Relationship Between Drug Concentration in Plasma or Serum and Amount of Drug in the Body

MILO GIBALDI, RENPEI NAGASHIMA, and GERHARD LEVY

Abstract □ It is shown that the apparent volume of distribution at the steady state $(V_d)_{ss}$ in a two-compartmental open system cannot be used to relate the drug concentration in the plasma to the amount of drug in the body, except at the one point in time when the rate of change of the amount of drug in the peripheral compartment is zero. A new concept of apparent volume of distribution, recently introduced for the pharmacokinetic analysis of a three-compartmental open system, is now applied to the two-compartmental open system. This concept leads to the definition of the constant $(V_d)_\beta$, which relates drug concentration in the plasma to the total amount of drug in the body at all times during the terminal exponential elimination phase (β phase). $(V_d)_\beta$ is shown to be identical to the apparent volume of distribution obtained from the area under the plasma curve equation for a two-compartmental open system. Since the area equation is independent of route of administration, $(V_d)_\beta$ can be obtained readily without having to resort to intravenous injection and very intensive blood sampling.

Keyphrases □ Apparent volume of distribution $(V_d)_\beta$—β phase, drug elimination □ Plasma-body drug concentration relationship—β phase □ Pharmacokinetic model—two compartment □ Plasma curve area—$(V_d)_\beta$ relationship □ Volume of distribution relationship—plasma, body drug concentration

The apparent volume of distribution is an important parameter in the pharmacokinetic characterization of drugs. While the terminology is unfortunate (since it usually has no relationship to a real volume) the apparent volume of distribution should serve ideally as a proportionality constant to relate the plasma or serum concentration of drug to the total amount of drug in the body.

Nagashima *et al.* (1) have recently defined this type of constant. The appropriate equations were developed for a three-compartmental open model in which the plasma itself is the first compartment. In the present report this constant is defined with respect to the more commonly used two-compartmental open model, and its significance and utility are compared to those of the so-called steady-state volume of distribution, $(V_d)_{ss}$.

THEORETICAL

Two-Compartmental Open System—A semilogarithmic plot of plasma concentration *versus* time after intravenous administration of a drug frequently yields a biexponential curve similar to that shown in Fig. 1. The linear portion of the curve has a slope which may be defined as $-\beta/2.303$ and an extrapolated zero-time intercept of B. Resolving the curve into its two components by the method of residuals yields a second linear segment with a slope which may be defined as $-\alpha/2.303$ and a zero-time intercept of A. Accordingly, the concentration of drug in the plasma (C_p) as a function of time is given by the equation

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

Equation 1 may also be derived from the two-compartment system depicted schematically in Fig. 2. As has been pointed out by many others (2–6), the terms A, B, α, and β are actually hybrid constants which may be defined in terms of the pharmacokinetic parameters of the two-compartmental open model.

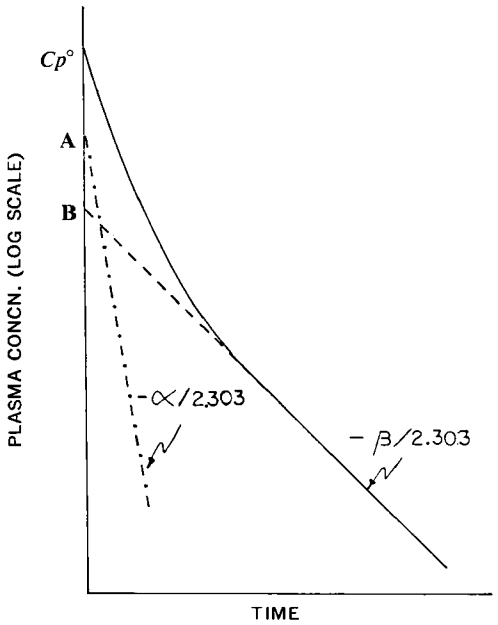

Figure 1—*Typical drug concentration in the plasma* versus *time curve (solid line) after intravenous administration of a drug which follows the kinetics of the two-compartmental open system.*

Equation 1 may be transformed readily (see *Appendix*) to Eq. 2 which consists of fraction of dose rather than drug concentration terms, so that

$$X_c/X^\circ = C_1e^{-\alpha t} + C_2e^{-\beta t} \qquad \text{(Eq. 2)}$$

where X_c/X° is the fraction of the initial dose X°) in the central compartment at time t, $C_1 = A/C_p^\circ$, $C_2 = B/C_p^\circ$, and C_p° is the plasma concentration at $t = 0$, *i.e.*, $C_p^\circ = A + B$.

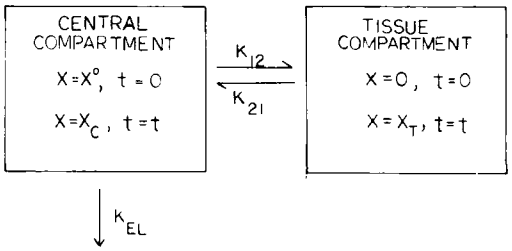

Figure 2—*Schematic representation of the body as a two-compartmental open system. The dose* (X°) *is introduced into the central compartment at* t = 0 *where it distributes instantaneously.* X *is the amount of drug in a given compartment,* k_{12} *is the transfer rate constant from the central compartment to the tissue compartment,* k_{21} *is the transfer rate constant from the tissue compartment to the central compartment, and* k_{el} *is the elimination rate constant of the drug. All rate constants are assumed to be first-order rate constants. Elimination is assumed to occur exclusively from the central compartment.*

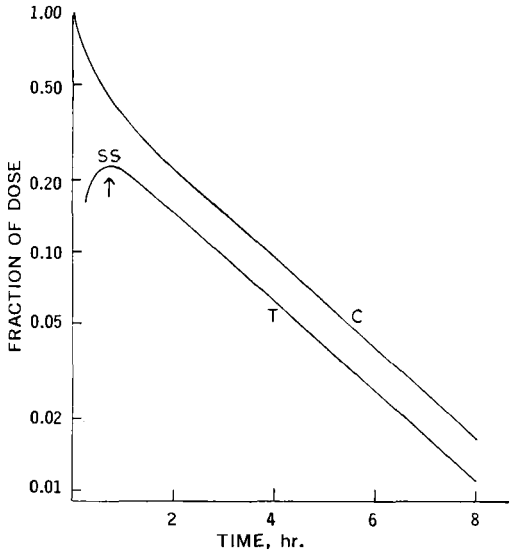

Figure 3—*Semilogarithmic plot of the fraction of a 500-mg. dose of spectinomycin in central (Curve C) and tissue (Curve T) compartments as a function of time after intravenous administration. The arrow (SS) denotes steady state in the tissue compartment* (i.e., d X_T/dt = 0). *Based on data in* Reference 7, *calculated by means of Eqs. 2 and 3.*

The fraction of the initial dose in the tissue compartment (X_T/X°) of a two-compartmental open model as a function of time is described by a similar equation

$$X_T/X^\circ = C_1'e^{-\alpha t} + C_2'e^{-\beta t} \qquad \text{(Eq. 3)}$$

where $C_1' = k_{12}/(\beta - \alpha)$ and $C_2' = k_{12}/(\alpha - \beta)$ as shown in the *Appendix*.

Pharmacokinetic evaluation of plasma level data after intravenous administration of a drug yields A, B, α, and β directly, and k_{12}, k_{21}, and k_{el} by calculation, and permits the determination of C_1, C_2, C_1', and C_2'. It is therefore possible to construct plots of the amount of drug (as a fraction of the initial dose) in the central and tissue compartments as a function of time.

Semilogarithmic plots for spectinomycin, calculated from the data and constants reported by Wagner (7), are shown in Fig. 3. The fraction of dose in the central compartment declines rapidly over the first few hours. After 3 hr. the term $C_1e^{-\alpha t}$ in Eq. 2 is essentially zero and the plot becomes linear. This linear portion of the curve will be referred to as the β phase. The equation for the fraction of the initial dose in the central compartment in the β phase is

$$X_c/X^\circ = C_2e^{-\beta t} \qquad \text{(Eq. 4)}$$

In Fig. 3, the fraction of initial dose in the tissue compartment is seen to increase initially, reach a maximum at about 0.75 hr., and then decline. After 3 hr., the plot becomes linear and may then be described by the equation

$$X_T/X^\circ = C_2'e^{-\beta t} \qquad \text{(Eq. 5)}$$

The linear portion of each plot has a slope of $-\beta/2.303$.

It is also convenient to determine the fraction of the total amount of drug in the body in a given compartment at any time. The fraction in each of the two hypothetical compartments may be defined as

$$f_c = X_c/(X_c + X_T) = X_c/X_B \qquad \text{(Eq. 6)}$$

and

$$f_T = X_T/(X_c + X_T) = X_T/X_B \qquad \text{(Eq. 7)}$$

where f_c and f_T are the fractions of the amount of drug in the body (X_B) in the central and tissue compartments, respectively. Substituting the appropriate terms from Eqs. 2 and 3 into Eqs. 6 and 7 yields

$$f_c = \frac{C_1e^{-\alpha t} + C_2e^{-\beta t}}{(C_1 + C_1')e^{-\alpha t} + (C_2 + C_2')e^{-\beta t}} \qquad \text{(Eq. 8)}$$

Table I—Relationship Between Amount of Spectinomycin in the Body (X_B) After Intravenous Administration and Quantities $[(V_d)_{ss} \cdot C_p]$ and $[(V_d)_\beta \cdot C_p]$

Time, hr.	X_B, mg.[a]	$[(V_d)_{ss} \cdot C_p]$, mg.[b]	$[(V_d)_\beta \cdot C_p]$, mg.[b]
0	500	—	—
0.50	371	397	437
(0.72)[c]	(332)[c]	(332)[c]	365
1.0	292	277	304
	β Phase[d]		
2.0	187	170	187
3.0	120	109	120
4.0	78	70	78

[a] The amount of spectinomycin in the body was calculated by means of the equation, $X_B = X^\circ[(C_1 + C_1')e^{-\alpha t} + (C_2 + C_2')e^{-\beta t}]$, which is a summation and rearrangement of Eqs. 2 and 3 in the text. [b] As reported in *Reference 7*, the mean plasma level data of six subjects may be fitted by the equation, $C_p = 37.8\,e^{-3.21t} + 43.9\,e^{-0.438t}$, and $(V_d)_{ss}$ = 9.27 l. [c] Parenthetical values denote steady-state values. [d] $(V_d)_\beta \cdot C_p = X_B$ only in the β phase.

and

$$f_T = \frac{C_1'e^{-\alpha t} + C_2'e^{-\beta t}}{(C_1 + C_1')e^{-\alpha t} + (C_2 + C_2')e^{-\beta t}} \qquad \text{(Eq. 9)}$$

In the β phase, Eqs. 8 and 9 reduce to Eqs. 10 and 11,

$$f_c = C_2/(C_2 + C_2') \qquad \text{(Eq. 10)}$$

$$f_T = C_2'/(C_2 + C_2') \qquad \text{(Eq. 11)}$$

Volume of Distribution at the Steady State—The volume of distribution, $(V_d)_{ss}$, defined by Riggs (2) and most recently discussed by Wagner *et al.* (5, 7) and Riegelman *et al.* (8), is determined when the rate of change of the amount of drug in the tissue compartment is zero (*i.e.*, $dX_T/dt = 0$), and corresponds to the maximum in the log X_T/X° *versus* time plot shown in Fig. 3. At this point

$$dX_T/dt = k_{12}X_c - k_{21}X_T = 0 \qquad \text{(Eq. 12)}$$

$$k_{12}V_cC_p = k_{21}X_T \qquad \text{(Eq. 13)}$$

$$\frac{k_{12}}{k_{21}} \cdot V_c = \frac{X_T}{C_p} = V_{T/P} \qquad \text{(Eq. 14)}$$

where C_p is the drug concentration in the central compartment[1] and V_c is the apparent volume of distribution of drug in the central compartment, *i.e.*, the amount of drug (X_c) divided by the concentration (C_p), which is equivalent to $X^\circ/(A + B)$.

The term $V_{T/P}$ has been defined by Riggs (2) as the volume of distribution of drug in the tissue compartment with reference to its concentration in the central compartment as deduced from plasma-concentration data. Consequently, the total volume of distribution of drug at steady state as given by Riggs (2), is

$$(V_d)_{ss} = V_c + V_{T/P} \qquad \text{(Eq. 15)}$$

or, from Eq. 14

$$(V_d)_{ss} = \frac{k_{21} + k_{12}}{k_{21}} \cdot V_c \qquad \text{(Eq. 16)}$$

Riegelman *et al.* (8) define the situation where $dX_T/dt = 0$ as a steady-state condition. Riggs (2), on the other hand, defines this single point as distribution equilibrium since at this time only is the rate of drug transfer into the tissue compartment equal to the rate of drug transfer back to the central compartment.

A fundamental problem arises when volume of distribution is calculated at the steady state. It has been suggested above that the volume of distribution (V_d) should represent a proportionality constant relating plasma concentration to the amount of drug in the

[1] From a mathematical point of view it is assumed that the plasma concentration corresponds to the drug concentration in the central compartment of the two-compartmental open model.

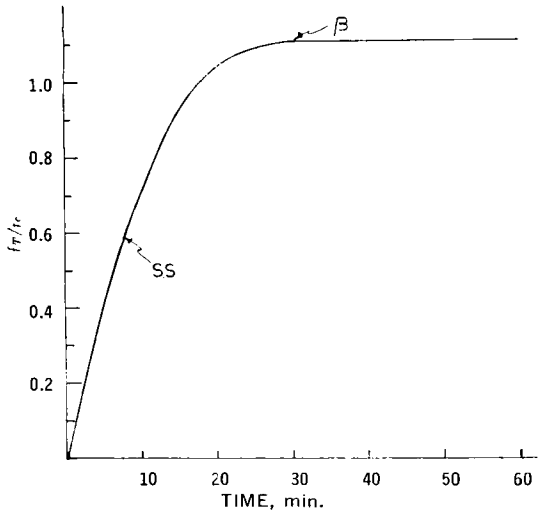

Figure 4—*The ratio of the fraction of aspirin in the tissue compartment to the fraction in the central compartment* (f_T/f_c) versus *time after intravenous administration of a 650-mg. dose. The arrow* (SS) *denotes steady state in the tissue compartment. The arrow* (β) *denotes the attainment of pseudo-distribution equilibrium. Based on the data for Subject 1 in* Reference 8, *calculated by means of Eqs. 8 and 9.*

body, *i.e.*, $V_d \times C_p = X_B$. However, as pointed out in a previous report from these laboratories (1), $(V_d)_{ss}$ multiplied by C_p equals the amount of drug in the body only at one instant, *viz.*, when $dX_T/dt = 0$. This is illustrated in Table I with respect to spectinomycin. It may be seen in the table that $(V_d)_{ss} \times C_p$ corresponds to the amount of drug in the body only at $t = 0.72$ hr. At all other times X_B is either overestimated (before steady state) or underestimated (after steady state).

Volume of Distribution at Pseudo-Distribution Equilibrium $(V_d)_\beta$—Nagashima *et al.* (1) have indicated that a pseudo-distribution equilibrium occurs at some time after drug administration when the terminal segment of a log C_p *versus* time plot becomes linear (β phase). In the two-compartmental open system, the attainment of pseudo-distribution equilibrium is that time when the exponential terms containing α in Eqs. 1–3 approach zero, corresponding to the beginning of the β phase. This concept of pseudo-distribution equilibrium in an open system provides an analogy to the concept of equilibrium in a closed system and fulfills one of the requirements for an equilibrium state in that the fraction of total drug in the body in any given compartment is constant and independent of time. In the two-compartmental open model, it is evident from Eqs. 4 to 7 that at pseudo-distribution equilibrium

$$X_T/X_c = C_2'/C_2 \qquad \text{(Eq. 17)}$$

and

$$f_T/f_c = C_2'/C_2 \qquad \text{(Eq. 18)}$$

Plots of f_T/f_c *versus* time calculated from Eqs. 8 and 9 using data from the literature for aspirin (8), griseofulvin (8), and spectinomycin (7) are presented in Figs. 4–6. These plots show that f_T/f_c increases with time and reaches a maximum value at a time corresponding to the pseudo-distribution equilibrium and thereafter remains constant (Eq. 18). In each figure the first arrow (*SS*) denotes the time at which steady state occurs (*i.e.*, $dX_T/dt = 0$). It is quite clear that at steady state the distribution of the drug is still proceeding (*i.e.*, f_T and f_c have not yet attained a constant value).

It may be seen from Eq. 6 that at pseudo-distribution equilibrium the amount of drug in the body (X_B) is given by the following equation.

$$X_B = \frac{X_c}{f_c} = \frac{V_c \cdot C_p}{f_c} \qquad \text{(Eq. 19)}$$

Defining $(V_d)_\beta$ as a proportionality constant to relate plasma concentration (C_p) to the amount of drug in the body (X_B) at any time after

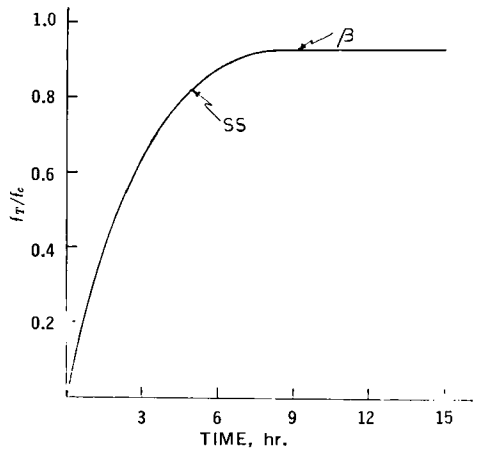

Figure 5—*The ratio of the fraction of griseofulvin in the tissue compartment to the fraction in the central compartment* (f_T/f_c) versus *time after intravenous administration of a 142-mg. dose. Arrows as in Fig. 4. Based on the data for Subject 1 in* Reference 8, *calculated by means of Eqs. 8 and 9.*

attainment of pseudo-distribution equilibrium, then

$$(V_d)_\beta \cdot C_p = X_B \qquad \text{(Eq. 20)}$$

Combining Eqs. 19 and 20, and rearranging, yields

$$(V_d)_\beta = \frac{V_c}{f_c} \qquad \text{(Eq. 21)}$$

where V_c is the volume of the central compartment, *i.e.*, $X^\circ/(A + B)$, and f_c is the constant fraction of drug in the body present in the central compartment after attainment of pseudo-distribution equilibrium, as stated in Eq. 10.[2] $(V_d)_\beta$ serves the important and desired function of a proportionality constant in that once pseudo-distribution equilibrium is attained, $(V_d)_\beta$ multiplied by C_p provides a correct estimate of the amount of drug in the body at all times thereafter. On the other hand, the use of volume of distribution at steady state, $(V_d)_{ss}$, for such calculations will underestimate the amount of drug in the body. A comparison of $(V_d)_{ss}$ and $(V_d)_\beta$ for aspirin, griseofulvin, and spectinomycin shows that $(V_d)_{ss} < (V_d)_\beta$ in each case (Table II).

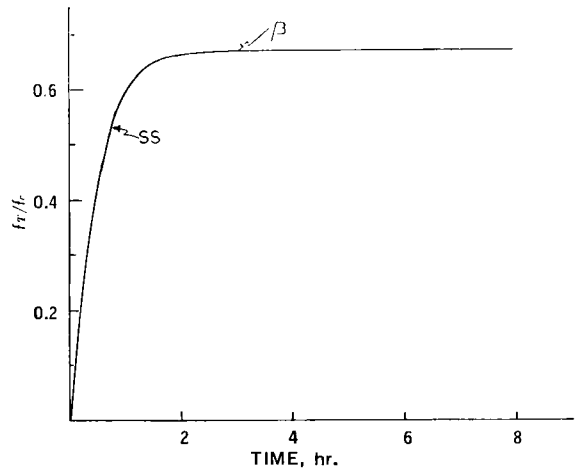

Figure 6—*The ratio of the fraction of spectinomycin in the tissue compartment to the fraction in the central compartment* (f_T/f_c) versus *time after intravenous administration of a 500-mg. dose. Arrows as in Fig. 4. Based on mean data from six subjects reported in* Reference 7, *calculated by means of Eqs. 8 and 9.*

[2] On the basis of a three-compartmental open model, Nagashima *et al.* (1) have shown that $(V_d)_\beta$ is equal to the plasma volume divided by the constant fraction of drug in the plasma compartment at pseudo-distribution equilibrium.

Table II—Comparison of $(V_d)_{ss}$, $(V_d)_\beta$, and $(V_d)_{area}$[a]

Drug	Ref.	Subject	$[(V_d)_{ss}]$[b]	$[(V_d)_\beta]$[c]	$[(V_d)_{area}]$[b]
Aspirin	(8)	1	10.4	13.8	13.8
		2	11.7	13.9	14.1
		3	10.1	14.0	13.9
Griseofulvin	(8)	1	112	120	120
		2	104	118	118
		3	103	122	118
Spectinomycin	(7)	—[d]	9.3	10.2	—[e]

[a] Volumes are expressed in liters. [b] Values reported in the literature. [c] Calculated from literature data by means of Eqs. 10 and 21. [d] Six subjects were studied and the data averaged. [e] Not reported.

Relationship Between $(V_d)_{area}$ and $(V_d)_\beta$—A method of determining a volume of distribution of a drug is by means of the area equation (8, 9)

$$(V_d)_{area} = \frac{\text{dose}}{\beta\,(\text{area})} \qquad \text{(Eq. 22)}$$

where (area) is the area under a plasma level *versus* time curve from $t = 0$ to $t = \infty$. The application of Eq. 22 to the pharmacokinetic analysis of data that are consistent with the two-compartmental open model has been criticized (8).

It is shown in the *Appendix* that in the two-compartmental open model the term (area) may be expressed as follows

$$(\text{area}) = C_p^\circ/k_{e1} \qquad \text{(Eq. 23)}$$

If, therefore, Eq. 22 is applied to data that are describable by the two-compartmental open model, then

$$(V_d)_{area} = \frac{\text{dose} \cdot k_{e1}}{\beta \cdot C_p^\circ} = \frac{V_c \cdot k_{e1}}{\beta} \qquad \text{(Eq. 24)}$$

Nagashima *et al.* (1) have shown that β is equal to the product of the elimination rate constant and the fraction of drug present in the compartment in which elimination occurs. As shown in the *Appendix*, this relationship yields the following equation for the two-compartmental open model

$$\beta = k_{e1} \cdot f_c \qquad \text{(Eq. 25)}$$

Substituting Eq. 25 in Eq. 24, yields[3]

$$(V_d)_{area} = \frac{V_c}{f_c} \qquad \text{(Eq. 26)}$$

This equation is identical to Eq. 21 for $(V_d)_\beta$. Hence, the area equation (Eq. 22) provides a volume of distribution which is absolutely equivalent to the volume of distribution at pseudo-distribution equilibrium, $(V_d)_\beta$, as rigorously defined in the two-compartmental open model. This is verified by the experimental data shown in Table II which shows also the discrepancy between $(V_d)_{ss}$ and $(V_d)_{area}$.

Since (area) is independent of route of administration (see *Appendix*) there is great practical significance to the equivalence of $(V_d)_{area}$ and $(V_d)_\beta$ in that the apparent volume of distribution, $(V_d)_\beta$, may be calculated from plasma data regardless of the route of drug administration. The ease of obtaining experimental data for the determination of $(V_d)_\beta$ is in marked contrast to the difficulty in the determination of the volume of distribution at steady state, $(V_d)_{ss}$. An accurate assessment of $(V_d)_{ss}$ requires intravenous administration of a drug, which in many cases because of solubility limitations is not a practical possibility. The estimation of $(V_d)_\beta$ by means of the area equation (Eq. 22) also requires much less intensive blood sampling than the estimation of $(V_d)_{ss}$. The latter requires the resolution of the plasma level *versus* time curve, after intravenous administration, into its exponential components. Hence, very frequent blood sampling is needed in the period immediately after administration of the drug in order to assess accurately the relatively fast α phase. This intensive sampling protocol presents problems which may be resolved in many instances in a research laboratory but which may be insurmountable in the clinical situation. This difficulty is now obviated by the pharmacokinetic approach outlined here.

[3] Equation 26 corresponds to Eq. 11*a* in *Reference 8*.

APPENDIX

Two-Compartmental Open-System Model—The appropriate differential equations to describe the model shown in Fig. 2 are as follows:

$$dX_c/dt = -(k_{e1} + k_{12})X_c + k_{21}X_T \qquad \text{(Eq. 1}a\text{)}$$

and

$$dX_T/dt = k_{12}X_c - k_{21}X_T \qquad \text{(Eq. 2}a\text{)}$$

where X_c and X_T are the amounts of drug in the central and tissue compartments, respectively, after intravenous administration of a dose, X°, into the central compartment at $t = 0$, and the various rate constants are as defined in Fig. 2. Integration and further development of these equations yields

$$X_c/X^\circ = C_1e^{-\alpha t} + C_2e^{-\beta t} \qquad \text{(Eq. 3}a\text{)}$$

and

$$X_T/X^\circ = C_1'e^{-\alpha t} + C_2'e^{-\beta t} \qquad \text{(Eq. 4}a\text{)}$$

where X_c/X° and X_T/X° are the fractions of the initial dose, X°, in the central and tissue compartments, respectively, at time t after administration,

$$C_1 = (k_{21} - \alpha)/(\beta - \alpha) \qquad \text{(Eq. 5}a\text{)}$$

$$C_2 = (k_{21} - \beta)/(\alpha - \beta) \qquad \text{(Eq. 6}a\text{)}$$

$$C_1' = k_{12}/(\beta - \alpha) \qquad \text{(Eq. 7}a\text{)}$$

$$C_2' = k_{12}/(\alpha - \beta) \qquad \text{(Eq. 8}a\text{)}$$

The terms α and β are defined in the course of integration and solution of Eqs. 1*a* and 2*a* as,

$$\alpha\beta = k_{21} \cdot k_{e1} \qquad \text{(Eq. 9}a\text{)}$$

$$\alpha + \beta = k_{e1} + k_{12} + k_{21} \qquad \text{(Eq. 10}a\text{)}$$

Since the amount of drug in the central compartment at any time is the product of concentration in the central compartment (C_p) and the volume of the central compartment (V_c), then Eq. 3*a* is equivalent to Eq. 1 in the text, where $A = C_p^\circ \cdot C_1$ and $B = C_p^\circ \cdot C_2$.

Definition of Area on the Basis of the Two-Compartmental Open Model—The total area under a plasma concentration *versus* time plot is defined in terms of the two-compartmental model in the following manner:

$$(\text{area}) = \int_{t=0}^{t=\infty} C_p dt = \left[\int_0^\infty Ae^{-\alpha t} + \int_0^\infty Be^{-\beta t}\right] dt \qquad \text{(Eq. 11}a\text{)}$$

Integration of Eq. 11*a* from $t = 0$ to $t = \infty$ yields

$$(\text{area}) = \frac{A}{\alpha} + \frac{B}{\beta} \qquad \text{(Eq. 12}a\text{)}$$

Substituting for A and B in terms of C_p°, α, β, and k_{21} yields

$$(\text{area}) = \frac{C_p^\circ k_{21}}{\alpha\beta} \qquad \text{(Eq. 13}a\text{)}$$

However, from Eq. 9*a* it is evident that $k_{21}/\alpha\beta = 1/k_{e1}$. Hence,

$$(\text{area}) = C_p^\circ/k_{e1} \qquad \text{(Eq. 14}a\text{)}$$

Relationship of β and k_{e1}—During the β phase of drug elimination the plasma concentration may be expressed as

$$C_p = Be^{-\beta t} \qquad \text{(Eq. 15}a\text{)}$$

Since at any time $C_p \times V_c = X_c$, it may be written that

$$X_c = V_cBe^{-\beta t} \qquad \text{(Eq. 16}a\text{)}$$

From Eq. 6 in the text it is evident that at any time $X_B = X_c/f_c$; hence,

$$X_B = \frac{V_cB}{f_c}e^{-\beta t} \qquad \text{(Eq. 17}a\text{)}$$

Since as stated in Eq. 10 in the text, f_c is a constant during the β phase then

$$dX_B/dt = -\beta X_B \qquad \text{(Eq. 18}a\text{)}$$

The two-compartmental open model also indicates that the rate of loss of drug from the body (dX_B/dt) may be expressed as

$$dX_B/dt = -k_{e1}X_c \qquad \text{(Eq. 19}a\text{)}$$

or

$$dX_B/dt = -k_{e1}f_cX_B \qquad \text{(Eq. 20}a\text{)}$$

Comparing Eqs. 18*a* and 20*a*, one concludes that

$$\beta = k_{e1} \cdot f_c \qquad \text{(Eq. 21}a\text{)}$$

(Area) as a Function of Route of Administration—The total area under a plasma concentration of drug *versus* time curve upon intravenous administration is given by Eq. 14*a* for the two-compartmental open system. If a drug is given by a route other than the intravenous one, the amount of drug absorbed to time t, $(A)_t$, is given by the material balance equation

$$(A)_t = C_pV_c + X_T + \int_0^t k_{e1} \cdot V_c \cdot C_p\,dt \qquad \text{(Eq. 22}a\text{)}$$

where C_pV_c is the amount of drug in the central compartment, X_T is the amount of drug in the tissue, and the integral term is the amount of drug eliminated. At $t = \infty$ Eq. 22*a* reduces to

$$(A)_\infty = k_{e1}V_c \int_0^\infty C_p dt \qquad \text{(Eq. 23}a\text{)}$$

or, assuming absorption of a dose X° is complete,

$$X^\circ = k_{e1}V_c(\text{area}) \qquad \text{(Eq. 24}a\text{)}$$

Rearranging and substituting for X°/V_c, yields

$$(\text{area}) = C_p^\circ/k_{e1} \qquad \text{(Eq. 25}a\text{)}$$

which is identical to Eq. 14*a*. Hence, assuming the body to behave as a two-compartmental open system, the total area under the plasma level of drug *versus* time curve is independent of route of administration.

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Anthraquinone Drugs I: Thin-Layer Chromatographic Identification of Aloes, Cascara, Senna, and Certain Synthetic Laxatives in Pharmaceutical Dosage Forms

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Abstract □ A new procedure for the identification of aloes, cascara, and senna is presented. The constituent glycosides are converted to aglycones and separated into acidic and nonacidic fractions. Identification is achieved by thin-layer chromatography. The method is also applicable to the mixture of these drugs and various pharmaceutical dosage forms containing danthron, phenolphthalein, and dioctyl sodium sulfosuccinate.

Keyphrases □ Anthraquinone dosage forms—analysis □ Glucosides, anthraquinone—aglycone conversion □ TLC—identification □ UV light—TLC spot visualization

Various color reactions and microscopic methods of identification of aloes, cascara, and senna prescribed by the official compendia (*e.g.*, the British Pharmacopoeia, the NF, and the USP) are often nonspecific, unreliable, and time-consuming. Paper chromatography has been applied with limited success for the identification of certain constituents of these drugs (1). With the advent of thin-layer chromatography (TLC), various attempts have been made at characterizing anthraquinone drugs employing silica gel-coated plates (2). Hoerhammer *et al.* have made a systematic attempt at their characterization on the basis of glycosides, resins, *etc.* (3), but the chromatograms exhibit a large number of spots whose resolution is markedly affected by slight variations in chromatographic conditions. In pharmaceutical preparations containing mixtures of these drugs along