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A Simple Method for Determining Whether Absorption and Elimination Rate Constants Are Equal in the One-Compartment Open Model with First-Order Processes

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A simple method is presented by which one may determine if the absorption and the elimination rate constants are equal (in the one-compartment body model) using only plasma drug data. This method suggests the pertinent equation to calculate the relevent pharmacokinetic parameters.

KEY WORDS: first-order process; equal absorption and elimination rate constants; one-compartment body model.

In a one-compartment open body model with first-order processes, the determination of the absorption and elimination rate constants (k_a and k_e, respectively) using only plasma drug concentration data is dependent on the magnitude of the differences between k_a and k_e.

In the case where $k_a \gg k_e$, k_e can be determined from the slope of the terminal phase of the log C_b vs. t plot (C_b is concentration of the drug in the body and t is time) and k_a can be determined by the method of residuals (the "feathering" technique). Similarly, when $k_e \gg k_a$ (the so-called flip-flop case) k_a can be determined from the slope of the terminal phase of a log C_b vs. t plot and k_e can be determined by the method of residuals (1,2).

However, in the case where k_a is equal or close to k_e, absorption continues throughout the elimination phase, and the terminal slope of the log C_b vs. t plot is not linear and therefore cannot be used to determine a rate constant. Obviously the method of residuals cannot be used.

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In the special case where the absorption rate constant (k_a) is equal to the elimination rate constant (k_e), the general Bateman equation (equation 1) for a one-compartment body model with first-order absorption and elimination is indeterminable (mathematically cannot be determined) and therefore cannot be used to determine the relevant pharmacokinetic parameters (1,2).

$$C_b = \frac{FDk_a}{V(k_a - k_e)}(e^{-k_e t} - e^{-k_a t}) \tag{1}$$

where C_b is the concentration of drug in the body, D is the dose administered, F is the fraction of dose absorbed, and V is the apparent volume of distribution.

When $k_a = k_e = k$, the drug concentration in the body is characterized by equation 2 (1,2):

$$C_b = FDkt\,e^{-kt}/V \tag{2}$$

This communication presents a simple method for determining, from a single linear plot of C_b vs. t data following drug administration by any first-order processes e.g., oral, intramuscular, or sustained release administration, whether absorption and elimination rate constants are equal (assuming a one-compartment open body model).

From equation 2, relationships can be derived for the parameters t_{max} (time of peak drug concentration) and C_{bmax} (peak drug concentration) (1,2).

$$t_{max} = 1/k \tag{3}$$

$$C_{bmax} = FD/Ve \qquad e = \text{base of natural logarithms} \tag{4}$$

The product of $t_{max} \cdot C_{bmax}$ is equal to AUC/e as is shown in equation 5:

$$t_{max} \cdot C_{bmax} = FD/kVe = FD/\mathrm{CL}e = \mathrm{AUC}/e \tag{5}$$

where CL is total body clearance and AUC is the area under the curve of C_b vs. t.

From a plot of C_b vs. t, t_{max} and C_{bmax} can be determined by inspection and AUC can be calculated by the trapezoidal rule.

Thus, whenever $t_{max} \cdot C_{bmax}$ can be shown to be equal to AUC/e, the rate constants k_a and k_e must be equal and the Bateman equation (equation 1) cannot be used; in this case, k can be calculated using equation 6, which is derived from equation 3:

$$k = k_a = k_e = 1/t_{max} \tag{6}$$

This method is demonstrated in Fig. 1, where a hypothetical curve was

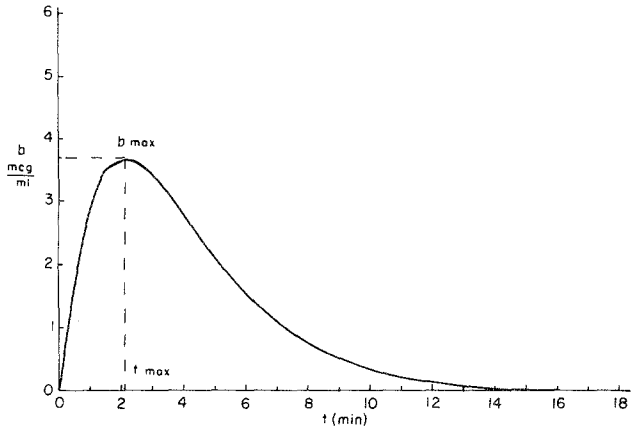

Fig. 1. Hypothetical curve generated by an analog computer.

generated by an analog computer (PACE model TR-9, Electronics Associated, Inc., Long Branch, New Jersey) with initial conditions set at $k_a = k_e = 0.5\ \text{min}^{-1}$.

By inspection, $t_{\max} = 2.1$ min, $C_{b\max} = 3.7\ \mu$g/ml, and AUC, calculated by the trapezoidal rule, was found to be 20.6 μg-min/ml.

The product $C_{b\max} \cdot t_{\max}$ equals (2.1 min) (3.7 μg/ml) = 7.77 μg-min/ml. The quotient AUC/e equals 20.6 μg-min/ml/2.718 = 7.58 μg-min/ml. The fact that these two values, as predicted by equation 5, are equal, demonstrates that k_a must be equal to k_e.

In summary, a simple scheme is suggested to determine the equivalence of k_a to k_e using only plasma drug data, which in turn determines which equation (equation 1 or equation 2) must be used to calculate the relevant pharmacokinetic parameters.

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