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Report

Application of Moment Analysis to Nonlinear Drug Disposition Described by the Michaelis–Menten Equation

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An equation for the mean residence time (MRT) of drug in the body is derived for the system where drug is injected intravenously into a one-compartment model and eliminated by a single, capacity-limited process. This MRT is a complex function of dose, volume, V_m, and K_m but degenerates into the classical volume/clearance expression under limiting low-dose conditions ($K_m \gg C_0$). The equation was validated by comparison of the MRT obtained by direct calculation versus numerical area estimation for simulated data. The equation may be useful analytically in the estimation of the fundamental Michaelis–Menten parameters, V_m and K_m, from experimental data.

KEY WORDS: mean residence time; pharmacokinetics; Michaelis–Menten elimination; one-compartment model.

INTRODUCTION

Statistical moment analysis has become extensively used as a noncompartmental approach to the estimation of pharmacokinetic parameters such as plasma clearance (CL), mean residence time (MRT), and steady-state volume of distribution (V_{ss}) (1–4). The generation of these parameters by conventional methods has been limited to linear pharmacokinetic systems, and they have been qualified as dose- and time-average values when drug disposition is nonlinear (4,5). The purpose of this communication is to derive the mathematical equation for the MRT of a drug injected intravenously into a one-compartment system and eliminated by a single, capacity-limited process based on the Michaelis–Menten equation. Also, we will demonstrate the analytical applicability of the derived MRT equation for generating the relevant pharmacokinetic parameters for this type of disposition system.

THEORETICAL

The condition is assumed of intravenous injection of a dose of drug (D) into a one-compartment system of apparent volume of distribution, V. Drug elimination occurs by a single saturable, Michaelis–Menten process with a capacity constant, V_m (units = amount/time), and coefficient, K_m (units = concentration). The rate of decline of drug concentrations (C) with time (t) can be described by the equation

$$-V \cdot \frac{dC}{dt} = \frac{V_m \cdot C}{K_m + C} \tag{1}$$

with drug concentration at the initial condition of

$$C_0 = D/V \tag{2}$$

The objective is to derive the coefficients of MRT as defined (1) by

$$\text{MRT} = \int_0^\infty t \cdot C \cdot dt \,/\, \int_0^\infty C \cdot dt \tag{3a}$$

or

$$\text{MRT} = \text{AUMC/AUC} \tag{3b}$$

The AUC value has been derived previously by Wagner (6) for this system as

$$\text{AUC} = V \cdot \frac{C_o}{V_m} \cdot \left(\frac{C_o}{2} + K_m\right) \tag{4}$$

[However, it should be noted that Wagner's equation differs from Eq. (4) by his incorporation of V into V_m to produce a hybrid V_m term with units of amount/volume/time rather than amount/time.]

In order to generate AUMC, rearrangement of Eq. (1) gives

$$-V \cdot \frac{K_m + C}{V_m} \cdot dC = C \cdot dt \tag{5}$$

Multiplying both sides of Eq. (5) by the variable, t, yields

$$\frac{-V}{V_m} \cdot K_m \cdot t \cdot dC - \frac{V}{V_m} \cdot C \cdot t \cdot dC = t \cdot C \cdot dt \tag{6}$$

It follows that

$$-V \cdot \frac{K_m}{V_m} \int_0^\infty t \cdot dC - \frac{V}{V_m} \int_0^\infty C \cdot t \cdot dC = \int_0^\infty t \cdot C \cdot dt \tag{7}$$

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which, when solved over the integration limits of $C = C_0$ at $t = 0$ and $C = 0$ at $t = \infty$ using the method of integration by parts, becomes

$$V \cdot \frac{K_m}{V_m} \int_0^\infty C \cdot dt + \frac{V^2}{2V_m} \cdot \left(\frac{K_m \cdot C_0^2}{2V_m} + \frac{C_0^3}{3V_m} \right) = \int_0^\infty t \cdot C \cdot dt \quad (8)$$

By substituting the components of Eqs. (3) and (4) into Eq. (8), the result is

$$V \cdot \frac{K_m}{V_m} \cdot \text{AUC} + V \cdot \frac{C_0}{6V_m} \cdot \frac{2C_0 + 3K_m}{C_0 + 2K_m} \cdot \text{AUC} = \text{AUMC} \quad (9)$$

And on rearranging the final relationship is

$$\text{MRT} = \frac{\text{AUMC}}{\text{AUC}} = V \cdot \frac{K_m}{V_m} + \frac{V \cdot C_0}{6V_m} \cdot \frac{2C_0 + 3K_m}{C_0 + 2K_m} \quad (10)$$

In the limiting low-dose case such that K_m is much larger than C_0, Eq. (10) reduces to

$$\text{MRT} = V \cdot K_m / V_m \quad (11)$$

Also, when $K_m \gg C$, Eq. (1) can be shown to yield

$$\text{CL} = V_m / K_m = D/\text{AUC} \quad (12)$$

The latter two equations are compatible with the classic dispositional MRT relationship for a mammillary system having a linear clearance process occurring from the plasma compartment:

$$\text{MRT} = V_{ss}/\text{CL} \quad (13)$$

where $V = V_{ss}$ for a one-compartment model.

METHODS

An integrated form of the Michaelis–Menten equation describing the time course of drug concentration in a one-compartment system was initially presented by Henri in 1902 (7):

$$V \cdot \frac{C_0 - C}{V_m} + V \cdot \frac{K_m}{V_m} \cdot \ln \frac{C_0}{C} = t \quad (14)$$

Simulated concentration, time data based on Eq. (14) were generated by assigning numerical values of V_m (433.2 mg/da), K_m (3.62 mg/liter), and C_0. For the latter, a V of 57 liters and doses (D) of 30, 100, 600, 1200, and 1800 mg were used.

To validate Eq. (10), values of MRT at different doses were generated by two approaches: (a) calculation of AUMC and AUC by LaGrange cubic polynomial approximation (8) for the sets of simulated C, t data and (b) calculation of MRT directly from Eq. (10). Values of MRT obtained from both methods for the same sets of parameters, V_m, K_m, and C_0, were compared.

To illustrate the analytical applicability of Eq. (10), values of V_m and K_m were iteratively fitted (9), where MRT values calculated by means of the LAGRAN program at different doses were employed as the dependent variable and C_0 (D/V) served as the independent variable.

RESULTS

The simulated concentration versus time data shown in Fig. 1 for five drug dose levels were generated using Eq. (14). The curves show the typical Michaelis–Menten pattern, with linear disposition occurring at the low dose and a saturation curve seen as the drug concentrations appreciably exceed the K_m value of 3.62 mg/liter. The parameters, D, C_0, AUC, AUMC, and MRT, which characterize the curves in Fig. 1 are listed in Table I. As shown in the table, both methods of calculating MRT, namely, numerical integration and direct use of Eq. (10), give the same values at each dose.

We next sought to recapture the assigned V_m and K_m values by means of iterative fitting of Eq. (10) to the measured values of MRT. The results obtained were V_m = 432.06 mg/da and K_m = 3.60 mg/liter, which are essentially identical to the corresponding values used to originally generate the curves.

DISCUSSION

The pharmacokinetic term MRT, the average duration of time that drug molecules remain in the body after introduction into the plasma compartment, is a constant in linear pharmacokinetic systems as it relates directly to constant parameters such as V_{ss} and CL as shown in Eq. (13). The calculation of MRT using Eq. (3) has not been considered to be directly meaningful for a saturable elimination process. Indeed, this has been verified by our demonstration that the AUMC/AUC ratio for a plasma disposition profile of a Michaelis–Menten process is related to dose, V_m, and K_m in a complex fashion [Eq. (10)]. However, by knowing the structure of the MRT equation for a nonlinear process, it is possible to utilize such a relationship in an iterative analytical fashion, i.e., to estimate values of V_m and K_m given C_0, AUC, and AUMC. Unfortunately, because the function produces a cubic polynomial, it is not convenient to rearrange Eq. (10) to generate V_m and K_m.

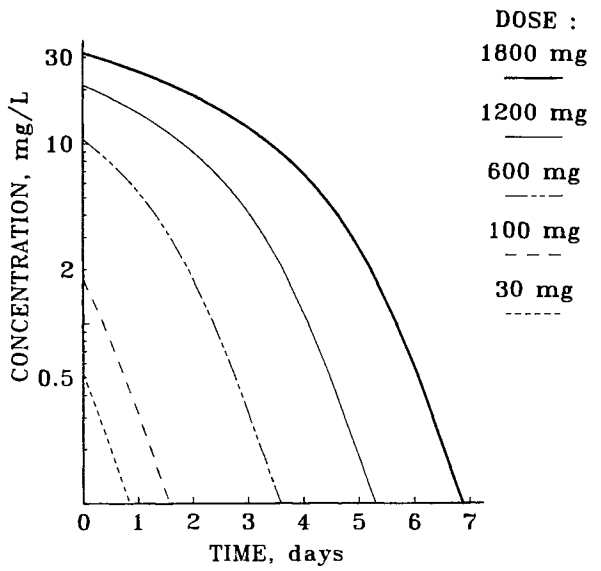

Fig. 1. Simulated concentration–time profiles using Eq. (14) with V_m = 433.20 mg/da, K_m = 3.62 mg/liter, V_d = 57 liters, and the indicated drug doses.

Table I. Comparison of MRT Values Predicted by Eq. (10) and Those Obtained by Numerical Integration of Simulated Data at Different Doses of Drug

Dose (mg)	C_0 (mg/liter)	AUC[a] (mg · da/liter)	AUMC[a] (mg · da²/liter)	MRT[a] (da)	MRT[b] (da)
1800	31.58	80.75	145.25	1.80	1.80
1200	21.05	39.16	52.44	1.34	1.34
600	10.53	12.29	10.96	0.89	0.89
100	1.75	1.03	0.56	0.54	0.54
30	0.53	0.27	0.13	0.49	0.49

[a] Estimated by numerical integration using Eq. (3) and data from Fig. 1.
[b] Predicted from Eq. (10).

This report further demonstrates the utility of moment analysis as an analytical method for resolving the fundamental parameters of any pharmacokinetic model. Moment analysis can often be used along with the more conventional approaches of deriving explicit equations to describe the time course of plasma, tissue, and excretory drug concentrations or amounts and the use of computer numerical integration techniques to arrive at parameters of assigned differential equations. As indicated here it is often feasible to develop solutions for the moments of a pharmacokinetic function which, in turn, can be used to solve for the basic clearance and volume parameters of interest (4). Further efforts are needed to extend this approach to additional routes of administration and polyexponential disposition processes.

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REFERENCES

1. K. Yamaoka, T. Nakagawa, and T. Uno. *J. Pharmacokin. Biopharm.* 6:547–558 (1978).
2. L. Z. Benet and R. L. Galeazzi. *J. Pharm. Sci.* 68:1071–1074 (1979).
3. N. A. Lassen and W. Perl. *Tracer Kinetic Methods in Medical Physiology,* Raven Press, New York, 1979, pp. 40–99.
4. W. J. Jusko. In W. E. Evans, J. J. Schentag, and W. J. Jusko (eds.), *Applied Pharmacokinetics,* Applied Therapeutics, Spokane, 1986, pp. 9–54.
5. A. Mangione, D. Boudinot, R. M. Schultz, and W. J. Jusko. *Antimicrob. Agents Chemother.* 21:428–435 (1982).
6. J. G. Wagner. *J. Pharmacokin. Biopharm.* 1:103–121 (1973).
7. V. Henri. *C.R. Hebd. Seanc. Acad. Sci. (Paris)* 135:916–919 (1902).
8. M. L. Rocci and W. J. Jusko. *Comp. Prog. Biomed.* 16:203–216 (1983).
9. C. M. Metzler, G. L. Elfring, and A. J. McEwen. *Biometrics* 30:562 (1974).