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Short Communications

Theoretical consideration for the cases where absorption rate constant approaches elimination rate constant in the linear one-compartment open models

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The drug concentrations in blood for the linear one-compartment open models with unequal and equal absorption and elimination rate constants are described by Eqns. 1, and 2, respectively (Gibaldi and Perrier, 1975)

$$C = \frac{k_aFD}{(k_a - K)V}[\exp(-Kt) - \exp(-k_at)] \qquad (1)$$

$$C = \frac{kFD}{V}t\exp(-kt) \qquad (2)$$

where C is drug concentration in blood at time t, k_a is a first-order absorption rate constant of drug, K is a first-order elimination rate constant of drug, F is fraction of dose D absorbed, V is the apparent volume of distribution of drug, and k is either absorption or elimination rate constant (for the case when $k_a = K$).

Recently Bialer (1980) has derived an equation for determining whether k_a is equal to K and therefore for deciding which equation (Eqn. 1 or 2) must be used to calculate the relevant pharmacokinetic parameters. For the cases when $k_a = K$, the equation of Bialer (1980) states that:

$$C_{max} \cdot t_{max} = \frac{F \cdot D}{e \cdot V \cdot k} = \frac{(AUC)_0^\infty}{e} \qquad (3)$$

in which C_{max} is peak drug concentration, t_{max} is time of peak drug concentration, $(AUC)_0^\infty$ is area under the blood level curve between times 0 and ∞ (infinity), and e is base of natural logarithms.

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In order to check Eqn. 3, data was generated by means of an electronic calculator based on Eqn. 1 (assuming $FD/V = 50$ units, $k_a = 0.8$ units, $K = 0.5$ units) and Eqn. 2 (assuming $FD/V = 50$ units, $k = 0.5$ units). The necessary parameters for Eqn. 3 are given below:

Eqn.	C_{max}	t_{max}	$C_{max} \cdot t_{max}$	$(AUC)_0^\infty/e$
1	22.8389	1.6	36.5422	36.7879
2	18.3940	2	36.7880	36.7879

The values of $(AUC)_0^\infty$ were calculated from the following model-independent equation:

$$(AUC)_0^\infty = \frac{FD}{k' \cdot V} \tag{4}$$

where for Eqn. 1 $k' = K$ and for Eqn. 2 $k' = k$.

It is seen from the data given above that, when the ratios of k_a/K are $0.8/0.5 = 1.6$ and $0.5/0.5 = 1$, the products $C_{max} \cdot t_{max}$ are 99.3% and 100% of the corresponding $(AUC)_0^\infty/e$ values, respectively for the error-free data. Therefore, the use of Eqn. 3 may not be a suitable way of the determination of the equivalence of k_a to K.

It is the intention of this communication to prove that, theoretically the limit of the product $C_{max} \cdot t_{max}$ for the cases represented by Eqn. 1 is also equal to FD/eVK and/or $(AUC)_0^\infty/e$ when k_a approaches K over certain ranges, one of which tested above. Mathematically, this statement can be expressed by the following equation:

$$\lim_{k_a \to K} (C_{max} \cdot t_{max}) = \frac{FD}{eVK} \tag{5}$$

Details of the proof of Eqn. 5 are as follows:
The values of C_{max} and t_{max} for the cases represented by Eqn. 1 are given by Eqns. 6 and 7 (Gibaldi and Perrier, 1975).

$$C_{max} = \frac{FD}{V} \exp(-Kt_{max}) \tag{6}$$

$$t_{max} = \frac{\ln(k_a/K)}{k_a - K} \tag{7}$$

Multiplying both sides of Eqn. 6 by Eqn. 7 and applying the statement made above to the resulted equation will give Eqn. 8

$$\lim_{k_a \to K} (C_{max} \cdot t_{max}) = \frac{FD}{V} \lim_{k_a \to K} \left[\frac{\ln(k_a/K)}{k_a - K} \exp(-Kt_{max}) \right] \tag{8}$$

For the sake of simplicity it is assumed that $\lim_{k_a \to K} (C_{max} \cdot t_{max})$ is equal to L.

Substituting for t_{max} from Eqn. 7 into the right-hand side of Eqn. 8 yields:

$$L = \frac{FD}{V} \lim_{k_a \to K} \left[\frac{\ln(k_a/K)}{k_a - K} \exp \frac{-K \ln(k_a/K)}{k_a - K} \right] \tag{9}$$

It is obvious that:

$$\exp \frac{-K \ln(k_a/K)}{k_a - K} = \left(\frac{k_a}{K} \right)^{\frac{-K}{k_a - K}} = \frac{1}{\left(\frac{k_a}{K} \right)^{\frac{1}{\frac{k_a}{K} - 1}}} \tag{10}$$

Thus, Eqn. 9 may be written as:

$$L = \frac{FD}{V} \lim_{k_a \to K} \left[\frac{\ln(k_a/K)}{k_a - K} \cdot \frac{1}{\left(\frac{k_a}{K} \right)^{\frac{1}{\frac{k_a}{K} - 1}}} \right] \tag{11}$$

Applying the theorem:

$$\lim_{x \to b} [f(x) \cdot g(x)] = \lim_{x \to b} f(x) \cdot \lim_{x \to b} g(x) \tag{12}$$

to the right-hand side of Eqn. 11 gives:

$$L = \frac{FD}{V} \lim_{k_a \to K} \left[\frac{\ln(k_a/K)}{k_a - K} \right] \cdot \lim_{k_a \to K} \left[\frac{1}{\left(\frac{k_a}{K} \right)^{\frac{1}{\frac{k_a}{K} - 1}}} \right] \tag{13}$$

According to L'Hospital's rule

$$\lim_{k_a \to K} \frac{\ln(k_a/K)}{k_a - K} = \lim_{k_a \to K} \left(\frac{1}{k_a} \right) = \frac{1}{K} \tag{14}$$

Therefore, Eqn. 13 is simplified to:

$$L = \frac{FD}{VK} \lim_{k_a \to K} \left[\frac{1}{\left(\frac{k_a}{K} \right)^{\frac{1}{\frac{k_a}{K} - 1}}} \right] \tag{15}$$

It is assumed that $(k_a/K) - 1 = u$, thus Eqn. 15 can be written as Eqn. 16

$$L = \frac{FD}{VK} \lim_{u \to 0} \left[\frac{1}{(1+u)^{\frac{1}{u}}} \right] \tag{16}$$

Again, it is assumed that $1/u = n$. Thus,

$$L = \frac{FD}{VK} \lim_{n \to \infty} \frac{1}{\left(1 + \frac{1}{n}\right)^n} \tag{17}$$

or

$$L = \frac{FD}{VK} \cdot \frac{1}{\lim_{n \to \infty} \left(1 + \frac{1}{n}\right)^n} \tag{18}$$

But, $\lim_{n \to \infty} (1 + 1/n)^n$ is equal to e. Therefore, Eqn. 18 becomes Eqn. 19

$$L = \frac{FD}{VK} \cdot \frac{1}{e} \tag{19}$$

Substituting $\lim_{k_a \to K} (C_{max} \cdot t_{max})$ for L will result in the following equation:

$$\lim_{k_a \to K} (C_{max} \cdot t_{max}) = \frac{FD}{VK} \cdot \frac{1}{e}$$

which is the required Eqn. 5.

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