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Letter

Calculations and Application of Mean Residence Times for Drugs Which Demonstrate One-Compartment Distribution and Michaelis–Menten Elimination

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In a recent report (1) the mean residence time (MRT) for a drug which demonstrates one-compartment distribution and Michaelis-Menten elimination was defined incorrectly as

$$\text{MRT} = \text{AUMC/AUC} \tag{1}$$

where AUC is the area under the plasma concentration–time curve and AUMC is the area under the corresponding first-moment curve. One of the assumptions of this equation is that clearance is linear (2,3). Using the derivation of Gillespie and Veng-Pedersen (3) (not presented here for sake of brevity), this crucial assumption is manifested in the following equation [corresponding to Eq. (8) in Ref. 4]:

$$\text{MRT} = \frac{\int t \cdot \text{CL}(t) \cdot c(t)\, dt}{\int \text{CL}(t) \cdot c(t)\, dt} \tag{2}$$

where t is time, CL(t) is clearance, and $c(t)$ is systemic drug concentration. If CL(t) is constant, as it is with linear kinetics, it may be brought outside the integral in both the numerator and the denominator and Eq. (1) follows immediately. However, with Michaelis–Menten kinetics CL(t) is not constant, but is a function of $c(t)$, and so the clearance term may not be taken outside of the integral and divided out of Eq. (2).

Nevertheless, the MRT of a drug which conforms to a single compartment of distribution can be calculated. The MRT of a drug can be decomposed into the following equation:

$$\text{MRT} = \text{MRTC} + \text{MRTP} \tag{3}$$

where MRTC is the mean residence time of the drug in the central compartment and MRTP is the mean residence time of the drug in the peripheral compartments. In the case where the kinetics of a drug follow a one-compartment model, MRTP is nonexistent, thus rendering MRT equivalent to MRTC. Veng-Pedersen and Gillespie (4) proved that the MRTC (and hence the MRT of a one-compartment model) can be calculated by

$$\text{MRTC} = \text{MRT (one-compartment model)} = \text{AUC}/C_o \tag{4}$$

In Eq. (4), C_o is defined by the following equation:

$$C_o = D/V \tag{5}$$

where D is the dose and V is the volume of distribution. These authors showed that Eq. (4) holds irrespective of whether the drug undergoes linear or nonlinear disposition kinetics. The AUC for a drug following single-compartment distribution with Michaelis–Menten elimination was shown by Wagner (5) to be

$$\text{AUC} = V(C_o/V_m)(C_o/2 + K_m) \tag{6}$$

where V_m and K_m are the capacity constant and coefficient of the nonlinear elimination process. The MRT can then be calculated as

$$\text{MRT} = (V/V_m)(C_o/2 + K_m) \tag{7}$$

Recently this equation has also been independently developed by other investigators (6–8).

By substituting Eq. (5) into Eq. (7), one can obtain

$$\text{MRT} = D/2V_m + K_m(V/V_m) \tag{8}$$

As indicated by Cutler (7), a plot of MRT versus dose will be linear, with a slope of $\frac{1}{2}V_m$ and an intercept of $K_m/(V/V_m)$.

Application of Eq. (1) rather than Eq. (7) or (8) will result in underestimation of the MRT for a one-compartment model with Michaelis–Menten elimination.

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