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Research Article

Application of Mean Residence-Time Concepts to Pharmacokinetic Systems with Noninstantaneous Input and Nonlinear Elimination

Haiyung Cheng[1,2] and William J. Jusko[1,3]

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Equations describing the mean residence time (MRT) of drugs in the body are derived for drugs that are administered by first- and zero-order rates into systems with Michaelis–Menten elimination. With computer simulations, the validity of these equations, the differences between them, and the conventional approach using the AUMC/AUC or the summation of mean times are demonstrated by examining calculations of the percentage of the administered dose eliminated at the MRT and AUMC/AUC. The effects of the absorption rate on the AUC and on the approximate and true MRT values in a nonlinear pharmacokinetic system are also illustrated with computer simulations. It was previously found that the true $MRT_{iv} = V_{ss} \cdot AUC_{iv}/dose$ for an iv bolus. The total MRT (sum of input and disposition) of a drug after noninstantaneous administration was found to be a function of the MRT_{iv}, two values of AUC (iv and non-iv), and exactly how the drug is administered expressed as the mean absorption time (MAT). In addition, a theoretical basis is proposed for calculation of the bioavailability of drugs in both linear and nonlinear pharmacokinetic systems.

KEY WORDS: mean residence time; moment analysis; Michaelis–Menten elimination; compartmental models; bioavailability; mean absorption time.

INTRODUCTION

Application of moment theory to the evaluation of drug absorption in linear pharmacokinetic systems has been explored (1–3). When drug absorption is a zero- or first-order process, the total mean residence time for an oral dose of drug (MRT_{po}) can be described by the following equation:

$$MRT_{po} = MRT_{iv} + MAT \quad (1)$$

where MRT_{iv} is the mean residence time after intravenous (iv) bolus administration and MAT is the mean absorption time. The MAT can be described for zero- and first-order absorption processes (1–3), as follows:

$$MAT_0 = \frac{\tau}{2} \quad (2)$$

and

$$MAT_1 = \frac{1}{k_a} \quad (3)$$

where τ is the time over which the zero-order absorption takes place and k_a is an apparent first-order absorption rate constant.

The mean residence time (MRT), after any mode of administration of drug into a *linear* disposition system, can also be described by the following equation (4):

$$MRT = \frac{\int_0^\infty t \cdot C(t)dt}{\int_0^\infty C(t)dt} = AUMC/AUC \quad (4a, b)$$

where $C(t)$ is the drug concentration at time t, AUC is the area under the plasma concentration–time curve, and AUMC is the area under the first moment curve. Recently, it has been shown that the application of Eq. (4) in calculating the exact MRT is limited to linear pharmacokinetic systems (5). For a drug administered by any route into the body and eliminated from the central compartment by either a linear or a single Michaelis–Menten process, the MRT can be calculated according to (5)

$$MRT = \frac{\int_0^\infty t \cdot CL(t) \cdot C(t)dt}{\int_0^\infty CL(t) \cdot C(t)dt} \quad (5)$$

where $CL(t)$ is the plasma clearance at time t. After an iv dose, the specific MRT becomes

[1] Department of Pharmaceutics, School of Pharmacy, State University of New York at Buffalo, Buffalo, New York 14260.
[2] Department of Pharmacokinetics and Drug Metabolism, Merrell Dow Pharmaceuticals Inc., Indianapolis, Indiana 46268.
[3] To whom correspondence should be addressed.

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$$MRT_{iv} = V_{ss} \cdot AUC_{iv}/D \quad (6)$$

where V_{ss} is the steady-state volume of distribution, AUC_{iv} is the AUC following intravenous bolus administration of a drug, and D is the dose administered.

The purpose of this report is to derive the MRT_{po} of a drug which enters the body (central compartment) by an apparent zero- or first-order absorption process, follows a one- or two-compartment distribution system, and is eliminated by a single, Michaelis–Menten process:

$$MRT_{po} = MRT_{iv} \cdot \frac{AUC_{po}}{F \cdot AUC_{iv}} + MAT \quad (7)$$

where F is the bioavailability and AUC_{po} is the area under the oral plasma concentration–time curve. Computer simulations are used to verify that the calculation of MRT_{po} using Eq. (7) is valid in both linear and nonlinear pharmacokinetic systems. We also show that the apparent MRT_{po} calculated using Eq. (1) or (4) does not provide the true MRT_{po} for nonlinear systems. In addition, the effects of the absorption rate on AUC_{po} and the approximation of MRT_{po} values by Eq. (1) and by $AUMC_{po}/AUC_{po}$ are demonstrated with computer simulations.

THEORETICAL

One-Compartment Model

First-Order Absorption

For a drug which enters the body by an apparent first-order absorption process and follows a one-compartment model having only Michaelis–Menten elimination (Fig. 1), the rate of change of drug concentration [$C(t)$] with time (t) can be described by the following equation:

$$V \cdot \frac{dC(t)}{dt} = F \cdot D \cdot k_a \cdot e^{-k_a \cdot t} - \frac{V_m \cdot C(t)}{K_m + C(t)} \quad (8)$$

where V is the apparent volume of distribution, V_m is the theoretical maximum rate of the elimination process, and K_m is the Michaelis constant. For Michaelis–Menten systems, clearance as a time-dependent function (5) CL(t) is given by Eq. (9):

$$CL(t) = \frac{V_m}{K_m + C(t)} \quad (9)$$

Substituting Eq. (9) into Eq. (8) yields

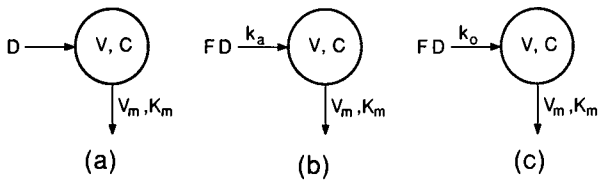

Fig. 1. The basic one-compartment models used for elaboration of MRT relationships. (a) Intravenous bolus administration; (b) oral administration with a first-order absorption process; (c) administration with a zero-order absorption or infusion process. Symbols are defined in the text.

$$V \cdot \frac{dC(t)}{dt} = F \cdot D \cdot k_a \cdot e^{-k_a \cdot t} - CL(t) \cdot C(t) \quad (10)$$

Rearranging terms yields

$$CL(t) \cdot C(t) = F \cdot D \cdot k_a \cdot e^{-k_a \cdot t} - V \cdot \frac{dC(t)}{dt} \quad (11)$$

Multiplying both sides of Eq. (11) by $t \cdot dt$ yields

$$CL(t) \cdot t \cdot C(t)dt = F \cdot D \cdot t \cdot k_a \cdot e^{-k_a \cdot t}dt - V \cdot t \cdot dC(t) \quad (12)$$

It follows that

$$\int_0^\infty CL(t) \cdot t \cdot C(t)dt = \int_0^\infty F \cdot D \cdot t \cdot k_a \cdot e^{-k_a \cdot t}dt - \int_0^\infty V \cdot t \cdot dC(t) \quad (13)$$

which, when solved using the method of integration by parts, becomes

$$\int_0^\infty CL(t) \cdot t \cdot C(t)dt = V \cdot AUC_{po} + \frac{F \cdot D}{k_a} \quad (14)$$

Multiplying both sides of Eq. (11) by dt yields

$$CL(t) \cdot C(t)dt = F \cdot D \cdot k_a \cdot e^{-k_a \cdot t}dt - V \cdot dC(t) \quad (15)$$

Integrating Eq. (15) from $t = 0$ to ∞ yields

$$\int_0^\infty CL(t) \cdot C(t)dt = F \cdot D \quad (16)$$

Substituting Eqs. (14) and (16) into Eq. (5) and denoting MRT as MRT_{po} yields

$$MRT_{po} = \frac{V \cdot AUC_{po}}{F \cdot D} + 1/k_a \quad (17)$$

For this one-compartment system, since V equals V_{ss}, Eq. (6) can be rearranged to

$$V/D = MRT_{iv}/AUC_{iv} \quad (18)$$

Substituting for V/D and $1/k_a$ in Eq. (17) according to Eqs. (18) and (3) then gives Eq. (7). It can be noted in comparing Eqs. (6) and (17) that, as $k_a \rightarrow \infty$ and if $F = 1$, then as expected, $MRT_{po} = MRT_{iv}$.

Zero-Order Absorption

When the drug is absorbed by a zero-order process (Fig. 1), the rate of change of drug with time can be described by the following equations:

$$V \cdot \frac{dC(t)}{dt} = k_o - \frac{V_m \cdot C(t)}{K_m + C(t)} \quad \text{(when } t < \text{or} = \tau\text{)} \quad (19)$$

and

$$V \cdot \frac{dC(t)}{dt} = -\frac{V_m \cdot C(t)}{K_m + C(t)} \quad \text{(when } t > \tau\text{)} \quad (20)$$

where k_o equals $F \cdot D/\tau$.

Substituting Eq. (9) into Eqs. (19) and (20) yields

$$V \cdot \frac{dC(t)}{dt} = k_o - CL(t) \cdot C(t) \quad \text{(when } t < \text{or} = \tau\text{)} \tag{21}$$

or

$$CL(t) \cdot C(t) = k_o - V \cdot \frac{dC(t)}{dt} \quad \text{(when } t < \text{or} = \tau\text{)} \tag{22}$$

and

$$V \cdot \frac{dC(t)}{dt} = -CL(t) \cdot C(t) \quad \text{(when } t > \tau\text{)} \tag{23}$$

or

$$CL(t) \cdot C(t) = -\frac{V \cdot dC(t)}{dt} \quad \text{(when } t > \tau\text{)} \tag{24}$$

Multiplying both sides of Eqs. (22) and (24) by $t \cdot dt$ yields

$$CL(t) \cdot t \cdot C(t)dt = k_o \cdot t \cdot dt - V \cdot t \cdot dC(t) \quad \text{(when } t < \text{or} = \tau\text{)} \tag{25}$$

and

$$CL(t) \cdot t \cdot C(t)dt = -V \cdot t \cdot dC(t) \quad \text{(when } t > \tau\text{)} \tag{26}$$

It follows that

$$\int_0^\infty CL(t) \cdot t \cdot C(t)dt = \int_0^\tau CL(t) \cdot t \cdot C(t)dt + \int_\tau^\infty CL(t) \cdot t \cdot C(t)dt = \int_0^\tau k_o \cdot t \cdot dt + \int_\tau^\infty V \cdot t \cdot dC(t) \tag{27a, b}$$

which, when solved using the method of integration by parts, becomes

$$\int_0^\infty CL(t) \cdot t \cdot C(t)dt = V \cdot AUC_{po} + k_o \cdot \tau^2/2 \tag{28}$$

Similarly, the following equation can be derived from Eqs. (22) and (24):

$$\int_0^\infty CL(t) \cdot C(t)dt = k_o \cdot \tau = F \cdot D \tag{29a, b}$$

Substituting Eqs. (29) and (30) into Eq. (16) and denoting MRT as MRT_{po} yields

$$MRT_{po} = \frac{V \cdot AUC_{po}}{F \cdot D} + \frac{\tau}{2} \tag{30}$$

Substituting for V/D and $\tau/2$ in Eq. (30) according to Eqs. (19) and (2) again yields Eq. (7).

Two-Compartment Model

First-Order Absorption

For a drug that enters the central compartment by an apparent first-order absorption process and follows a two-compartment model having only Michaelis–Menten elimination from the central compartment (Fig. 2), the rates of decline of the drug concentration in plasma [$C(t)$] and in tissue [$C_T(t)$] can be described by the following equations:

$$V_c \cdot \frac{dC(t)}{dt} = F \cdot D \cdot k_a \cdot e^{-k_a \cdot t} - \frac{V_m \cdot C(t)}{K_m + C(t)} - CL_D \cdot C(t) + \frac{CL_D}{R} \cdot C_T(t) \tag{31}$$

$$\frac{V_T}{R} \cdot \frac{dC_T(t)}{dt} = CL_D \cdot C(t) - \frac{CL_D}{R} \cdot C_T(t) \tag{32}$$

where V_c and V_T are the apparent volumes of distribution of the central and tissue compartments, CL_D is the distribution clearance, and R is the tissue:plasma distribution ratio. Using the derivation technique shown previously (5) and above, the following equation can be derived for this system:

$$MRT_{po} = \frac{V_{ss} \cdot AUC_{po}}{F \cdot D} + \frac{1}{k_a} \tag{33}$$

In addition, Eq. (7) can also be derived from Eqs. (3), (6), and (33).

Zero-Order Absorption/Infusion

When the drug enters the central compartment by a zero-order process (Fig. 2), the rate of change of drug concentrations in plasma and in tissue with time can be described by the following equations:

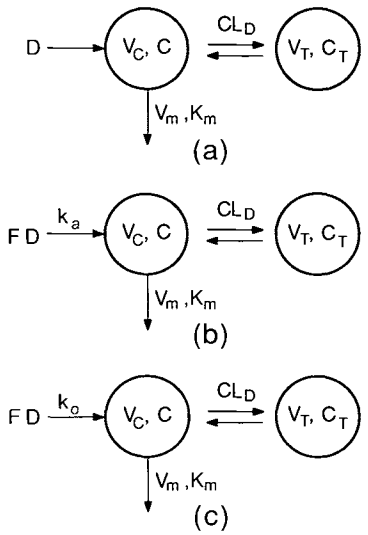

Fig. 2. The basic two-compartment models used for elaboration of MRT relationships. (a) Intravenous bolus administration; (b) oral administration with a first-order absorption process; (c) administration with a zero-order absorption or infusion process. Symbols are defined in the text.

$$V_c \cdot \frac{dC(t)}{dt} = k_o - \frac{V_m \cdot C(t)}{K_m + C(t)} - CL_D \cdot C(t) + \frac{CL_D}{R} \cdot C_T(t) \quad (\text{when } t < \text{or} = \tau) \tag{34}$$

$$V_c \cdot \frac{dC(t)}{dt} = -\frac{V_m \cdot C(t)}{K_m + C(t)} - CL_D \cdot C(t) + \frac{CL_D}{R} \cdot C_T(t) \quad (\text{when } t > \tau) \tag{35}$$

$$\frac{V_T}{R} \cdot \frac{dC_T(t)}{dt} = CL_D \cdot C(t) - \frac{CL_D}{R} \cdot C_T(t) \tag{36}$$

For zero-order drug absorption, the following equation and Eq. (7) can be shown to be valid:

$$MRT_{po} = \frac{V_{ss} \cdot AUC_{po}}{F \cdot D} + \frac{\tau}{2} \tag{37}$$

For a one-compartment system, since V equals V_{ss}, Eqs. (16) and (30) are identical to Eqs. (33) and (37). Thus, when drug is administered orally and exhibits nonlinear behavior, Eqs. (7), (33), and (37) are meaningful for both one- and two-compartment Michaelis–Menten systems.

The following equations describe the mean residence time of a drug after a constant-rate intravenous infusion (MRT_{if}):

$$MRT_{if} = \frac{V_{ss} \cdot AUC_{if}}{D} + \frac{\tau}{2} \tag{38}$$

$$MRT_{if} = MRT_{iv} \cdot \frac{AUC_{if}}{AUC_{iv}} + \frac{\tau}{2} \tag{39}$$

METHODS

Numerical integrations of the appropriate equations [Eqs. (8), (19), (20), (31), (32), and (34–36)] were performed using the Runge–Kutta method (6) and an IBM XT microcomputer system to obtain plasma concentration–time data after oral administration of a hypothetical drug for the following models: (a) one-compartment Michaelis–Menten system (Fig. 1) and (b) two-compartment Michaelis–Menten system (Fig. 2). In the first case, simulations were performed with V_m = 433.2 mg/da, K_m = 3.62 mg/liter, V = 57 liters, D = 1, 600, and 1800 mg, F = 1, and k_a = 16 da^{-1} or k_o = 2000 mg/da. Similarly, in the two-compartment case, simulations were carried out by using the following values: V_m = 54.2 mg/hr, K_m = 36.2 mg/liter, CL_D = 28.7 liters/hr, R = 1, F = 1, D = 50, 1000, and 30,000 mg, V_c = 29.5 liters, V_T = 20.7 liters, and k_a = 0.4 hr^{-1} or k_o = 100 mg/hr for D = 50 and 1000 mg as well as 1000 mg/hr for D = 30,000 mg. In addition, simulated intravenous bolus data which were generated previously (5) using the above parameter values were used for calculations. In the case of the two-compartment system, apparent tissue concentrations of drug were also generated to calculate the percentage of the dose eliminated at MRT and AUMC/AUC [i.e., A_e(MRT)% and A_e(AUMC/AUC)%]. Three doses were used in both the one- and two-compartment cases to assure that pseudo-first-order, true Michaelis–Menten, and initial pseudo-zero-order elimination behavior would be observed in the limiting low-dose, middle, and limiting high-dose cases. The values of k_a and k_o used in simulations also ensure that the absorption half-time is less than or equal to $MRT_{iv}/5$.

The values of AUC and AUMC were calculated by Lagrange cubic polynomial approximation (7) from the simulated data. Values of MRT were calculated directly from Eqs. (1), (6), and (7). These values and A_e(MRT)% and A_e(AUMC/AUC)% obtained from intravenous and oral administration of drug for each model were compared.

To illustrate the effect of the absorption rate or absorption half-time of a drug on the AUC_{po}, and the approximation of MRT_{po} values, additional simulations were performed for the one-compartment Michaelis–Menten system with the zero-order absorption process. The k_o was changed from 200 to ∞ mg/da, while the rest of the parameters were kept constant at values mentioned above. The dose used in these simulations was 600 mg. Values of AUC_{po}, MRT_{po}, and $AUMC_{po}/AUC_{po}$ calculated for the various zero-order absorption conditions were compared. In addition, the percentage deviation from the true MRT_{po} values was also calculated.

RESULTS

One-Compartment Model

The simulated concentration–time data shown in Fig. 3 were generated using Eqs. (8), (19), and (20) as well as the following equation for disposition of an iv bolus dose:

$$-V \cdot \frac{dC(t)}{dt} = \frac{V_m \cdot C(t)}{K_m + C(t)} \tag{40}$$

where $C(t)$ is the drug concentration at time t after intravenous bolus administration and the initial condition is $C(0) = D/V$.

These data were used to calculate values of MRT, AUMC/AUC, A_e(MRT)%, and A_e(AUMC/AUC)% for both intravenous and oral administration as specified in Table I. Except at the limiting low-dose case, values of MRT_{po} calculated using Eq. (1) versus $AUMC_{po}/AUC_{po}$ are different from those calculated using Eq. (7). In addition, as doses increase from 1 to 1800 mg, $A_e(MRT_{iv})$% decreases from 63.2 to 52.7%. The same is true for $A_e(MRT_{po})$% when MRT_{po} is calculated using Eq. (7). However, when MRT_{po} is calculated using Eq. (1), the corresponding $A_e(MRT_{po})$% values decrease from 63.2 to 58.1 for the zero-order and 53.6 for the first-order absorption processes. In the same dose range, $A_e(AUMC_{po}/AUC_{po})$% also decreases from the iv value of 63.2 to 41.7 and 38.3% for these two absorption processes.

Two-Compartment Model

Using the same procedures described above for the one-compartment model, simulated data and an array of parameter values were obtained for a hypothetical drug obeying the two-compartment model shown in Fig. 2. Equations (31), (32), and (34)–(36) as well as the following equations for

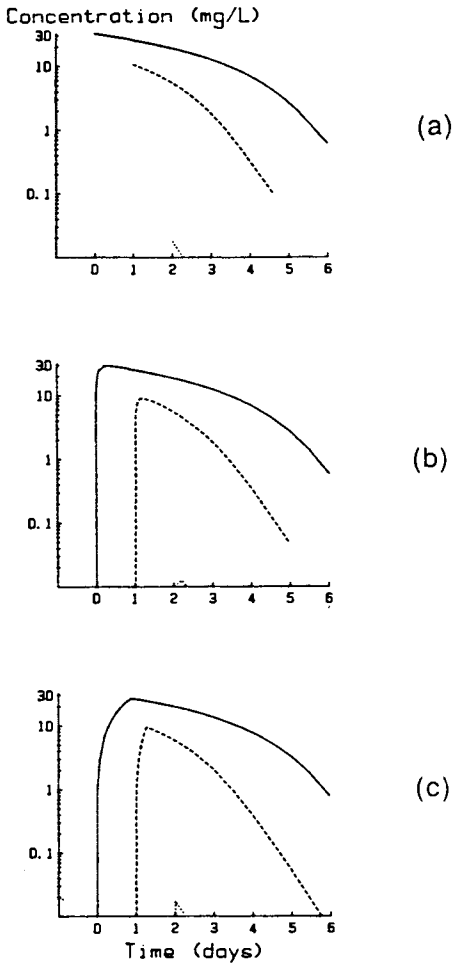

Fig. 3. Simulated concentration–time profiles for the corresponding one-compartment models shown in Fig. 1 (a, b, c) using Eqs. (8), (19), (20), and (40) with D = 1, 600, and 1800 mg (curves in ascending order) and parameter values described in the text. For clarity, the data for each dose are displaced by 1 day on the time axis from the preceding data.

disposition of an iv bolus were used to generate the simulated concentration–time profiles plotted in Fig. 4:

$$V_c \cdot \frac{dC(t)}{dt} = -\frac{V_m \cdot C(t)}{K_m + C(t)} - CL_D \cdot C(t) + \frac{CL_D}{R} \cdot C_T(t) \quad (41)$$

$$\frac{V_T}{R} \cdot \frac{dC_T(t)}{dt} = CL_D \cdot C(t) - \frac{CL_D}{R} \cdot C_T(t) \quad (42)$$

where the initial conditions are $C(0) = D/V_c$ and $C_T(0) = 0$. Table II lists the values of MRT, AUMC/AUC, A_e(MRT)%, and A_e (AUMC/AUC)% for intravenous and oral administration along with specification of the calculation methods. As shown in Table II, again, except at the limiting low-dose case, the methods of calculating the MRT_{po} [Eqs. (1) and (7)] and the approach using the $AUMC_{po}/AUC_{po}$ [Eq. (4)] yield different values for the oral drug. Also, for the dose range studied and regardless of the kinetic order of the absorption processes, Eq. (7) yields MRT_{po} values for which calculated values of $A_e(MRT_{po})$% equal those of $A_e(MRT_{iv})$%. However, the same is not true at the apparent MRT_{po} calculated using Eq. (1) and at $AUMC_{po}/AUC_{po}$; at these times, $A_e(MRT_{po})$% ranges from 53.4 and 52.0 to 63.1%, while A_e(AUMC/AUC)% lies in the range of 35.7–63.1 and 35.9–63.0% for the zero- and first-order absorption processes.

Effects of Absorption Rate on AUC_{po} and Approximation of MRT_{po}

Simulations were performed to demonstrate the effects of the absorption rate or the absorption half-time (time at which 50% absorption occurs) on the AUC_{po} and the approximation of MRT_{po} by Eq. (1) and $AUMC_{po}/AUC_{po}$. Figure 5 presents plots of the concentration–time profiles generated for the one-compartment model. Values of the parameters obtained from these data for various k_o are listed in Table III. As k_o increases from 200 mg/da to infinity or the absorption half-time decreases from 1.5 to 0 day, values of AUC_{po} increase from 7.77 to 12.3 mg · da/liter, while values of MRT_{po} calculated using Eq. (7) decrease from 2.24 to 1.17 days. In addition, as the absorption half-time decreases, the calculation error of MRT_{po} by using Eq. (1) decreases from 19.2 to 0%, while the error related to using $AUMC_{po}/AUC_{po}$ increases from 0.9 to 23.9%.

DISCUSSION

In linear pharmacokinetic systems, MRT_{iv} is constant and independent of dose, as it relates only to two constant parameters, V_{ss} and CL. Similarly, according to Eq. (1), MRT_{po} in these systems is also dose independent. In contrast, as reported previously (5), in nonlinear pharmacokinetic systems, MRT_{iv} increases with dose. The newly derived Eqs. (33) and (37) indicate that MRT_{po} is also dose dependent in these systems. According to the more general Eq. (7), MRT_{po} is a function of AUC_{po} and $F \cdot AUC_{iv}$. When equal doses are given intravenously and orally, in middle- and high-dose cases, AUC_{po} is smaller than $F \cdot AUC_{iv}$, as the time-average clearance (5) for intravenous administration ($\overline{CL}_{iv}$) is smaller than that after oral administration ($\overline{CL}_{po}$). Thus, values of MRT_{po} for nonlinear systems estimated using Eq. (7) are expected to be smaller than those obtained from Eq. (1), which pertains to linear elimination. However, in limiting low-dose cases, Eq. (7) degenerates to Eq. (1) as AUC_{po} approaches $F \cdot AUC_{iv}$. For middle- and high-dose situations, Eq. (1) overestimates the MRT_{po} (Tables I and II).

The common approach for calculating MRT_{po} using $AUMC_{po}/AUC_{po}$ is similarly valid only in limiting low-dose cases. For middle- and high-dose situations, this method underestimates MRT_{po}. If one uses Eq. (1) to calculate the MRT_{po} for a drug eliminated nonlinearly from the body, under the simulation conditions, the calculation error will range from negligible (0%) at low doses to small (1–5%) at middle and high doses. In contrast, the corresponding error caused by using $AUMC_{po}/AUC_{po}$ [Eq. (4)] will range from negligible (0%) to moderate (31.0%). Thus, Eq. (1) gives a better approximation of MRT_{po} values than does $AUMC_{po}/AUC_{po}$. However, it also necessitates more experimental data after both iv and oral doses.

As pointed out by Riegelman and Collier (2), in a linear pharmacokinetic system, if the absorption half-time is less than or equal to $MRT_{iv}/5$, values of $A_e(MRT_{po})$% are exper-

Table I. Comparison of Residence Time Values Obtained from Different Modes of Drug Administration for a One-Compartment Michaelis–Menten System

Dose (mg)	Dosing mode	MRT (da)[a]	MRT (da)[b]	AUMC/AUC (da)	A_e (MRT) (%)[c]	A_e (MRT) (%)[d]	A_e (AUMC/AUC) (%)[e]
1	iv	0.48	—	0.48	63.2	—	63.2
	po: k_o	0.48	0.48	0.48	63.2	63.2	63.2
	po: k_a	0.54	0.54	0.54	63.2	63.2	63.2
600	iv	1.17	—	0.89	56.2	—	52.3
	po: k_o	1.26	1.32	1.02	56.2	58.6	45.1
	po: k_a	1.20	1.23	0.94	56.2	57.3	45.1
1800	iv	2.55	—	1.80	52.7	—	37.9
	po: k_o	2.72	3.00	2.16	52.7	58.1	41.7
	po: k_a	2.57	2.61	1.84	52.7	53.6	38.3

[a] Calculated using Eq. (6) (iv) and Eq. (7) (po).
[b] Calculated using Eq. (1).
[c] Obtained using MRT as described in footnote *a;* calculated as $\{1 - [V \cdot C(t)/D]\} \times 100\%$ at t = MRT.
[d] Obtained using MRT as described in *b;* calculated as $\{1 - [V \cdot C(t)/D]\} \times 100\%$ at t = MRT.
[e] Calculated as $\{1 - [V \cdot C(t)/D]\} \times 100\%$ at t = AUMC/AUC.

imentally indistinguishable from $A_e(MRT_{iv})\%$, which equals 63.2%. This implies that in those cases where the rate-limiting step is elimination instead of absorption, $A_e(MRT_{po})\%$ equals $A_e(MRT_{iv})\%$. This concept can be extended to nonlinear pharmacokinetic systems, which allows us to verify Eq. (7) by computer simulations. Indeed, using Eq. (7) to calculate MRT_{po}, we have shown that $A_e(MRT)\%$ values for drugs exhibiting one- and two-compartment Michaelis–Menten characteristics are independent of the mode of drug administration (Tables I and II). Thus, MRT_{po} defined by Eq. (7) is meaningful in both linear and nonlinear systems.

Since our initial simulations were performed under the condition that the absorption half-time is less than or equal to $MRT_{iv}/5$, the validity of the observation that Eq. (1) gives a better approximation of MRT_{po} values than $AUMC_{po}/AUC_{po}$ when absorption was slower was uncertain. Thus, the effects of varying the absorption half-time relative to $MRT_{iv}/5$ on the calculation of MRT_{po} values by using Eq. (1) or $AUMC_{po}/AUC_{po}$ were examined. As shown in Table III, when the absorption half-time is less than or close to $MRT_{iv}/5$, Eq. (1) performs better than $AUMC_{po}/AUC_{po}$ to approximate the true MRT_{po} values. However, when the absorption half-time is larger than $MRT_{iv}/5$, the converse holds. Thus, in nonlinear pharmacokinetic systems, the accuracy of the conventional methods using Eq. (1) or $AUMC_{po}/AUC_{po}$ to approximate the MRT_{po} values depends not only on the severity of the nonlinear condition but also on the relative absorption rate.

In these simulations, we also examined the effect of the absorption rate of a drug on the AUC_{po} in a nonlinear system. As indicated in Table III, the slower the absorption rate, the smaller the AUC_{po}. This is consistent with observations by Wagner *et al.* (8).

Although the equations derived and simulations performed in this work have been based only on one- and two-compartment Michaelis–Menten elimination, they are also valid (by extrapolation) for multiple-compartment distribution systems. According to Eqs. (7) and (39), in nonlinear systems, the MRT of a drug after noninstantaneous administration is a function of the MRT_{iv}, two AUC values (iv and

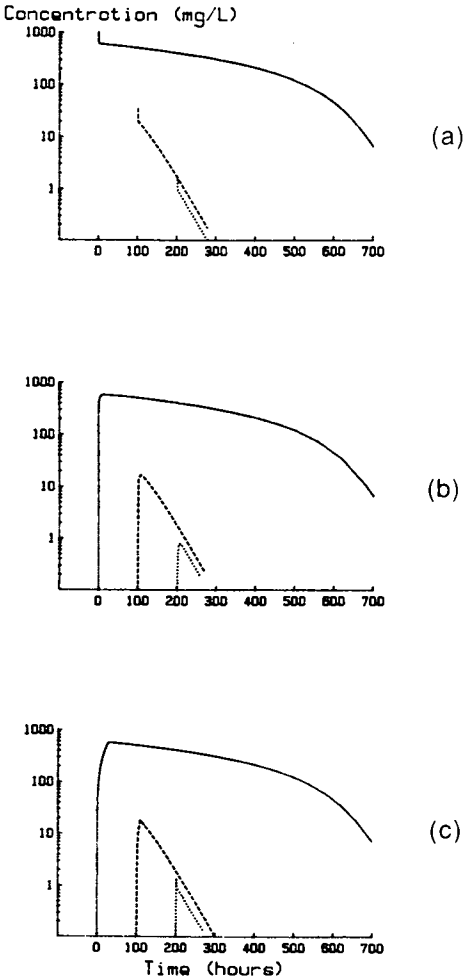

Fig. 4. Simulated concentration–time profiles for the corresponding two-compartment models shown in Fig. 2 (a, b, c) using Eqs. (31), (32), (34)–(36), (41), and (42) with D = 50, 1000, and 30000 mg (curves in ascending order) and parameter values described in the text. For clarity, the data for each dose are displaced by 100 hr on the time axis from the preceding data.

Table II. Comparison of Residence Time Values Obtained from Different Modes of Drug Administration for a Two-Compartment Michaelis–Menten System

Dose (mg)	Dosing mode	MRT (hr)[a]	MRT (hr)[b]	AUMC/AUC (hr)	A_e (MRT) (%)[c]	A_e (MRT) (%)[d]	A_e (AUMC/AUC) (%)[e]
50	iv	34.0	—	33.9	63.1	—	63.0
	po: k_o	34.2	34.2	34.2	63.1	63.1	63.1
	po: k_a	36.5	36.5	36.0	63.1	63.1	63.0
1,000	iv	42.8	—	38.5	60.9	—	56.7
	po: k_o	47.1	47.8	43.4	60.9	61.6	57.3
	po: k_o	44.7	45.1	40.8	60.9	61.4	57.0
30,000	iv	310.0	—	214.0	51.6	—	36.0
	po: k_o	313.6	325.0	223.9	51.6	53.4	35.7
	po: k_a	310.4	312.5	214.2	51.6	52.0	35.9

[a] Calculated using Eq. (6) (iv) and Eq. (7) (po).
[b] Calculated by using Eq. (1).
[c] Obtained using MRT as described in footnote *a*; calculated as $\{1 - [V \cdot C(t) + V_T \cdot C_T(t)]/D\} \times 100\%$ at t = MRT.
[d] Obtained using MRT as described in footnote *b*; calculated as $\{1 - [V_c \cdot C(t) + V_T \cdot C_T(t)]/D\} \times 100\%$ at t = MRT.
[e] Calculated as $\{1 - [V_c \cdot C(t) + V_T \cdot C_T(t)]/D\} \times 100\%$ at t = AUMC/AUC.

non-iv), and exactly how the drug is administered. Since the process of intravenous infusion can be treated as a special case of zero-order absorption process, the simulations performed in this report for the latter are also meaningful for the former.

Bioavailability Considerations

The classical method for estimating bioavailability is based on the following equation for F (3):

$$F = \frac{D_{iv} \cdot AUC_{po}}{D_{po} \cdot AUC_{iv}} \tag{43}$$

However, this method assumes linearity in drug elimination and hence is not applicable to estimate F in Eq. (7). Martis and Levy (9) have shown that F calculated by using Eq. (43) for a drug which actually exhibits nonlinear elimination kinetics could involve large errors. They proposed the following equation as the basis for calculating F of drugs which are orally administered and show simultaneous first- order and Michaelis–Menten elimination kinetics in a one-compartment system:

$$F = (1/V) \cdot \left[\int_0^\infty (dA_e/dt)dt\right]_{po} \Big/ \left[\int_0^\infty - (dC/dt)dt\right]_{iv} \tag{44}$$

assuming that equal doses are given intravenously and orally.

Irrespective of the linearity of a pharmacokinetic system, the bioavailability of drugs after oral administration can be described by the following (see Appendix):

$$F = \frac{D_{iv} \cdot \left[\int_0^\infty (dA_e/dt)dt\right]_{po}}{D_{po} \cdot \left[\int_0^\infty (dA_e/dt)dt\right]_{iv}} = \frac{D_{iv} \cdot \int_0^\infty CL_{po}(t) \cdot C_{po}(t)dt}{D_{po} \cdot \int_0^\infty CL_{iv}(t) \cdot C_{iv}(t)dt} \tag{45a, b}$$

Since the calculation of F using Eq. (45) is based only on the assumption that elimination of drug occurs from the central compartment, this relationship is applicable for single- and multiple-compartment systems as well as for linear and nonlinear systems. In linear systems, plasma clearance is constant, which results in Eq. (45b) degenerating to Eq. (43). Otherwise Eq. (43) does not follow from Eq. (45b) and is no longer meaningful for the calculation of F. Assuming that $D_{iv} = D_{po}$, Eq. (44) evolves from Eq. (45). Thus, Eq. (44) is not limited to one-compartment Michaelis–Menten systems. The utility of Eq. (44) to calculate F for drugs showing one-compartment Michaelis–Menten kinetics has been illustrated by computer simulations (9). It has also been applied to the determination of phenytoin bioavailability (10). Similarly, Eq. (44) or (45) can be used to determine F in Eq. (7) or F of drugs eliminated nonlinearly from a multiple-compartment body model. It should be noted, however, that this method requires estimates of V_m and K_m from intravenous doses

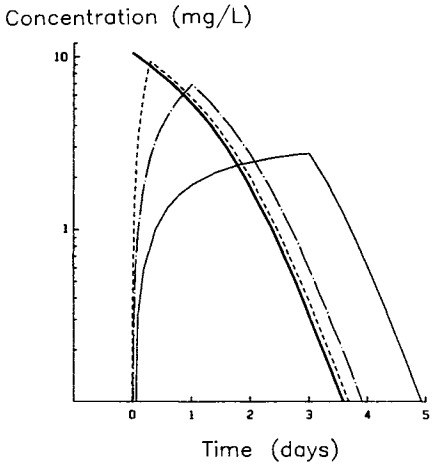

Fig. 5. Simulated concentration–time profiles for the one-compartment model shown in Fig. 1c using Eqs. (19), (20), and (40) with D = 600 mg and parameter values described in the text. (——) k_o = 200; (—·—) k_o = 600; (– – –) k_o = 2000; (——) k_o = ∞ mg/da.

Table III. Effects of Absorption Rate or Absorption Half-Time on AUC_{po} and the Calculation of Residence Time Values

k_o (mg/da)	Absorption half-time (da)	$MRT_{iv}/5$ (da)	AUC_{po} (mg · da/liters)	MRT_{po} (da)[a]	MRT_{po} (da)[b]	$AUMC_{po}/AUC_{po}$ (da)
200	1.5	0.23	7.77	2.24	2.67 (19.2)[c]	2.22 (0.9)
600	0.5	0.23	10.37	1.48	1.67 (12.8)	1.33 (10.1)
2000	0.15	0.23	11.66	1.26	1.32 (4.8)	1.02 (19.0)
—[d]	0	0.23	12.30	1.17	1.17 (0)	0.89 (23.9)

[a] Calculated using Eq. (7).
[b] Calculated using Eq. (1).
[c] Number in parentheses is the percentage deviation (abs. value) from the true MRT_{po} values.
[d] Values of parameters generated for an intravenous bolus were used.

plasma data, which in practice, may not be necessarily easy or accurate.

Recently, Cutler proposed a broader definition of MRT based on cumulative amounts of drug eliminated that applies to both linear and nonlinear systems (11). He also pointed out that the additive properties of moment theory described in Eq. (1) applied only to linear pharmacokinetic systems. In this report we have shown that the similar but more complex additive properties described in Eq. (7) apply to linear and nonlinear pharmacokinetic systems. We have also demonstrated that, in a nonlinear system, absorption rate has a pronounced effect on AUC_{po} and alters the accuracy of using either Eq. (1) or $AUMC_{po}/AUC_{po}$ to approximate MRT_{po} values. In addition, this report provides a more general method for calculation of the bioavailability of a drug exhibiting either linear or nonlinear behavior.

APPENDIX

Derivation of the Bioavailability Equation 45

The bioavailability (F) of the drug can be defined as

$$F = \frac{[A_b]_{po}/D_{po}}{[A_b]_{iv}/D_{iv}} \tag{A1}$$

where $[A_b]_{po}$ and $[A_b]_{iv}$ are the total amounts of drug in the body after oral and iv routes.

Since

$$A_b(t) = D - A_e(t) \tag{A2}$$

where $A_b(t)$ and $A_e(t)$ are the amounts of drug in the body and eliminated at time t. It follows that

$$dA_b(t)/dt = -dA_e(t)/dt \tag{A3}$$

By definition

$$dA_e(t)/dt = CL(t) \cdot C(t) \tag{A4}$$

Combining Eqs. (A3) and (A4) yields

$$dA_b(t)/dt = -dA_e(t)/dt = -CL(t) \cdot C(t) \quad \text{(A5a, b)}$$

Multiplying both sides of Eq. (A5) by dt and integrating the results from time 0 to ∞ yields

$$\int_0^\infty [dA_b(t)/dt]dt = -\int_0^\infty [dA_e(t)/dt]dt = -\int_0^\infty CL(t) \cdot C(t)dt \tag{A6a, b}$$

Now

$$[A_b] = \int_0^\infty [dA_b(t)/dt]dt \tag{A7}$$

Combining Eqs. (A6) and (A7) yields

$$[A_b] = \int_0^\infty [dA_b(t)/dt]dt = -\int_0^\infty [dA_e(t)/dt]dt = -\int_0^\infty CL(t) \cdot C(t)dt \tag{A8a, b, c}$$

Substituting Eq. (A8) into Eq. (A1) for both oral and iv routes yields Eq. (45).

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