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Simple relationships between parameters representing input and output rates in linear one-compartment open model

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The available classical relationships between parameters of input and output rates for the linear one-compartment model are of a complex semilogarithmic nature. One such relationship is given below (Gibaldi and Perrier, 1975)

$$t_{max} = \frac{\ln(k_a/K)}{k_a - K} \qquad (1)$$

where t_{max} is time of peak blood level or peak urinary excretion rate of drug, and k_a and K are first-order absorption (input) and elimination (output) rate constants, respectively. In the cases where the value of t_{max} is known and the value of either k_a or K is unknown, the calculation of the unknown parameter from Eqn. 1 is not easy and is based on trial and error (Carstensen, 1977).

In this report some simple non-logarithmic relationships between the parameters representing rates of input (absorption rate constant and absorption half-life) and output (elimination rate constant and biological half-life) as well as a readily solvable semilogarithmic relationship between t_{max} and the parameters for the model are derived. Some theoretical conclusions drawn from the latter relationship are also given.

The drug concentration in the blood, C, for the model when $k_a > K$ is given by Eqn. 2 (Gibaldi and Perrier, 1975)

$$C = \frac{k_a FD}{V(k_a - K)} \cdot (e^{-Kt} - e^{-k_a t}) \qquad (2)$$

in which t is time, F is fraction of dose D absorbed, and V is the apparent volume of distribution of the drug.

The equation describing the residual plot for the estimation of the value of k_a is as follows (Gibaldi and Perrier, 1975):

$$C_r = \frac{k_a FD}{V(k_a - K)} \cdot e^{-k_a t} \tag{3}$$

where C_r is the residual concentration.

It is obvious that the residual plot and/or the extrapolated residual plot can intersect the absorptive phase of the blood level curve and that at the point of intersection C_r equals C. Therefore,

$$\frac{k_a FD}{V(k_a - K)} \cdot e^{-k_a T} = \frac{k_a FD}{V(k_a - K)} \cdot (e^{-KT} - e^{-k_a T}) \tag{4}$$

where T is the corresponding time for the point of intersection. Simplification and rearrangement of Eqn. 4 would yield:

$$2 \cdot e^{-k_a T} = e^{-KT} \tag{5}$$

Taking logarithms of both sides of Eqn. 5 and solving the resulting equation for T would give Eqn. 6.

$$T = \frac{\ln 2}{k_a - K} \tag{6}$$

and since $\ln 2 = 0.693$, therefore:

$$T = \frac{0.693}{k_a - K} \tag{7}$$

According to Eqn. 7 the relationship between k_a and K is given by:

$$k_a = K + \frac{0.693}{T} \tag{8}$$

Using the relationships $k_a = 0.693/(t_{1/2})_a$ and $K = 0.693/(t_{1/2})_b$, Eqn. 8 can be converted into Eqn. 9.

$$\frac{1}{(t_{1/2})_a} = \frac{1}{(t_{a/2})_b} + \frac{1}{T} \tag{9}$$

or

$$(t_{1/2})_a = \frac{T(t_{1/2})_b}{T + (t_{1/2})_b} \tag{10}$$

where $(t_{1/2})_a$ and $(t_{1/2})_b$ are the absorption and biological half-lives of the drug, respectively.

Combination of Eqns. 1 and 6 will result in Eqn. 11 from which one may draw some theoretical conclusions.

$$t_{max} = T\frac{\ln(k_a/K)}{\ln 2} \quad (11)$$

As is evident from Eqn. 11, when $k_a/K = 2$ the value of T is equal to t_{max}. In other words, the residual line will pass through the peak of the blood level curve. Also, when $2 > k_a/K > 1$ and $k_a/K > 2$, the residual plot will intersect the blood level curve at $T > t_{max}$ and $T < t_{max}$, respectively.

When there is not enough data at the absorptive phase, the value of T can be calculated from the peak blood level or peak urinary excretion rate and the postabsorptive data as follows.

The following equations have been given an a previous report (Barzegar-Jalali, 1982):

$$k_a = \frac{KC_{t_{max}}}{C_{t_{max}} - C_{max}} \quad (12)$$

$$k_a = \frac{K\dot{U}_{t_{max}}}{\dot{U}_{t_{max}} - \dot{U}_{max}} \quad (13)$$

where C_{max} = peak blood level, $C_{t_{max}}$ = a concentration on extrapolated linear post-absorptive blood level plot corresponding to t_{max}, $\dot{U}_{max}$ = maximum value of urinary excretion rate, and $\dot{U}_{t_{max}}$ = an excretion rate on extrapolated linear postabsorptive urinary excretion rate plot corresponding to t_{max}.

Substitution for k_a from Eqn. 8 into Eqns. 12 and 13 and solving the resulting equations for T would result in Eqns. 14 and 15

$$T = \frac{0.693}{K} \cdot \left(\frac{C_{t_{max}}}{C_{max}} - 1\right) \quad (14)$$

$$T = \frac{0.693}{K} \cdot \left(\frac{\dot{U}_{t_{max}}}{\dot{U}_{max}} - 1\right) \quad (15)$$

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