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CALCULATIONS OF OPTIMUM PHARMACOKINETIC DRUG SUPPLY RATES FOR MAXIMUM DURATION DURING MULTIPLE DOSE THERAPY BY PRODRUG ADMINISTRATION

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SUMMARY

For a drug that is repetitively dosed in order to maintain a certain minimum effective concentration in blood (MEC) there exists an optimum rate-determining drug input constant, $(k_{rds})_{opt}$, which will result in the maximum time between doses (τ_{max}). By defining $Q^{\infty} = [A^{\infty}_{max}/(MEC)Vd)]$, where A^{∞}_{max} is the steady-state maximum amount in the site of administration and Vd is the volume of distribution of drug, the $(k_{rds})_{opt}$ may be estimated from e/Q^{∞}, provided $Q^{\infty} \geqslant 8$. This estimate applies to all of the 1- and 2-compartment models considered in the report. The relative onset time is shown to be 4 to 5 times the rate-determining half-life defined as $t_{0.5} = 0.693/k_{rds}$. Thus, a prodrug with an ideal rate-limiting input constant will increase the onset time relative to the drug itself unless a compensatory loading dose is employed. Equations are provided for estimating the loading dose, maintenance dose, onset time, optimum k_{rds} and τ. The applicability and significance of the methods are discussed.

INTRODUCTION

Equations normally used for calculating multiple dosage regimens assume that absorption is faster than the elimination of drug (Kruger-Thiemer, 1966, 1969). If duration is to be extended, it is necessary to intentionally reduce the input rate so that it becomes slower than elimination. The input rate constant must be made rate-determining (Byron and Notari, 1976).

Notari (1977) has reviewed the potential for extending duration by developing prodrugs with rate-limiting first-order drug delivery (k_{rds}) due to either absorption of prodrug or its subsequent conversion to drug. Byron et al. (1978) have demonstrated that the value of the optimum first-order drug input constant $(k_{rds})_{opt}$ which provides the maximum duration of drug activity following administration of a single fixed dose of prodrug,

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may be easily estimated a priori. The optimum values for the cases reported varied from 0.013 to ≈0.8 × the elimination rate constant ($0.693/t_{0.5}$). Thus, when rate-limiting input is used to extend the duration, the optimum value may be extremely small relative to elimination.

There are several problems which arise in the design, evaluation and use of such a prodrug. If input is very slow, then single dose screening procedures may reject an ideal prodrug as 'inactive'. Repetitive multiple dosing of a very slow input prodrug would also result in a long onset period during which there will be no therapeutic effect. The optimum rate-determining drug input constant for multiple dose therapy may differ from that reported for a single dose (Byron et al., 1978).

The present study has established a simple method for estimating the optimum input constant during multiple dose administration of drugs described by 1- and 2-compartment models. Equations derived for these systems allow calculation of the loading dose, maintenance dose and dosing interval to provide immediate therapeutic effect and the maximum time between doses (i.e. $(k_{rds})_{opt}$ and maximum duration). The approach can be used to define the optimum characteristics for a prodrug of any given drug. Optimum theoretical results may be appraised for feasibility of prodrug design. Several questions can be examined a priori. For example, it is possible to calculate the input rate and the dose size necessary to provide a desired dosage interval. A specific dosage interval might be considered as ideal for a particular drug from a clinical viewpoint. It may be immediately apparent, using these calculations, that such a system could not be achieved. Conversely, it might appear feasible until some systems are tested. At this point the test itself can be evaluated using the theory. If the test is adequate then the possibility of optimizing the system can be considered relative to the theoretical optimum. If the system cannot be improved beyond certain limits of rate-determining input, then the optimum regimen can be calculated for the system as it is and its potential may then be appraised.

This treatment is intended primarily for i.m. injections for several reasons. The two most important factors are the dosage interval and accumulation at the site of administration. The optimum dosage interval is often too long for oral administration. For very slow input constants a large number of doses must accumulate at the site of administration. If these methods are to be employed for an oral dosage form both of these limitations must be imposed on the equations and a compromise in ideality may be required.

EXPERIMENTAL

The optimum absorption constant for τ_{max}

Scheme I represents extravascular administration of a drug described by a 1-compartment model with first-order absorption (k_a) and elimination (k). Repetitive administration of an infinite number of equal doses at a constant dosage interval (τ) will provide

$$A \xrightarrow{k_a} B \xrightarrow{k} C$$

Scheme I

a steady-state time course for the concentration of drug in plasma (C_p) which may be

defined

$$C_p^{\infty} = \left[\frac{k_a F D_0}{Vd(k_a - k)}\right]\left\{\left(\frac{e^{-kt}}{1 - e^{-k\tau}}\right) - \left(\frac{e^{-k_a t}}{1 - e^{-k_a \tau}}\right)\right\} \quad (1)$$

where the limits of time are $0 \leqslant t \leqslant \tau$, and the bioavailable dose (FD_0), the apparent volume of distribution (Vd) and the first-order rate constants (k_a and k) are held constant (Gibaldi and Perrier, 1975). Eqn. 1 may be written in terms of the amount in the body, $D_t^{\infty} = C_p^{\infty}$ Vd, and solved for the steady-state minimum, D_{min}^{∞}, when $t = \tau$, F = 1, to give

$$D_{min}^{\infty} = \left[\frac{k_a D_0}{k_a - k}\right]\left\{\left(\frac{e^{-k\tau}}{1 - e^{-k\tau}}\right) - \left(\frac{e^{-k_a \tau}}{1 - e^{-k_a \tau}}\right)\right\} \quad (2)$$

The amount of drug in the depot during steady state may be defined by

$$A_t^{\infty} = \left[\frac{D_0}{1 - e^{-k_a \tau}}\right] e^{-k_a t} \quad (3)$$

which may be solved for a maximum at t = 0 to give

$$A_{max}^{\infty} = \frac{D_0}{(1 - e^{-k_a \tau})} = \frac{D_0}{1 - f} \quad (4)$$

where $f = e^{-k_a \tau}$ is the fraction of each A_0 remaining in the depot at the end of each dosage interval. By setting $r = k/k_a = 1/R$, Eqn. 2 may be written in terms of f and r as follows:

$$D_{min}^{\infty} = \left[\frac{D_0}{r - 1}\right]\left\{\left(\frac{f}{1 - f}\right) - \left(\frac{f^r}{1 - f^r}\right)\right\} \quad (5)$$

which may be expressed as

$$D_{min}^{\infty} = \left[\frac{A_{max}^{\infty}}{r - 1}\right]\left\{\frac{f - f^r}{1 - f^r}\right\} \quad (6)$$

Eqn. 6 may be simplified by setting $Q^{\infty} = (A_{max}^{\infty})/(D_{min}^{\infty})$, which is the maximum allowable number of effective doses (D_{min}^{∞}) to be stored in the depot, so that

$$Q^{\infty} = (r - 1)\left\{\frac{1 - f^r}{f - f^r}\right\} \quad (7)$$

where $r = k/k_a > 1$ and f has the limits $0 < f < 1$.

For a chosen Q^{∞} value, it is possible to assess τ as a function of the ratio of the rate constants, r. This was accomplished by digital computer reiteration to estimate the value of f which satisfied Eqn. 7 at each chosen value for Q^{∞} and r. Since the limits of f are $0 < f < 1$, its value was increased by an optimum increment from $f \approx 0$ to an f value which provided a calculated Q^{∞} in Eqn. 7 which did not differ significantly from the chosen Q^{∞}. To ensure that this was the desired f value, the iteration was repeated from f = 1 toward f = 0 until Eqn. 7 was again satisfied. Results were the same indicating that no other values in the range $0 < f < 1$ will satisfy Eqn. 7 at each fixed value for $r > 1$ and

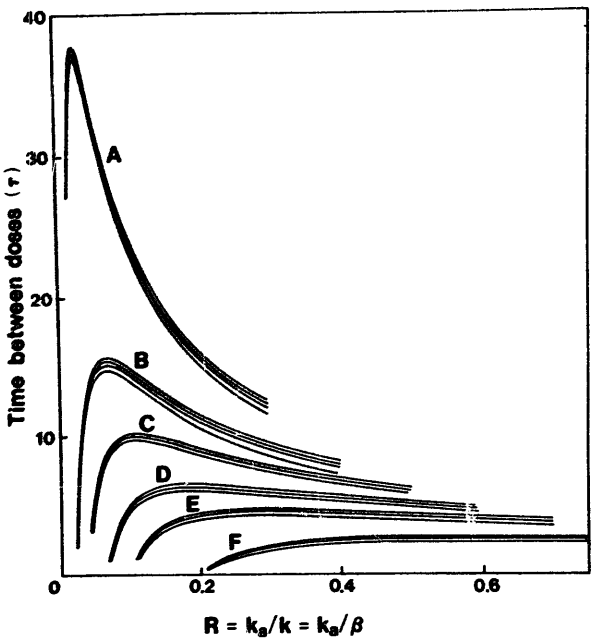


Fig. 1. The effect of rate-limiting first-order absorption (k_a) on the time between doses (τ) to maintain a constant MEC. Each group of curves represents 1-compartment model drugs (Scheme I) and 2-compartment model drugs (Scheme II; Table 3) at constant $Q^\infty = A^\infty_{max}/MEC \cdot Vd$. When $(A^\infty_{max}/Vd) = 1$ then $Q^\infty = 1/MEC$ and MEC values are: A = 0.01; B = 0.025; C = 0.04; D = 0.067; E = 0.1, and F = 0.2. Case no. 7 in Table 3 (lowest curve in A and B) has been omitted from C through F for clarity. All cases had similar r_{opt} values as listed in Table 1.

Q^∞. The value for τ was then calculated from $\tau = -\ln f/k_a$ after choosing a value for k to define k_a. Typical results are shown in Fig. 1, where τ is seen to pass through a maximum value for a given set of values for Q^∞ and k.

If f^r is insignificant compared to f then Eqn. 7 becomes

$$Q^\infty = (r - 1)/e^{-k_a\tau} \tag{8}$$

which may be solved for τ to give

$$\tau = \ln[Q^\infty/(r - 1)]/k_a \tag{9}$$

By taking the first derivative of Eqn. 9 and regarding Q^∞ and k as constants, one obtains

$$\frac{d\tau}{dk_a} = \frac{\ln[Q^\infty/(r - 1)]}{-k_a^2} + \frac{k}{k_a^2(k - k_a)} \tag{10}$$

Attempts to solve for k_a at τ_{max} by setting $d\tau/dk_a$ (Eqn. 10) equal to zero were not successful. However, estimates were obtained by digital simulations of Eqn. 10 as shown in Fig. 2. The maximum time between doses, τ_{max}, is obtained when $(d\tau/dk_a)$ passes through zero in each plot. This represents the optimum k_a value for maximum duration when k and Q^∞ are fixed. It was observed that the product $(r_{opt}) \cdot e$ approaches Q^∞ when the assumption $k >> k_a$ is satisfied. This would be predicted since setting Eqn. 10 equal

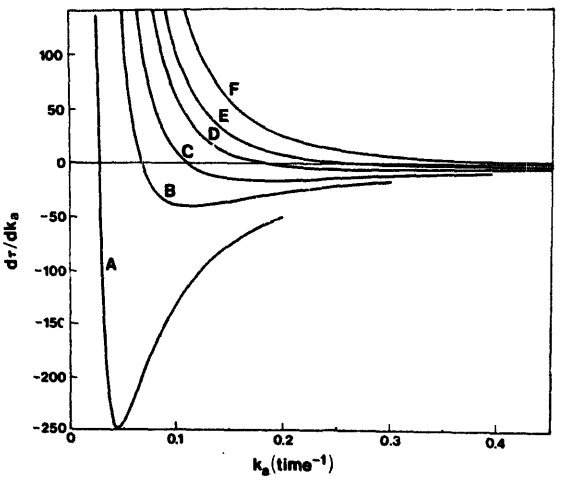


Fig. 2. The derivative ($d\tau/dk_a$) as defined by Eqn. 10 as a function of rate-limiting k_a in Scheme I. It contains the assumption, $f >> f^r$, which was invoked to derive Eqn. 8. Q^∞ values for A through F are identical to those in Fig. 1.

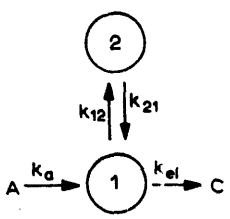
to zero and solving for Q^∞ yields

$$Q^\infty = (r_{opt} - 1)(e)^{[r_{opt}/(r_{opt}-1)]} \tag{11}$$

which approaches $(r_{opt}) \cdot e$ as $(r_{opt} - 1)$ approaches r_{opt}.

Comparison of 1- and 2-compartment models

In the 2-compartment model with first-order absorption (Scheme II) D_t^∞ cannot be assumed to be equal to C_p^∞ Vd as was done for Eqn. 2 in order to define Q^∞.



Scheme II

The product, C_p^∞ Vd, where Vd is Vd_{area}, is only equal to D_t^∞ when $Vd_{ss} = Vd$, i.e. $[(k_{12} + k_{21})/\alpha] = 1$ (Perrier and Gibaldi, 1973). Only two of the cases simulated approach this limit ($[k_{12} + k_{21}]/\alpha = 0.99$ for case no. 6 and 0.98 for case no. 2 in Table 3). Curves for the plasma concentration of drug during repetitive dosing in the steady-state may be described in terms of Vd and β by equations analogous to those for Scheme I. The 1- and 2-compartment model systems were normalized by holding Vd constant and evaluating the effect of $r = k/k_a = \beta/k_a$. Comparisons were thus carried out using the normal equations for C_p^∞ as a function of time (Gibaldi and Perrier, 1975) by holding F = 1 and A_{max}^∞, the steady-state maximum mass in the depot, constant. Eqn. 6 may be rewritten as

$$MEC = \frac{A_{max}^\infty}{(r-1)Vd}\left\{\frac{f - f^r}{1 - f^r}\right\} \tag{12}$$

since $D^{\infty}_{min} = (C^{\infty}_p)_{min} Vd$ and $(C^{\infty}_p)_{min}$ is set equal to the minimum effective concentration (MEC) of drug. Similarly for Scheme II

$$MEC = \left[\frac{A^{\infty}_{max} k_a k_{e1}}{\beta Vd}\right]\left\{Xf + Y\left[\frac{f^{r'r}(1-f)}{(1-f^{r'r})}\right] + Z\left[\frac{f^{r}(1-f)}{(1-f^{r})}\right]\right\} \tag{13}$$

where $X = (k_{21} - k_a)/(\alpha - k_a)(\beta - k_a)$; $Y = (k_{21} - \alpha)/(k_a - \alpha)(\beta - \alpha)$; $Z = (k_{21} - \beta)/(k_a - \beta)(\alpha - \beta)$; $r' = \alpha/\beta$ and $r = \beta/k_a$. The effect of r on τ was evaluated by reiteration of Eqns. 12 and 13 to determine that value for f which produced the MEC value at each value for r and at constant A^{∞}_{max}, and Vd. The desired solution for f was assured as described under Eqn. 7. The value for τ was then calculated from $\tau = -\ln f/k_a$. This represents the duration obtained at fixed Q^{∞} which is defined as $A^{\infty}_{max}/(C^{\infty}_p)_{min}$ Vd. The denominator, $(C^{\infty}_p)_{min}$ Vd does not equal D^{∞}_{min} for most of the 2-compartment cases studied. In these cases the definition of Q^{∞} is not defined $Q^{\infty} = A^{\infty}_{max}/D^{\infty}_{min}$ as it was for Eqn. 7. When $(A^{\infty}_{max}/Vd) = 1$, Q^{∞} corresponds to 1/MEC.

Estimating τ for a specific therapeutic ratio

In the simulations for Scheme I the optimum ratio (k/k_a) and maximum τ result in D^{∞}_{max} values that are roughly equal to $(e) \cdot (D^{\infty}_{min})$ when r values are large. The following approach examined the situation where the desired $(D^{\infty}_{max}/D^{\infty}_{min})$ ratio is a property of the drug.

The maximum amount of drug in the body (D^{∞}_{max} in B of Scheme I) during steady-state may be described as

$$D^{\infty}_{max} = \frac{D_0}{1 - e^{-k\tau}} e^{-kt'_p} \tag{14}$$

where F = 1 and t'_p, the time at which the maximum occurs during the steady-state, is defined

$$t'_p = \frac{1}{(k_a - k)} \ln\left[\frac{k_a(1 - e^{-k\tau})}{k(1 - e^{-k_a\tau})}\right] \tag{15}$$

If $(1 - f^r)$ approaches one, t'_p may be expressed

$$t'_p = \frac{1}{(k_a - k)} \ln\left[\frac{k_a}{k(1 - e^{-k_a\tau})}\right] \tag{16}$$

Substituting Eqn. 16 into Eqn. 14 and setting $(1 - f^r)$ equal to one yields

$$D^{\infty}_{max} = D_0[(k/k_a)^{[k/(k_a-k)]}][(1 - e^{-k_a\tau})^{[k/(k_a-k)]}] \tag{17}$$

When absorption is rate-limiting and $k >> k_a$

$$D^{\infty}_{max} = D_0/r(1 - e^{-k_a\tau}) \tag{18}$$

Similarly, as $(1 - f^r)$ approaches one, Eqn. 5 becomes

$$D^{\infty}_{min} = \left[\frac{D_0 k_a}{k - k_a}\right]\left[\frac{e^{-k_a\tau}}{1 - e^{-k_a\tau}}\right] \tag{19}$$

When $k >> k_a$ this becomes

$$D^{\infty}_{min} = \left[\frac{D_0}{r}\right]\left[\frac{e^{-k_a\tau}}{1 - e^{-k_a\tau}}\right] \tag{20}$$

Dividing Eqn. 18 by Eqn. 20 yields

$$[D^{\infty}_{max}/D^{\infty}_{min}] = (1/e^{-k_a\tau}) = 1/f \tag{21}$$

which is an approximation of the therapeutic ratio under conditions wherein $k >> k_a$ and $(1 - f^r) \approx 1$.

Assuming that a minimum therapeutic (D_{min}) and a maximum desirable (D_{max}) bioavailable dose are known from clinical observations, we can define a desired therapeutic index, T.I., as follows:

$$T.I. = D_{max}/D_{min} \tag{22}$$

An optimum dosage regimen must not exceed this ratio (i.e. $[(D^{\infty}_{max})/(D^{\infty}_{min})]$ = T.I.) in the steady state. Substitution of T.I. into Eqn. 21 yields

$$T.I. = [1/e^{-k_a\tau}] \tag{23}$$

which may be rearranged to provide an equation to estimate the dosage interval

$$\tau' = [\ln(T.I.)/k_a] \tag{24}$$

where τ' may be expected to approach the actual value, τ, when the assumptions are suitably met.

An estimated value for the maintenance dose, D'_0, may then be calculated using τ' in Eqn. 19 to give

$$D'_0 = D^{\infty}_{min}\left[\frac{1 - e^{-k_a\tau'}}{e^{-k_a\tau'}}\right]\left[\frac{k - k_a}{k_a}\right] \tag{25}$$

In order to avoid a long onset time, a loading dose, D*, is often employed.

$$D^* = D_0/(1 - e^{-k\tau})(1 - e^{-k_a\tau}) \tag{26}$$

Since we have assumed $e^{-k\tau}$ approaches zero, the estimated loading dose, D*', may be calculated from

$$D^{*\prime} = D'_0/(1 - e^{-k_a\tau'}) \tag{27}$$

In order to assess the suitability of Eqns. 24, 25 and 27, the values for D^{∞}_{min} and D^{∞}_{max} were calculated for various combinations of k_a, k, τ and D_0 using Eqns. 2, 15 and 14. The estimated values were then compared to the known values.

The onset time

When absorption is not rate-limiting, the onset time is generally regarded to be about 4 to 5 times the biological half-life of the drug. This would be expected to change in the case of rate-limiting absorption.

Since infinite time is required to mathematically satisfy the steady-state assumption, a practical onset time must be chosen. We have arbitrarily defined onset time as the time at

which the plasma level *permanently* surpasses 95% of the minimum plasma level at steady-state during multiple dosing. Thus onset occurs when plasma levels never again fall below 95% of steady-state minimum. The relative onset time, t_{on}, is then defined as the ratio of the onset time when $k_a < k$ (or β) to the onset time where $k_a = 100k$ (or β) as shown in Eqn. 28 where $R = 1/r$.

$$t_{on} = \frac{\text{onset time, } R < 1}{\text{onset time, } R = 100} \tag{28}$$

Scheme III illustrates the simplest model for extravascular administration of a prodrug of a one-compartment model drug

$$[PD] \xrightarrow[\text{dose}]{k'_a} PD \xrightarrow{k'_c} D \xrightarrow{k} \underset{\text{Loss}}{\text{Drug}}$$

Scheme III

The amount of drug in the body during multiple dosing of prodrug may be expressed as

$$D_t^n = D_0 k'_a k'_c [A_1 e^{-k'_a t}(1 - e^{-nk'_a \tau})/(1 - e^{-k'_a \tau}) + A_2 e^{-k'_c t}(1 - e^{-nk'_c \tau})/(1 - e^{-k'_c \tau}) + A_3 e^{-kt}(1 - e^{-nk\tau})/(1 - e^{-k\tau})] \tag{29}$$

when F = 1, n = the number of doses and $A_1 = 1/[(k'_a - k'_c)(k'_a - k)]$; $A_2 = 1/[(k'_c - k'_a)(k'_c - k)]$; and $A_3 = 1/[(k'_a - k)(k'_c - k)]$. This equation, which was adapted from a single dose equation, (Kruger-Thiemer and Eriksen, 1966) has a symmetrical structure with respect to k'_a and k'_c. That is, the two constants may be interchanged without altering the equation. The value for k was held constant at unity while the ratio k'_c/k was varied between 0.1 and 100 and k'_a/k was varied from 1 to 20. For each case a digital simulation based on Eqn. 29 was employed to determine the onset time and the *relative* onset time was then defined similarly to that in Eqn. 28 except that the reference state (or denominator) was taken to be $(k'_a/k) = 99$ and $(k'_c/k) = 100$, i.e. neither input function in Scheme III is rate-limiting. (Note that Eqn. 29 is not valid when any two or all three of the rate constants are equal.)

RESULTS AND DISCUSSION

The optimum absorption constant for τ_{max}

For a given MEC, A^{∞}_{max} and Vd, there is only one optimum first-order input constant (k_a) for all of the cases studied. This is illustrated in Fig. 1 where τ passes through a maximum value as a function of k_a. Fig. 2 is a graphical representation of Eqn. 10 where it is assumed that $(f - f^r)$ in Eqn. 7 approaches f. Results shown in Table 1 indicate that the observed values for $(k_a)_{opt}$ will agree with those based on Eqn. 10 (Fig. 2) if Q^{∞} is sufficiently large. Eqn. 11 implies that a sufficiently large value for Q^{∞} would result in the relationship, $r_{opt} \approx Q^{\infty}/e$. Table 1 shows that the observed values for r_{opt} may be estimated from Q^{∞}/e when $r_{opt} \geq 3$. The high % error at $Q^{\infty} < 8$ is due to the fact that f^r becomes significant in Eqn. 7 at low values for Q^{∞}. Table 2 shows that at $Q^{\infty} = 5$, the assumption that $[Q^{\infty}/r - 1]$ may be approximated by $1/f$ (Eqn. 8) has a 29% error.

TABLE 1

COMPARISON (%Δ) OF OBSERVED AND CALCULATED VALUES FOR THE MAXIMUM DOSAGE INTERVAL, τ_{max}, AND THE RATIO AT WHICH IT OCCURS, $r_{opt} = k/(k_a)_{opt} = \beta/(k_a)_{opt}$ WHEN Q^∞ IS CONSTANT

τ_{max} [a]				r_{opt}			
(Q^∞) [b]	Obs [c]	Calcd [d]	% Δ	Obs [c]	Calcd [e]	% Δ	Approx. [f]
100	37.80	37.80	0.00	37.0	36.8	−0.54	37.0
50	19.42	19.42	0.00	18.5	18.4	−0.54	18.5
40	15.75	15.75	0.00	14.7	14.7	0.00	14.7
25	10.25	10.25	0.00	9.09	9.20	1.21	9.26
20	8.43	8.43	0.00	7.25	7.36	1.52	7.30
15	6.60	6.62	0.30	5.43	5.52	1.66	5.43
12	5.51	5.55	0.73	4.26	4.42	3.76	4.26
10	4.76	4.84	1.68	3.59	3.68	4.25	3.53
8	4.01	4.16	3.74	2.78	2.94	5.76	2.70
5	2.81	3.28	16.7	1.67	1.84	10.2	–

[a] To convert to real time: $\tau_{max}/(k \text{ or } \beta)$.
[b] $Q^\infty = A^\infty_{max}/(MEC)(Vd)$.
[c] From Fig. 1 which has no approximation.
[d] From Eqn. 31.
[e] From $r_{opt} = Q^\infty/e$.
[f] From Fig. 2 which assumes $f >> f^r$ (Eqn. 10).

Eqn. 9 may be solved for τ_{max} when the ratio k/k_a is at its optimum and τ in real time (Eqn. 9) equals τ_{max}/k.

$$\tau_{max} = r_{opt} \ln\left[\frac{Q^\infty}{r_{opt} - 1}\right] \tag{30}$$

As discussed above r_{opt} approaches the value Q^∞/e when k becomes 3 times larger than

TABLE 2

COMPARISON OF (1/f) TO $[(1-f^r)/(f-f^r)]$ AT r_{opt}. [a]

Q^∞	f	1/f	$\left[\frac{1-f^r}{f-f^r}\right]$	%Δ
100	0.358	2.79	2.79	0
40	0.340	2.94	2.94	0
25	0.328	3.04	3.04	0
20	0.315	3.17	3.17	0
15	0.294	3.40	3.40	0
12	0.278	3.60	3.64	1.10
10	0.261	3.83	3.93	2.54
8	0.234	4.27	4.54	5.95
5	0.192	5.21	7.29	28.5

[a] In Eqn. 7, which has no assumptions, $Q^\infty = (r-1)(1-f^r)/(f-f^r)$. In Eqn. 8, which assumes f^r is insignificant, $Q^\infty \approx (r-1)/f$.

$(k_a)_{opt}$. Substitution for r_{opt} in Eqn. 30 yields

$$\tau_{max} = \left(\frac{Q^\infty}{e}\right) \ln\left[\frac{eQ^\infty}{Q^\infty - e}\right] \tag{31}$$

Eqn. 31 was used to predict the values for τ_{max} at the various Q^∞ values employed in Table 1. The values obtained agreed ($\Delta < 4\%$) with the observed values when $Q^\infty \geqslant 8$. The values calculated for r_{opt} were in agreement ($\Delta \leqslant 4\%$) with observed values when $Q^\infty \geqslant 10$. Even when r_{opt} is 2.78 ($Q^\infty = 8$) the error in Q^∞/e was less than 6%. From a practical point of view, r_{opt} and τ_{max} may be estimated as in Table 1 when $Q^\infty \geqslant 8$. At low values for Q^∞ the curves in Fig. 1 become flat making errors in the estimates even less critical.

Effect of rate-limiting input on the onset time for 1- and 2-compartment model drugs

The effect of variation of rate-limiting input on the time taken to surpass 95% of the plasma minimum drug level at steady-state during multiple dosing with a constant maintenance dose and dosing interval is summarized in Fig. 3. It is apparent that when absorption is rate-limiting, the onset time is proportional to r. The open circles in Fig. 3 represent the *relative* onset times for five of the seven 2-compartment cases (Table 3) simulated from combinations of k_{12}, k_{21}, and k_{el} and all 1-compartment cases. In these cases the values for the *relative* onset time are similar when r ratios are equal regardless of differences in the individual constants (k_{12}, k_{21} and k_{el}) or model. The slope is 1.05 for the plot t_{on} versus r. The two exceptions both represent cases where k_{12} is smaller than k_{el} (i.e. $k_{el}/k_{12} = 10$). This variation may be said to be a property of the drug itself (i.e. the k_{12}, k_{21}, k_{el} ratio) rather than an effect due to the drug input constant, k_a (Byron and Notari, 1976).

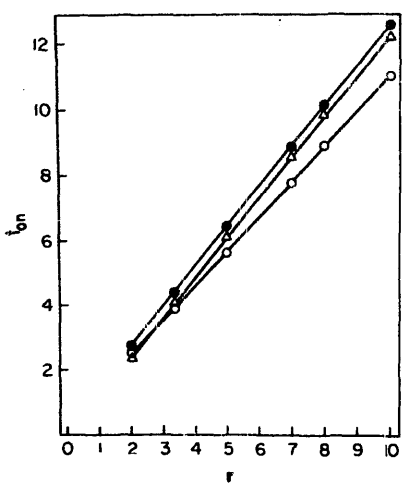


Fig. 3. The open circles (o) show the relative onset time (t_{on}; Eqn. 28) as a function of $r = k/k_a$ (Scheme I), β/k_a (Scheme II, case nos. 1, 2, 3, 5, and 6 in in Table 3) and k/k'_c or k/k'_a (whichever is rate-limiting in Scheme III). The two exceptions from Table 3 are case no. 4 (•) and case no. 7 (△).

TABLE 3

THE VALUES OF THE SLOPES AND INTERCEPTS OF LINEAR REGRESSION LINES FOR THE DATA SHOWN IN FIG. 6 FOR 1- AND 2-COMPARTMENT MODEL DRUGS

Case	k_{12}	k_{21}	k_{e1}	α	β	Linear regression [a]	
						Slope	Intercept
1	1.0	1.0	1.0	2.62	0.382	0.964	−3.6
2	1.0	1.0	0.1	2.05	0.0488	0.965	−4.1
3	1.0	0.1	1.0	2.05	0.0488	0.964	−3.2
4	0.1	1.0	1.0	1.37	0.730	0.964	−3.5
5	1.0	0.1	0.1	1.19	0.00839	0.965	−4.0
6	0.1	1.0	0.1	1.11	0.0901	0.961	−4.0
7	0.1	0.1	1.0	1.11	0.0901	0.963	−1.1
				1-compartment model drugs		0.965	−4.1

[a] From Fig. 6 where τ' versus τ and $\tau > 10$ ($t_{0.5}$).

Effect of rate-limiting input on the onset time of the drug after administration of the prodrug as shown in Scheme III

Eqn. 29 has a symmetrical structure with respect to k'_a and k'_c. In other words, if the values for these two constants are interchanged, the identical equation for drug in the body is obtained. Fig. 3 illustrates the results obtained when the absorption rate constant for the prodrug, k'_a, is kept three or more times greater than the elimination rate constant for the drug, k. As the ratio, r, of the elimination rate constant (k) to the conversion rate constant from the prodrug to the drug, k'_c, becomes greater than 2, the line observed in Fig. 3 becomes identical with those for Schemes I and II (open circles). That is, the conversion rate constant, k'_c, has become the rate-limiting input step. So long as the absorption rate constant for prodrug, k'_a, is three or more times greater than the elimination rate constant for the drug, k, it will not contribute to the onset time. However, when the value for k'_a/k is less than 3, the k'_a value causes a deviation in the t_{on} versus k/k'_c plot. The degree of this deviation increases as the ratio k'_a/k decreases. In all cases in Fig. 3 the onset time is roughly 4–5 X the $t_{0.5}$ for rate-limiting input.

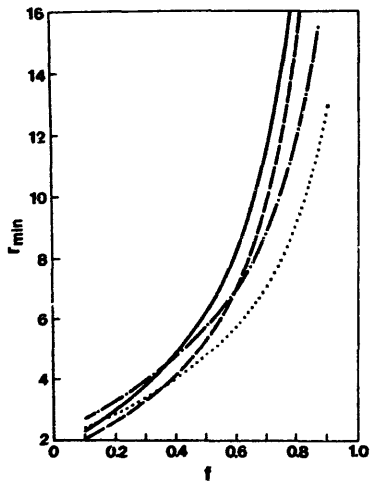
Estimating τ for a specific therapeutic index

Eqn. 9 represents an approximation for τ when Q^∞ approaches $(r-1)/f$. This condition is satisfied when X, defined as

$$X = \left[\frac{1 - f^r}{f - f^r}\right] \tag{32}$$

approaches the value 1/f so that Eqn. 7 may be written as $[Q^\infty/(r-1)] \approx 1/f$. At r_{opt}, $X \approx 1/f$ when $Q^\infty \geq 8$ (Table 2).

The approximation based on a therapeutic index (Eqn. 24) shows that (D_{max}/D_{min}) approaches 1/f when $k \gg k_a$ and f^r is insignificant as assumed in the derivation of



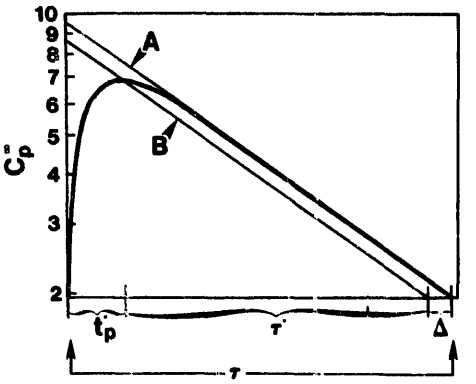


Fig. 4. The minimum r (k/k_a) necessary for $Q^{\infty} \approx (r-1)/f$ (Eqn. 8) within an error of 2% (· – · – ·) and 4% (· · · · ·) and for $\tau \approx \ln[Q^{\infty}/(r-1)]/k_a$ (Eqn. 9) within 2% (———) and 4% (– – – –) as a function of $f = e^{-k_a\tau}$.

Fig. 5. Illustration of a steady-state drug plasma time course (C_p^{∞} versus t where $0 < t < \tau$) and the errors in the τ estimates associated with Eqn. 9 (line A) or Eqn. 24 (line B). τ' in Eqn. 24 is based on the correct $[(C_p^{\infty})_{max}/(C_p^{\infty})_{min}]$ ratio but it underestimates τ by t_p' (Eqn. 15) and Δ (Eqn. 34). Eqn. 9 calculates the time required for the intercept value in line A to decrease to $(C_p^{\infty})_{min}$. It will correctly estimate τ if the time is sufficiently long for τ to lie on the portion of the C_p^{∞} curve that is common to both the curve and line A.

Eqn. 19. Thus, the approximations become identical in the limits where $\tau = -\ln f/k_a$.

Fig. 4. shows the minimum values required for r as a function of f in order to ensure a maximum error of 2 or 4% in the assumption that $X = 1/f$ and in the resulting τ estimates using Eqn. 9. If the fraction remaining at the end of each dosage interval is limited to $f \leqslant 0.36$ as observed in Table 1, then $r \geqslant 3$ will ensure the estimation of both $Q^{\infty} \approx (r-1)/f$ and $\tau \approx \ln[Q^{\infty}/(r-1)]/k_a$ within a 4% error (Fig. 4).

The limits on Eqn. 24 are more restrictive. In addition to requiring that $(f - f^r) \approx f$ it is also necessary that $k >> k_a$. Assuming that $f >> f^r$, the sole difference in the estimates from Eqn. 9 and Eqn. 24 stems from the intercepts as illustrated in Fig. 5. The intercept associated with the derivation of Eqn. 9 is $[D_0/(1-f)(r-1)]$ while that for Eqn. 24 is $[D_0/(1-f)r]$. Thus Eqn. 9 will provide good estimates for τ so long as $(f - f^r) \approx f$ as shown in Fig. 5. As observed in Fig. 4 this will occur whenever $f \leqslant 0.5$ and $r \geqslant 6$. In contrast, Eqn. 24 underestimates τ. This is illustrated in Fig. 5, where it can be observed that

$$\tau' = \tau - t_p' - \Delta \tag{33}$$

where t_p' is defined by Eqn. 15, τ' by Eqn. 24 and Δ is calculated from

$$\Delta = \ln\left[\frac{r}{r-1}\right]/k_a \tag{34}$$

which can be derived from the equations for the reference lines in Fig. 5. Table 4 sum-

TABLE 4

COMPARISON OF THE ESTIMATED VALUES, τ', TO THE ACTUAL VALUES, τ, AND THE SEGMENTS WHICH ARE OMITTED IN THE τ' ESTIMATE, t'_p (Eqn. 15) AND Δ (Eqn. 34) WHEN k = 1 hr^{-1}.

r	τ hr	t'_p		τ'		Δ		Estimate sum	
		hr	% [a]	hr	% [a]	hr	% [a]	hr	% [a]
100	138.6	4.36	3.15	133.1	96.1	1.00	0.726	138.5	99.9
100	69.3	3.95	5.70	64.3	92.9	1.00	1.45	69.3	100.0
100	34.6	3.41	9.84	30.2	87.3	1.00	2.90	34.6	100.0
10	13.9	2.24	16.2	10.5	76.2	1.05	7.62	13.8	99.3
10	3.46	1.23	34.1	1.32	36.6	1.05	29.3	3.60	104.0
5	6.93	1.65	23.9	4.16	60.0	1.12	16.1	6.93	100.0
5	3.46	1.19	32.8	1.32	36.4	1.12	30.8	3.63	104.9
5	1.73	0.72	32.7	0.36	16.5	1.12	50.7	2.20	129.4

[a] These are the % of the sums. Both τ' and Δ have the assumption $(f-f^r) \approx f$ and $k >> k_a$.

marizes the % contribution of t'_p, τ' and Δ to the sum which would equal τ if the assumptions were met which is true for most of the cases in the Table. As the ratio, r, is increased the % contribution of t'_p and Δ decrease and τ' becomes a better estimate of τ provided that $(f - f^r) \approx f$. Therefore at r = 100, τ' is a reasonable estimate when f = 0.25 (τ = 138.6 hr) and f = 0.5 (τ = 59.3) but when f = 0.71 (τ = 34.6) the estimate is only good to 87% of τ. All three of these examples would be suitably estimated from Eqn. 9 as is obvious from Fig. 4 where r_{min} (4%) = 3, 5 and 10 for f = 0.25, 0.5 and 0.7.

A comparison between the estimated values, τ', and the actual values for τ is shown

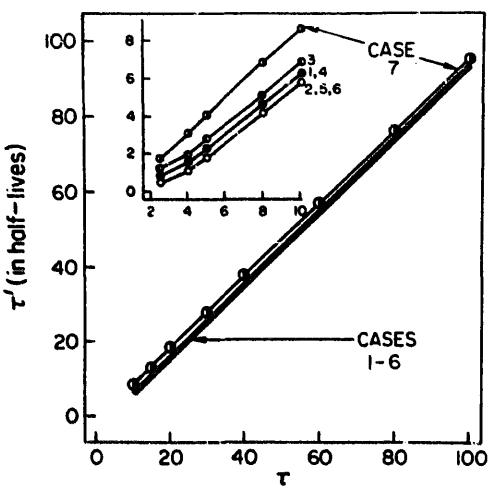


Fig. 6. Relationship between the estimates for τ' expressed in biological half-lives (Eqn. 24) and the actual τ values for seven 2-compartment model drugs (defined in Table 3) and 1-compartment model drugs (open circles in inset and lower margin of band).

in Fig. 6. Equations for C_p^∞ versus t were reiterated for maximum and minimum C_p^∞ values as a function of various τ values. The resulting MAX : MIN ratio was set equal to T.I. to calculate the estimated dosage interval, τ', from Eqn. 24 as discussed previously. The values were normalized by expressing τ and τ' in units of biological half-lives where $t_{0.5} = 0.693/\beta = 0.693/k$.

Fig. 6 summarizes the results for the seven cases in Table 3 and the 1-compartment model. Six of the seven cases are described by a narrow range shown as a band in the figure. The 1-compartment case is also included in this band. Once again the odd case (7) represents a (k_{e1}/k_{12}) ratio of 10. All of the cases are linear when τ exceeds 10 times the half-life. The slopes are reasonably constant at 0.96 and the primary difference is in the intercept values (Table 3). The lowest line in Fig. 6 (i.e. case nos. 2, 5 and 6 shown as open circles in the inset) is identical to that for the 1-compartment model. Due to the multiplicity of results it is not possible to have a single equation to correct the estimates.

In view of the restrictive nature of Eqn. 24 it may be more reasonable to use Eqn. 9 and regard the intercept as D_{max}^∞ which, although incorrect, will err on the safe side. Thus, if $(f - f^r)$ approaches f, the intercept is defined as $[D_0/(1 - f)(r - 1)]$. Thus to convert Eqn. 9 we note that

$$[D_{min}^\infty][Q^\infty/(r - 1)] = [D_0/(1 - f)(r - 1)] \tag{35}$$

Since we will assume the intercept to be D_{max}^∞ (recognizing that the actual maximum is always less) we can then set

$$\left[\frac{Q^\infty}{r - 1}\right] = \left[\frac{D_{max}^\infty}{D_{min}^\infty}\right] = \text{T.I.} \tag{36}$$

Thus, if Q^∞ is defined as $(r - 1)$ (T.I.), a known value for T.I. and a chosen value for Q^∞ will set the value for r and Eqn. 9 will then estimate τ provided $f \leqslant 0.5$ and $r \geqslant 6$.

Conclusions

The significance of this study is best illustrated by examining a hypothetical example. Consider a drug of $t_{0.5} = 8.8$ hr where $t_{0.5} = 0.693/k$ (Scheme I) or $t_{0.5} = 0.693/\beta$ (Scheme II). What is the feasibility of extending the duration of action by a first-order release i.m. prodrug if the MEC is 0.01 μg/ml, the Vd is 50 liters and the amount which may be allowed to accumulate in the muscle is 50 mg? The optimum rate-limiting input constant may be estimated from $r_{opt} \approx Q^\infty/e$. Since $Q^\infty = A_{max}^\infty/(MEC)(Vd) = 50$ mg/(0.01 μg/ml) (50 liters) = 100, r_{opt} is 36.8. The ideal prodrug must therefore provide a rate-determining first-order rate constant for drug input equal to [(0.693)/(8.8 hr)(36.8)] = 2.14×10^{-3} hr^{-1}. The value for τ_{max} as estimated from Eqn. 31, is 37.8 which must be divided by k or β to provide the estimate in real time equal to 480 hr which may also be calculated directly from Eqn. 9. The value of f may now be calculated since $f = e^{-k_a\tau} = 0.36$. The maintenance dose of $D_0 = 32$ mg is then calculated from Eqn. 4 $[D_0/(1 - f) = 50$ mg]. Therefore if a prodrug with a rate-determining rate constant for release from the muscle or conversion to drug equal to 2.14×10^{-3} hr^{-1} can be achieved, it will maintain the required MEC with an i.m. loading dose of 50 mg and a maintenance dose of 32 mg administered every 20 days.

Suppose experimentation shows that a rate constant of 2.14×10^{-3} hr^{-1} is not pos-

sible but $\approx 1 \times 10^{-2}$ might be achieved. Since r = 7.9, Eqn. 9 may be used to approximate $\tau \approx 268$ hr and f = 0.07. This results in a 50 mg i.m. loading dose and a 46 mg maintenance dose given every 11 days.

The problem might also begin by choosing an ideal dosage regimen from a clinical viewpoint. For example, it might be considered desirable to provide weekly administration of a prodrug of the drug described above. Thus τ_{max} (Table 1) would be calculated from $\tau_{max} = [(\text{desired } \tau)\ (0.693)/t_{0.5}] = 13.23$. A plot of the τ_{max} values in Table 1 versus the r_{opt} values is linear and may be described by $\tau_{max} = 1.237 + 0.987\, r_{opt}$. Therefore $r_{opt} = 12.1$ and $Q^{\infty} = (r_{opt})\ (e) = 33$. Since $\tau = 168$ hr and $k_a = 6.51 \times 10^{-3}$ hr^{-1}, f = 0.335. $A^{\infty}_{max} = Q^{\infty}(MEC)Vd = 16.5$ mg; $D_0 = A^{\infty}_{max}\ (1 - f) = 11$ mg. A prodrug with rate-limiting input of 0.00651 hr^{-1}, administered i.m. with an initial dose of 16.5 mg and weekly administration of 11 mg, will maintain an MEC of 0.01 μg/ml.

These examples illustrate the use of the results in the present paper for solving typical situations which may arise in product development. The methods allow the a priori estimation of the maximum duration which may be achieved by design of the optimum prodrug for a given set of conditions. The drug itself would define the MEC, $t_{0.5}$ and Vd. The value for A^{∞}_{max} must be chosen, but once it is fixed only one k_{rds} (rate-constant for rate-limiting input) is optimum. The k_{rds} value is easily estimated from $r_{opt} = Q/e$ (provided $Q^{\infty} \geqslant 8$) and the corresponding τ_{max} and D_0 are then calculated. This allows one to consider the feasibility of achieving success a priori and then to define the optimum result as a reference standard against which prodrug performance may be measured.

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