BIOPHARMACEUTICS & DRUG DISPOSITION, VOL. 13, 229–232 (1992)

SHORT COMMUNICATION

EQUATIONS FOR THE FRACTION OF BIOAVAILABLE DOSE REMAINING IN THE BODY IN THE ONE-COMPARTMENT MODEL

P. MACHERAS, M. SYMILLIDES AND C. REPPAS

Department of Pharmacy, University of Athens, 106 80 Athens, Greece.

KEY WORDS One-compartment model First-order absorption Zero-order absorption

In a recent paper,[1] we reported an equation for the calculation of the fraction of the bioavailable dose remaining in the body at t_{max}, $F_{sys,t_{max}}$, assuming that the drug follows one-compartment model disposition and first-order absorption. It was shown[1] that this fraction is solely dependent on the ratio k_a/k_e where k_a and k_e are the first-order absorption and elimination rate constants, respectively. However, this equation can be applied only to a specific time point, i.e. t_{max}.

In the present communication equations are derived for the calculation of the fraction of the bioavailable dose, $F_{sys,t}$, remaining in the body at any time t after drug's administration. These equations can be applied to drugs obeying one compartment model kinetics assuming either first- or zero-order absorption. In addition, an alternative and simpler method of derivation of the equation relating $F_{sys,t_{max}}$ with the ratio k_a/k_e is proposed.

In the previous communication[1] a lengthy procedure based on material balance relationships was used to derive equations (1) and (2) for $F_{sys,t_{max}}$ in the linear one-compartment model:

$$F_{sys,t_{max}} = \Phi^{1/(1-\Phi)} \qquad \text{when } k_a \neq k_e \tag{1}$$

$$F_{sys,t_{max}} = 0{\cdot}368 \qquad \text{when } k_a = k_e \tag{2}$$

where $\Phi = k_a/k_e$.

However, the fraction of the bioavailable dose, $F_{sys,t}$, remaining in the body at any time t, can be defined by the equation (3):

$$F_{sys,t} = (C_t V)/(F\mathrm{D}) \tag{3}$$

where C_t is the plasma concentration at time t, F is the fraction of the dose absorbed, D is the administered dose and V is the apparent volume of distribu-

Correspondence to: Dr. P. Macheras, Department of Pharmacy, University of Athens, 104 Solonos Street, 106 80 Athens, Greece.

0142–2782/92/030229–04$05.00

Received 20 May 1991
Accepted 29 October 1991

tion. Also, equations (4) and (5) describe the plasma concentration versus time in the linear one-compartment model when $k_a \neq k_e$ and when $k_a = k_e = k$, respectively:[2]

$$C_t = \frac{FDk_a}{V(k_a - k_e)}(e^{-k_e t} - e^{-k_a t}) \tag{4}$$

$$C_t = \frac{FD}{V} kte^{-kt} \tag{5}$$

Considering equations (3), (4), and (5) for $t = t_{max}$ and using[2] $t_{max} = [1/(k_a - k_e)][\text{Ln}(k_a/k_e)]$ (when $k_a \neq k_e$) or $t_{max} = 1/k$ (when $k_a = k_e = k$), the equations (1) and (2) for $F_{sys,t_{max}}$ are obtained.

The derivation of equations (1) and (2) can be now extended to equations for $F_{sys,t}$ which is the fraction of the bioavailable dose remaining in the body at any time t, after drug's administration. This can be accomplished by expressing time in multiples (n) of drug's half-life ($t_{1/2}$). In reality, n is a continuous variable and does not represent only integral multiples of half-life. The derivation for both first- and zero-order absorption kinetics follows.

First order absorption. Substituting t with $nt_{1/2} = n(\text{Ln}2)/k_e$ in equations (3), (4), and (5), the following equations for $F_{sys,nt_{1/2}}$ result:

$$F_{sys,nt_{1/2}} = \frac{\Phi}{\Phi - 1}[(0{\cdot}5)^n - (0{\cdot}5)^{n\Phi}] \qquad (k_a \neq k_e) \tag{6}$$

$$F_{sys,nt_{1/2}} = n\,\text{Ln}2\,(0{\cdot}5)^n \qquad (k_a = k_e = k) \tag{7}$$

It is worth mentioning that, as previously shown[1] for $t = t_{max}$, $F_{sys,t}$ is independent of k when $k_a = k_e = k$. In Figure 1 the $F_{sys,nt_{1/2}}$ is expressed as per cent ($100 \times F_{sys,nt_{1/2}}$) and plotted against multiples of elimination half-life using various ratios of k_a/k_e.

Zero order absorption. Equations (8) and (9) describe the concentration of the drug in plasma as a function of time in a one-compartment model:[2]

$$C_t = \frac{FD}{V\tau k_e}(1 - e^{-k_e t}) \qquad (t \leq \tau) \tag{8}$$

$$C_t = \frac{FD}{V\tau k_e}(e^{-k_e(t-\tau)} - e^{-k_e t}) \qquad (t > \tau) \tag{9}$$

where τ is the duration of the absorptive phase. By combining equations (8) and (9) with equation (3) and substituting t with $nt_{1/2}$, $= n(\text{Ln}2)/k_e$ the following equations can be derived:

$$F_{sys,nt_{1/2}} = \frac{1}{m\,\text{Ln}2}[1 - (0{\cdot}5)^n] \qquad (n \leq m) \tag{10}$$

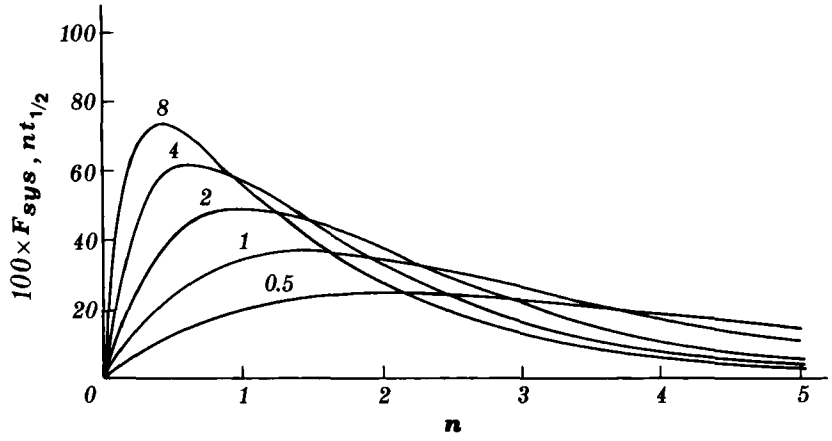

Figure 1. Family of curves for the fraction of the bioavailable dose remaining in the body, 100 $\times$ ($F_{sys,nt_{1/2}}$), as function of multiples (n) of elimination half-life when first-order absorption kinetics is operating. The numbers correspond to different values of k_a/k_e

$$F_{sys,nt_{1/2}} = \frac{1}{m\,\mathrm{Ln}2}[(0{\cdot}5)^{(n-m)} - (0{\cdot}5)^n] \qquad (n > m) \tag{11}$$

where $m = \tau/t_{1/2}$. In Figure 2 the $F_{sys,nt_{1/2}}$ is expressed as per cent ($100 \times F_{sys,nt_{1/2}}$) and plotted against multiples of elimination half-life using various values of m.

Figures 1 and 2 and the accompanying equations can be used in various topics of biopharmaceutical studies. The design of conventional or sustained

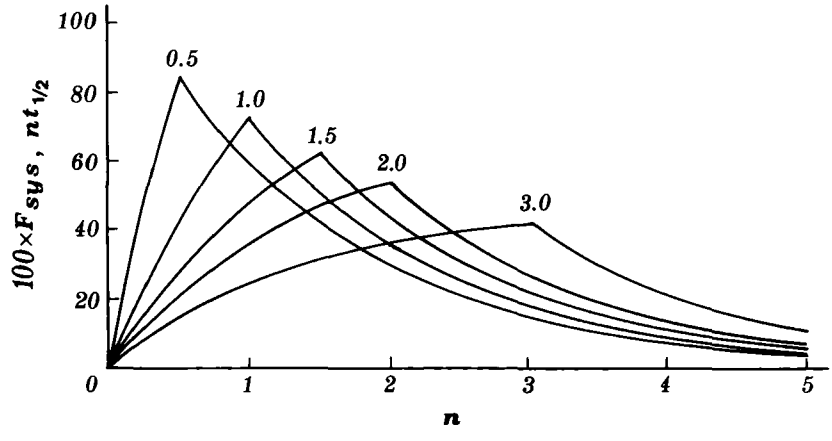

Figure 2. Family of curves for the fraction of the bioavailable dose remaining in the body, 100 $\times$ ($F_{sys,nt_{1/2}}$), as function of multiples (n) of elimination half-life when zero-order absorption kinetics is operating. The numbers correspond to different values of m ($m = \tau/t_{1/2}$)

release formulations during the preformulation stage, can be greatly facilitated. For example, the development of a formulation with a release pattern such that 40–50 per cent of the bioavailable dose remains in the body at time longer than two half-lives, requires, according to Figure 2, a zero-order release with a duration two to three times the half-life of drug. In this case an estimate of m, with fixed values for n and $F_{sys,nt_{1/2}}$, can be derived from equation (10); subsequently, the appropriate value of the duration of the absorption process, τ, can be obtained from the simple relationship, $\tau = mt_{1/2}$.

In conclusion, it was shown that in the context of one-compartment model, after normalizing the time-scale to the elimination half-life, the fraction of the bioavailable dose remaining in the body can be expressed solely in terms of the ratio of absorption to elimination rate constants. This is of interest to investigators working in the area of formulation development.

REFERENCES

1. P. Macheras, C. Reppas and M. Symillides, Fraction of the bioavailable dose remaining in the body at Tmax in a linear open one-compartment model. *J. Pharm. Sci.*, **81**, 110 (1992).
2. M. Gibaldi, and D. Perrier, *Pharmacokinetics*, Marcel Dekker, New York, 1982, pp. 27, 34, 38, 41, 170.