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Research Article

Mean Residence Time Concepts for Pharmacokinetic Systems with Nonlinear Drug Elimination Described by the Michaelis–Menten Equation

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Equations for the mean residence time (MRT) of drug in the body and related functions are derived for drugs which are intravenously administered into a one- or two-compartment system with Michaelis–Menten elimination. This MRT is a function of the steady-state volume of distribution and time-average clearance obtained from the dose and area under the curve (dose/AUC). The differences between the MRT calculated by the proposed method and by using the moment theory method (AUMC/AUC) are demonstrated both mathematically and by computer simulations. The validity of the proposed method for calculation of MRT and its relationship to the moment theory result have also been assessed by examining the percentage of the administered dose eliminated and the percentage of the total area attained at MRT and at AUMC/AUC in relation to the dose. The equations evolved should be helpful in clarifying residence time derivations and in defining the disposition characteristics and differences between linear and nonlinear systems. Direct methods are provided for calculation of Michaelis–Menten parameters based on the relationship between MRT and dose.

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

INTRODUCTION

Application of moment theory to linear pharmacokinetics (1–3) has become increasingly popular because of the ease of estimation of commonly used pharmacokinetic parameters such as mean residence time (MRT), plasma clearance (CL), and steady-state volume of distribution (V_{ss}). As frequently used to describe drug disposition, the moment theory approach utilizes the area under the plasma concentration–time curve (AUC) and the area under the first moment curve (AUMC) to calculate MRT and V_{ss} as shown below:

$$\text{MRT} = \text{AUMC/AUC} = \int_0^\infty t \cdot C(t) \cdot dt \Big/ \int_0^\infty C(t) \cdot dt \qquad \text{(1a, b)}$$

and

$$V_{ss} = \text{MRT} \cdot \text{CL} = D \cdot \text{AUMC/AUC}^2 \qquad \text{(2a, b)}$$

where $C(t)$ is the drug concentration at time t, and D is the intravenous bolus dose administered.

Calculation of MRT and V_{ss} using Eqs. (1) and (2) is based upon two assumptions (2): (a) the drug must exhibit a linear disposition process; and (b) the drug must be administered to and eliminated from only the sampling (central) compartment. The first of these assumptions implies that in nonlinear systems the calculation of MRT using Eq. (1) is not valid. Moreover, since plasma clearance is not constant in nonlinear systems, the V_{ss} calculated using Eq. (2) has also been suspect.

Rescigno (4) has defined the time of exit (Z_x) characterizing tracer kinetics as

$$Z_x = \frac{\int_0^\infty \tau \cdot K^{irr} \cdot X(\tau) d\tau}{\int_0^\infty K^{irr} \cdot X(\tau) d\tau} \qquad (3)$$

where K^{irr} is the fraction of material leaving a compartment irreversibly per unit time, and $X(\tau)$ is the amount of tracer present in the compartment at time τ. In terms of pharmacokinetic analysis, the analogous expression for Z_x is

$$Z_x = \frac{\int_0^\infty t \cdot \text{CL}(t) \cdot C(t) dt}{\int_0^\infty \text{CL}(t) \cdot C(t) dt} \qquad (4)$$

For the case of intravenous bolus administration of a drug, Z_x equals MRT (4). Thus, besides Eq. (1), MRT can also be defined as follows:

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

It should be noted that Eq. (5) has recently been mathematically verified. Gillespie and Veng-Pedersen (5) clarified this as the most appropriate starting point in deriving MRT values and have pointed out that Eq. (1a) follows from Eq. (5), if plasma clearance relative to plasma concentration is constant. In terms of compartmental analysis, the occurrence of constant clearance satisfies the assumption previously mentioned that the drug must exhibit linear disposition. However, if plasma clearance is not constant (e.g., clearance follows the Michaelis–Menten equation), Eq. (1a) cannot be obtained from Eq. (5) and is no longer valid for calculation of the true MRT. Thus Eq. (5) is the correct equation to derive MRT values for drugs exhibiting either linear or nonlinear behavior. It should be noted that calculation of MRT using Eq. (5) is based only upon the second assumption mentioned previously, that administration and elimination of drug occur from the central compartment.

For drugs which are administered intravenously into the body and eliminated by a single, capacity-limited process, the concept of dose- and time-averaged parameters and the following relationship between MRT and V_{ss} have been proposed (6–8):

$$\text{MRT} = V_{ss}/\overline{\text{CL}} \quad (6)$$

where $\overline{\text{CL}}$ has been defined as the time-average clearance (7,8) according to

$$\overline{\text{CL}} = D/\text{AUC} \quad (7)$$

Since $\overline{\text{CL}}$ must decrease as the dose increases, MRT would be expected to increase. Therefore, Eq. (6) appears to bear some relevance to nonlinear pharmacokinetics. Indeed, MRT based on Eq. (6) has been shown to be meaningful in computer simulation studies (7,8). However, Eq. (6) has not been mathematically verified.

The purpose of this report is to derive and clarify Eq. (6) for a drug injected intravenously into a one- or two-compartment system and eliminated by a single, Michaelis–Menten process. Also, mathematical derivations and computer simulations are used to demonstrate differences between two approaches for calculating MRT, namely, the use of Eqs. (1) and (6). We show that the apparent MRT calculated using AUMC/AUC does not provide the true MRT for these nonlinear systems.

THEORETICAL

One-Compartment Model

For a drug which follows a one-compartment model having only Michaelis–Menten elimination, the rate of decline of drug concentration [$C(t)$] with time (t) after intravenous bolus administration can be described by the equation

$$-V \cdot \frac{dC(t)}{dt} = \frac{V_m \cdot C(t)}{K_m + C(t)} = \text{CL}(t) \cdot C(t) \quad (8a, b)$$

where V is the apparent volume of distribution, V_m is the theoretical maximum rate of the process, K_m is the Michaelis constant, and CL(t) is the plasma clearance relative to the drug concentration at time t. The mean residence time of drug in the body, MRT, can be calculated according to Eq. (5). Multiplying both sides of Eq. (8b) by dt yields

$$-V \cdot dC(t) = \text{CL}(t) \cdot C(t)dt \quad (9)$$

Since at $t = 0$, $C(t) = C_0$, and at $t = \infty$, $C(t) = 0$, it follows that

$$-\int_{C_0}^0 V \cdot dC(t) = \int_0^\infty \text{CL}(t) \cdot C(t)dt \quad (10)$$

or

$$\int_0^\infty \text{CL}(t) \cdot C(t)dt = V \cdot C_0 = D \quad (11a, b)$$

Multiplying both sides of Eq. (8b) by $t \cdot dt$ yields

$$-V \cdot t \cdot dC(t) = \text{CL}(t) \cdot t \cdot C(t)dt \quad (12)$$

Integrating over the limits $C(t) = C_0$ at $t = 0$ and $C(t) = 0$ at $t = \infty$ yields

$$-\int_{C_0}^0 V \cdot t \cdot dC(t) = \int_0^\infty \text{CL}(t) \cdot t \cdot C(t)dt \quad (13)$$

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

$$V \cdot \int_0^\infty C(t)dt = \int_0^\infty \text{CL}(t) \cdot t \cdot C(t)dt \quad (14)$$

or

$$\int_0^\infty \text{CL}(t) \cdot t \cdot C(t)dt = V \cdot \text{AUC} \quad (15)$$

By substituting the components of Eqs. (11) and (15) into Eq. (5), the result is

$$\text{MRT} = \frac{\text{AUC}}{C_0} = \frac{V \cdot \text{AUC}}{D} \quad (16a, b)$$

Also, combining Eqs. (7) and (16b) yields

$$\text{MRT} = V/\overline{\text{CL}} \quad (17)$$

where $\overline{\text{CL}}$ is the time-average clearance obtained from D/AUC as elaborated on further below.

The following equation has been derived previously by Wagner (9) for the present model:

$$\text{AUC} = V \cdot C_0 \cdot \left(\frac{C_0}{2} + K_m\right)/V_m = D \cdot \left(\frac{C_0}{2} + K_m\right)/V_m \quad (18)$$

Rearranging terms yields

$$\frac{D}{\text{AUC}} = V_m/\left(\frac{C_0}{2} + K_m\right) \quad (19)$$

Therefore, substituting for D/AUC in Eq. (7) according to Eq. (19) gives

$$\overline{\text{CL}} = V_m/\left(\frac{C_0}{2} + K_m\right) = V_m/\left(\frac{D}{2V} + K_m\right) \quad (20a, b)$$

Substitution for $\overline{CL}$ in Eq. (17) according to Eq. (20) yields

$$MRT = V \cdot \left(\frac{C_0}{2} + K_m\right)/V_m = V \cdot \left(\frac{D}{2V} + K_m\right)/V_m \quad (21a, b)$$

Analogous expressions for $\overline{CL}$ and MRT have been described by Smith (7) and Cutler (10). Recently, Chow and Jusko (11) have derived the AUMC/AUC value for this system as

$$AUMC/AUC = V \cdot \frac{K_m}{V_m} + \frac{V \cdot C_0(2\,C_0 + 3\,K_m)}{6 \cdot V_m \cdot (C_0 + 2\,K_m)} \quad (22)$$

or

$$AUMC/AUC = V \cdot \frac{K_m}{V_m} + \frac{D(2\,C_0 + 3\,K_m)}{6 \cdot V_m \cdot (C_0 + 2\,K_m)} \quad (23)$$

Subtracting Eq. (23) from Eq. (21) yields

$$MRT - (AUMC/AUC) = \frac{D \cdot (C_0 + 3\,K_m)}{6 \cdot V_m \cdot (C_0 + 2\,K_m)} \quad (24)$$

Here, we define this relationship as ΔMRT:

$$\Delta MRT = MRT - (AUMC/AUC) \quad (25)$$

By substituting the components of Eq. (24) into Eq. (25), the result is

$$\Delta MRT = \frac{D \cdot (C_0 + 3\,K_m)}{6 \cdot V_m \cdot (C_0 + 2\,K_m)} \quad (26)$$

Dividing both sides of Eq. (26) by Eq. (21) yields

$$\Delta MRT/MRT = \frac{C_0 \cdot (C_0 + 3\,K_m)}{3 \cdot (C_0 + 2\,K_m)^2} \quad (27)$$

Two-Compartment Model

For this model (see Appendix), it can be shown that

$$MRT = \frac{V_{ss} \cdot AUC}{D} = \frac{V_{ss}}{\overline{CL}} \quad (28a, b)$$

Equation (28b) is identical to Eq. (6). For one-compartment systems, since V equals V_{ss}, Eq. (17) is also identical to Eq. (6). Therefore, the calculation of MRT using Eq. (6) is valid for drugs exhibiting nonlinear kinetic behavior.

The following equations, which are similar to Eqs. (20) and (21), have been shown with computer simulations to be meaningful for the two-compartment Michaelis–Menten system (8).

$$AUC = D \cdot \left(\frac{D}{2V_{ss}} + K_m\right)/V_m \quad (29)$$

$$\overline{CL} = V_m/\left(\frac{D}{2\,V_{ss}} + K_m\right) \quad (30)$$

$$MRT = V_{ss} \cdot \left(\frac{D}{2\,V_{ss}} + K_m\right)/V_m \quad (31)$$

Similarly, from simulation, it can be shown that for two-compartment Michaelis–Menten systems,

$$AUMC/AUC = V_{ss} \cdot \frac{K_m}{V_m} + \frac{D \cdot [(2D/V_{ss}) + 3\,K_m]}{6 \cdot V_m[(D/V_{ss}) + 2\,K_m]} \quad (32)$$

Therefore, it follows that

$$\Delta MRT = MRT - (AUMC/AUC) = \frac{D \cdot [(D/V_{ss}) + 3\,K_m]}{6 \cdot V_m \cdot [(D/V_{ss}) + 2\,K_m]} \quad (33a, b)$$

Dividing both sides of Eq. (33b) by Eq. (31) yields

$$\Delta MRT/MRT = \left[\frac{D}{V_{ss}} \cdot \left(\frac{D}{V_{ss}} + 3\,K_m\right)\right]\Big/\left[3 \cdot \left(\frac{D}{V_{ss}} + 2\,K_m\right)^2\right] \quad (34)$$

It should be noted that Eqs. (32), (33), and (34) are similar to Eqs. (23), (26), and (27) and Eqs. (30)–(34) are valid for both one- and two-compartment Michaelis–Menten systems.

In the limiting low-dose case such that D/V_{ss} is much smaller than K_m, MRT [Eq. (31)] reduces to $V_{ss} \cdot K_m/V_m$. Similarly, AUMC/AUC [Eq. (32)] reduces to $(4\,V_{ss} \cdot K_m + D)/4\,V_m$. Because in this limiting case, D is much smaller than $V_{ss} \cdot K_m$ and is negligible compared to the latter, AUMC/AUC reduces further to $V_{ss} \cdot K_m/V_m$. Thus,

$$MRT = AUMC/AUC \simeq V_{ss} \cdot K_m/V_m \quad (35a, b)$$

and

$$\Delta MRT = MRT - (AUMC/AUC) \simeq 0 \quad (36)$$

Also, in the limiting high-dose case such that D/V_{ss} is much larger than K_m, Eqs. (31), (33b), and (34) reduce to

$$MRT \cong D/2 \cdot V_m \quad (37)$$

$$\Delta MRT \cong \frac{D}{6 \cdot V_m} \quad (38)$$

$$\Delta MRT/MRT \cong 0.333 \quad (39)$$

or

$$(\Delta MRT/MRT) \times 100\% \cong 33.3\% \quad (40)$$

METHODS

Based on intravenous bolus administration, plasma concentrations of drug were generated by numerical integration of the appropriate differential equations [Eqs. (8a) or (A1) and (A2)]. The fourth-order Runge–Kutta method was used on an IBM XT system for the following models: (a) the one-compartment Michaelis–Menten system and (b) the two-compartment Michaelis–Menten system (Fig. 1). In the first case, simulated data were obtained by assigning numerical values of V_m (433.2 mg/day), K_m (3.62 mg/liter), V (57 liters), and various doses (1–1800 mg). Similarly, in the second case, numerical integrations were carried out by assigning values of V_m (54.2 mg/hr), K_m (36.2 mg/liter), CL_D (distribution clearance, 28.7 liters/hr), V_c (29.5 liters), V_T (20.7 liters), $R = 1$, and various doses (50–30,000 mg). 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)%]. The range of doses used in both cases ensures that typical be-

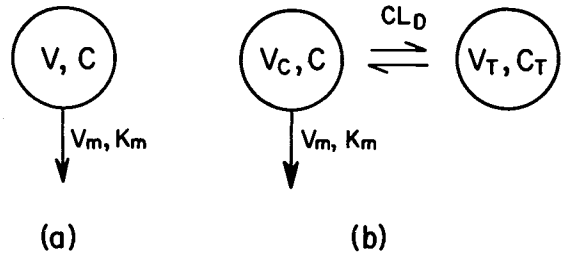

Fig. 1. The basic one (a)- and two (b)-compartment models used for elaboration of MRT relationships. Symbols are defined in the text.

havior would be observed in the limiting low-dose case (pseudo-first-order elimination), for middle doses (the Michaelis–Menten pattern), and in the limiting high-dose case (initial pseudo-zero-order decline). The values of AUC, AUMC, $AUC_{0\rightarrow MRT}$, and $AUC_{0\rightarrow AUMC/AUC}$ were calculated using the LAGRAN program (12). Values for $\overline{CL}$ at different doses were also generated using Eq. (30).

To illustrate differences between MRT and AUMC/AUC, values of MRT, AUMC/AUC, ΔMRT, and (ΔMRT/MRT) × 100% at different doses were calculated by numerical integration to obtain AUC and AUMC and direct use of Eqs. (31) and (25). Values of MRT and AUMC/AUC obtained for the same sets of data were compared.

To confirm that calculations of MRT using AUMC/AUC differ from the newly derived MRT value [Eqs. (21) and (31)], A_e(MRT)% and A_e(AUMC/AUC)% were calculated by using simulated concentration data. In addition, the percentage of the total AUC attained at MRT and the AUMC/AUC were also calculated.

RESULTS

One-Compartment Model

Simulations were performed to demonstrate the relationships between derived and computer-generated values of the pharmacokinetic and moment parameters. Using Eq. (8a), the simulated plasma concentration–time data shown in Fig. 2 were obtained for five drug dose levels. The lower linear curve and the upper saturation curves indicate first-order behavior at the lowest dose and pseudo-zero-order behavior at early time values for the highest dose. Included also in Fig. 2 are curves which show the intermediate Michaelis–Menten behavior at middle doses.

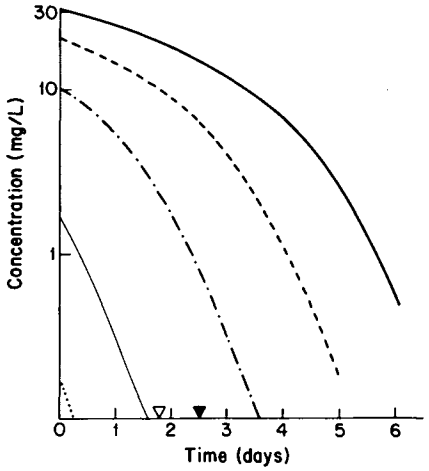

Fig. 2. Simulated concentration–time profiles for the one-compartment model using Eq. (8a) with parameter values of V_m = 433.2 mg/day, K_m = 3.62 mg/liter, V = 57 liters, and D = 1, 100, 600, 1200, and 1800 mg (in ascending order). Triangles denote AUMC/AUC (▽) and MRT (▼) for the 1800-mg dose function.

Table I lists the doses and the parameters, $\overline{CL}$, MRT, and AUMC/AUC calculated using Eqs. (20) and (21) for the simulated data plotted in Fig. 2. As shown in Table I, as the dose decreases, $\overline{CL}$ increases and MRT decreases. In addition, calculations using AUMC/AUC give different values from the method of calculating MRT using Eq. (21). Table I also shows the relationship of ΔMRT to dose. As the dose increases, ΔMRT increases and values of (ΔMRT/MRT) × 100% increase from 0 to 29.4%. This trend is well illustrated by the plot of MRT and AUMC/AUC vs dose shown in Fig. 3. According to Eq. (21b), a plot of MRT versus dose yields a straight line with a slope of $1/(2V_m)$ and an intercept of $V \cdot K_m/V_m$. This leads to one method for calculation of the Michaelis–Menten parameters from such a graph. If V is generated from D/C_0, then

$$V_m = 1/(2 \cdot \text{slope}) \tag{41}$$

Table I. Comparison of MRT and AUMC/AUC Values at Different Doses of Drug for a One-Compartment Michaelis–Menten System

Dose (mg)	$\overline{CL}$ (liters/day)[a]	MRT (days)[b]	AUMC/AUC (days)[c]	ΔMRT (days)[d]	(ΔMRT/MRT) × 100% (%)
1	118.8	0.48	0.48	0	0
100	96.3	0.59	0.54	0.05	8.47
600	48.8	1.17	0.89	0.28	23.9
1200	30.6	1.86	1.34	0.52	28.0
1800	22.3	2.55	1.80	0.75	29.4

[a] Calculated using Eq. (20).
[b] Calculated using Eq. (21).
[c] Calculated by numerical integration using Eq. (1) and data from Fig. 2.
[d] Calculated using Eq. (25).

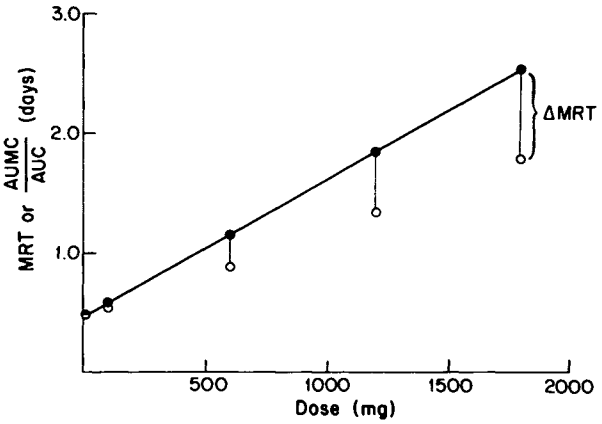

Fig. 3. MRT (●) and AUMC/AUC (○) as a function of dose for the one-compartment Michaelis–Menten system. ΔMRT is denoted by the vertical bar.

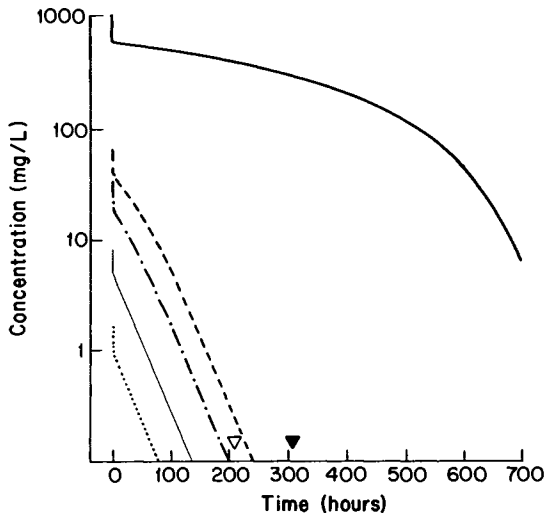

Fig. 4. Simulated concentration–time profiles for the two-compartment model using Eqs. (A1) and (A2) with parameter values of V_m = 54.2 mg/hr, K_m = 36.2 mg/liter, CL_D = 28.7 liters/hr, V_c = 29.5 liters, V_T = 20.7 liters, R = 1, and D = 50, 250, 1000, 2000, and 30,000 mg (in ascending order). Triangles denote AUMC/AUC (▽) and MRT (▼) for the 30,000-mg dose function.

and

$$K_m = V_m \cdot \text{intercept}/V \qquad (42)$$

Recently, the use of Eq. (21) to estimate K_m and V_m has also been suggested by Cutler (10). Alternatively, these parameters can be obtained by nonlinear least-squares regression. The AUMC/AUC relationship to dose in Fig. 3 is nonlinear as anticipated from Eq. (23) but converges to the same low-dose intercept as the MRT value.

Table II contains additional calculations which demonstrate various relationships between MRT and AUMC/AUC as viewed from the perspective of percentages of the dose eliminated and of the total AUC attained at these times. It can be seen that A_e(MRT)% decreases from 63.2 to 52.7%, while A_e(AUMC/AUC)% decreases from 63.2 to 37.9% as the dose increases. Also, the percentage of the total area attained at MRT increases from 63.2 to 73.2%, while the percentage of the total area attained at AUMC/AUC decreases from 63.2 to 57.0% over the same dosage range.

Two-Compartment Model

The same procedures used for the one-compartment model were carried out for a system exhibiting two-compartment distribution and Michaelis–Menten elimination. Figure 4 presents a plot of the simulated concentration–time profiles. As shown in Table III, the relationships among dose, $\overline{CL}$, and MRT observed for the one-compartment system also hold for the two-compartment model. Except at the limiting low-dose case, the methods of calculating MRT and AUMC/AUC yield different values. As also shown in Table III, as the dose increases, ΔMRT diverges and (ΔMRT/MRT) × 100% increases from 0 to 31%. This trend is also illustrated in Fig. 5, showing the linear relationship between MRT and dose, with a slope of $\frac{1}{2} \cdot V_m$ and an intercept of $V_{ss} \cdot K_m/V_m$. In this instance, if low-dose data are available to generate V_{ss} from Eq. (2), then V_m and K_m can be calculated from the slope [Eq. (41)] and intercept [Eq. (42)], where V_{ss} is now used instead of V.

Values of percentage drug eliminated at MRT and AUMC/AUC are listed in Table IV. For the range of doses studied, A_e(MRT)% lies between 51.6 and 63.1%, while A_e(AUMC/AUC)% ranges from 36.0 to 63.0%. In addition, as the dose increases from 50 to 30,000 mg, the percentage

Table II. Comparison of the Percentage of the Administered Dose Eliminated and the Percentage of the Total AUC Attained at MRT and at AUMC/AUC for a One-Compartment Michaelis–Menten System

Dose (mg)	MRT (days)	AUMC/AUC (days)	A_e (MRT) (%)[a]	A_e (AUMC/AUC) (%)[b]	$AUC_{0\to MRT}/AUC$ (%)	$AUC_{0\to AUMC/AUC}/AUC$ (%)
1	0.48	0.48	63.2	63.2	63.2	63.2
100	0.59	0.54	61.0	57.4	65.8	62.4
600	1.17	0.89	56.2	52.3	70.6	58.7
1200	1.86	1.34	53.8	39.7	72.3	57.5
1800	2.55	1.80	52.7	37.9	73.2	57.0

[a] Calculated as $\left[1 - \frac{V \cdot C(t)}{D}\right] \times 100\%$ at t = MRT.

[b] Same as footnote *a* except t = AUMC/AUC.

Table III. Comparison of MRT and AUMC/AUC Values at Different Doses of Drug for a Two-Compartment Michaelis–Menten System

Dose (mg)	$\overline{CL}$ (liters/hr)[a]	MRT (hr)[b]	AUMC/AUC (hr)[c]	ΔMRT (hr)[d]	(ΔMRT/MRT) × 100% (%)
50	1.48	34.0	33.9	0.01	0.03
250	1.40	35.8	34.8	1.00	2.79
1,000	1.17	42.8	38.5	4.30	10.0
2,000	0.97	52.0	43.8	8.20	15.8
30,000	0.16	310.0	214.0	96.0	31.0

[a] Calculated using Eq. (30).
[b] Calculated using Eq. (31).
[c] Calculated by numerical integration using Eq. (1).
[d] Calculated using Eq. (25).

of the total area attained at MRT increases from 63.1 to 73.8%, while the corresponding value at AUMC/AUC decreases from 63.0 to 56.3%.

DISCUSSION

Equations for the MRT of drug in the body have been derived for drugs which follow one- or two-compartment models and are eliminated by single, capacity-limited processes. As shown in Eqs. (28a) and (31), this MRT can be generalized as the quotient of V_{ss} and $\overline{CL}$ as well as a more specific function of V_{ss}, D, V_m, and K_m. In addition, a general, multicompartment equation defining AUMC/AUC was also obtained. This AUMC/AUC is also a complex function of V_{ss}, D, V_m, and K_m but does not equal MRT.

As shown in Tables I and III, the conventional moment approach using Eq. (1) is adequate for estimating the true MRT only in limiting low-dose cases. For middle- and high-dose situations, the AUMC/AUC method underestimates MRT. If one uses AUMC/AUC to calculate the MRT for a drug eliminated from the body in a nonlinear fashion, the calculation error of MRT will range from negligible (0%) at low doses to moderate (33.3%), depending on the severity of the nonlinear condition.

In the limiting cases MRT corresponds to the time for 50.0% (high dose) or 63.2% (low dose) of the administered dose to be eliminated (3). This allows Eq. (6) to be verified by computer simulations. Indeed, we directly examined this (Tables II and IV). In addition, differences in results using the traditional moment method have also been demonstrated. The percentage of the dose eliminated at AUMC/AUC from both the one- and the two-compartment Michaelis–Menten systems ranges from 36.0 to 63.2% instead of from 50.0 to 63.2%. Similarly, Eq. (6) was also verified by computer simulations by examining the percentage of the total AUC attained at MRT (Tables II and IV). In the limiting low-dose case, MRT represents the time required for 63.2% of the total AUC to be attained, while in the limiting high-dose case, the MRT occurs at 75.0% time. Therefore, it can be observed that the MRT in Michaelis–Menten systems is not a constant as occurs in a linear disposition system, but the true MRT values fall in a specific, limited range of times.

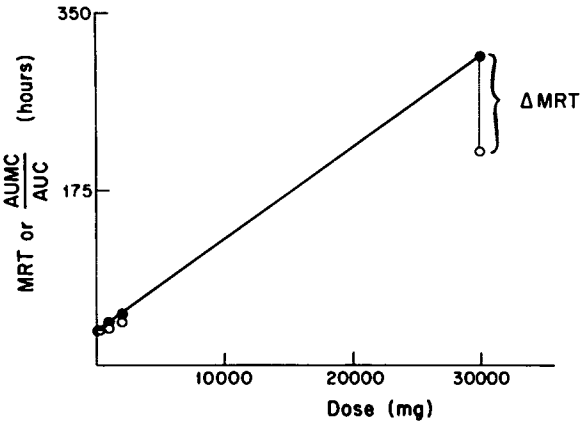

Fig. 5. MRT (●) and AUMC/AUC (○) as a function of dose for the two-compartment Michaelis–Menten system. ΔMRT is denoted by the vertical bar.

Thus, by examining the one- and two-compartment Michaelis–Menten models, we have shown that utilization of AUMC/AUC to calculate the true MRT is limited to linear pharmacokinetics. In contrast, MRT defined by $V_{ss} \cdot AUC/D$ is meaningful in both linear and nonlinear systems. It should be noted that, although the equations developed in this report have been based only on one- and two-compartments, the principal relationships using $\overline{CL}$ and V_{ss} can also be applied to other multiple-compartment systems with linear distribution and Michaelis–Menten elimination. While the derivation methods are not as general as a purely "noncompartmental" approach, they assist in defining the properties of two important models and ease the verification of the relationships by computer simulations.

For multiple-compartment models the upper restriction of A_e(MRT)% or A_e(AUMC/AUC)% of 63.2% is applicable only in those cases where the rate-limiting step is elimination instead of tissue-to-plasma distribution (unpublished observations). Thus, even in the limiting low-dose case, the use of cumulative urinary excretion data will not necessarily give a valid estimate for MRT of drugs following a multiple-compartment model.

One of the major advantages of moment analysis in linear pharmacokinetics is that the area and moment (AUMC) of any curve after intravenous administration of drug can be used to calculate directly CL (D/AUC) and V_{ss} [Eqs. (1) and (2)]. We now can view the complexities which ensue when drug disposition is nonlinear. Firstly, the AUMC no longer easily generates V_{ss} and $\overline{CL}$ is, of course, not a constant. If drug distribution is one compartmental, the calculations of the cardinal pharmacokinetic parameters be-

Table IV. Comparison of the Percentage of the Administered Dose Eliminated and the Percentage of the Total AUC Attained at MRT and at AUMC/AUC for a Two-Compartment Michaelis–Menten System

Dose (mg)	MRT (hr)	AUMC/AUC (hr)	A_e (MRT) (%)[a]	A_e (AUMC/AUC) (%)[b]	$AUC_{0\rightarrow MRT}/AUC$ (%)	$AUC_{0\rightarrow AUMC/AUC}/AUC$ (%)
50	34.0	33.9	63.1	63.0	63.1	63.0
250	35.8	34.8	62.5	61.4	64.0	62.9
1,000	42.8	38.5	60.9	56.7	66.1	62.0
2,000	52.0	43.8	59.5	52.1	68.0	61.0
30,000	310.0	214.0	51.6	36.0	73.8	56.3

[a] Calculated as $\left[1 - \frac{V_c \cdot C(t) + V_T \cdot C_T(t)}{D}\right] \times 100\%$ at t = MRT.

[b] Same as footnote *a* except t = AUMC/AUC.

come modestly involved. First, the true MRT must be obtained from AUC/C_0. Then, $\overline{CL}$ is a concentration-average value when generated from D/AUC but can be related to the fundamental parameters, V_m and K_m, via Eq. (20). The volume of distribution must be obtained from D/C_0. Of value is the ability then to obtain V_m and K_m from a plot of MRT versus dose as depicted in Fig. 3 and using Eqs. (41) and (42). According to Eq. (41), the accuracy of this approach to estimate K_m depends on the certainty of both V_m and V. In a real situation where drug elimination is nonlinear and sampling times are not close to zero, it should be noted that the extrapolation back to zero time to estimate V may not be easy or sufficiently exact.

For multicompartmental drugs, further complications exist. The AUMC/AUC is slightly smaller than the true MRT, and both change with the dose (Fig. 5). A problem is that the MRT cannot be independently generated for all dose levels. First, V_{ss} must be calculated at a low dose using conventional methods such as Eq. (2). This, however, does require that the realities of assay sensitivity versus saturable kinetics be treated. Then this V_{ss} value can be employed to obtain the true MRT for larger doses using Eq. (28). Thus we lose the ease of handling data regardless of the dose and in visualizing the MRT as a constant value on the time axis. However, we gain a direct approach to calculation of V_m and K_m from the slope and intercept of a graph such as shown in Fig. 5. Trying to fit these parameters for multicompartment systems using traditional approaches is otherwise difficult.

We have shown that the AUMC/AUC is an apparent, and not the true, MRT for nonlinear pharmacokinetic systems. However, the AUMC/AUC parameter remains of analytical value owing to its ease of computation and the ability to relate it to the fundamental parameters of the system. It was shown previously (11) and in Eq. (22) for a one-compartment system that AUMC/AUC is defined by the D, V_m, K_m, and V of the drug. As indicated in Eq. (32), we now find that V_{ss} may be substituted for V in this relationship for application to multiple-compartment systems. Together with the AUC value [Eq. (29)], it is feasible to employ these equations in nonlinear regression analysis to generate either least-squares or population average values of V_m, K_m, and V_{ss} for multiple nonlinear drug disposition profiles (11). In addition, since pseudo-first-order elimination occurs at limiting low-dose situations, estimating V_{ss} by using AUMC/AUC and Eq. (2) is feasible for weakly nonlinear systems. It can be noted that in linear pharmacokinetic systems which may actually constitute limiting low-dose nonlinear conditions, $\overline{CL}$ is dose or concentration independent:

$$\lim_{D\rightarrow 0} \overline{CL} = CL = V_m/K_m \qquad (43a, b)$$

where CL is a constant plasma clearance.

Further clarification of the meaning of $\overline{CL}$ is possible. By substituting Eq. (11b) into Eq. (7), we can define $\overline{CL}$ more specifically as follows:

$$\overline{CL} = \frac{\int_0^\infty CL(t) \cdot C(t)dt}{\int_0^\infty C(t)dt} \qquad (44)$$

Although Eq. (7) is analogous to Eq. (44), the latter equation mathematically more rigorously defines $\overline{CL}$. Thus, the so-called "time-average clearance" is actually better described as the "concentration-average" clearance.

The concept of $\overline{CL}$ is of value for several reasons. The $\overline{CL}$ parameter allows two useful parameters, MRT and V_{ss}, to be closely related regardless of the linearity of the system. As shown in Eqs. (7) and (30), D/AUC can also be related to V_m, K_m, and V_{ss} through the $\overline{CL}$ parameter. This allows us to generate values of V_m, K_m, and V_{ss} by computer iteration to characterize nonlinear systems with Michaelis–Menten elimination. Moreover, of considerable importance is that this concept can be applied to any nonlinear processes associated with drug disposition.

Veng-Pedersen and Gillespie (13) and Benet (14) have pointed out that for drugs exhibiting Michaelis–Menten elimination following an intravenous bolus dose, the mean residence time in the central compartment (MRT_c) can be calculated according to the following equation:

$$MRT_c = AUC/C_0 \qquad (45)$$

From Eqs. (28) and (45) it follows that

$$\frac{MRT}{MRT_c} = \frac{V_{ss}}{V_c} \qquad (46)$$

While Eq. (46) has been given for linear systems (14), here we show that this relationship is also true for nonlinear systems.

Although, historically, evidence of nonlinear pharmacokinetics has been discovered as early as those of linear systems, the theoretical development of nonlinear pharmacokinetic concepts has lagged owing to the mathematical and experimental complexity of such systems. This report shows the interrelationships between linear and nonlinear plasma clearance models, amplifies the definition and relevance of the time-average (concentration-average) clearance parameter, derives and further examines the meaning of MRT and AUMC/AUC for these systems, and provides new methods for calculation of Michaelis–Menten parameters in these complex systems.

APPENDIX: MRT FOR THE TWO-COMPARTMENT MODEL

For a drug which follows a two-compartment model having only Michaelis–Menten elimination from the central compartment, the rates of change of drug concentration in plasma [$C(t)$] and in tissue [$C_T(t)$] with time after intravenous bolus administration can be described by the following equations:

$$V_c \cdot \frac{dC(t)}{dt} = \frac{V_m \cdot C(t)}{K_m + C(t)} - CL_D \cdot C(t) + \frac{CL_D}{R} \cdot C_T(t) \quad (A1)$$

$$\frac{V_T}{R} \cdot \frac{dC_T(t)}{dt} = CL_D \cdot C(t) - \frac{CL_D}{R} \cdot C_T(t) \quad (A2)$$

where V_c and V_T are the apparent volumes of distribution of the central and tissue compartments, CL_D is the intercompartmental or distribution clearance, and R is the tissue:plasma distribution ratio. It is assumed that an intravenous bolus dose of drug into the central compartment produces initial conditions of $C_0 = D/V_c$ and $C_T(0) = 0$.

Multiplying both sides of Eq. (A2) by $R \cdot dt$ yields

$$V_T \cdot dC_T(t) = R \cdot CL_D \cdot C(t)dt - CL_D \cdot C_T(t)dt \quad (A3)$$

Since $C_T(0) = 0$ and $C_T(\infty) = 0$, it follows that

$$0 = R \cdot CL_D \cdot \int_0^\infty C(t)dt - CL_D \cdot \int_0^\infty C_T(t)dt \quad (A4)$$

or

$$AUC_T = R \cdot AUC \quad (A5)$$

Multiplying both sides of Eq. (A2) by $R \cdot t \cdot dt$ yields

$$V_T \cdot t \cdot dC_T = R \cdot CL_D \cdot t \cdot C(t)dt - CL_D \cdot t \cdot C_T(t)dt \quad (A6)$$

Integrating over the limits $t = 0$ and $t = \infty$ and solving the equation using the method of integration by parts yields

$$-V_T \cdot AUC_T = R \cdot CL_D \cdot AUMC - CL_D \cdot AUMC_T \quad (A7)$$

or

$$CL_D \cdot AUMC_T - R \cdot CL_D \cdot AUMC = V_T \cdot AUC_T \quad (A8)$$

Multiplying both sides of Eq. (A1) by $t \cdot dt$ yields

$$V_c \cdot t \cdot dC(t) = -\frac{V_m \cdot t \cdot C(t)dt}{K_m + C(t)} - CL_D \cdot t \cdot C(t)dt + \frac{CL_D}{R} \cdot t \cdot C_T(t)dt \quad (A9)$$

or

$$\frac{V_m \cdot t \cdot C(t)dt}{K_m + C(t)} = -V_c \cdot t \cdot dC(t) - CL_D \cdot t \cdot C(t)dt + \frac{CL_D}{R} \cdot t \cdot C_T(t)dt \quad (A10)$$

Integrating from $t = 0$ to $t = \infty$ yields

$$\int_0^\infty \frac{V_m \cdot t \cdot C(t)dt}{K_m + C(t)} = -V_c \cdot \int_0^\infty t \cdot dC(t) - CL_D \cdot \int_0^\infty t \cdot C(t)dt + \frac{CL_D}{R} \cdot \int_0^\infty t \cdot C_T(t)dt \quad (A11)$$

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

$$\int_0^\infty \frac{V_m \cdot t \cdot C(t)dt}{K_m + C(t)} = V_c \cdot AUC - CL_D \cdot AUMC + \frac{CL_D}{R} AUMC_T \quad (A12)$$

Substituting Eq. (A8) into Eq. (A12) yields

$$\int_0^\infty \frac{V_m \cdot t \cdot C(t)dt}{K_m + C(t)} = V_c \cdot AUC + \frac{V_T}{R} \cdot AUC_T \quad (A13)$$

Substituting Eq. (A5) into Eq. (A13) yields

$$\int_0^\infty \frac{V_m \cdot t \cdot C(t)dt}{K_m + C(t)} = AUC \cdot (V_c + V_T) = AUC \cdot V_{ss} \quad (A14a, b)$$

where V_{ss} for this model is $V_c + V_T$.

Multiplying both sides of Eq. (A1) by dt gives

$$V_c \cdot dC(t) = \frac{-V_m \cdot C(t)dt}{K_m + C(t)} - CL_D \cdot C(t)dt + \frac{CL_D}{R} \cdot C_T(t)dt \quad (A15)$$

or

$$\frac{V_m \cdot C(t)dt}{K_m + C(t)} = -V_c \cdot dC(t) - CL_D \cdot C(t)dt + \frac{CL_D}{R} \cdot C_T(t)dt \quad (A16)$$

Integrating over the limits $C(t) = C_0$ at $t = 0$ and $C(t) = 0$ at $t = \infty$ yields

$$\int_0^\infty \frac{V_m \cdot C(t)dt}{K_m + C(t)} = C_0 \cdot V_c - CL_D \cdot AUC + \frac{CL_D}{R} \cdot AUC_T \quad (A17)$$

Substituting Eq. (A5) into Eq. (A17) for AUC_T yields

$$\int_0^\infty \frac{V_m \cdot C(t)dt}{K_m + C(t)} = C_0 \cdot V_c = D \quad (A18a, b)$$

Substituting Eqs. (A14b) and (A18b) into Eq. (5) yields

$$\text{MRT} = \frac{V_{ss} \cdot \text{AUC}}{D} = \frac{V_{ss}}{\overline{\text{CL}}} \qquad (28a, b)$$

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NOMENCLATURE

A_e	Amount of drug eliminated from time zero to the specified time
AUC	Area under the plasma concentration versus time curve
AUC_T	Area under the tissue concentration versus time curve
AUMC	Area under the time · plasma concentration versus time curve
$AUMC_T$	Area under the time · tissue concentration versus time curve
$C(t)$	Plasma concentration at time t
C_0	Zero-time plasma concentration (iv bolus dose)
$C_T(t)$	Tissue concentration at time t
CL	Plasma clearance
$\overline{\text{CL}}$	Time-average or concentration-average clearance
CL(t)	Time-dependent plasma clearance
CL_D	Intercompartmental or distribution clearance
D	Dose
K^{irr}	Fraction of material leaving a compartment per unit of time
K_m	Michaelis–Menten constant
MRT	Mean residence time of drug in the body
ΔMRT	Difference between MRT and AUMC/AUC
MRT_c	Mean residence time of drug in the central compartment
R	Tissue-to-plasma distribution ratio
τ	Time
t	Time
V_c	Apparent volume of distribution, central compartment
V_m	Michaelis–Menten capacity constant
V_T	Apparent volume of distribution, tissue compartment
V_{ss}	Steady-state volume of distribution
$X(\tau)$	Amount of drug in a compartment at time τ
Z_x	Time of exit of drug from a compartment

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