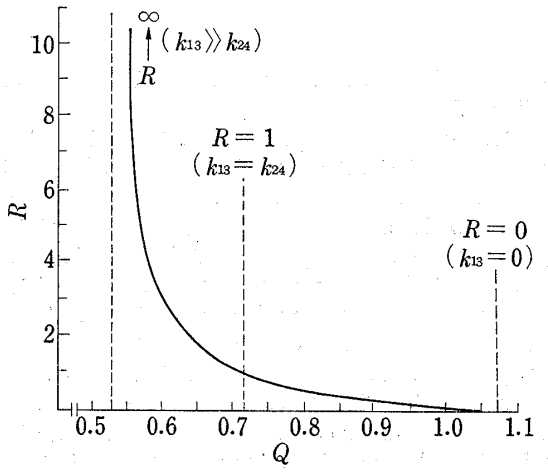

Fig. 1. Relationship between $Q=k_{12}/k_{21}$ and $R=k_{13}/k_{24}$ as Calculated with Eq. 9 using $m=0.713$ and $n=11.6$ based on the Average Values for Sulfisoxazole in Reference 13

$$M = \frac{D}{m+1}[(m-\sqrt{mQ})e^{-n\beta t}+(\sqrt{mQ}+1)e^{-\beta t}] \qquad (11)$$

where, the amount of drug in the body as a function of time can not be calculated by only m, n, and β values, if a Q value is not specified. Similar derivation yields Eq. 14 and 15 representing the amounts of drug in the body for models II and III, respectively (Table II). The equations for the amounts of drug in special

Table II. Drug Amount in the Body *versus* Time Expressed in Terms of m, n, β, and Q after a Single Intravenous Injection

Model		Drug amount in the body	
I	$k_{12}=Qk_{21}$	$\frac{D}{m+1}[(m-\sqrt{mQ})e^{-n\beta t}+(\sqrt{mQ}+1)e^{-\beta t}]$	(11)
I	$k_{13}=k_{24}$	$De^{-\beta t}$	(12)
I	$k_{12}=k_{21}$	$\frac{D}{m+1}[(m-\sqrt{m})e^{-n\beta t}+(\sqrt{m}+1)e^{-\beta t}]$	(13)
II		$\frac{D}{m+n}(me^{-n\beta t}+ne^{-\beta t})$	(14)
III		$\frac{D}{n-1}(-e^{-n\beta t}+ne^{-\beta t})$	(15)

Q is defined as a ratio of k_{12} to k_{21}.

cases ($k_{13}=k_{24}$ and $k_{12}=k_{21}$) of model I are shown by Eq. 12 and 13 which are obtained by substituting m and unity for Q in Eq. 11, respectively.

13) S.A. Kaplan, R.E. Weinfeld, C.W. Abruzzo, and M. Lewis, *J. Pharm. Sci.*, **61**, 773 (1972).

If the distribution rate constants (k_{12} and k_{21}) are very much larger than the elimination rate constants (k_{13} and k_{24}) in the two-compartment model, the faster rate constant (α) of the corresponding biexponential equation will be very much larger than the slower rate constant (β). The term with the faster rate constant may make only a very small contribution to C_1, since it becomes negligible very rapidly. Neglecting the blood level data in the early period after rapid intravenous administration yields a monoexponential equation. In that case, the total amount of drug present in the body at any time may be approximated by Eq. 16.

$$M = V_m B e^{-\beta t} \tag{16}$$

Here, V_m is the apparent volume of distribution (D/B) calculated from extrapolating the blood level to the ordinate.[14]

The curves representing Eq. 14 and 16 do not cross except at time zero. The amount of drug in the body calculated with Eq. 14 based on model II is always less than that calculated with Eq. 16 derived from the one-compartment model as an approximate. The contribution of the first terms, $Dme^{-n\beta t}/(m+n)$, of Eq. 14 to the amount of drug becomes negligibly small with time, since $n \gg m$ in many cases and $n \gg 1$, and the amount of drug approaches $n/(m+n)$ times that calculated with Eq. 16 as time becomes large. Therefore, the ratio of the amount of drug calculated with Eq. 14 to that calculated with Eq. 16 rapidly approaches a limiting value $n/(m+n)$ with increasing n. The limiting ratio becomes progressively smaller with increasing m and decreasing n. On the other hand, the total drug in the body calculated with Eq. 15 (model III) is always larger than that calculated with Eq. 16. The former approaches $n/(n-1)$ times the latter as time becomes large. The total amount of drug at any time calculated with Eq. 11 based on Model I will be found between the values calculated with Eq. 14 and 15 based on models II and III. Typical values of $n/(m+n)$ and $n/(n-1)$ for various drugs are shown in Table III. The drug amounts of several for these drugs were found to be predictable satisfactorily from the approximated equation.

Table III. Limiting Value ($n/m+n$ and n/n-1) of Ratio of Drug Amount Remaining in the Body Calculated from the Biexponential Equation (Models II and III) to That Calculated with the Monoexponentical Approximation

Drug	Species	Dose	n	m	$n/(m+n)$	$n/(n$-1)
Diphenylhydantoin sodium[a]	man	250 mg	79.0	1.62	0.980	1.01
Trimethoprim[b]	dog	5.7 mg/kg	43.2	0.91	0.979	1.02
Lidocaine[c]	man	50 mg	18.3	3.29	0.847	1.06
Griseofulvin[d]	dog	50 mg	12.4	3.21	0.794	1.09
Nortriptyline[e]	man	1 mg/kg	9.49	0.01	0.999	1.12
Dicloxacillin[f]	man	250 mg	6.71	2.84	0.703	1.18
Ampicillin[g]	man	250 mg	6.67	5.23	0.561	1.18
Ethoxybenzamide[h]	rabbit	200 mg	6.58	0.35	0.949	1.18
Acetysalicylic acid[i]	man	325 mg	5.42	2.71	0.667	1.23
Chlordiazepoxide[j]	dog	10 mg/kg	5.07	1.26	0.801	1.25
Oxacillin[k]	man	250 mg	5.00	7.35	0.405	1.25

Pharmacokinetic parameters of the above drugs (A μg/ml, B μg/ml, α hr^{-1}, and β hr^{-1}) are taken as it is or as average values from their references and are shown as follows:
a) 12.2, 7.5, 6.0, 0.076[15]; *b*) 3.0, 3.3, 10.1, 0.234[16]; *c*) 1.38, 0.42, 7.38, 0.404[17]; *d*) 3.05, 0.95, 10.4, 0.84[18]; *e*) 0.4, 40.0, 0.258, 0.0272[5]; *f*) 42.0, 14.8, 5.3, 0.79[19]; *g*) 20.0, 6.2, 4.6, 0.69[19]; *h*) 19.7, 56.8, 23.0, 3.49[11]; *i*) 42.0, 15.5, 15.6, 2.88[20]; *j*) 13.5, 10.7, 2.18, 0.43[3]; *k*) 25.0, 3.4, 5.0, 1.0[19]

It was shown that if a two-compartment model (model II) is appropriate to be applied, a semilogarithmic plot of the amount of drug (M) in the body *versus* time has a smaller curvature than that of blood levels *versus* time after rapid intravenous administration and that the semilogarithmic M-plot gives a better estimate of the parameter β than the terminal linear segment of the semilogarithmic plot of blood levels.[3b]

14) $V_m = D/B = V_1(m+1)$, since $V_1 = D/(m+1)B$.
15) T. Suzuki, Y. Saitoh, and K. Nishihara, *Chem. Pharm. Bull.* (Tokyo), **18**, 405 (1970).
16) S.A. Kaplan, R.E. Weinfeld, S. Cotler, C.W. Abruzzo, and K. Alexander, *J. Pharm. Sci.*, **59**, 358 (1970).
17) M. Rowland, P.D. Thomson, A. Guichard, and K.L. Melmon, *N.Y. Acad. Sci.*, **179**, 383 (1971).
18) P.A. Harris and S. Riegelman, *J. Pharm. Sci.*, **58**, 93 (1969).
19) L.W. Dittert, W.O. Griffen, Jr., J.C. LaPiana, F.J. Shainfeld, and J.T. Doluisio, *Antimicrob. Agents Chemother.*, **1969**, 42.
20) M. Rowland and S. Riegelman, *J. Pharm. Sci.*, **57**, 1313 (1968).

However, this semilogarithmic M-plot also deviates from the straight line representing Eq. 16 with increasing n and decreasing $n/(m+n)$, and may have a significant curvature over a considerable period of time depending upon n and relative size of m and n.

Estimation of Rate and Extent of Drug Absorption——Wagner and Nelson[21] proposed an equation for calculating absorption rates of a drug from an extravascular depot into the general circulation. This equation was derived on the assumption that the distribution and elimination of the drug can be described by a one-compartment model and a first-order rate for overall loss of drug from the blood. Loo and Riegelman[7] reported that the Wagner-Nelson (W-N) absorption equation does not give an acceptable estimate for the case where a drug is distributed according to a two-compartment model. In this section, an error in estimation of the amount of drug absorbed using the one-compartment model as an approximate will be expressed in terms of m, n, and β.

If a blood level-time curve is represented by a biexponential equation after rapid intravenous injection, the amount of drug absorbed after a single oral administration may be given by the following equation:

$$(A)_t = C_1V_1 + M_2 + k_{13}V_1\int_0^t C_1dt + k_{24}\int_0^t M_2dt \tag{17}$$

where, M_2 is the amount of drug (C_2V_2) in compartment 2 at any time. The amount of drug absorbed up to time t is evaluated as being the sum of the drug amounts in the body plus the sum of the drug amounts eliminated from both compartments. Since model I is a linear model, whose system is described by first-order linear differential equations, the blood level function Eq. 2 after intravenous administration of a drug is the weighting function between an input function showing the absorption rate of drug into compartment 1 and the resulting blood level function.[22] Therefore, the rate and extent of drug absorption is independent of the ratio R. The total drug absorbed into compartment 1 is calculated to be as follows:

$$(A)_\infty = k_{13}V_1\int_0^\infty C_1dt + k_{24}\int_0^\infty M_2dt = \frac{n(m+1)}{m+n}\beta V_1\int_0^\infty C_1dt \tag{18}$$

the latter half of which is derived in the Appendix. Kaplan reported that the estimates of the total coumermycin A_1 absorbed were practically the same, when calculated using model II or model III in this study and also that the percent drug amount absorbed with time was calculated to be almost equal for both models.[23] However, the calculated values based on both models should be identical theoretically as described above.

For the single-compartment approximation, the amount of drug absorbed up to time t after oral administration may be approximated by the following W-N equation:

$$(A_{app})_t = C_1V_m + \beta V_m\int_0^t C_1dt \tag{19}$$

The ratio $(A)_\infty/(A_{app})_\infty$ of the total amounts of drug absorbed is given by Eq. 20. Since $V_m = V_1(m+1)$[14], the ratio of the true amount of drug absorbed to the apparent amount of drug absorbed, which is calculated

$$\frac{(A)_\infty}{(A_{app})_\infty} = \frac{k_{13}V_1\int_0^\infty C_1dt + k_{24}\int_0^\infty M_2dt}{\beta V_m\int_0^\infty C_1dt} = \frac{n}{m+n} \tag{20}$$

with the approximated model, is shown to be $n/(m+n)$ and independent of the ratio R.

A two-compartment model (model I) with first-order absorption into compartment 1 was used to examine whether the amount of drug calculated with Eq. 19 is an adequate approximation. The drug level in compartment 1 at time t is given by Eq. 21, which is derived in the Appendix.

$$C_1 = \frac{k_aD}{V_1}\left[\frac{(k_{21}+k_{24}-k_a)}{(k_a-\alpha)(k_a-\beta)}e^{-k_at} - \frac{(k_{21}+k_{24}-\alpha)}{(k_a-\alpha)(\alpha-\beta)}e^{-\alpha t} + \frac{(k_{21}+k_{24}-\beta)}{(k_a-\beta)(\alpha-\beta)}e^{-\beta t}\right] \tag{21}$$

Let p denote a ratio of the absorption rate constant k_a to β. Substituting α, $k_{21}+k_{24}$, and k_a from Eq.

$$k_a = p\beta \tag{22}$$

4, 7, and 22 into Eq. 21 and rearranging give:

21) J.G. Wagner and E. Nelson, *J. Pharm. Sci.*, **52**, 610 (1963).
22) G. Segre, *Ann. N.Y. Acad. Sci.*, **96**, 913 (1962).
23) S.A. Kaplan, *J. Pharm. Sci.*, **59**, 309 (1970).

$$C_1 = \frac{pD}{V_1(m+1)(p-n)(p-1)}[(p-1)me^{-n\beta t}+(p-n)e^{-\beta t} + \{(m+n)-p(m+1)\}e^{-p\beta t}] \quad (23)$$

Substitution of Eq. 23 and $V_m = V_1(m+1)$ into Eq. 17 results in:

$$(A_{app})_t = \frac{D(m+n)}{n}\left[1-\left\{\frac{mp(n-1)}{(n-p)(m+n)}e^{-n\beta t}+\frac{n(n-p)-mn(p-1)}{(n-p)(m+n)}e^{-p\beta t}\right\}\right] \quad (24)$$

This means that the amount of drug remaining to be absorbed in the gastrointestinal tract is not represented by the true monoexponential equation $De^{-k_a t}$, but a biexponential equation.[24]

Loo and Riegelman[7] reported that an analog computer was programmed for distribution and elimination of griseofulvin with selected half-lives for the first-order absorption and that the semilogarithmic simulated plots based on the W-N equation resulted in concave descending curves to which it was usually difficult to assign a half-life. When the half-lives for the absorption process was small relative to the disposition half-life of griseofulvin set at 9.5 hr, then the W-N calculation yielded an apparent first-order. The relative error in the estimated half-life, however, varied with each simulated situation. The simulated curves for the absorption half-lives adjusted from 3.8 to 7 hr approached the theoretical half-lives near the end of the absorption process. Using the W-N equation, the computed plot of the percent amount of drug remaining to be absorbed was shown to be $0.45e^{-0.77t}+0.55e^{-0.183t}$ for the theoretical absorption process with a half-life of 3.8 hr.

The above results of the simulation by the computer are conveniently explained in terms of Eq. 24, which is represented by the two exponential terms with the exponents α and k_a. The equation showing the unabsorbed amount of drug consists of a sum or difference of the two exponential terms.[25] Theoretical absorption half-lives can be estimated from the end of the absorption process, only when the equation is a sum of the two exponential terms. It can be shown using Eq. 24 that the use of the single-compartment approximation results in an underestimation of the time, up to which any fraction of the administered drug is absorbed, and an overestimation of the drug amount absorbed up to any time t. The percent amount of drug remaining to be absorbed was calculated to be $0.44e^{-0.688t}+0.56e^{-0.182t}$ from Eq. 24 using the rate constants of the two-compartment model for griseofulvin,[26] and was in agreement with the simulated results of Loo and Riegelman.[7]

Table IV. Time (hr) Required to Absorb Half the Administered Drug as Calculated with Eq. 24

$n \backslash m$	Diphenylhydantoin			Acetylsalicylic acid		
	0.5	2.0	10.0	0.5	2.0	10.0
5	4.9	3.1	1.6	18.1	14.0	7.3
20	5.6	4.6	1.2	19.3	17.9	11.3
100	5.9	4.7	4.7	19.7	19.4	17.8

Assignments made are $\beta=0.076$ hr^{-1} [15] and $ka=0.116$ hr^{-1} (half-life: 6.0 hr)[27] for diphenylhydantoin, and $\beta=0.048$ min^{-1} and $ka=0.035$ min^{-1} (half-life: 19.8 min) based on data of Subject A and plain tablets of Fig. 1 in References 20 and 28, respectively, for acetylsalicylic acid.

24) If $k_a=\alpha$(*i.e.* $p=n$) and $k_a=\beta$(*i.e.* $p=1$), Eq. 24 becomes:

$$(A_{app})_t = \frac{D(m+n)}{n}\left[1-\frac{m+n-mn\beta t(n-1)}{m+n}e^{-n\beta t}\right] \quad \text{and}$$

$$(A_{app})_t = \frac{D(m+n)}{n}\left[1-\frac{1}{m+n}\{me^{-n\beta t}+ne^{-\beta t}\}\right]$$

25) $$\frac{D(m+n)}{n}-(A_{app})_t = D\left[\frac{mp(n-1)}{n(n-p)}e^{-\alpha t}+\frac{(n-p)-m(p-1)}{(n-p)}e^{-k_a t}\right] = Te^{-\alpha t}+Se^{-k_a t}$$

where, $T>0$ and $S>0$ for $\alpha>k_a$ and $k_{21}>k_a$, $T>0$ and $S<0$ for $\alpha>k_a>k_{21}$, and $T<0$ and $S>0$ for $k_a>\alpha$ and $k_a>k_{21}$.

26) $k_{12}=0.29$ hr^{-1}, $k_{21}=0.31$ hr^{-1}, and $k_{13}=0.16$ hr^{-1}.[7]

27) Y. Saitoh, Ph. D. thesis, Faculty of Pharmaceutical Sciences, University of Tokyo, 1971.

The time $t_{1/2}$ required to absorb half the administered drug was calculated with Eq. 24. The results of calculations were presented in Table IV using the data of diphenylhydantoin[15,27] and acetylsalicylic acid.[20,28] As true values for k_a, 0.116 hr^{-1} (half-life=6.0 hr, $p=8.55$) and 0.048 min^{-1} (half-life=19.8 min, $p=0.73$) were used for diphenylhydantoin and acetylsalicylic acid, respectively. The calculations were made by means of a digital computer[29] for several m and n values chosen arbitrarily. The results are shown to be in underestimation for all the combinations of p, m, and n in Table IV. The calculated time $t_{1/2}$ of acetylsalicylic acid ($m=2.71$ and $n=5.42$) was 12.8 min for the true value of 19.8 min, while that of diphenylhydantoin ($m=1.62$ and $n=79.0$) was 5.7 hr for the true value of 6.0 hr. The calculated time $t_{1/2}$ was $0.693/k_a$ for $n=1$ or ∞ and less than $0.693/k_a$ for $1<n<\infty$ at constant m values, while the $t_{1/2}$ decreased with increasing m at constant n values.

Prediction of Blood Levels after Multiple Doses——If N doses are given compartment 1 of the two-compartment model in a first-order fashion with a rate constant of k_a, the blood level C_1^N in the compartment 1 at time t after the last dose is given by Eq. 25.

$$C_1^N = \frac{Dk_a}{V_1}\left[\left\{\frac{1-e^{-Nk_a\tau}}{1-e^{-k_a\tau}}\right\}\left\{\frac{k_{21}+k_{24}-k_a}{(k_a-\alpha)(k_a-\beta)}\right\}e^{-k_at} - \left\{\frac{1-e^{-N\alpha\tau}}{1-e^{-\alpha\tau}}\right\}\left\{\frac{k_{21}+k_{24}-\alpha}{(k_a-\alpha)(\alpha-\beta)}\right\}e^{-\alpha t} + \left\{\frac{1-e^{-N\beta\tau}}{1-e^{-\beta\tau}}\right\}\left\{\frac{k_{21}+k_{24}-\beta}{(k_a-\beta)(\alpha-\beta)}\right\}e^{-\beta t}\right] \quad (25)$$

Equation 25 is derived in the Appendix. Here, N doses of size D are given at uniform time intervals (τ). Since a sum of k_{21} plus k_{24} in model I is equal to $(m+n)\beta/(m+1)$, the drug level in compartment 1 after the n-th dose remains independent of the R value. If the number of doses prior to time zero is assumed to be infinite (*i.e.* equilibrium has been reached with periodic doses), and if Eq. 4, 7, and 22 are used, Eq. 25 can be reduced to the following form:

$$C_1^\infty = \frac{pD}{V_1(m+1)(p-n)(p-1)}\left[\left\{\frac{1}{1-e^{-n\beta\tau}}\right\}m(p-1)e^{-n\beta t} + \left\{\frac{1}{1-e^{-\beta\tau}}\right\}(p-n)e^{-\beta t} + \left\{\frac{1}{1-e^{-p\beta\tau}}\right\}\{m+n-p(m+1)\}e^{-p\beta t}\right] \quad (26)$$

where, C_1^∞ is the steady-state blood level at time t after dosing. On the other hand, if the one-compartment model with the first-order rate constant k_a for absorption and the first-order rate constant β for elimination is used as an approximation, the estimated blood level (C_{app}^∞) at time t after an infinite number of doses was given by the following equation.[30]

$$C_{app}^\infty = \frac{k_aD}{V_m(k_a-\beta)}\left[\left(\frac{1}{1-e^{-\beta\tau}}\right)e^{-\beta t} - \left(\frac{1}{1-e^{-k_a\tau}}\right)e^{-k_at}\right] \quad (27)$$

Equation 27 may be rewritten by substituting $p\beta$ and $V_1(m+1)$ for k_a and V_m, respectively, as follows:

$$C_{app}^\infty = \frac{pD}{V_1(m+1)(p-1)}\left[\left(\frac{1}{1-e^{-\beta\tau}}\right)e^{-\beta t} - \left(\frac{1}{1-e^{-p\beta\tau}}\right)e^{-p\beta t}\right] \quad (28)$$

The ratio of C_1^∞ to C_{app}^∞ at time t after an infinite number of doses is given by Eq. 29. The ratio $(C_1^\infty)_{min}/(C_{app}^\infty)_{min}$ of predicted minimum steady-state levels after an infinite number of doses is formed by replacing

$$\frac{C_1^\infty}{C_{app}^\infty} = 1 + \frac{m(p-1)(1-e^{-\beta\tau})\{e^{-n\beta t}(1-e^{-p\beta\tau}) - e^{-p\beta t}(1-e^{-n\beta\tau})\}}{(p-n)(1-e^{-n\beta\tau})\{e^{-\beta t}(1-e^{-p\beta\tau}) - e^{-p\beta t}(1-e^{-\beta\tau})\}} \quad (29)$$

t by τ in Eq. 29.

$$\frac{(C_1^\infty)_{min}}{(C_{app}^\infty)_{min}} = 1 + \frac{m(p-1)(1-e^{(p-n)\beta\tau})(1-e^{-\beta\tau})}{(p-n)(1-e^{(p-1)\beta\tau})(1-e^{-n\beta\tau})} \quad (30)$$

The average blood level ($\bar{C}_1^\infty$) over a time interval (τ) after an infinite number of doses may be obtained by integration of C_1^∞ over the interval and subsequent division by τ, as shown in the following equation:

28) G. Levy, J.R. Leonards, and J.A. Procknal, *J. Pharm. Sci.*, **54**, 1719 (1965).
29) Hitachi 5020E in The Computer Center of University of Tokyo.
30) R.G. Wiegand, J.D. Buddenhagen, and C.J. Endicott, *J. Pharm. Sci.*, **52**, 268 (1963).

$$\bar{C}_1^{\infty} = \frac{\int_0^{\tau} C_1^{\infty} dt}{\tau} = \frac{D}{\tau V_1 \frac{n(m+1)}{m+n}\beta} \tag{31}$$

This equation is obtained by substituting V_1 and $n(m+1)\beta/(m+n)$ for V_m and β in the following equation:

$$\bar{C}_{app}^{\infty} = \frac{\int_0^{\tau} C_1^{\infty} dt}{\tau} = \frac{D}{\tau V_m \beta} \tag{32}$$

which represents the average blood level over a time interval (τ) after an infinite number of doses based on the one-compartment analysis.[4] If data are derived from Model I and analyzed by the single-compartment approximation, then

$$\frac{\bar{C}_1^{\infty}}{\bar{C}_{app}^{\infty}} = 1 + \frac{m}{n} \tag{33}$$

TABLE V. Ratios $(C_1^{\infty})_{\min}/(C_{app}^{\infty})_{\min}$ and $\bar{C}_1^{\infty}/\bar{C}_{app}^{\infty}$ as Calculated with Eq. 30 and 33

Drug	p	$(C_1^{\infty})_{\min}/(C_{app}^{\infty})_{\min}$	$\bar{C}^{\infty}/\bar{C}_{app}^{\infty}$
Nortriptyline[5]	21.69	1.002	1.001
Griseofulvin[7]	5.66	1.052	1.168
Dicloxacillin[19,32]	1.10	1.000	1.423
Diphenylhydantoin Sodium[27]	1.53	1.012	1.021

Pharmacokinetic parameters of the above drugs (m and n values) are shown in the Table III, and those of griseofulvin ($m=1.59$ and $n=9.49$) were calculated with $k_{12}=0.29$ hr^{-1}, $k_{21}=0.31$ hr^{-1}, $k_{13}=0.16$ hr^{-1}, and $\beta=0.0725$ hr^{-1}.[7]

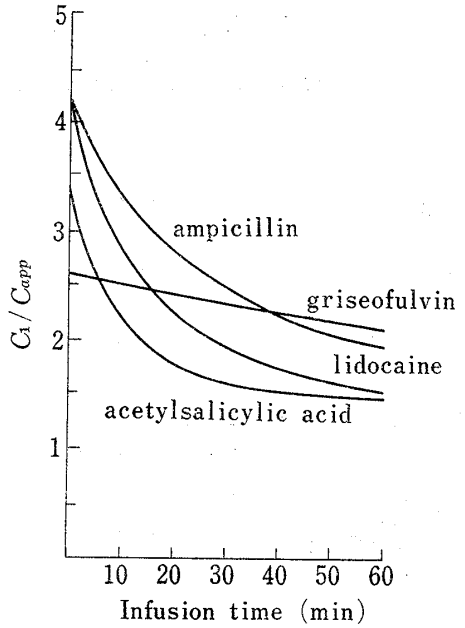

Fig. 2. Ratios C_1/C_{app} *versus* Infusion Time as Calculated with Eq. 34

Assignments made (m and n values) are shown in the Table III, and those of griseofulvin ($m=1.59$ and $n=9.49$) were calculated with $k_{12}=0.29$ hr^{-1}, $k_{21}=0.31$ hr^{-1}, $k_{13}=0.16$ hr^{-1}, and $\beta=0.0725$ hr^{-1}.[7]

Equations 30 and 33 show that the predicted ratios $(C_1^{\infty})_{\min}/(C_{app}^{\infty})_{\min}$ and $\bar{C}_1^{\infty}/\bar{C}_{app}^{\infty}$ will always be more than unity. An error of the calculated asymptotic minimum level $(C_{app}^{\infty})_{\min}$ based on the singlecompartment approximation increases with increasing m and decreasing n and also decreases with increasing p (except $1<p<n$).[31] The ratios were calculated based on the reported data for several drugs and a desirable time interval of administering. The results of calculation are shown in Table V. It can be seen that the minimum blood levels at the steady-state condition predicted by the single-compartment approximation agrees satisfactorily with those calculated from the two-compartment model.

Prediction of Blood Level during Constant-Rate Intravenous Infusion——The blood level in compartment 1 of the two-compartment model (model I) during constant-rate intravenous infusion of a drug are given by the following equation:

$$C_1 = \frac{k_0}{V_1 \frac{\alpha\beta}{k_{21}+k_{24}}}\left[1 + \frac{\beta\{(k_{21}+k_{24})-\alpha\}}{(\alpha-\beta)(k_{21}+k_{24})}e^{-\alpha t} + \frac{\alpha\{\beta-(k_{21}+k_{24})\}}{(\alpha-\beta)(k_{21}+k_{24})}e^{-\beta t}\right] \tag{34}$$

31) If $p=\infty$(*i.e.* intravenous injection), $p=n$ (*i.e.* $k_a=\alpha$), $p=1$ (*i.e.* $k_a=\beta$), and $p=0$, the ratio becomes: $1+m(1-e^{-\beta\tau})e^{-(n-1)\beta\tau}/(1-e^{-n\beta\tau})$, $1+m(1-e^{-\beta\tau})(n-1)\beta\tau e^{-(n-1)\beta\tau}/(1-e^{-n\beta\tau})(1-e^{-(n-1)\beta\tau})$, $1+m(1-e^{-\beta\tau})(1-e^{-(n-1)\beta\tau})/(1-e^{-n\beta\tau})(n-1)\beta\tau$, and $1+m/n$, respectively.

which is derived in the Appendix. Here, k_0 is the constant intravenous infusion rate. On the other hand, the blood level in the body compartment based on the single-compartment approximation is given by Eq. 35.[3c]

$$C_{app} = \frac{k_0}{V_m\beta}(1-e^{-\beta t}) \tag{35}$$

Equation 31 may be rewritten by substitution of Eq. 4 and 7 into Eq. 32 as follows:

$$C_1 = \frac{k_0}{V_1(m+1)n\beta}\{(m+n)-me^{-n\beta t}-ne^{-\beta t}\} \tag{36}$$

Therefore, the ratio of C_1 to C_{app} at time t after the start of infusion is given by Eq. 37.

$$\frac{C_1}{C_{app}} = 1 + \frac{m(1-e^{-n\beta t})}{n(1-e^{-\beta t})} \tag{37}$$

Equation 37 shows that this ratio of the blood levels is always more than unity, reaches to $1+m$ with approaching time zero, and decreases to $1+m/n$ with the increasing t value. Application of Eq. 37 were presented in Fig. 2 using the data of am picillin,[19] lidocaine,[17] acetylsalicylic acid,[20] and griseofulvin.[7] An error of the calculated blood level based on the single-compartment approximation is predominantly dependent on the m value in the early period and decrease rapidly after the start of infusion.

Notation

A, B=Intercepts of two resolvable exponential lines of blood level curve plotted on a semilogarithmic scale at time zero. α, β=Slopes of the individual exponential lines ($\alpha>\beta$). C_1, C_2=Drug levels in compartments 1 and 2 of the two-compartment model. V_1, V_2=Volumes of distribution of compartments 1 and 2. k_{12}, k_{21}=First-order rate constants of drug transfer from compartment 1 to 2 and from compartment 2 to 1. k_{13}, k_{24}=First-order rate constants of drug elimination from compartments 1 and 2. m, n, p=Ratios of A to B, α to β, and k_a to β. Q, R=Ratios of k_{12} to k_{21} and k_{13} to k_{24}. D=Dose. M=Total drug in the body numerically equivalent to a sum of M_1 and M_2. M_1, M_2=Drug amounts in compartments 1 and 2. V_m=Apparent volume of distribution in the body compartment based on the single-compartment approximation numerically equivalent to D/B. $(A)_t$, $(A)_\infty$=Drug amounts absorbed up to time t and infinity due to the method of calculation (Eq. 17) derived from the two-compartment model. $(A_{app})_t$, $(A_{app})_\infty$=Drug amounts absorbed up to time t and infinity due to the W-N equation (Eq. 19) based on the single-compartment approximation. k_a=First-order rate constant of drug absorption (introduction of the dose D of drug into compartment 1 or the body compartment based on the single-compartment approximation at the rate $k_aDe^{-k_at}$). C_1^N, C_1^∞=Drug levels in compartment 1 after N doses and infinite number of doses. N=Number of doses. τ=Dosage interval. C_{app}^∞=Drug level in the body compartment based on the single-compartment approximation after an infinite number of doses. $(C_1^\infty)_{min}$=Asymptotic minimum drug level in compartment 1. $(C_{app}^\infty)_{min}$=Asymptotic minimum drug level in the body based on the single-compartment approximation. k_0=Constant intravenous infusion rate of drug.

Appendix

The appropriate differential equations for model I shown in Chart 1 after instantaneous injection of a drug into compartment 1 are as follows:

$$\frac{dM_1}{dt} = k_{21}M_2 - (k_{13}+k_{12})M_1 \tag{1A}$$

$$\frac{dM_2}{dt} = k_{12}M_1 - (k_{21}+k_{24})M_2 \tag{2A}$$

where, M_1 and M_2 are the amounts of drug in compartments 1 and 2 after administration of dose (D), respectively, and all the the rate constants are as defined in Fig. 1. Applying Laplace transformation to Eq. 1A and 2A for $M_1=D$ and $M_2=0$ at $t=0$, and combining give:

32) J.T. Doluisio, J.C. LaPiana, G.R. Wilkinson, and L.W. Dittert, *Antimicrob. Agents Chemother.*, **1969**, 49.

$$m_1(s) = \frac{D(s+k_{21}+k_{24})}{[s^2+s(k_{12}+k_{21}+k_{13}+k_{24})+k_{13}k_{21}+k_{13}k_{24}+k_{12}k_{24}]} \quad (3A)$$

$$m_2(s) = \frac{Dk_{12}}{[s^2+s(k_{12}+k_{21}+k_{13}+k_{24})+k_{13}k_{21}+k_{13}k_{24}+k_{12}k_{24}]} \quad (4A)$$

The denominator of Eq. 3A may be simplified by Eq. 5 and 6 in the text. Rewriting Eq. 3A in terms of α and β results in:

$$m_1(s) = \frac{D(s+k_{21}+k_{24})}{(s+\alpha)(s+\beta)} \quad (5A)$$

similarly,

$$m_2(s) = \frac{Dk_{12}}{(s+\alpha)(s+\beta)} \quad (6A)$$

The inverse transforms of Eq. 5A and 6A are:

$$M_1 = D\left\{\left(\frac{k_{21}+k_{24}-\alpha}{\beta-\alpha}\right)e^{-\alpha t}+\left(\frac{k_{21}+k_{24}-\beta}{\alpha-\beta}\right)e^{-\beta t}\right\} \quad (7A)$$

$$M_2 = D\left\{\frac{k_{12}}{\beta-\alpha}e^{-\alpha t}+\frac{k_{12}}{\alpha-\beta}e^{-\beta t}\right\} \quad (8A)$$

The total drug (M) in the body is expressed by combining with Eq. 7A and 8A as follows:

$$M = M_1 + M_2 = D\left\{\left(\frac{\beta-k_{13}}{\beta-\alpha}\right)e^{-\alpha t}+\left(\frac{\alpha-k_{13}}{\alpha-\beta}\right)e^{-\beta t}\right\} \quad (9A)$$

which is Eq. 10 in the text. Dividing M_1 by the volume (V_1) of distribution of compartment 1 gives:

$$C_1 = \frac{D}{V_1}\left\{\left(\frac{k_{21}+k_{24}-\alpha}{\beta-\alpha}\right)e^{-\alpha t}+\left(\frac{k_{21}+k_{24}-\beta}{\alpha-\beta}\right)e^{-\beta t}\right\} \quad (10A)$$

Equation 11A is obtained from Eq. 1 and 10A.

$$\frac{D(k_{21}+k_{24}-\alpha)}{V_1(\beta-\alpha)} = A \quad (11A)$$

Equation 12A is derived from Eq. 11A and $V_1=D/B(m+1)$

$$k_{21} + k_{24} = \frac{A\beta+B\alpha}{A+B} \quad (12A)$$

Combining Eq. 12A and 5 yields:

$$k_{12} + k_{13} = \frac{A\alpha+B\beta}{A+B} \quad (13A)$$

Equations 12A and 13A are represented as Eq. 7 and 8 in the text, respectively. If the drug (dose=D) is administered at the first-order rate (rate constant=k_a) and the constant rate (k_0) instead of instantaneous injection, the Laplace transform of the amount of drug in Compartment 1 is described for $M_1=0$ and $M_2=0$ at $t=0$ by Eq. 14A and 15A.[33a)]

$$m_1(s) = c_1(s)V_1 = D\left(\frac{k_a}{s+k_a}\right)\frac{(s+k_{21}+k_{24})}{(s+\alpha)(s+\beta)} \quad (14A)$$

33) A. Rescigno and G. Segre, "Drug and Tracer Kinetics," Blaisdell Publishing Co., Waltham, Mass., 1966, *a*) p. 102; *b*) p. 88.

$$m_1(s) = c_1(s)V_1 = \frac{D}{s}\left\{\frac{s+k_{21}+k_{24}}{(s+\alpha)(s+\beta)}\right\} \tag{15A}$$

The inverse transforms of Eq. 14A and 15A are:

$$C_1 = \frac{k_a D}{V_1}\left\{\frac{(k_{21}+k_{24}-k_a)}{(k_a-\alpha)(k_a-\beta)}e^{-k_a t} - \frac{(k_{21}+k_{24}-\alpha)}{(k_a-\alpha)(\alpha-\beta)}e^{-\alpha t} + \frac{(k_{21}+k_{24}-\beta)}{(k_a-\beta)(\alpha-\beta)}e^{-\beta t}\right\} \tag{16A}$$

$$C_1 = \frac{k_0}{V_1\dfrac{\alpha\beta}{k_{21}+k_{24}}}\left[1+\frac{\beta\{(k_{21}+k_{24})-\alpha\}}{(\alpha-\beta)(k_{21}+k_{24})}e^{-\alpha t} + \frac{\alpha\{\beta-(k_{21}+k_{24})\}}{(\alpha-\beta)(k_{21}+k_{24})}e^{-\beta t}\right] \tag{17A}$$

which are given as Eq. 21 and 34 in the text. The Laplace transform of the drug level in compartment 1 of model I with first-order absorption after N doses of size D administered at uniform time intervals (τ) is given by the following equation.[33b)]

$$c_1{}^N(s) = \frac{D}{V_1}\left\{\frac{k_a(s+k_{21}+k_{24})}{(s+k_a)(s+\alpha)(s+\beta)}\right\}(1+e^{\tau s}+e^{2\tau s} \cdots\cdots + e^{(N-1)\tau s}) \tag{18A}$$

Equation 18A is equal to:

$$c_1{}^N(s) = \left(\frac{1-e^{N\tau s}}{1-e^{\tau s}}\right)\frac{D}{V_1}\left\{\frac{k_a(s+k_{21}+k_{24})}{(s+k_a)(s+\alpha)(s+\beta)}\right\} \tag{19A}$$

The inverse transform of Eq. 19A is:

$$C_1{}^N = \frac{Dk_a}{V_1}\left[\left\{\frac{1-e^{-Nk_a\tau}}{1-e^{-k_a\tau}}\right\}\left\{\frac{k_{21}+k_{24}-k_a}{(k_a-\alpha)(k_a-\beta)}\right\}e^{-k_a t} - \left\{\frac{1-e^{-N\alpha\tau}}{1-e^{-\alpha\tau}}\right\}\left\{\frac{k_{21}+k_{24}-\alpha}{(k_a-\alpha)(\alpha-\beta)}\right\}e^{-\alpha t} + \left\{\frac{1-e^{-N\beta\tau}}{1-e^{-\beta\tau}}\right\}\left\{\frac{k_{21}+k_{24}-\beta}{(k_a-\beta)(\alpha-\beta)}e^{-\beta t}\right\}\right] \tag{20A}$$

which is Eq. 25 in the text.

Equation 2A holds also after a single oral dose into compartment 1. Integrating Eq. 2A between time zero and time t after substitution of C_1V_1 for M_1 gives:

$$M_2 = k_{12}V_1\int_0^t C_1 dt - (k_{21}+k_{24})\int_0^t M_2 dt \tag{21A}$$

The area under the curve of drug amount in compartment 2 between time zero and time infinity is given by Eq. 22A.

$$\int_0^\infty M_2 dt = \frac{k_{12}V_1}{k_{21}+k_{24}}\int_0^\infty C_1 dt \tag{22A}$$

Substitution from 22A and the individual rate constants represented by m, n, β, and Q in Table I into the first half of Eq. 18 in the text gives:

$$(A_b)_\infty = \frac{(k_{13}+k_{12})V_1}{k_{21}+k_{24}}\int_0^\infty C_1 dt = \frac{n(m+1)}{m+n}V_1\beta\int_0^\infty C_1 dt \tag{23A}$$

which is the latter half of Eq. 18 in the text.