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*Technical Note*

# Mean Residence Time of Drugs Showing Simultaneous First-Order and Michaelis–Menten Elimination Kinetics

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## INTRODUCTION

The mean residence time (MRT) has been used to assess the persistence of drug in the body and as a means of generating other pharmacokinetic parameters. Most such attention has focused on linear pharmacokinetic systems (1–8). Recently, MRT concepts for pharmacokinetic systems with nonlinear drug elimination described by the Michaelis–Menten equation have been proposed (9). The purposes of this communication are (a) to point out that MRT concepts can be extended to pharmacokinetic systems with simultaneous first-order and Michaelis–Menten elimination from the central compartment and (b) to derive the following equation for a drug intravenously injected into a one- or two-compartment system and eliminated from the central compartment by one or more first-order processes in parallel with one or more Michaelis–Menten elimination processes (Fig. 1):

$$\text{MRT} = \frac{V_{ss} \cdot \text{AUC}}{D} \tag{1a}$$

$$= \frac{\text{CL}_1 \cdot \text{AUMC} + \int_0^\infty \text{CL}_N(t) \cdot t \cdot C(t)dt}{\text{CL}_1 \cdot \text{AUC} + \int_0^\infty \text{CL}_N(t) \cdot C(t)dt} \tag{1b}$$

$$= \frac{\text{CL}_1 \cdot \text{AUMC}}{D} + \frac{\int_0^\infty \text{CL}_N(t) \cdot t \cdot C(t)dt}{D} \tag{1c}$$

where $V_{ss}$ is the volume of distribution at steady state, AUC is the area under the plasma concentration–time curve, $D$ is the dose, $\text{CL}_1$ is the sum of clearances for all linear (i.e., first-order) elimination processes of the drug, AUMC is the area under the first moment curve, and $\text{CL}_N(t)$ is the sum of clearances for all nonlinear (i.e., Michaelis–Menten) elimination processes of the drug {i.e., $\text{CL}_N(t) = \Sigma_{i=1}^{n} V_{m,i}/[K_{m,i} + C(t)]$, where $V_{m,i}$ and $K_{m,i}$ are the theoretical maximum rate and the Michaelis constant of the $i$th nonlinear elimination process}.

## THEORETICAL

Let $C(t)$ denote the plasma concentration resulting from an intravenous administration of a drug into a one-compartment model with apparent volume of distribution $V$ (Fig. 1). The rate of change of drug concentration with time ($t$) can be described by the following equation:

$$V \cdot \frac{dC(t)}{dt} = -\text{CL}_1 \cdot C(t) - \text{CL}_N(t) \cdot C(t) \tag{2a}$$

$$= -\text{CL}(t) \cdot C(t) \tag{2b}$$

where $\text{CL}(t)$ is the sum of clearances of the drug from the body and equals $\text{CL}_1 + \text{CL}_N(t)$. By integration techniques, the following equations can be derived from Eqs. (2a) and (2b):

$$\int_0^\infty \text{CL}(t) \cdot t \cdot C(t)dt = V \cdot \text{AUC} = \text{CL}_1 \cdot \text{AUMC} + \int_0^\infty \text{CL}_N(t) \cdot t \cdot C(t)dt \tag{3}$$

$$\int_0^\infty \text{CL}(t) \cdot C(t)dt = D = \text{CL}_1 \cdot \text{AUC} + \int_0^\infty \text{CL}_N(t) \cdot C(t)dt \tag{4}$$

Dividing Eq. (3) by Eq. (4) yields

$$\frac{\int_0^\infty \text{CL}(t) \cdot t \cdot C(t)dt}{\int_0^\infty \text{CL}(t) \cdot C(t)dt} = V \cdot \text{AUC}/D \tag{5a}$$

$$= \frac{\text{CL}_1 \cdot \text{AUMC} + \int_0^\infty \text{CL}_N(t) \cdot t \cdot C(t)dt}{\text{CL}_1 \cdot \text{AUC} + \int_0^\infty \text{CL}_N(t) \cdot C(t)dt} \tag{5b}$$

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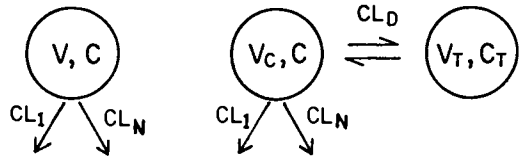


Fig. 1. The one- and two-compartment models used for evaluation of MRT of drugs. Symbols are defined in the text.

$$= \frac{CL_1 \cdot AUMC}{D} + \frac{\int_0^\infty CL_N(t) \cdot t \cdot C(t)dt}{D} \quad (5c)$$

For an intravenous drug, the MRT can be calculated as follows (9):

$$MRT = \frac{\int_0^\infty CL(t) \cdot t \cdot C(t)dt}{\int_0^\infty CL(t) \cdot C(t)dt} \quad (6)$$

Substituting Eq. (6) into Eq. (5) yields

$$MRT = \frac{V \cdot AUC}{D}$$

$$= \frac{CL_1 \cdot AUMC + \int_0^\infty CL_N(t) \cdot t \cdot C(t)dt}{CL_1 \cdot AUC + \int_0^\infty CL_N(t) \cdot C(t)dt}$$

$$= \frac{CL_1 \cdot AUMC}{D} + \frac{\int_0^\infty CL_N(t) \cdot t \cdot C(t)dt}{D} \quad (7a, b, c)$$

For a one-compartment system, since $V$ equals $V_{ss}$, Eq. (7) is identical to Eq. (1).

The following equation has been derived for drugs obeying a one-compartment system with simultaneous first-order and Michaelis–Menten elimination (10,11):

$$AUC = \frac{D}{CL_1} - \frac{V_m \cdot V}{CL_1^2} \cdot ln\left[1 + \frac{CL_1 \cdot D}{V \cdot (V_m + CL_1 \cdot K_m)}\right] \quad (8)$$

Substituting Eq. (8) into Eq. (7a) yields

$$MRT = \frac{V}{CL_1} - \frac{V_m \cdot V^2}{D \cdot CL_1^2} \cdot ln\left[1 + \frac{CL_1 \cdot D}{V \cdot (V_m + CL_1 \cdot K_m)}\right] \quad (9)$$

An analogous expression for MRT has been described by Cutler (7). Similarly, for a drug following an analogous two-compartment system (Fig. 1), Eq. (4) and the following equation can also be derived by using the derivation technique shown previously (9):

$$\int_0^\infty CL(t) \cdot t \cdot C(t)dt = V_{ss} \cdot AUC = CL_1 \cdot AUMC + \int_0^\infty CL_N(t) \cdot t \cdot C(t)dt \quad (10)$$

Dividing Eq. (10) by Eq. (4) yields

$$\frac{\int_0^\infty CL(t) \cdot t \cdot C(t)dt}{\int_0^\infty CL(t) \cdot C(t)dt} = V_{ss} \cdot AUC/D \quad (11a)$$

$$= \frac{CL_1 \cdot AUMC + \int_0^\infty CL_N(t) \cdot t \cdot C(t)dt}{CL_1 \cdot AUC + \int_0^\infty CL_N(t) \cdot C(t)dt} \quad (11b)$$

$$= \frac{CL_1 \cdot AUMC}{D} + \frac{\int_0^\infty CL_N(t) \cdot t \cdot C(t)dt}{D} \quad (11c)$$

Combining Eqs. (6) and (11) yields Eq. (1).

For both the one- and the two-compartment systems, let $f_1$ and $f_N$ be the fractions of the dose eliminated linearly and nonlinearly. From Eq. (4), it follows that:

$$f_1 = CL_1 \cdot AUC/D \quad (12)$$

and

$$f_N = 1 - f_1$$
$$= 1 - (CL_1 \cdot AUC/D)$$
$$= \int_0^\infty CL_N(t) \cdot C(t)dt/D \quad (13a, b, c)$$

Let $MRT_1$ and $MRT_N$ be the mean residence times of drug molecules eliminated linearly and nonlinearly. From Eqs. (1c), (12), and (13), it follows that

$$MRT_1 = CL_1 \cdot AUMC/D = f_1 \cdot AUMC/AUC \quad (14a, b)$$

and

$$MRT_N = \int_0^\infty CL_N(t) \cdot t \cdot C(t)dt/D \quad (15a)$$

$$= f_N \cdot \left(\int_0^\infty CL_N(t) \cdot t \cdot C(t)dt / \int_0^\infty CL_N(t) \cdot C(t)dt\right) \quad (15b)$$

Substituting Eqs. (14a) and (15a) into Eq. (1c) yields

$$MRT = MRT_1 + MRT_N \quad (16)$$

Dividing both sides of Eq. (16) by MRT yields

$$1 = MRT_1/MRT + MRT_N/MRT \quad (17)$$

Let $MRT_{th,1}$ be the theoretical mean residence time which would have occurred had $CL_1$ been the sole elimination process. Thus,

$$MRT_{th,1} = V_{ss}/CL_1 \quad (18)$$

or

$$CL_1 = V_{ss}/MRT_{th,1} \quad (19)$$

Substituting Eq. (19) into Eq. (12) yields

$$f_1 = V_{ss} \cdot AUC/(D \cdot MRT_{th,1}) \quad (20)$$

or

$$f_1 \cdot MRT_{th,1} = V_{ss} \cdot AUC/D \quad (21)$$

Table I. Mean Residence Times and Elimination Fractions of Three Drugs

| Drug | Dose (mg) | $MRT_I$ (hr) | $MRT_N$ (hr) | $f_I$ | $f_N$ | $MRT_I/MRT$ | $MRT_N/MRT$ | MRT (hr) |
|---|---|---|---|---|---|---|---|---|
| Phenytoin[a] | 322 | 0.1 | 26.4 | 0.002 (0.24, 0.10)[b] | 0.998 (0.76, 0.90) | 0.002 | 0.998 | 26.5 |
| Salicylic acid[a] | 3000 | 2.76 | 12.01 | 0.25 (0.27) | 0.75 (0.73) | 0.19 | 0.81 | 14.77 |
| 4-Hydroxybutyric-acid[a] | 1500 | 0.23 | 0.17 | 0.65 | 0.35 | 0.56 | 0.44 | 0.40 |
| 4-Hydroxybutyric acid | 2900 | 0.30 | 0.16 | 0.74 | 0.26 | 0.64 | 0.36 | 0.46 |

[a] Values of parameters for simulations were obtained from Refs. 12–14.
[b] Values in parentheses are mean elimination fractions obtained from Refs. 13, 15, and 16.

Combining Eqs. (1a) and (21) gives

$$MRT = f_I \cdot MRT_{th,I} \tag{22}$$

It should be noted that, although Eqs. (1), (16), and (22) derived in this report have been based only on one- and two-compartment systems, they are also meaningful for any multicompartment model exhibiting simultaneous nonlinear and linear elimination kinetics from the central compartment. In limiting low-dose or pseudo-first-order situations where $CL_N(t)$ becomes constant, $CL_N$, Eq. (1) reduces to

$$MRT = \frac{V_{ss} \cdot AUC}{D} = \frac{AUMC}{AUC} = \frac{(CL_I + CL_N) \cdot AUMC}{D} \tag{23a, b, c}$$

Thus, Eq. (1) yields the expected relationships for drugs exhibiting linear disposition kinetics. In contrast, when all elimination occurs by Michaelis–Menten processes, Eq. (1) reduces to

$$MRT = V_{ss} \cdot AUC/D = \int_0^\infty CL_N(t) \cdot t \cdot C(t)dt / \int_0^\infty CL_N(t) \cdot C(t)dt = \int_0^\infty CL_N(t) \cdot t \cdot C(t)dt/D \tag{24a, b, c}$$

An analogous expression for MRT has been derived previously for bolus drugs exhibiting only Michaelis–Menten elimination (9).

*Applications.* Using Eqs. (1), (14a), (16), (12), and (13a), the residence time parameters and fractions were calculated for three drugs (12–14) whose elimination from a one-compartment model occurs by one or more apparent first-order processes in parallel with one or more Michaelis–Menten processes (Table I). The influence of the dose on elimination patterns has been readily demonstrated with salicylic acid (13); $f_I$ increases and $f_N$ decreases with the dose. The same applies to 4-hydroxybutyric acid and any other drug with similar parallel elimination processes. As doses of 4-hydroxybutyric acid increase from 1500 to 2900 mg, $f_N$ decreases from 0.35 to 0.26, while $f_I$ increases from 0.65 to 0.74 (Table I). As expected, as the dose increases, more of the drug is removed by linear rather than nonlinear pathways. This is also demonstrated by the increase in $MRT_I$/MRT and decrease in $MRT_N$/MRT with the increase in dose. Table I also lists mean elimination fractions for phenytoin (15,16) and salicylic acid (13) obtained from renal excretion of a metabolite(s) of these two drugs. Phenytoin is at least 76–90% hydroxylated (15,16). Assuming that this is the sole saturable metabolic pathway, one would expect the fraction $f_N$ to exceed the value of 0.9. Indeed, the $f_N$ value (0.998) obtained for phenytoin from the simulated plasma data is reasonably close to this range. As shown in Table I, the fractions $f_I$ and $f_N$ calculated for salicylic acid from simulated plasma data also agree well with the values obtained from renal excretion of metabolites by Levy *et al.* (13). No $f_I$ and $f_N$ values for 4-hydroxybutyric acid obtained from renal excretion data have been reported. Thus, no comparison was made.

Simulations were also performed to demonstrate the additive properties of the mean residence time described in Eq. (16). The plasma amount–time curves shown in Fig. 2 were constructed by numerical integration of Eq. (2) for a hypothetical drug based on the properties of salicylic acid (13). The upper plasma amount–time profile of total drug shows a distinct nonlinear decline characteristic of a compound eliminated by a substantive nonlinear process. The plasma amount–time profiles of the two fractions of the drug eliminated linearly and nonlinearly show the expected nonparallel decline, reflecting the concentration-dependent effects of the nonlinear process causing unequal removal of the two portions of drug. As shown in Table I and Fig. 2, the MRT of salicylic acid is the summation of its $MRT_I$ and $MRT_N$.

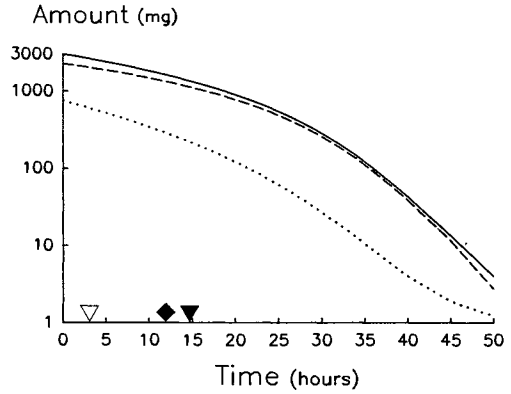


Fig. 2. Simulated amount–time profiles for a hypothetical drug based on the properties of salicylic acid (see Table I). Lines depict (——) total drug eliminated by simultaneous linear and nonlinear processes, (- - -) drug eliminated nonlinearly, (· · ·) drug eliminated linearly. Symbols denote MRT (▼), $MRT_N$ (◆), and $MRT_I$ (▽).

In summary, equations to calculate the MRT of intravenous drugs following one- or two-compartment systems with simultaneous first-order and Michaelis–Menten elimination have been derived. This MRT can be calculated from $V_{ss}$, AUC, and $D$; it can be partitioned into $MRT_I$ and $MRT_N$ and is also related to $MRT_{th,I}$ by $f_I$. In addition, the influences of the dose on elimination and residence time patterns of actual and hypothetical drugs have been demonstrated.

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