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Short Communications

On the calculation of absorption rate constant of linear one-compartment open models using peak blood level or peak urinary excretion rate and post-absorptive data

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Pidgeon and Pitlick (1977) have employed a unique method of derivation to obtain an equation from which it is possible to calculate the absorption rate constant, k_a, of linear one-compartment open models using the peak blood level, C_{max}, and post-absorptive data. They have also used a similar technique to derive an equation from urine data (Pidgeon and Pitlick, 1980). In deriving the equations, the authors have assumed that more than one first-order rate process is occurring simultaneously with absorption (e.g. chemical degradation). However, it is possible to derive the equations from the standard classical equations without making such an assumption as follows:

(1) The Wagner-Nelson equation (Wagner and Nelson, 1963) for the peak of the blood level is:

$$C_{max} + K\int_0^{t_{max}} C \cdot dt = \frac{FD}{V} - \frac{FD}{V} e^{-k_a t_{max}} \quad (1)$$

where K is a first-order elimination rate constant of the drug, the integral is the area under the blood level curve between times 0 and t_{max} (the peak time), F is fraction of dose D absorbed, and V is the apparent volume of distribution of the drug.

Dividing both sides of Eqn. 1 by K and substituting $\int_0^\infty C \cdot dt$ (area under the blood level curve between times 0 and ∞) for one of the FD/KV terms in the resultant equation will give Eqn. 2

$$\frac{C_{max}}{K} + \int_0^{t_{max}} C \cdot dt = \int_0^\infty C \cdot dt - \frac{FD}{KV} e^{-k_a t_{max}} \quad (2)$$

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The value of C_{max} is given by Eqn. 3 (Gibaldi and Perrier, 1975)

$$C_{max} = \frac{FD}{V} e^{-Kt_{max}} \tag{3}$$

or

$$\frac{FD}{V} = C_{max} \cdot e^{Kt_{max}} \tag{4}$$

Also, the value of t_{max} for the model is calculated from Eqn. 5 (Gibaldi and Perrier, 1975)

$$t_{max} = \frac{\ln(k_a/K)}{k_a - K} \tag{5}$$

Substituting for FD/V and t_{max} from Eqns. 4 and 5 into the right-hand side of Eqn. 2 and simplification will yield:

$$\frac{C_{max}}{K} + \int_0^{t_{max}} C \cdot dt = \int_0^{\infty} C \cdot dt - \frac{C_{max}}{K} e^{-\ln(k_a/K)} \tag{6}$$

But

$$e^{-\ln(k_a/K)} = \frac{1}{e^{\ln(k_a/K)}} = \frac{1}{k_a/K} = \frac{K}{k_a} \tag{7}$$

Therefore, Eqn. 6 is simplified to Eqn. 8

$$\frac{C_{max}}{K} + \int_0^{t_{max}} C \cdot dt = \int_0^{\infty} C \cdot dt - \frac{C_{max}}{k_a} \tag{8}$$

Re-arrangement of Eqn. 8 gives:

$$\frac{C_{max}}{K} + \frac{C_{max}}{k_a} = \int_0^{\infty} C \cdot dt - \int_0^{t_{max}} C \cdot dt = \int_{t_{max}}^{\infty} C \cdot dt \tag{9}$$

Solving Eqn. 9 for k_a will result in Eqn. 10 which is the equation of Pidgeon and Pitlick (1977):

$$k_a = \frac{C_{max}}{\int_{t_{max}}^{\infty} C \cdot dt - C_{max}/K} \tag{10}$$

in which the integral is the area under the blood level curve between times t_{max} and ∞.

Applying a similar technique of derivation to the Wagner-Nelson equation for urinary excretion data will give Eqn. 11 which is identical to another equation of Pidgeon and Pitlick (1980):

$$k_a = \frac{\dot{U}_{max}}{U^{\infty}_{t_{max}} - \dot{U}_{max}/K} \tag{11}$$

where $\dot{U}_{max}$ is the maximum value of the urinary excretion rate of drug, and $U^{\infty}_{t_{max}}$ is the cumulative drug amount excreted via the urine from t_{max} (peak time of the urinary excretion rate) to time ∞.

(2) The drug concentration, C, in blood for the model is given by Eqn. 12 (Gibaldi and Perrier, 1975)

$$C = \frac{k_a FD}{(k_a - K)V} e^{-Kt} - \frac{k_a FD}{(k_a - K)V} e^{-k_a t} \tag{12}$$

The integration of Eqn. 12 between times t_{max} and ∞ yields:

$$\int_{t_{max}}^{\infty} C \cdot dt = \frac{k_a FD}{K(k_a - K)V} e^{-Kt_{max}} - \frac{FD}{(k_a - K)V} e^{-k_a t_{max}} \tag{13}$$

Substituting for $(FD/V)\, e^{-Kt_{max}}$ from Eqn. 3 into the first term and for FD/V and t_{max} from Eqns. 4 and 5 into the second term of the right-hand side of Eqn. 13, simplifications, and subsequent solution of the resultant equation for k_a will result in Eqn. 10.

Also, applying a similar technique of derivation to the equation describing the drug urinary excretion rate will yield Eqn. 11.

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