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PHARMACOKINETIC PREDICTIONS OF OPTIMUM DRUG DELIVERY RATES FROM PRODRUGS DESIGNED FOR MAXIMUM DURATION

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SUMMARY

Recent interest in prodrugs as well as other drug delivery systems has included the control of drug release for the purpose of extending the duration of therapeutic blood levels. While zero-order release rates are generally considered ideal, many systems approach apparent first-order kinetics. These cases may successfully prolong duration if the rate constant for drug delivery (k_a) is rate-limiting relative to the elimination rate constant (k or β). For a given drug there is only one optimum rate-limiting input constant which will provide the maximum duration of therapeutic activity for a given dose. This was demonstrated using computer simulations to examine the effect of variations in dose and R ($R = k_a/k$ or k_a/β) upon the duration, T, of 1- and 2-compartment model drugs administered by rate-determining first-order input. When dose is held constant, an optimum R, R_{opt}, exists at which duration is maximal ($T = T_{max}$). When k_a is fixed, an optimum value for dose, $[D_0]_{opt}$, provides the greatest duration per unit mass. Equations were derived which enable estimation of R_{opt}, T, T_{max}, and $[D_0]_{opt}$ when input is rate-determining. The accuracy of these estimates was determined as a function of R. The equations provide estimates with less than 5% error when $R \leqslant 0.09$. The administration of a 1- or 2-compartment model drug at estimates within the limit, $0.09 < R \leqslant 0.34$, provides a duration $T \geqslant 0.95\ T_{max}$. A practical approach for maximizing duration by manipulation of dose and k_a is described for drugs with known biological half-life, Vd and minimum effective concentration. The results are significant in that they provide a means for both assessing the feasibility of increasing the duration of drug action by prodrug formation and for evaluating the experimental results by comparison with the theoretical optimum.

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INTRODUCTION

Duration of drug action is extended by slow release drug delivery systems (DDS) such as osmotic pumps (Theeuwes, 1975), implants (Chien and Lau, 1976), encapsulated cosolvents (Theeuwes et al., 1976), drug and prodrug depot injections (Dreyfuss et al., 1976) and a variety of oral sustained release dosage forms (Notari, 1975). The ideal drug input rate is generally considered to be zero-order. The rate constant may be calculated from known pharmacokinetic parameters for the drug (the minimum effective blood level, the $t_{0.5}$ and the apparent volume of distribution) using methods similar to those for calculations of constant i.v. infusion rates (Notari, 1975). In practice, the kinetics of drug release varies widely among the delivery systems and zero-order release is infrequently achieved. A decreasing exponential rate of supply (apparent first-order) is encountered in many instances including encapsulated solutions (Baker and Lonsdale, 1974), sustained release dosage forms (Meier et al., 1974; Kruger-Thiemer and Eriksen, 1966; Robinson and Eriksen, 1966) and prodrugs (Notari, 1977; Morozowich et al., 1977).

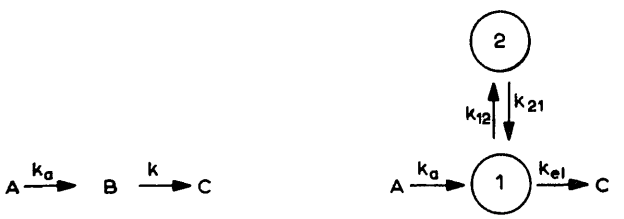
It is well recognized that the first-order input rate constant (k_a) can affect the efficacy of a dosage form. Given a fixed dose, a value for k_a that is too small can mean that the MEC is never reached. Toxic side-effects may result when it is too high. This implies that an optimum k_a exists for the administration of a known dose. This report demonstrates that for a given drug, dose and MEC, there is only one optimum apparent first-order input constant which will provide the maximum duration of therapeutic activity. This k_a may be estimated a priori from the relationship $R'_{opt} = e \cdot MEF$ where R'_{opt} is the ratio (input constant)/(output constant), MEF is the minimum effective fraction of bioavailable dose, and the estimate is made within the limits of applicability outlined in the discussion. A discussion is included to illustrate the effect of prodrug loss to non-drug on the equations. Equations have been derived primarily for the cases where all of the prodrug is absorbed and converted to drug. This is most likely limited to i.m. injections but the equations are easily altered for other kinetic situations.

EXPERIMENTAL

Plasma concentrations resulting from rate-limiting first-order input

Assuming first-order kinetics the concentration of drug in the body for a drug whose pharmacokinetics are described by Scheme I obeys the equation

$$C_p = [D_0F/Vd]\,[k_a/(k - k_a)]\,[e^{-k_at} - e^{-kt}] \qquad (1)$$



Scheme I Scheme II

while, in the case of the 2-compartment drug in Scheme II, the concentration of drug in

the sampled compartment, may be described by

$$C_p = [D_0 F k_a / V_1] \{X e^{-k_a t} + Y e^{-\alpha t} + Z e^{-\beta t}\} \quad (2)$$

where

$$X = (k_{21} - k_a)/(\alpha - k_a)(\beta - k_a) \quad (3)$$

$$Y = (k_{21} - \alpha)/(k_a - \alpha)(\beta - \alpha) \quad (4)$$

$$Z = (k_{21} - \beta)/(k_a - \beta)(\alpha - \beta) \quad (5)$$

and α and β have the usual definitions (Gibaldi and Perrier, 1975). Eqn. 2 may be written in terms of the volume of distribution using the identity $k_{el} V_1 = \beta$ Vd to give

$$C_p = (D_0 F k_a k_{el} / Vd\beta) \{X e^{-k_a t} + Y e^{-\alpha t} + Z e^{-\beta t}\} \quad (6)$$

where the volume of distribution for Scheme II is determined by the area method (Gibaldi and Perrier, 1975; Notari, 1975).

In a previous publication (Byron and Notari, 1976) we observed that the negative value of the terminal log-linear slope, S, for the plasma-profile of a 1- or 2-compartment model drug with first-order absorption provides an estimate of k_a ($S \rightarrow k_a$) with less than 2% error when $k_a < 0.3k$ or $k_a < 0.3\beta$, respectively. Thus, input controls the plasma decay curve when $k_a < 0.3k$ for a 1-compartment drug or $k_a < 0.3\beta$ for a 2-compartment drug.

In the limit, as $k >> k_a$, Eqn. 1 may be written

$$C_p \approx [D_0 F k_a / Vdk] e^{-k_a t} \quad (7)$$

and as $\beta >> k_a$, Eqn. 6 becomes

$$C_p \approx (D_0 F k_a k_{el} / Vd\beta) \{(k_{21} - k_a)/\alpha\beta\} e^{-k_a t} \quad (8)$$

which can be simplified to Eqn. 9 since $k_{21} > \beta$ and $\alpha\beta = k_{21} k_{el}$. *

$$C_p \approx [D_0 F k_a / Vd\beta] e^{-k_a t} \quad (9)$$

Since total body clearance, Cl, may be defined as kVd for Scheme I and βVd for Scheme II, Eqns. 7 and 9 may be written as a single equation

$$C_p \approx [D_0 F k_a / Cl] e^{-k_a t} = [RFD_0 / Vd] e^{-k_a t} \quad (10)$$

where R is the ratio of the rate constants: $R = k_a/k$ (Scheme I) and $R = k_a/\beta$ (Scheme II). The advantage is the potential for describing both 1- and 2-compartment drugs by a single equation. When Eqn. 10 is applicable, plots for C_p versus t should be similar for Schemes I and II provided that $[RFD_0/Vd]$ and k_a are held constant.

The adequacy with which C_p is described by Eqn. 10 will be shown to depend upon the value of R which is an indication of the degree of rate-determination by absorption. An example where both a 1- and 2-compartment model curve may be approximated by Eqn. 10 is illustrated in Fig. 1. The dashed curve represents the C_p versus t profile

* $k_{21} > \beta$ may be demonstrated using the 2-compartment i.v. bolus equation: $C_p = Ae^{-\alpha t} + Be^{-\beta t}$ where $B = [D_0(k_{21} - \beta)/V_1(\alpha - \beta)]$. Therefore $k_{21} = \beta + [BV_1(\alpha - \beta)/D_0]$.

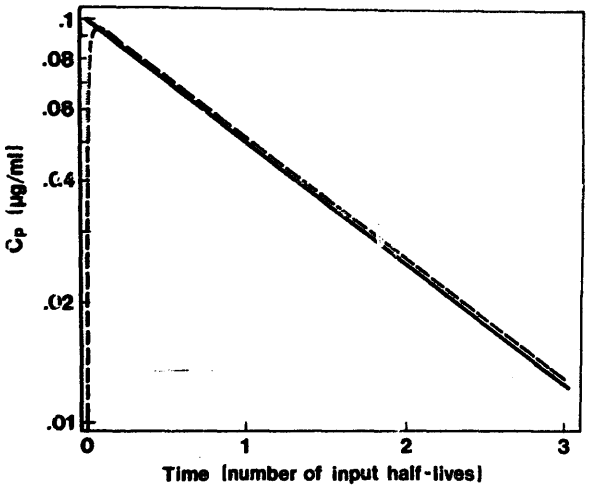


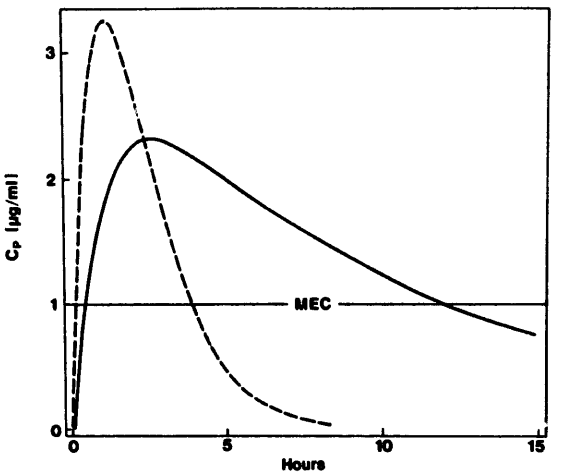
Fig. 1. Rate-limiting first-order input is shown to produce a single curve (– – – –) for Scheme I (k_a/k = 0.01) and Scheme II (k_a/β = 0.01) when D_0 = 500 mg, F = 1, Vd = 50 liters and the time scale is normalized using ($0.693/k_a$) = 1 unit. The solid line, approximating most of the curve, was generated using Eqn. 10. By imposing these conditions on Scheme II any 2-compartment model in Table 1 (except case no. 5) will provide a similar curve.

observed when D_0 = 500 mg, F = 1, Vd = 50 liters, R = 0.01 and k_a is held constant. Under these conditions both Schemes I and II have the same C_p time course. The solid line results from Eqn. 10. The ability of Eqn. 10 to describe most of the profile for the 1- and 2-compartment model drugs administered with the same high degree of rate-determination (R = 0.01 = k_a/k = k_a/β) is demonstrated by the similarity between the solid line and the simulated data (dashed curve).

Input:output (R) ratios for maximum duration of 1- and 2-compartment drugs

The dashed curve of Fig. 2 illustrates the plasma-concentration time course described by Eqn. 1 when R = 0.8 and the solid curve represents the same drug under conditions of rate-limited administration (R = 0.1) and 3 times the dose. The horizontal line represents an arbitrary assignment for the *minimum effective concentration* (MEC) of the drug. The duration, T, in each case may be defined as the time spent above the MEC or ($t_2 - t_1$) where t_1 is the onset time and t_2 is the time at which C_p falls below the MEC. Eqns. 1 and 2 cannot be solved explicitly for t_1 or t_2. However, the duration (as illustrated in Fig. 2) was found by numerical analysis as follows.

Eqns. 1 and 2 were used to determine the actual duration, T, by iterative digital simulation of C_p versus t, after choosing 15 representative values for MEC. In each simulation D_0, F, Vd, MEC and β = k were held constant. The value for t in Eqn. 1 or 2 was increased from $t \approx 0$ to t_1 as evidenced by C_p becoming nearly equal to MEC. The incremental values for t were optimized so as to make the difference between $(C_p)_t$ and MEC insignificant. The process was continued from $t > t_1$ until t_2 as indicated by the second point at which C_p equals MEC. The values for $T = t_2 - t_1$ were determined as a function of R = 0 to 1 by setting β = k = 1 and changing k_a values. The ratios employed in Scheme II for k_{12}, k_{21} and k_{e1} are listed in Table 1.



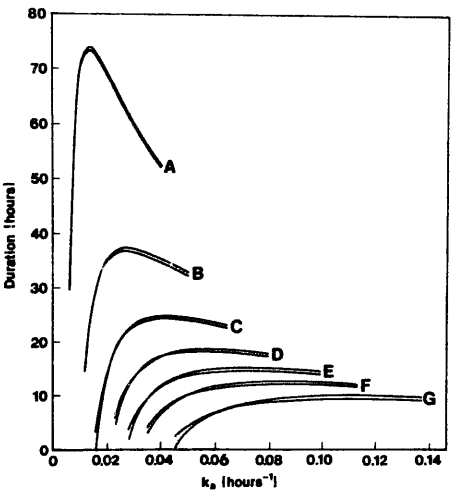


Fig. 2. Typical plasma-concentration time profiles for the 1-compartment drug whose k = 1 hr^{-1} and Vd = 10 liters. Solid line: $k_a/k = 0.1$, $D_0 = 300$ mg. Dashed line: $k_a/k = 0.8$, $D_0 = 100$ mg.

Fig. 3. Duration of action (T) in hours for all 1- and seven 2-compartment drugs at MEC values (in μg/ml) of: A = 0.005; B = 0.01; C = 0.015; D = 0.02; E = 0.025; F = 0.03 and G = 0.04 as a function of k_a. D_0, Vd, k and β are constant at 50 mg, 50 liters, 1 hr^{-1} and 1 hr^{-1}, respectively. To scale these curves for different drugs: (1) multiply the known MEC (μg/ml or mg/l) by [(Vd in liters)/(D_0 in mg)] to convert to the MEC in the figure (50 mg D_0 with Vd = 50 liters); (2) multiply duration in hours taken from the appropriate curve by 1/k or 1/β (in hr^{-1}) to obtain predicted duration. At a fixed MEC value all cases are described by a single curve except case no. 5 (Table 1) which is represented by the lower curve adjacent to each identifying letter.

Except for case number 5 in Table 1, a single model-independent curve was obtained for T versus k_a at fixed values for D_0, F, Vd, MEC and $k = \beta$. Examples are shown in Fig. 3 where $D_0 = 50$ mg, F = 1, Vd = 50 liters and $k = \beta = 1$ hr^{-1}. The lower curve adjacent to each identifying letter represents case no. 5 and the upper curve represents all 1-compartment model cases and the remaining 2- compartment model cases in Table 1.

TABLE 1

RATE-CONSTANT RATIOS CHOSEN TO REPRESENT A CROSS SECTION OF 2-COMPARTMENT DRUGS

Case no.	k_{12}	k_{21}	k_{e1}
1	1.0	1.0	1.0
2	1.0	1.0	0.1
3	1.0	0.1	1.0
4	0.1	1.0	1.0
5	0.1	0.1	1.0
6	1.0	0.1	0.1
7	0.1	1.0	0.1

Testing validity of the approximations

In the case of rate-determining input, Eqn. 10 may be used to estimate the duration (T) by solving for the time (T′) at which C_p = MEC or

$$MEC = [RFD_0/Vd]\, e^{-k_a T'} = [FD_0 k_a/Cl]\, e^{-k_a T'} \quad (11)$$

The duration, T, may be approximated from T′,

$$T' = [\ln(RFD_0/Vd\ MEC)]/k_a = [\ln(FD_0/Cl\ MEC)]/k_a \quad (12)$$

if the conditions of rate-limiting input wherein T′ approaches T can be imposed. Eqn. 12, in the clearance form, may be differentiated with respect to k_a to give

$$dT'/dk_a = [1 - \ln k_a - \ln(FD_0/MEC \cdot Cl)]/k_a^2 \quad (13)$$

which may be set equal to zero to estimate R_{opt} at T'_{max}. When $dT'/dk_a = 0$, Eqn. 13 becomes: $1 - \ln k_a - \ln(FD_0/Cl \cdot MEC) = 0$ which may be solved for k_a to give

$$k_a = e[Cl \cdot MEC/FD_0] \quad (14)$$

TABLE 2

DURATION IN HOURS (T_{max} AND T) AT R_{opt} AND R'_{opt} (EQN. 15) FOR 1- AND 2-COMPARTMENT [a] DRUGS [D_0 = mg; Vd = 50 LITERS: $\beta = k = 1\ HR^{-1}$] AT VARIOUS VALUES FOR THE MINIMUM EFFECTIVE CONCENTRATIONS (MEC)

Case no.	MEC (μg/ml)	R_{opt}	R'_{opt}	T_{max}	T [b]	% Error [c]	T'_{max}	$(T'_{max}-T)$ [d]
1	0.005	0.013	0.0136	74.1	74.1	0	73.5	−0.6
2	0.01	0.028	0.0272	37.4	37.4	0	36.8	−0.6
3	0.015	0.042	0.0408	25.1	25.1	0	24.5	−0.6
4	0.02	0.056	0.0544	19.0	19.0	0	18.4	−0.6
5	0.025	0.072	0.068	15.3	15.3	0	14.7	−0.6
6	0.03	0.086	0.082	12.9	12.9	0	12.2	−0.7
7	0.04	0.117	0.109	9.84	9.84	0	9.17	−0.7
8	0.06	0.183	0.163	6.79	6.75	−0.6	6.14	−0.6
9	0.08	0.258	0.217	5.27	5.20	−1.3	4.61	−0.6
10	0.10	0.338	0.272	4.31	4.23	−1.9	3.68	−0.6
11	0.12	0.433	0.326	3.68	3.56	−3.3	3.07	−0.5
12	0.14	0.518	0.381	3.20	3.06	−4.4	2.63	−0.4
13	0.16	0.638	0.435	2.84	2.66	−6.3	2.30	−0.4
14	0.18	0.758	0.489	2.54	2.36	−7.1	2.05	−0.3
15	0.20	0.873	0.544	2.29	2.08	−9.2	1.84	−0.2

[a] Defined in Table 1.
[b] Observed value at R'_{opt}.
[c] $[(T-T_{max})/T_{max}] \times 100\%$.
[d] Values in Table apply to other cases of k or β when adjusted: $(T'_{max}-T)/k$ for Scheme I or $(T'_{max})/\beta$ for Scheme II.

Since $Cl = \beta Vd = kVd$ and $R = k_a/\beta = k_a/k$ substitution for Cl allows Eqn. 15 to be written

$$R'_{opt} = e[Vd \cdot MEC/FD_0] \quad (15)$$

where R'_{opt} is the ratio when T' is at its maximum, i.e. T'_{max}. R'_{opt} may provide an estimate for the true optimum ratio, R_{opt}, when T'_{max} approaches T_{max}. Substitution of R'_{opt} (Eqn. 15) for R (Eqn. 12) shows that at this input:output ratio

$$T'_{max} = 1/k_a \quad (16)$$

The validity of Eqn. 15 has been assessed by comparing the observed values for R_{opt} to the calculated values (R'_{opt}) for each of the MEC values in Table 2. The potential decrease in duration was estimated by comparing the actual duration (T) which would result from administering the drug at R'_{opt} to the values for T_{max} which is the observed duration at R_{opt}. The differences are listed as % error in Table 2.

Eqn. 16 suggests that the maximum duration (T_{max}) might be estimated from k_a when $k_a \ll k$ (or β) and R'_{opt} approaches R_{opt}. Estimates were made using R'_{opt} values and these were compared to the observed duration (T) as determined in the previous section. The last column in Table 2 summarizes the differences between T'_{max} and T.

RESULTS AND DISCUSSION

Plasma concentrations resulting from rate-limiting first-order input

Eqn. 12 estimates duration for 1- and 2-compartment drugs when first-order input is truly rate-determining. This equation, like Eqn. 10, assumes extremely low values of R. The slope of the line $\ln C_p$ versus time, based on Eqn. 10, is $-k_a$. The negative log-linear slope, S, of a plasma profile described by Eqn. 1 or 2 has been shown to provide an estimate of k_a when $R \leqslant 0.3$ (Byron and Notari, 1976). Thus, if elimination is at least 3.3 times faster than input, then $S \rightarrow k_a$ and the plot of $\ln C_p$ versus time based on Eqn. 10 is parallel to that obtained from Eqns. 1 and 2 (see Fig. 4).

The monoexponential curve described by Eqn. 10 may be shown to pass through $(C_p)_{max}$, the maximum concentration of drug at t_{max} using Eqn. 1 irrespective of R. Several texts (Gibaldi and Perrier, 1975) have shown that, for Scheme I,

$$(C_p)_{max} = [D_0 F/Vd] R^{[k/(k-k_a)]} \quad (17)$$

since

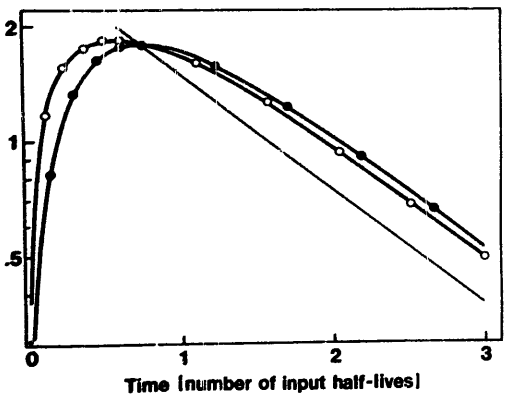
$$t_{max} = [\ln R]/(k_a - k) \quad (18)$$

At t_{max} Eqn. 10 becomes

$$C_p \approx [RFD_0/Vd]\, e^{[k_a/(k-k_a)]\ln R} \quad (19)$$

which upon rearrangement becomes identical to Eqn. 17. This intersection of the curves described by Eqns. 1 and 10 is illustrated in Fig. 4.

Plasma-profiles for a 2-compartment drug ($k_{12} = k_{21} = k_{el}$) administered with different degrees of rate determination are illustrated in Fig. 1 (R = 0.01) and Fig. 4 (R = 0.3). These profiles have been simulated with D_0F and Vd held constant. The 1- and 2-compartment profiles shown by Fig. 1 are indistinguishable. This is not the case in Fig. 4 when



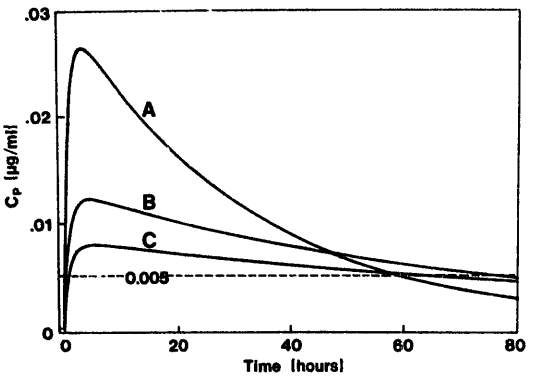


Fig. 4. Computer generated semi-logarithmic plots of drug concentration in plasma for a 1-compartment (•; $k_a/k = 0.3$; Vd = 50 liters) and a typical 2-compartment (○; $k_a/\beta = 0.3$; $k_{12} = k_{21} = k_{el}$; Vd = 50 liters) drug administered as a single 500 mg dose by first-order absorption. Solid line was generated using Eqn. 10 for these cases.

Fig. 5. Time course for concentration of drug in plasma for a drug described by Scheme I where D_0 = 50 mg, Vd = 50 liters and k = 1 hr^{-1}. Curve A: R = 0.03; curve B: R = 0.013; curve C: R = 0.008.

R = 0.3. For drugs described by Scheme II, Eqn. 10 only passes through $(C_p)_{max}$ under conditions of extreme rate-limitation ($R \rightarrow 0$) when Eqns. 1 and 2 can both be reduced to Eqn. 10.

The solid line in Fig. 1 shows that Eqn. 10 is a good approximation of the terminal portion of the plasma-profile when R = 0.01. When R = 0.01, Eqn. 12 will provide a good estimate of T independent of the MEC value. Fig. 4 shows the other extreme. When R = 0.3 the solid line from Eqn. 10 is a poor approximation of the examples shown. Despite the difference in the appearance of the 1- and 2-compartment profiles in Fig. 4, the observed duration for an MEC of 1 μg/ml equals 1.85 input half-lives for both cases. The estimated duration, T', is 1.58 input half-lives. As seen in Fig. 4, T' underestimates t_2, the time at which C_p falls below the MEC, but also includes the onset time t_1. The errors are compensatory and although T' estimates are aided by this effect, T' underestimates T in this example.

Input:output (R) ratios for maximum duration of 1- and 2-compartment drugs

Fig. 3 shows the observed duration, T, as a function of R for various MEC values where F, D_0 and Vd are held constant. The duration T can be seen to pass through a maximum defined as T_{max} at R_{opt}. The presence of this maximum duration is increasingly obvious as input becomes more rate-limiting as noted at the lower values for R_{opt}.

The explanation for this maximum and the reason for the existence of an optimum input:output ratio can be visualized through the example in Fig. 5. Dose, Vd and k have been held constant. Fig. 5 shows plasma-profiles for a drug described by Scheme I and administered with R = 0.03, 0.013 (R_{opt}) and 0.008 (curves A, B and C). If the MEC is 0.005 μg/ml then T can be observed in Fig. 5 as 60, 74.1 and 60 hr for these three cases (which may also be read from the A group in Fig. 3).

Two factors, $(C_p)_{max}$ and k_a, are operative in the determination of the duration, T. An

increase in $(C_p)_{max}$ tends to increase duration. Increased values of k_a result in a more rapid decrease in plasma levels ($t > t_{max}$) since $S = k_a$ under conditions of rate-determining input. Thus, increasing k_a increases $(C_p)_{max}$ which has a positive effect on T but also increases S which has a negative effect. Thus, when $R < R_{opt}$, duration increases with increasing R because increasing $(C_p)_{max}$ has a greater contribution to T than does the increased value of the terminal slope S. When $R > R_{opt}$, however, S assumes more importance and the converse becomes true.

Testing validity of the approximations

The duration, T, for 1-compartment and 2-compartment model drugs (as defined by the k_{12}, k_{21} and k_{e1} ratios shown in Table 1 and adjusted so that $\beta = 1.0\ hr^{-1}$) was determined as a function of R at various values for MEC. Results are illustrated in Fig. 3.

Although F, D_0, β or k, Vd and MEC have been held constant at arbitrary values (50 mg, $1\ hr^{-1}$, 50 liters and the MEC as indicated for each curve), the information may be generalized. Fig. 3 can be used to determine the duration for any drug described by Schemes I and II if the MEC can be adjusted to the figure. Consider, for example, a drug with Vd = 60 liters normally dosed at 20 mg with a MEC of 0.01 μg/ml. This can be converted to a corresponding curve in Fig. 3 by calculating the MEC which would result if it were administered in a 50 mg dose with a volume of distribution of 50 liters. To do this simply multiply the MEC by (50 mg) (Vd in liters)/(D_0 in mg)·(50 liters) or the factor Vd/D_0 without units. The result in this case is (0.01 μg/ml) (3) = 0.03 μg/ml. The curve marked F in Fig. 3 will provide the duration in hours as a function of R if β or $k = 1\ hr^{-1}$. To convert the answer for other k or β values multiply T by $1/\beta$ or 1/k.

It is impractical to construct a nomogram such as Fig. 3 for every possible MEC. It is more reasonable to use Eqns. 12, 15 and 16 to estimate T', R'_{opt} and T'_{max} for a chosen drug. However, the upper limit of R, below which the equations provide reasonable estimates, must be established.

Provided that $R \leqslant 0.34$, Table 2 is applicable to all cases studied for both Schemes I and II with the exception of case no. 5 in Table 1. This exception represents the only case wherein the distribution constants are much smaller than the elimination constant ($k_{12} = k_{21} = 0.1\ k_{e1}$). Results in Table 2 are only applicable to case no. 5 when $R \leqslant 0.12$.

Table 2 provides a comparison of the observed values (R_{opt}, T_{max} and T) to the calculated values (R'_{opt} and T'_{max}). Eqns. 12, 15 and 16 require that $R'_{opt} \leqslant 0.09$ to provide estimates with less than 5% error. This can be observed in Table 2 where the errors in R'_{opt} exceed 5% at R_{opt} values greater than 0.086 (case no. 6 in the table).

However the above limitations are misleading when approaching a practical problem. Consider the decreased duration which would occur if a drug with known D_0, Vd and MEC were administered at an input:output ratio R'_{opt} instead of R_{opt}. To do this compare values of T to T_{max} in Table 2. The percent error tabulation shows that <2% loss in duration occurs when $R_{opt} \leqslant 0.34$ even though the drug is supplied at the inappropriate input rate constant based on R'_{opt}. The reason for this minimal error in duration when R'_{opt} varies significantly from R_{opt} may be realized from Fig. 3. As R values increase and R'_{opt} becomes less accurate, the peaks for T versus R become broader and accuracy is less critical.

When $R_{opt} \leqslant 0.34$, Eqn. 16 underestimates the duration, T, by a constant value deter-

mined empirically to be $0.6/\beta$ or $0.6/k$ (Table 2). Rewriting Eqn. 16 to include this empirical correction factor would yield

$$T'_{max} = 1/k_a + 0.6/\beta \tag{20}$$

Practical optimization of first-order input

Fig. 2 illustrates that changing R from 0.8 to 0.1 and simultaneously changing D_0 from 100 to 300 mg for a given drug increases the duration more than 3-fold (3.7 to 11.6 hr). That is, three times the dose provides more than three times the duration. In this case, 300 mg of this drug supplied at the slower k_a represents more efficient administration. Two variables, therefore, must be adjusted: R and D_0. If D_0 is progressively increased it is possible to use smaller and smaller input rates (see Eqn. 15). The limit is of course impractical ($D_0 \to \infty$ and $k_a \to 0$). While it is obvious that the larger the dose used, the longer the duration, a practical limit must be imposed. In order to maximize duration by optimizing k_a, it is first necessary to choose a maximum acceptable dose. Assuming that the drug-dependent parameters Vd and MEC are known, R'_{opt} may be calculated from Eqn. 15. The optimum input rate constant may then be calculated from $R'_{opt} = k_a/\beta = k_a/k$ provided $R_{opt} \leqslant 0.34$ (i.e. $R'_{opt} \leqslant 0.27$).

The question may also be considered in reverse. Given a known input:output ratio ($R \leqslant 0.34$) what is the *optimum dose*? Obviously the dose which will give the longest duration is the largest mass. The optimum dose, $[D_0]_{opt}$, may be defined as that amount of drug which, when administered at a known R value, provides the greatest duration per unit mass. It can be estimated by rearrangement of Eqn. 15 (F = 1) to give

$$[D'_0]_{opt} = e[Vd \cdot MEC/R] \tag{21}$$

which provides estimates of the optimum dose with less than 5% error when $R \leqslant 0.09$.

Under conditions of rate-limiting input, values for $(C_p)_{max}$ in Schemes I and II are approximately equal (see Fig. 1). For the drugs described by Scheme I, Eqn. 15 may be rewritten as

$$R'_{opt} = e \cdot MEF \tag{22}$$

where $MEF = Vd \cdot MEC/FD_0$ is the minimum effective fraction of bioavailable dose in the body and $(e \cdot MEF) < 0.27$. Substitution of $e[Vd \cdot MEC/FD_0]$ for R in Eqn. 10 provides $C_p \approx (e \cdot MEC)e^{-k_a t}$ which means that a semilog plot for C_p versus t has an intercept of $e \cdot MEC$. Thus the most efficient R for a given dose of drug would provide a $(C_p)_{max}$ approximately 2.7 times higher than the MEC when k_a is sufficiently rate-limiting to cause $(C_p)_{max}$ to approach the intercept value.

Consider the optimization of first-order input for drugs possessing a known therapeutic index, T.I., which may be defined

$$T.I. = MSC/MEC \tag{23}$$

where MSC is the maximum safe concentration of drug in the plasma. As noted above, optimum rate-determining administration of a known dose provides a $(C_p)_{max}$ approximately 2.7 times the MEC. If $T.I. \geqslant 2.7$ and a maximum acceptable dose is known, R'_{opt} can be calculated directly from Eqn. 15 provided that $R'_{opt} \leqslant 0.27$. Administration at the input rate constant specified by this ratio will achieve a duration, T, between the limits T_{max} and $0.95\ T_{max}$ without exceeding 2.7 MEC.

If T.I. < 2.7, it is not possible to employ R_{opt}. Administration must be at a value of k_a less than that calculated as R'_{opt} from Eqn. 15 in order to reduce $(C_p)_{max}$ to the maximum safe concentration. In this case the maximum duration will occur at a value for R such that $(C_p)_{max} = MSC$. It is therefore necessary to find that value for k_a which results in a $(C_p)_{max}$ of MSC. For a 1-compartment model, Eqn. 17 may be reiterated to estimate the value for $R = k_a/k$ which will result in $(C_p)_{max} \approx MSC$. For a 2-compartment model it would be necessary to simulate curves using Eqn. 2 and to reiterate k_a until the observed $(C_p)_{max} \approx MSC$. In the case of very small R values, when 1- and 2-compartment models provide similar profiles (Fig. 1) it may be feasible to approximate $(C_p)_{max}$ using Eqn. 10 by setting $MSC = RFD_0/Vd$ and solving for R since $(C_p)_{max}$ (Eqn. 17) $\approx$ the intercept of Eqn. 10 when $k >> k_a$.

A similar situation arises when R is known and is smaller than 0.34. It is now necessary to estimate the dose required to maximize duration. If T.I. > 2.7 the dose providing maximum duration, $[D_0]_{max}$, can be found by rearranging Eqn. 17 (using β for k in Scheme II provided that R is small) and setting $(C_p)_{max}$ equal to MSC. Thus, (assuming F = 1)

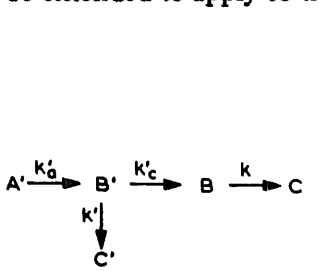
$$[D_0]_{max} = MSC \cdot Vd \cdot R^{[k/(k_a-k)]} \tag{24}$$

However the resulting duration will be less than the maximum duration which would be obtained if R were changed to R'_{opt} which, if sufficiently small, would cause $(C_p)_{max}$ to approach $e \cdot MEC$. Since T.I. > 2.7 the $(C_p)_{max}$ would remain less than MSC.

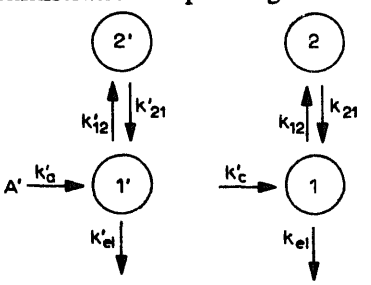
Subsequent to the optimization procedures described above, the duration T may be estimated with less than 0.5% error from T'_{max} (Eqn. 20) provided $R_{opt} \leqslant 0.34$. If $R \neq R'_{opt}$ however (for example when T.I. > 2.7 and $D_0 = [D_0]_{max}$), then Eqn. 12 will provide an estimate T' of T with less than 5% error when $R \leqslant 0.09$. At input:output ratios above this value ($R > 0.09$) T must be estimated by numerical analysis.

Increased duration by administration of prodrugs

Morozowich et al. (1977) have discussed the prolongation of drug plasma levels by inhibition of prodrug conversion rates for an example where both the drug and prodrug behave according to a 1-compartment open model. This increase in duration by bioreversible chemical modification was called *chemical sustained release.* Notari (1977) discussed the general case of 1- or 2-compartment model prodrugs releasing 1- or 2-compartment model drugs. In either case, in order to extend the activity of the drug through chemical sustained release, it is necessary that either absorption or conversion of prodrug must be rate-determining compared with elimination of drug itself. Schemes I and II may be extended to apply to the administration of prodrug as follows.



Scheme III



Scheme IV

A symbol with a prime, i.e. A′, indicates unconverted prodrug and the remainder of the schemes are identical with that shown in Schemes I and II. In both models, the rate-limiting step must be either absorption or conversion if duration is to be extended. However, in a series of rate processes such as this

$$\text{PRODRUG} \xrightarrow[\text{INPUT}]{\text{CONTROLLED}} \text{PRODRUG} \xrightarrow[\text{CONVERSION}]{\text{CONTROLLED}} \text{DRUG}$$

Scheme V

only *one* rate-limiting step can prevail. This was illustrated by comparing the observed percent of morphine antagonism in mice from administration of antagonist to that observed from its prodrug (Notari, 1977). When both were administered by i.v. bolus the prodrug extended the time profile from roughly 4 hr to more than 24 hr. By i.v. bolus the conversion of prodrug to drug appeared rate-limiting relative to the elimination of drug itself. When the same prodrug and drug were compared by i.m. injection, the prodrug provided antagonism for roughly 2 weeks while the drug itself lasted less than a day. The rate-determining step was transferred from conversion to absorption.

This same principle may be applied to Schemes III and IV. The fraction (f) of prodrug that is converted to drug is determined by the competing rate constants so that for Scheme III, $f = k'_c/(k'_c + k')$ and for Scheme IV, $f = k'_c/(k'_c + k'_{e1})$ and $\beta'_c = f\beta'$. In the ideal case where $f = 1$, the rate-determining constant, k'_{rds}, must be either k'_a or k'_c in Scheme III and k'_a or β'_c in Scheme IV. In this way one of the two steps in Scheme V is rate-limiting and the optimum value for k'_{rds} is defined as discussed in the previous section. For the case where $f < 1$, with rate-limiting conversion, the negative terminal slope of ln C_p versus time would become $k'_{rds} = [k'_c + k']$ (Scheme III) and $k'_{rds} = \beta'$ (Scheme IV) (Notari et al., 1972). The optimum value for k'_{rds} could be calculated as previously discussed. However, to obtain the expected blood levels the dosage actually administered would have to be increased, i.e. administered dose = D_0/f. Alternatively, D_0 could be held constant but R'_{opt} would have to be corrected i.e. $(R'_{opt})_{corr} = R'_{opt}/f$. For rate-limiting absorption the terminal slope would reflect k'_a and again corrections using f would be required.

Conclusions

If D_0 is progressively increased, it is possible to use successively decreasing values of k_a to prolong the duration indefinitely. As $D_0 \to \infty$ and $k_a \to 0$, the observation is of little value. If a maximum acceptable dose is chosen, the optimum input:output ratio, R_{opt}, for maximum duration can be estimated if input is rate-determining. In its simplest form when $F = 1$, $R_{opt} \approx 2.7$ times the minimum effective *fraction* of the dose. If k_a is fixed, then $[D_0]_{opt}$, the dose which provides the maximum duration per unit mass, is approximately (e/R) times the minimum effective *amount* of drug in the body. The values of k_a or D_0 calculated by these methods are sufficiently large to produce a maximum concentration in the plasma some 2.7 times higher than the MEC. Eqn. 20 allows the estimation of the duration which would be obtained from the optimum D_0 and k_a values.

This report provides a rational means of manipulating dose and the input rate constant to maximize duration for drugs administered by rate-determining first-order input.

Whether further attempts to increase duration by molecular modification (prodrugs) or formulation control is worthwhile may be evaluated by comparing the duration observed in practice to T'_{max} for the maximum acceptable dose.

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