Effect of Mode of Administration on Drug Distribution in a Two-Compartment Open System

MILO GIBALDI

Abstract □ The pharmacokinetics of drug distribution are evaluated for two types of drug administration, *viz.*, constant-rate intravenous infusion and instantaneous intravenous injection. Both modes of administration eventually result in a constant tissue compartment–central compartment distribution ratio of drug. However, the distribution ratio at pseudo-distribution equilibrium (after instantaneous intravenous injection) and at infusion equilibrium (some time after the start of infusion) are not equivalent. The consequence of this finding is that at equivalent plasma concentrations more drug will be in the tissue compartment during pseudo-distribution equilibrium than during infusion equilibrium although the total amount of drug which will enter the tissue compartment is independent of mode of administration. The present findings may have important implications for drug-distribution studies and with respect to the relative effectiveness of continuous and intermittent drug administration.

Keyphrases □ Drug distribution—instantaneous *versus* constant rate i.v. administration □ Model system—two compartment, open □ Pharmacokinetics—instantaneous, constant-rate drug administration □ Distribution ratios—pseudo-distribution, infusion equilibria

There is some controversy as to the most efficacious mode of administration of certain drugs. A recent commentary (1) on antibiotic administration, for example, records the debate over intravenous infusion *versus* intermittent intravenous therapy with penicillins. In the area of antineoplastic drugs, Liguori *et al.* (2) have suggested that drug uptake by a tumor may be influenced by the mode of administration. These workers have reported that administration of amethopterin by continuous intravenous drip was more effective than administration of the same amount of drug in a single daily dose. Hence, the delivery system by which a drug reaches a site of action or target organ may be as important a consideration as the size of a dose.

In the present report the pharmacokinetics of drug distribution in the two-compartment open system are analyzed for two types of drug administration, *viz.*, constant-rate intravenous infusion and instantaneous intravenous injection. In addition, the concept of volume of distribution as a proportionality constant relating amount of drug in the body and plasma concentration, which was developed in earlier reports (3, 4) is defined with respect to the constant-rate intravenous infusion model. The apparent volume of distribution obtained from intravenous infusion data is compared to the previously defined parameters $(V_d)_\beta$ and $(V_d)_{ss}$.

THEORETICAL

Instantaneous Intravenous Injection in Two-Compartment Open Model—A semilogarithmic plot of plasma concentration *versus* time after intravenous administration of a drug frequently yields a biexponential curve. 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 open model depicted schematically in Fig. 1 and may be transformed readily (see *Appendix*) to Eq. 2 which is expressed in terms of amount of drug in the central compartment (X_c), so that

$$X_c = X^0(C_1 e^{-\alpha t} + C_2 e^{-\beta t}) \qquad \text{(Eq. 2)}$$

where X^0 is the dose, $C_1 = A/C_p^0$, $C_2 = B/C_p^0$, and C_p^0 is the plasma concentration at $t = 0$, *i.e.*, $C_p^0 = A + B$.

The amount of drug in the tissue compartment (X_T) as a function of time is described by a similar equation

$$X_T = X^0(C_1' e^{-\alpha t} + C_2' e^{-\beta t}) \qquad \text{(Eq. 3)}$$

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

At some time after administration the terms $C_1 e^{-\alpha t}$ and $C_1' e^{-\alpha t}$ in Eqs. 2 and 3, respectively, are essentially zero. This situation gives rise to the β-phase (pseudo-distribution equilibrium), the significance of which has been considered in a previous report from these laboratories (4). In the β-phase the distribution ratio of the amount of drug in the tissue compartment to that in the central compartment is constant and is given by

$$(X_T/X_c)_\beta = C_2'/C_2 \qquad \text{(Eq. 4)}$$

Substituting for C_2' and C_2 (as defined in the *Appendix*) in Eq. 4 yields

$$(X_T/X_c)_\beta = k_{12}/(k_{21} - \beta) \qquad \text{(Eq. 5)}$$

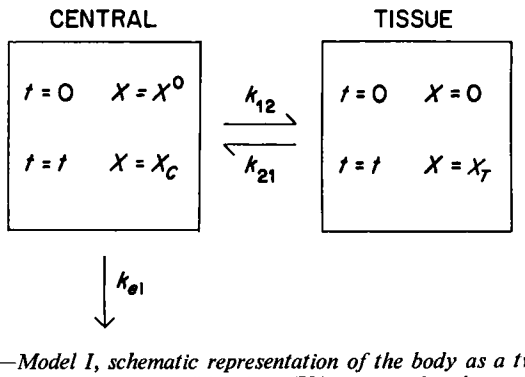

Figure 1—*Model I, schematic representation of the body as a two-compartment open system. The dose* (X^0) *is introduced into the central compartment at* t = 0 *where it distributes instantaneously.* X *is the amount of drug in a given compartment,* k_{12} *is the transfer rate constant from the central 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. Elimination is assumed to occur exclusively from the central compartment.*

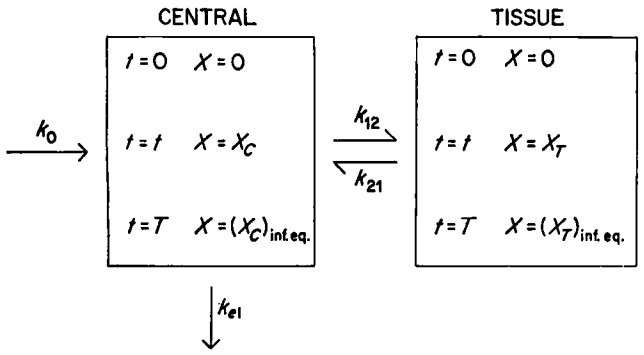

Figure 2—*Model II, intravenous infusion at a constant rate* (k_0), *representing the body as a two-compartment open system. Notation as in Fig. 1.*

Constant-Rate Intravenous Infusion in Two-Compartment Open Model—The model is shown in Fig. 2. The appropriate differential equations arising from this model are

$$dX_c/dt = k_0 - (k_{el} + k_{12})\,X_c + k_{21}\,X_T \qquad \text{(Eq. 6)}$$

and

$$dX_T/dt = k_{12}X_c - k_{21}X_T \qquad \text{(Eq. 7)}$$

The solution for X_c has been given by Gaudino (5). Rewritten in the nomenclature of Gibaldi *et al.* (4), X_c is given by the equation

$$X_c = k_0\left(\frac{k_{21}}{\alpha\beta} - \frac{C_1}{\alpha}\,e^{-\alpha t} - \frac{C_2}{\beta}\,e^{-\beta t}\right) \qquad \text{(Eq. 8)}$$

One may solve for X_T in a similar manner such that

$$X_T = k_0\left(\frac{k_{12}}{\alpha\beta} - \frac{C_1'}{\alpha}\,e^{-\alpha t} - \frac{C_2'}{\beta}\,e^{-\beta t}\right) \qquad \text{(Eq. 9)}$$

Equations 8 and 9 indicate that during infusion drug levels in both the central and tissue compartments increase until they approach asymptotic values which are given by

$$(X_c)_{\text{inf. eq.}} = k_0\,k_{21}/\alpha\beta \qquad \text{(Eq. 10)}$$

and

$$(X_T)_{\text{inf. eq.}} = k_0\,k_{12}/\alpha\beta \qquad \text{(Eq. 11)}$$

Aspirin levels calculated to be in the central and tissue compartments during intravenous infusion at a constant rate of 10 mg./min. are shown in Fig. 3.

The constant levels of drug in the central and tissue compartments occurring some time after initiation of a constant-rate intravenous infusion provide a strong analogy to the concept of equilibrium in a closed system and shall be referred to as a state of infusion equilibrium. The concept of infusion equilibrium in an open

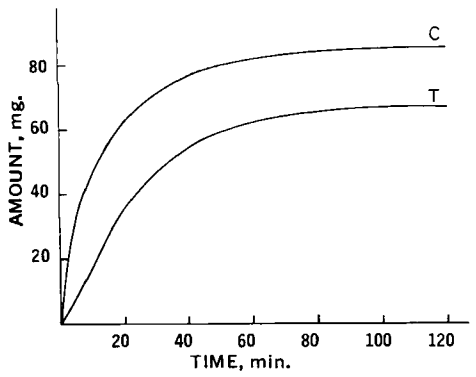

Figure 3—*Aspirin levels in the central* (C) *and tissue* (T) *compartments during intravenous infusion at a constant rate of 10 mg./min. Based on the data for Subject 3 in* Reference 8, *calculated by means of Eqs. 8 and 9.*

Table I—Comparison of Distribution Ratios (X_T/X_c) at Pseudo-Distribution Equilibrium and Infusion Equilibrium

Drug	Ref.	Subject	$(X_T/X_c)^a_{\text{inf. eq.}}$	$(X_T/X_c)_\beta{}^b$
Aspirin	(8)	1	0.62	1.13
		2	0.67	0.99
		3	0.79	1.47
Griseofulvin	(8)	1	0.81	0.94
		2	1.17	1.69
		3	0.72	1.06
Salicylic acid	(8)	1	0.78	0.82
		2	0.64	0.65
		3	0.61	0.62
Spectinomycin	(9)	—[c]	0.52	0.83

[a] Calculated from literature data by means of Eq. 12. [b] Calculated from literature data by means of Eq. 5. [c] Six subjects were studied and the data averaged.

system essentially fulfills the usual requirements for an equilibrium state in that the fraction of total drug in the body in any given compartment is constant and the rate of change of amount of drug in each compartment is equal to zero. At infusion equilibrium the distribution ratio of the amount of drug in the tissue compartment to that in the central compartment is given from Eqs. 10 and 11 by

$$(X_T/X_c)_{\text{inf. eq}} = k_{12}/k_{21} \qquad \text{(Eq. 12)}$$

Comparison of Pseudo-Distribution Equilibrium (β-Phase) and Infusion Equilibrium—Thus far it has been demonstrated in the two-compartment open model that a constant-distribution ratio exists under two different conditions, *viz.*, during the β-phase after instantaneous intravenous injection and some time after initiation of continuous constant-rate intravenous infusion. It is most important to note that the distribution ratios at pseudo-distribution equilibrium and at infusion equilibrium are not equivalent. Comparison of Eq. 5 with Eq. 12 reveals that

$$(X_T/X_c)_\beta > (X_T/X_c)_{\text{inf. eq.}} \qquad \text{(Eq. 13)}$$

The difference between the distribution ratio at pseudo-distribution equilibrium and at infusion equilibrium depends on the relative magnitudes of k_{21} and β and will vary from one drug to another. Values of the distribution ratios of various drugs, calculated from literature data, are shown in Table I. In each case a larger tissue compartment : central compartment distribution ratio is observed at pseudo-distribution equilibrium than at infusion equilibrium. The differences range from an average of 1.7-fold for aspirin to 1.03-fold for salicylic acid. Preliminary experiments in this laboratory suggest a two to threefold difference in the distribution ratio of penicillin G at pseudo-distribution equilibrium compared to infusion equilibrium (6).

The therapeutic implications of the present findings are most interesting and provide an insight to potential differences in efficacy of a drug as a function of mode of administration. If pharmacologic effect is related to the amount of drug in a target organ which exists within the tissue compartment, then *at equal plasma concentrations* a greater response may be elicited in a state of pseudo-distribution equilibrium than in a state of infusion equilibrium since a larger amount of drug will be in the target organ. This is readily shown by considering Eqs. 5 and 12. Assuming a given amount of drug in the central compartment at pseudo-distribution equilibrium, $(X_c)_\beta{}^*$, then the amount of drug in the tissue compartment is given by

$$(X_T)_\beta{}^* = (X_c)_\beta{}^*\,k_{12}/(k_{21} - \beta) \qquad \text{(Eq. 14)}$$

or

$$(X_T)_\beta{}^* = (C_p)_\beta{}^*\,V_c k_{12}/(k_{21} - \beta) \qquad \text{(Eq. 15)}$$

where V_c is the apparent volume of distribution of drug in the central compartment, *i.e.*, $X^0/(A + B)$, and C_p is the drug concentration in the plasma.[1] At a plasma concentration, $(C_p)^*_{\text{inf. eq.}}$, during

[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-compartment open model.

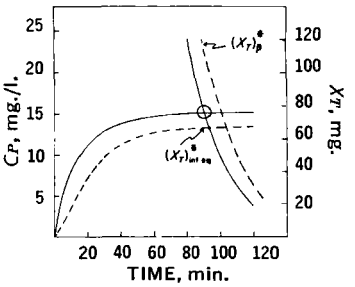

Figure 4—*Plasma concentrations (solid lines) and tissue levels (dashed lines) of aspirin during continuous constant-rate (10 mg./min.) intravenous infusion, and some time after a single dose of drug such that elimination is in the β-phase. The circle denotes the intersection of plasma concentrations of drug resulting from each mode of administration. The arrows denote tissue levels at equivalent plasma concentrations of drug. See text for further discussion. Based on the data for Subject 3 in* Reference 8, *calculated by means of Eqs. 2, 3, 8, and 9.*

infusion equilibrium, equivalent to $(C_p)_\beta^*$, it follows from Eq. 12 that

$$(X_T)^*_{inf.\ eq.} = (C_p)^*_{inf.\ eq.} V_c k_{12}/k_{21} \qquad \text{(Eq. 16)}$$

Hence, at equal plasma concentrations

$$\frac{(X_T)_\beta^*}{(X_T)^*_{inf.\ eq.}} = \frac{k_{21}}{k_{21} - \beta} > 1 \qquad \text{(Eq. 17)}$$

Figure 4 is a plot of plasma concentration and tissue level of aspirin during continuous constant-rate intravenous infusion and after an instantaneous intravenous dose. At equal plasma concentrations, the amount of drug in the tissue after instantaneous injection therapy is almost twice that found in the tissue during infusion. Assuming that the target organ resides within the tissue compartment, one concludes that significantly different intensities of pharmacologic response may be elicited at equal plasma concentrations depending on the mode of administration.

Drug Distribution and Elimination After Cessation of Constant-Rate Intravenous Infusion—Figure 5 shows a model describing drug distribution in a two-compartment open system after cessation of a constant-rate intravenous infusion which was administered over a sufficiently long period of time to achieve constant levels of drug in each compartment. Solution of the equations resulting from Model III (Fig. 5) is similar to that used in evaluating Model I (Fig. 1). The only difference from the previously discussed approach is a consideration of the initial conditions in Model III, *viz.*, at $t = 0$, $X_c = (X_c)_{inf.\ eq.}$, and $X_T = (X_T)_{inf.\ eq.}$. Integration and further development of the appropriate equations yields

$$X_c = (X_c)_{inf.\ eq.}\left(\frac{(\beta - k_{el})}{\beta - \alpha}e^{-\alpha t} - \frac{(\alpha - k_{el})}{\beta - \alpha}e^{-\beta t}\right) \qquad \text{(Eq. 18)}$$

and

$$X_T = (X_T)_{inf.\ eq.}\left(\frac{\beta e^{-\alpha t}}{\beta - \alpha} - \frac{\alpha e^{-\beta t}}{\beta - \alpha}\right) \qquad \text{(Eq. 19)}$$

where X_c and X_T represent the amounts of drug in the central and tissue compartments, respectively, in the postinfusion period. Equation 18 is analogous to Eq. 17 of Gaudino (5).

Figure 6 shows semilogarithmic plots of the loss of aspirin from the central and tissue compartments after discontinuing an intravenous infusion administered at a constant rate of 10 mg./min. The duration of infusion was sufficiently long to attain infusion equilibrium. The plots show clearly that when infusion is stopped, a redistribution occurs between the central and tissue compartments. The initial rate of loss of drug from the central compartment exceeds that from the tissue compartment and after a time the amount of drug in the tissue compartment is actually greater than the amount of drug in the central compartment. After 25 min. postinfusion both plots become linear and the compartments are in a state of pseudo-distribution equilibrium.

Apparent Volume of Distribution at Infusion Equilibrium—One concept of apparent volume of distribution is that it should serve

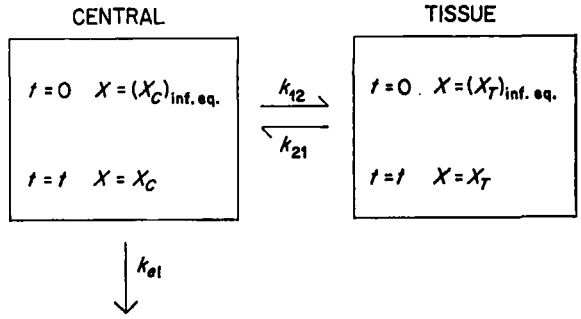

Figure 5—*Model III, drug distribution and elimination in a two-compartment open model after cessation of a constant-rate intravenous infusion which was administered over a sufficiently long period of time to achieve constant levels of drug,* viz. $(X_c)_{inf.\ eq.}$ *and* $(X_T)_{inf.\ eq.}$, *in each compartment. Notation as in Fig. 1.*

as a proportionality constant to relate the plasma or serum concentration of drug to the total amount of drug in the body. The appropriate equations to define this type of constant at pseudo-distribution equilibrium have been developed for a three-compartment open model (3) and a two-compartment open model (4). From the preceding discussion it is apparent that a proportionality constant between plasma concentration and total amount of drug at infusion equilibrium cannot be identical to $(V_d)_\beta$, the proportionality constant at pseudo-distribution equilibrium, since $(X_T/X_c)_\beta \neq (X_T/X_c)_{inf.\ eq.}$.

The total amount of drug in the body (X_B), at any time, is the sum of the amounts in the individual compartments, *i.e.*, $X_c + X_T$. At infusion equilibrium, it follows from Eqs. 10 and 11 that

$$(X_B)_{inf.\ eq.} = k_0(k_{21} + k_{12})/\alpha\beta \qquad \text{(Eq. 20)}$$

Plasma concentration of drug at infusion equilibrium may be expressed, from Eq. 10, as

$$(C_p)_{inf.\ eq.} = k_0 k_{21}/V_c(\alpha\beta) \qquad \text{(Eq. 21)}$$

Combining and rearranging Eqs. 20 and 21 yields

$$(V_d)_{inf.\ eq.} = (X_B)_{inf.\ eq.}/(C_p)_{inf.\ eq.} = (k_{21} + k_{12})V_c/k_{21} \qquad \text{(Eq. 22)}$$

where $(V_d)_{inf.\ eq.}$ is the apparent volume of distribution at infusion equilibrium.

The definition of $(V_d)_{inf.\ eq.}$ expressed in Eq. 22 is identical to the volume of distribution proposed by Riggs (7), *viz.*, $(V_d)_{ss}$. Unfortunately, the use of an incorrect differential equation (Eq. 14*a* in *Reference 8*) has led to the wrong conclusion in the literature that $(V_d)_{ss}$ is not equivalent to $(V_d)_{inf.\ eq.}$ (8). The correct derivation of this relationship is included in the *Appendix*.

In view of the equivalency of $(V_d)_{inf.\ eq.}$ and $(V_d)_{ss}$, it is possible to estimate $(V_d)_{ss}$ without the requirement of obtaining the parame-

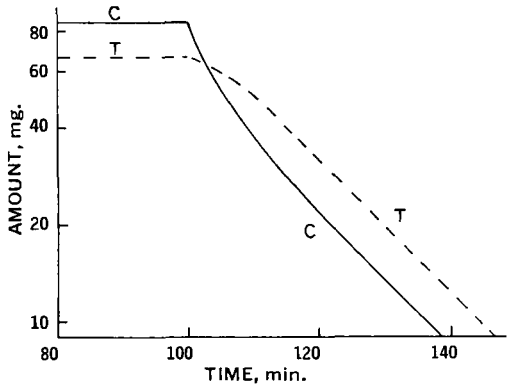

Figure 6—*Semilogarithmic plots of aspirin levels in the central* (C) *and tissue* (T) *compartments during and after intravenous infusion at a constant rate of 10 mg./min. Based on the data for Subject 3 in* Reference 8, *calculated by means of Eqs. 8, 9, 18, and 19.*

ters of Model I or the need for an instantaneous intravenous injection and subsequent intensive blood sampling to assess α.

It has been stated by Riegelman *et al.* (8), and it is shown in the *Appendix*, that the amount of drug in the body at infusion equilibrium, in a two-compartment open model, can be calculated from the ratio of the area under the plasma level curve from $t = 0$ to the end of the infusion ($t = T$), and the total area under the plasma concentration of drug *versus* time curve, so that

$$(X_B)_{\text{inf. eq.}} = \text{dose}\left(1 - \frac{\int_0^T C_p dt}{\int_0^\infty C_p dt}\right) \qquad \text{(Eq. 23)}$$

where dose $= k_0 T$. Hence, characterization of the complete plasma concentration of drug *versus* time curve during and after constant rate intravenous infusion of sufficient duration permits the estimation of $(C_p)_{\text{inf. eq.}}$ and the calculation of $(X_B)_{\text{inf. eq.}}$ and $(V_d)_{\text{inf. eq.}}$ or $(V_d)_{ss}$ according to Eqs. 22 and 23.

Area Under the Tissue Level Versus Time Curve as a Function of Mode of Administration—It has been shown in a preceding section that significant differences in tissue level may exist at a given plasma concentration of drug depending on the mode of administration. The total amount of drug reaching the tissue compartment may also be of therapeutic interest when the target organ for drug response resides in this compartment. An indication of the amount of drug reaching the tissue compartment from a given dose may be obtained by considering the total area under the tissue level of drug *versus* time curve.

A general equation for the area under the tissue level of drug *versus* time curve after administration of an instantaneous intravenous dose of X^0 is obtained by integrating Eq. 3, from $t = 0$ to $t = \infty$, so that upon simplification

$$\left(\int_0^\infty X_T dt\right)_{\text{instant}} = X^0 k_{12}/\alpha\beta \qquad \text{(Eq. 24)}$$

The amount of drug in the tissue compartment at any time during a constant-rate intravenous infusion is given by Eq. 9 and the amount of drug in the tissue compartment at any time during the postinfusion period is given by Eq. 19. Integrating Eq. 9 from $t = 0$ to $t = T$ where T is the total infusion time and $k_0 T = X^0$ yields

$$\int_0^T X_T dt = \frac{k_0 k_{12}}{\alpha\beta}\left[T - \frac{(\alpha + \beta)}{\alpha\beta}\right] \qquad \text{(Eq. 25)}$$

when T is sufficiently large to attain infusion equilibrium.

Integrating Eq. 19 from $t' = 0$ to $t' = \infty$, where t' is the time from cessation of infusion, yields

$$\int_{t'=0}^{t'=\infty} X_T dt = \frac{k_0 k_{12}}{\alpha\beta}\left(\frac{\alpha + \beta}{\alpha\beta}\right) \qquad \text{(Eq. 26)}$$

Combining Eqs. 25 and 26 yields the total area under the tissue level of drug *versus* time curve during and after constant-rate intravenous infusion, so that

$$\left(\int_0^\infty X_T dt\right)_{\text{inf.}} = k_0 T k_{12}/\alpha\beta = X^0 k_{12}/\alpha\beta \qquad \text{(Eq. 27)}$$

Comparing Eqs. 24 and 27, it is clear that

$$\left(\int_0^\infty X_T dt\right)_{\text{instant}} \Big/ \left(\int_0^\infty X_T dt\right)_{\text{inf.}} = 1 \qquad \text{(Eq. 28)}$$

The total amount of drug reaching the tissue compartment of the two-compartment open model is, therefore, independent of mode of administration. Since $\alpha\beta = k_{21}\, k_{e_1}$ (as noted in the *Appendix*), Eqs. 24 or 27 may be rewritten as

$$\int_0^\infty X_T dt = \frac{X^0}{k_{e_1}}\left(\frac{k_{12}}{k_{21}}\right) \qquad \text{(Eq. 29)}$$

Hence the area under the tissue level of drug *versus* time curve is simply a function of dose (X^0), the elimination rate constant of the drug (k_{e_1}) and the distribution ratio at infusion equilibrium (k_{12}/k_{21}), and independent of the manner in which the drug is administered.

Therapeutic Implications—The present report has important implications in cancer chemotherapy in particular and with respect to chemotherapeutics and pharmacodynamics in general. The fact that the same plasma concentration of drug may result in markedly different tissue levels of drug depending on the mode of administration provides a scientific rationale for the controversy as to the relative efficacy of intermittent *versus* continuous therapy. However, the theoretical relationships established herein do not provide a definitive answer as to which mode of administration is the most effective. The resolution of the problem resides in determining the site of drug action and this may be either in, or directly connected to, the central or tissue compartments, respectively.

APPENDIX

Instantaneous Injection in Two-Compartment Open Model—The appropriate differential equations to describe the model shown in Fig. 1 are as follows

$$dX_c/dt = -(k_{e_1} + k_{12})X_c + k_{21}X_T \qquad \text{(Eq. 1}a\text{)}$$

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^0, into the central compartment at $t = 0$, and the various rate constants are as defined in Fig. 1. Integration and further development of these equations yields Eqs. 2 and 3 in the text where

$$C_1 = (k_{21} - \alpha)/(\beta - \alpha) \qquad \text{(Eq. 3}a\text{)}$$

$$C_2 = (k_{21} - \beta)/(\alpha - \beta) \qquad \text{(Eq. 4}a\text{)}$$

$$C_1' = k_{12}/(\beta - \alpha) \qquad \text{(Eq. 5}a\text{)}$$

$$C_2' = k_{12}/(\alpha - \beta) \qquad \text{(Eq. 6}a\text{)}$$

and $\alpha\beta = k_{21}k_{e_1}$ and $(\alpha + \beta) = k_{e_1} + k_{12} + k_{21}$.

Definition of $(V_d)_{\text{inf.eq.}}$ from the Two-Compartment Open Model—After a constant-rate intravenous infusion is maintained for a sufficient length of time, an equilibrium is established. Under these conditions, the rate of drug entry to the central compartment is equal to the rate of drug loss from this compartment and $(V_d)_{\text{inf. eq.}}$ may be calculated as follows:

$$dX_c/dt = k_0 - (k_{e_1} + k_{12})X_c + k_{21}X_T = 0 \qquad \text{(Eq. 7}a\text{)}$$

$$k_{21}X_T = (k_{e_1} + k_{12})X_c - k_0 \qquad \text{(Eq. 8}a\text{)}$$

At infusion equilibrium, the rate in = the rate out and

$$k_0 = k_{e_1}X_c \qquad \text{(Eq. 9}a\text{)}$$

Substituting Eq. 9*a* in Eq. 8*a* and rearranging yields

$$X_T/X_c = k_{12}/k_{21} \qquad \text{(Eq. 10}a\text{)}$$

From Eq. 17*a* in *Reference 8*

$$(V_d)_{\text{inf. eq.}} = \frac{(X_B)_{\text{inf. eq.}}}{(C_p)_{\text{inf. eq.}}} = \frac{X_c + X_T}{(X_c/V_c)} \qquad \text{(Eq. 11}a\text{)}$$

or

$$(V_d)_{\text{inf. eq.}} = (1 + X_T/X_c)V_c \qquad \text{(Eq. 12}a\text{)}$$

Substituting for X_T/X_c from Eq. 10*a* yields

$$(V_d)_{\text{inf. eq.}} = (k_{21} + k_{12})V_c/k_{21} \qquad \text{(Eq. 13}a\text{)}$$

Therefore, according to the definition of $(V_d)_{ss}$ (Eq. 7 in *Reference 8*), it follows that

$$(V_d)_{\text{inf. eq.}} = (V_d)_{ss} \qquad \text{(Eq. 14}a\text{)}$$

Estimation of $(X_B)_{\text{inf. eq.}}$ in Two-Compartment Open Model—Rewriting Eqs. 8 and 18 in terms of plasma concentration of drug rather than amount of drug yields Eqs. 15*a* and 16*a*, respectively,

$$C_p = \frac{k_0}{k_{e1}V_c}\left[1 - \frac{(k_{e1} - \beta)}{\alpha - \beta}e^{-\alpha t} + \frac{(k_{e1} - \alpha)}{\alpha - \beta}e^{-\beta t}\right] \qquad \text{(Eq. 15}a\text{)}$$

and

$$C_p = \frac{k_0}{k_{e1}V_c}\left[\frac{(k_{e1} - \beta)}{\alpha - \beta}e^{-\alpha t'} - \frac{(k_{e1} - \alpha)}{\alpha - \beta}e^{-\beta t'}\right] \qquad \text{(Eq. 16}a\text{)}$$

where t' is the time from cessation of the infusion. Integrating Eqs. 15*a* and 16*a* from $t = 0$ to $t = T$ (where T is the total infusion time) and from $t' = 0$ to $t' = \infty$, respectively, yields

$$\int_{t=0}^{t=T} C_p dt = \frac{k_0}{k_{e1}V_c}\left[T - \frac{(k_{e1} - \beta)}{\alpha(\alpha - \beta)} + \frac{(k_{e1} - \alpha)}{\beta(\alpha - \beta)}\right] \qquad \text{(Eq. 17}a\text{)}$$

and

$$\int_{t'=0}^{t'=\infty} C_p dt = \frac{k_0}{k_{e1}V_c}\left[\frac{(k_{e1} - \beta)}{\alpha(\alpha - \beta)} - \frac{(k_{e1} - \alpha)}{\beta(\alpha - \beta)}\right] \qquad \text{(Eq. 18}a\text{)}$$

Combining Eqs. 17*a* and 18*a* yields the total area under the plasma concentration of drug *versus* time curve, so that

$$\int_0^\infty C_p dt = \frac{k_0 T}{k_{e1}V_c} = \frac{\text{dose}}{k_{e1}V_c} \qquad \text{(Eq. 19}a\text{)}$$

Dividing Eq. 17*a* by Eq. 19*a* and rearranging yields

$$\text{dose}\left[1 - \frac{\int_0^T C_p dt}{\int_0^\infty C_p dt}\right] = \frac{k_0(k_{21} + k_{12})}{\alpha\beta} \qquad \text{(Eq. 20}a\text{)}$$

which is equivalent to the definition of $(X_B)_{\text{inf. eq.}}$ as in Eq. 20.

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ACKNOWLEDGMENTS AND ADDRESSES

Received September 30, 1968, from the *Department of Pharmaceutics, School of Pharmacy, State University of New York at Buffalo, Buffalo, NY 14214*

Accepted for publication November 14, 1968.

The author wishes to thank Dr. Gerhard Levy and Dr. Renpei Nagashima for their valuable suggestions, and Mr. Stuart Feldman for his technical assistance, in the preparation of the manuscript.