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KINETIC CONSIDERATIONS RELATING TO THE USE OF DRUG PRECURSORS

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The pharmacological action which follows the administration of certain substances is due to their conversion in the body to an active metabolite, the parent substance being inactive. Such substances can be termed pro-drugs (Albert, 1958) or drug precursors and many examples of these are now known (Harper, 1962; Albert, 1965). In some instances the administration of the drug precursor has been abandoned in favour of the direct administration of the metabolite which has been formally introduced into clinical practice as a drug. In this manner, sulphanilamide replaced prontosil rubrum. In other instances the practice of administering the precursor has continued, thus proguanil remains the " drug " of choice, although its therapeutic effect is due to its conversion *in vivo* to a triazine derivative (Crowther & Levi, 1953).

These discoveries, in conjunction with other considerations, have fostered the attempt to prepare drug precursors for certain known drugs. The advantages which can arise from this procedure have been considered by Harper (1959, 1962, 1964) and by Albert (1965), thus the use of a precursor may prove of value in overcoming difficulties of pharmaceutical formulation, in reducing drug toxicity, in modifying the absorption, the duration of action, the transport and the distribution of a drug in the body. Furthermore, if the formation of the active metabolite is localized in certain cells or tissues, an action or effect may be obtained which is selective for these cells.

Little attention has, however, been given to the kinetic factors which govern the effective use of a precursor, thus there is no quantitative indication of the extent to which a precursor might successfully extend the duration of drug action or reduce drug toxicity. The present communication records the results obtained by a theoretical study of these factors. The study was designed to examine the effect of assigning different values to the rate constant governing the formation of drug from a model precursor and to compare the drug level resulting from the administration of single and multiple doses of precursor with those obtained by administration of the drug.

A preliminary report of this work was presented to the 5th International Congress of Chemotherapy, Vienna (Martin, 1967).

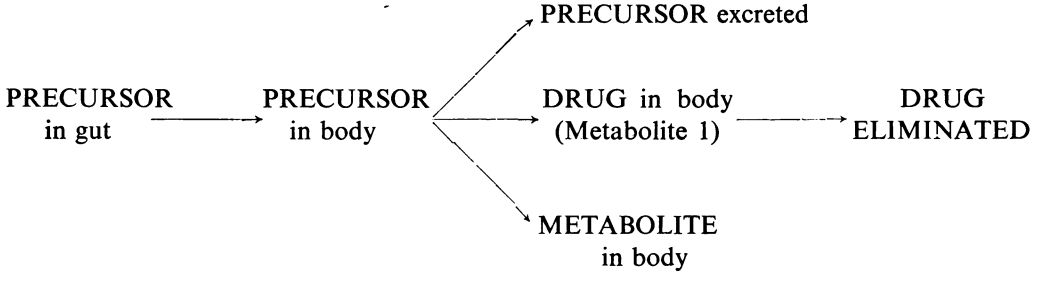
THEORETICAL CONSIDERATIONS

The *in vivo* conversion of a drug precursor to the active drug involves the same considerations as those which apply to any drug which is metabolized in the body, but in this instance special interest is directed to the metabolite. The ability of a metabolite to produce

a pharmacological effect depends not only on its intrinsic activity but also on the concentration which it attains in the body or, more specifically, the concentration at the site of action. Following the administration of a single dose of drug, the amount of metabolite in the body increases to a maximum value and this growth in the amount or concentration of metabolite has been termed metabolite accrual by Cummings & Martin (1963).

The term " drug " is normally applied to the substance administered. This is unsatisfactory for the present purpose and in the following considerations the term " drug " will be used to describe the pharmacological active substance, whether it is formed *in vivo* as a metabolite of the precursor, or directly administered.

In the following model system the elimination of the drug precursor (P) is a first order process and takes place by excretion and by the simultaneous formation of two metabolites, one of these is interpreted as the active drug (D), the other metabolite (M′) being inactive.



Let D_0 = Amount of drug administered as a dose,

D = Amount of drug in the body at time t,

P_0 = Amount of precursor administered as a dose,

P = Amount of precursor in body at time t.

All amounts are expressed in molar units.

K = First order rate constant governing the elimination of drug by all routes,

K_P = First order rate constant governing elimination of precursor by all routes,

k_p = First order rate constant governing urinary excretion of precursor,

k_f = First order rate constant governing formation of drug, D,

k'_f = First order rate constant governing formation of metabolite, M′,

so that, $K_P = k_p + k_f + k'_f$ ..... (1)

When the drug and precursors are administered orally, they may well exhibit different absorption patterns. Consideration will therefore be given in the first instance to a model precursor and a model drug which are instantaneously absorbed and attain equilibrium distribution in the body, so that at t=o, $P=P_0$ or $D=D_0$. The departures which arise in practice when the process of absorption extends over a period of time will be considered subsequently.

The elimination of drug from the body after administration of the drug is considered as a first order process and can be described by the equation:—

$$D = D_o e^{-Kt} \quad \ldots\ldots (2)$$

In the model system the rate constant governing the elimination of drug which is formed *in vivo* from a precursor is assigned the same value as that which applies when the drug is administered. This may not always be so in practice because the drug may well attain a different distribution when it is formed *in vivo* to that which it attains after direct administration and the drug elimination rate constant will then have a different value.

The equations employed by Cummings, Martin & Park (1967) to describe metabolite accrual are applicable, with certain changes of nomenclature, to the *in vivo* conversion of drug precursor to drug. The drug in the former treatment is now regarded as a precursor and the metabolite formally acquires the significance of a drug.

The following equations are applicable to the administration of a single dose of precursor:

$$P = P_o e^{-K_P t} \quad \ldots\ldots (3)$$

$$D = \frac{k_f P_o}{(K_P - K)} (e^{-Kt} - e^{-K_P t}) \quad \ldots\ldots (4)$$

or in the special case when $K_P = K$,

$$D = k_f P_o t\, e^{-Kt} \quad \ldots\ldots (5)$$

The fraction of the dose of precursor which is converted to drug and which is effectively utilized $= \frac{k_f}{K_P} = \frac{k_f}{k_f + k_p + k'_f}$ ..... (6)

Ideally therefore, both k_p and k'_f should be small relative to k_f—that is, the precursor should be eliminated predominantly by formation of drug.

Consideration of the drug level which results from the administration of precursor cannot be based only on the rate constant, k_f, which governs the rate of formation of drug from precursor, for equation (4) shows that the rate of growth and the rate of decline of drug in the body depends on the rate constants, K_P and K, which respectively govern the elimination of precursor and drug. Consideration will be given to a number of drug precursors which have different elimination rate constants and which *in vivo* give rise to the same drug, but the precursors will also be characterized by different values of the rate constant governing drug formation.

In considering the drug level which results from the administration of a precursor, it will be shown to be advantageous to perform the initial calculations on the basis that the precursor is eliminated only by the formation of drug—that is, there is no excretion of

precursor (k_p=o) and no other metabolite is formed (k'_f=o), so that $k_f = K_P$. Equations (4), (18) and (19) which relate to the amount of drug in the body after administration of precursor can be expanded so that they contain the factor (k_f/K_P)—for example, equation (4) can be written:

$$D = \left(\frac{k_f}{K_P}\right)\frac{K_P\,P_o}{K_P - K}\left(e^{-Kt} - e^{K_P t}\right) \qquad (7)$$

Such equations show that the drug level calculated on the basis that $k_f = K_P$ can subsequently be very simply adjusted for any value of k_f by multiplying by the factor k_f/K_P, thereby avoiding the necessity of repeating the entire calculation. When only a fraction of the precursor is converted to drug, the resulting drug level will be reduced by the factor k_f/K_P, but the relative rate of increase and the relative rate of decline of the drug will remain unchanged.

Figure 1 shows the decline in the amount of drug in the body after the administration of a single dose of drug. It also depicts the pattern of drug accrual which results from the administration of an equivalent dose of three precursors of the drug. The three precursors exemplify the situation when $K_P > K$, $K_P = K$ and when $K_P < K$. Various values have been assigned to the rate constant governing the elimination of the precursor (K_P), whereas the elimination rate constant of the drug (K) is maintained constant.

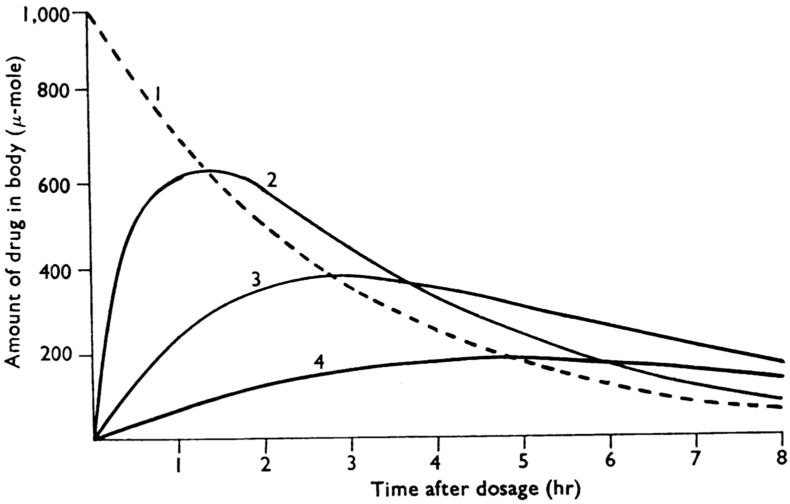


Fig. 1. Plots of the amount of drug in the body after the administration of a single 1 m-mole dose of drug and three precursors of the drug.

(1) Drug ($t_{0\cdot5}$ = 2 hr).
(2) Precursor ($t_{0\cdot5}$ = 0·5 hr), $K_P > K$.
(3) Precursor ($t_{0\cdot5}$ = 2·0 hr), $K_P = K$.
(4) Precursor ($t_{0\cdot5}$ = 8·0 hr), $K_P < K$.

Data calculated from equations (2), (4) and (5) on the basis that $k_f = K_P$ and that absorption is instantaneous.

There are two features of the drug level resulting from the administration of a precursor which are highly significant to the present considerations. The first is the pattern of drug accrual and the second is the rate of drug decline (Fig. 1). It is convenient to consider them as two separate features, although they are related, for both depend on the value of K_P and K.

The pattern of drug accrual

The maximum drug level obtained after administration of a precursor is less than that obtained by administration of drug, the time of attainment of the maximum is delayed, and the drug level declines more slowly (Fig. 1). This difference is particularly marked when the rate constant for the elimination of the predursor is less than the rate constant for drug elimination. Under these conditions ($K_P<K$), there is a period of time when the level of drug exhibits only a small fluctuation over a period of several hours. During this period the loss of drug by elimination is largely compensated by the continued formation of drug from precursor. This feature of " sustained formation " bears a resemblance in effect to the principal of sustained release which can be achieved by suitable pharmaceutical formulation of the drug. This characteristic pattern of drug accrual which results from the administration of precursor can appreciably reduce the fluctuations which occur in the drug level plateau in multiple dose therapy.

The rate of drug decline

Two particular cases can be considered, according to whether K_P is greater or smaller than K.

Figure 2 depicts the accrual of drug and its subsequent decline when $K_P>K$, that is when the precursor is rapidly converted to the drug, relative to the rate of drug elimination. The amount of drug in the body following the administration of the precursor is given by equation (4), which when $K_P>K$ and at high values of t, reduces in its log form to

$$\ln D_B = \ln \frac{k_f P_o}{K_P - K} - Kt \quad \text{.......} \quad (8)$$

A plot of log amount of drug in the body against time after administration of precursor (equation 8) exhibits a terminal linear section which is parallel to the corresponding log plot obtained when the drug is administered. Under these conditions ($K_P>K$) the decline of drug in the body after administration of the precursor ultimately occurs at the same relative rate as it does after direct administration of the drug.

An entirely different result is obtained when $K_P<K$—that is, when the precursor is slowly converted to the drug, relative to the rate of drug elimination. The amount of drug in the body following the administration of the precursor is again given by equation (4), but when $K_P<K$ and at high values of t, this equation reduces in its log form to:

$$\ln D = \ln \frac{k_f P_o}{K - K_P} - K_P t \quad \text{.......} \quad (9)$$

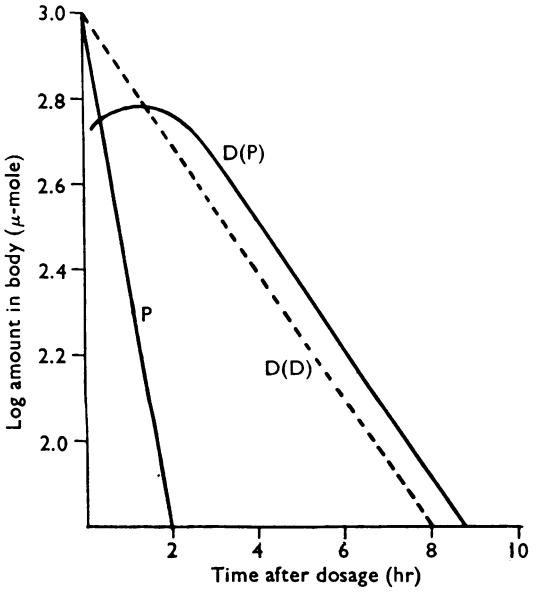


Fig. 2. Plots of log amount of drug in the body after drug administration D (D), after precursor administration D (P) and of log amount of precursor (P) in the body, when $K_P > K$.

$K = 0{\cdot}3466\ hr^{-1}$ ($t_{0{\cdot}5} = 2$ hr).

$k_f = K_P = 1{\cdot}3864\ hr^{-1}$ ($t_{0{\cdot}5} = 0{\cdot}5$ hr).

Data calculated from equations (2), (3) and (4) on the basis of instantaneous absorption of a single dose of 1 m-mole.

Under these conditions ($K_P < K$) a plot of log drug in the body against time after administration of precursor (equation 9), exhibits a terminal linear section, but in this instance its slope is equal to $-K_P$, the elimination rate constant of the precursor. The linear section of this plot is parallel to the plot of log amount of precursor in the body; this is apparent when equation (2) is written in its logarithmic form:

$$\ln P = \ln P_o - K_P t \quad \ldots\ldots (10)$$

This theoretical consideration, which is illustrated in Fig. 3, is of particular significance, for it suggests that, when a drug has a short half-life, the use of a precursor which has a longer half-life gives a drug level which declines relatively more slowly and at a rate which is never greater than that of the precursor. The frequency with which it is necessary to administer a drug depends on the rate of decline of drug in the body and the above considerations suggest that the use of a precursor which has a longer half-life than the drug can serve to extend the dosage interval.

Multiple dose therapy

In considering the drug level which results after the administration of multiple doses of drug or precursor, the following additional symbols are introduced:

$\overline{D}^n$ = Average value of the amount of drug in the body,

$\min D^n$ = Minimum value of the amount of drug in the body,

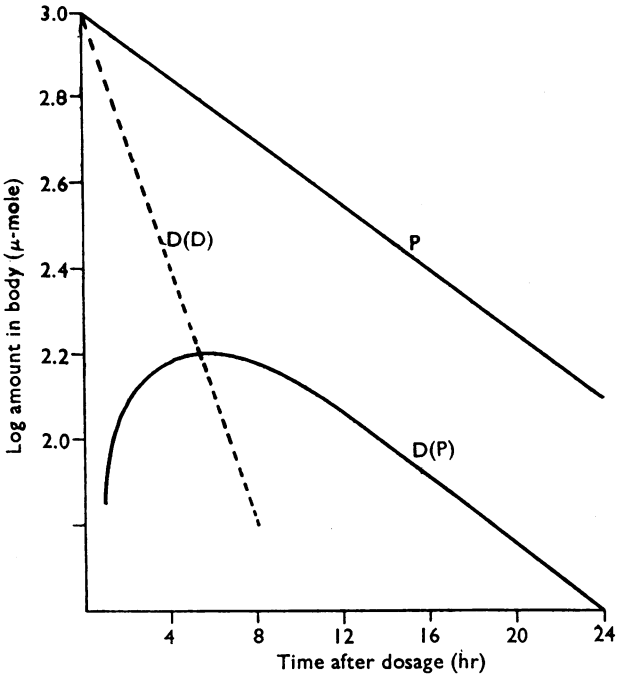


Fig. 3. Plots of log amount of drug in the body after drug administration D (D), after precursor administration D (P) and of log amount of precursor (P) in the body, when $K_P < K$.

$K = 0{\cdot}3466\ hr^{-1}$ ($t_{0{\cdot}5} = 2$ hr).
$k_f = K_P = 0{\cdot}0867\ hr^{-1}$ ($t_{0{\cdot}5} = 8$ hr).

Data calculated from equations (2), (3) and (4) on the basis of instantaneous absorption of a single dose of 1 m-mole.

$\max D^n$ = Maximum value of the amount of drug in the body, obtained after the administration of n doses of drug or precursor, when $n \rightarrow \infty$.

$D^n_{t'}$ = Amount of drug in the body at time t′ after administration of the n^{th} dose of drug or precursor,

t' = Time (hr) after the administration of the n^{th} dose of drug or precursor,

t'_m = Time (hr) after the administration of the n^{th} dose of precursor when the drug level attains its maximum value,

ΔT = Dosage interval (hr), the time between successive doses of drug or precursor.

The preceding considerations suggest that it would be necessary to administer a dose of precursor considerably in excess of the equivalent dose of drug in order to obtain a comparable drug concentration. This is true in respect of a single dose, but it does not apply to multiple dose therapy. This may be shown by considering the average value of the drug level plateau which is obtained after multiple doses of precursor.

The concept of the average asymptotic blood level has been employed by Widmark & Tandberg (1924) and more recently by Wagner, Northam, Alway & Carpenter (1965) and this can be modified and extended to apply to the drug level which results from the administration of precursors. At the steady state which applies at the plateau, the amount of drug formed in each dosage interval ($k_f P_o/K_P$) is equal to the amount which is eliminated in that interval ($K \overline{D}^n \Delta T$), so that,

$$\frac{k_f}{K_P} P_o = K \overline{D}^n \Delta T$$

$$\text{and } \overline{D}^n = \left(\frac{k_f}{K_P}\right) \frac{P_o}{K \Delta T} \quad \ldots\ldots (11)$$

In equation (11), (k_f/K_P) represents the fraction of the dose of precursor which is converted to drug and if the dose of each precursor is increased by the factor (K_P/k_f) to allow for this, all precursors when administered at the same dosage interval will give rise to the same average drug level plateau.

Minimum and maximum values of the drug level plateau

The administration of multiple doses of drug gives rise to a drug level plateau which exhibits a recurring series of maximum and minimum values as successive doses of drug are absorbed. The concept of the average plateau level is therefore inadequate for many purposes. for it does not reflect the fluctuation which occurs during each dosage interval. The maximum and the minimum values of the plateau obtained with any specified dosage schedule can frequently be predicted from kinetic data relating to the administration of a single dose of drug (Krüger-Thiemer, 1960a, b). In several instances, close agreement has been found between the calculated and the observed values (Boxer, Jelinek, Tompsett, DuBois & Edison, 1948; Swintosky, Bondi & Robinson, 1958; Bünger, Diller, Führ & Krüger-Thiemer, 1961; Wagner & Alway, 1964; Krüger-Thiemer & Bunger, 1965/66) and this prompts the present attempt to predict the drug level plateau which results from the administration of multiple doses of precursor.

Administration of drug

If the absorption of drug is considered to be instantaneous and complete, the maximum value of the drug level plateau (max D^n) is attained immediately after dosage and can be calculated by the method used by Widmark & Tandberg (1924), Boxer *et al.* (1948), Dost (1953) and others. After the administration of a large number of doses, each equal to D_o at equal intervals of time, ΔT, then

$$\max D^n = \frac{D_o}{1 - e^{-K\Delta T}} \quad \ldots\ldots (12)$$

and the minimum value is given by

$$\min D^n = \max D^n - D_o \quad \ldots\ldots (13)$$

Administration of precursor

The administration of several doses of precursor will give rise to a plateau level of precursor and a plateau level of drug in the body, and each will be characterized by certain minimum and maximum values. When the plateau level is attained the amount of precursor in the body will be at its maximum (max P^n) and the drug will be at its minimum (min D^n) immediately after each dose of precursor. During the dosage interval the change in the amount of drug in the body may be considered as the net result of the decline of the drug already present (A) and the increase due to the continued formation of drug from precursor (B).

Thus, $A = \min D^n e^{-Kt'}$ ..... (14)

and $B = \frac{k_f \max P^n}{K_P - K} (e^{-Kt'} - e^{-K_P t'})$ ..... (15)

where t′ is the time after the administration of the last dose of precursor, and so:

$$D^n{}_{t'} = \min D^n e^{-Kt'} + \frac{k_f \max P^n}{K_P - K} (e^{-Kt'} - e^{-K_P t'}) \quad \ldots\ldots (16)$$

The value of max P^n can be calculated on the same basis as equation (12), to give:

$$\max P^n = \frac{P_o}{(1 - e^{-K_P \Delta T})} \quad \ldots\ldots (17)$$

When the plateau region has been reached, the amount of drug in the body will return to the same value, min D^n, at the end of each dosage interval so that the sum of the values of A and B at time ΔT will again equal min D^n, and so:

$$\min D^n = \frac{k_f P_o}{K_P - K} (e^{-K\Delta T} - e^{-K_P \Delta T}) \Big/ (1 - e^{-K\Delta T})(1 - e^{-K_P \Delta T}) \quad \ldots\ldots (18)$$

The minimum value of the drug level plateau obtained after administration of precursor can therefore be calculated from equation (18).

Substitution of the value of min D^n in equation (16) gives an expression for the amount of drug in the body as a function of t′, thus:

$$D^n{}_{t'} = \frac{k_f P_o}{(K_P - K)(1 - e^{-K_P \Delta T})} \left\{ \frac{(e^{-K\Delta T} - e^{-K_P \Delta T}) e^{-Kt'}}{(1 - e^{-K\Delta T})} + (e^{-Kt'} + e^{-K_P t'}) \right\} \quad \ldots (19)$$

An approximate value of max D^n can be found by inspection of the values of $D^n_{t'}$ during the dosage interval. Alternatively, the time (t'_m) at which the maximum is attained can be calculated by setting $\frac{d(D^n_{t'})}{dt} = 0$, to give:

$$K \left[1 + \frac{(e^{-K\Delta T} - e^{-K_P \Delta T})}{(1 - e^{-K\Delta T})} \right] e^{-Kt'_m} = K_P \, e^{-K_P t'_m}$$

so that:

$$t'_m = \frac{1}{K - K_P} \ln \left\{ \frac{K \, (1 - e^{-K_P \Delta T})}{K_P \, (1 - e^{-K \Delta T})} \right\} \qquad (20)$$

and the calculated value of t'_m can then be inserted in equation (19) to obtain max D^n.

Dosage schedule of drug and precursor

In order to study the use of a drug precursor when the drug is rapidly eliminated, the mode drug is assigned a half-life of 2 hr ($K = 0.3466 \text{ hr}^{-1}$).

Initial considerations have suggested that it is advantageous to select a precursor which has a longer half-life than that of the drug and that the dosage interval might then be related to the half-life of the precursor. A regular dosage schedule can be most conveniently achieved in practice when the dosage interval is 8, 12 or 24 hr and consideration will therefore be given to three model precursors which have half-lives of 8 hr ($K_P = 0{\cdot}0867 \text{ hr}^{-1}$), 12 hr ($K_P = 0{\cdot}0578 \text{ hr}^{-1}$) and 25·8 hr ($K_P = 0{\cdot}0269 \text{ hr}^{-1}$) respectively. The precursor of half-life 25·8 hr was selected because a single dose would in this instance ($K = {\cdot}03466 \text{ hr}^{-1}$) give a maximum drug level at 8 hr. If dosage is repeated at 8-hourly intervals, the amount of drug in the body which is attributable to the previous dose will continue to increase throughout the entire dosage interval and the fluctuation in the drug level will then tend to be minimal.

Equations (18), (19) and (20) have been used to calculate the minimum and maximum values of the drug level plateau obtained when multiple doses of 1 m-mole of the drug and precursors are administered at various constant time intervals. The calculations have been performed on the basis that the drug and precursors are instantaneously absorbed and that the precursor is completely converted to drug ($k_f = K_P$). The results are given in Table 1 and the fluctuation which occurs in the drug level when the three precursors are administered at 8-hourly intervals is illustrated in Fig. 4.

Effective therapy frequently required that the concentration of drug in the body is not at any time below a certain minimum value. In order to compare the performance of the drug and its precursors, the doses must therefore be adjusted so that they all provide the same minimum plateau level of drug. This level is arbitrarily defined in the model system as 0·5 m-mole and the data relating to the adjusted dose levels are given in Table 2.

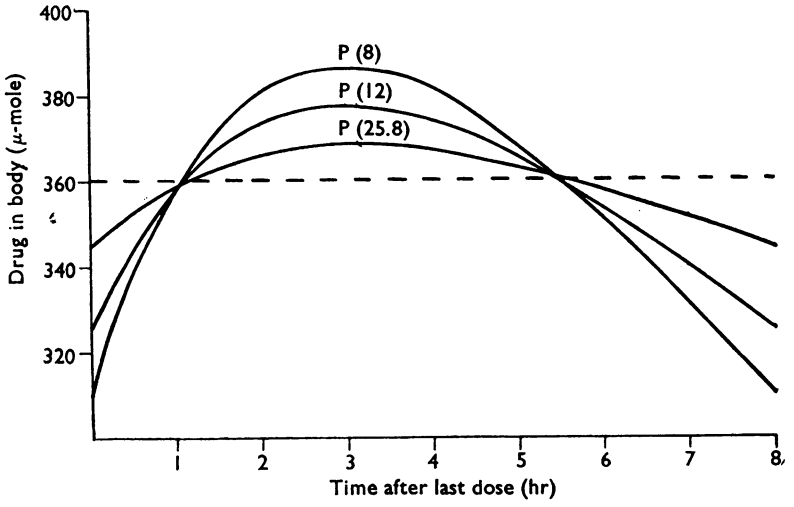


Fig. 4. The fluctuation in the amount of drug in the body during the dosage interval (8 hr) after multiple 1 m-mole doses of precursor. The plots relate to the use of three precursors, P (8), P (12) and P (25·8), which have half-lives of 8, 12 and 25·8 hr, respectively. The dotted line represents the average amount of drug in the body at the steady state. Data calculated from equation (19).

TABLE 1

MINIMUM AND MAXIMUM VALUES OF THE DRUG LEVEL PLATEAU AFTER THE ADMINISTRATION OF MULTIPLE 1 M-MOLE DOSES OF DRUG AND OF THREE DRUG PRECURSORS AT VARIOUS CONSTANT TIME INTERVA

The precursors have a half-life ($t_{0.5}$) of 8, 12 and 25·8 hr respectively. Data calculated on the basis that $k_f = K_P$ and that absorption is instantaneous, using equations (18), (19), and (20)

Substance administered	Dosage interval (hr)	Fluctuation of drug plateau (μ-mole)	Fluctuation of precursor plateau (μ-mole)
Drug	4	333–1333	—
$t_{0.5}$ = 2 hr	8	67–1067	—
Precursor	8	310–387	1000–2000
$t_{0.5}$ = 8 hr	12	177–280	547–1547
	24	48–188	143–1143
Precursor	8	326–378	1703–2703
$t_{0.5}$ = 12 hr	12	197–267	1000–2000
	24	67–164	333–1333
Precursor	8	345–369	4181–5181
$t_{0.5}$ = 25·8 hr	12	219–252	2623–3623
	24	93–140	1101–2101

The values given in Tables 1 and 2 relate to the special instance when $k_f = K_P$, but they can be very simply adjusted for any particular value of k_f. Since $k_f \leqslant K_P$, the drug levels obtained will usually be less than the calculated values by the factor (k_f/K_P), consequently the dose of each precursor must be increased by the factor (K_P/k_f) to obtain a drug level plateau identical to the values in Table 2.

TABLE 2

MULTIPLE DOSAGE SCHEDULE OF DRUG AND THREE DRUG PRECURSORS TO MAINTAIN A MINIMUM PLATEAU DRUG LEVEL OF 0·5 M-MOLE

Calculated on the basis that $k_f = K_P$ and that absorption is instantaneous

Substance administered	Dose (m-mole)	Dosage interval (hr)	Maximum amount of drug in body (m-mole)	Number of doses to attain 90% plateau	Fluctuation of precursor plateau (m-mole)
Drug	1·5	4	2·0	4	—
	7·5	8	8·0	1	—
Precursor $t_{0.5} = 8$ hr	1·6	8	0·63	4	1·6–3·2
	2·8	12	0·79	3	1·5–4·3
	10·5	24	1·97	2	1·5–12·0
Precursor $t_{0.5} = 12$ hr	1·5	8	0·58	5	2·6–4·1
	2·5	12	0·68	4	2·5–5·0
	7·5	24	1·23	3	2·5–10·0
Precursor $t_{0.5} = 25{\cdot}8$ hr	1·5	8	0·54	11	6·3–7·8
	2·3	12	0·58	7	6·0–8·3
	5·4	24	0·76	4	5·8–11·2

These results (Tables 1 and 2) have been calculated on the basis that the drug and precursor are instantaneously absorbed and immediately attain equilibrium distribution. This may be closely approached when administration is by intravenous injection. When administered orally the absorption of drug extends over a period of time and this has the effect of giving a smaller fluctuation in the drug level plateau, the maximum values being lower and minimum values higher than those calculated on the basis of instantaneous absorption. As a consequence the required dose of drug will be less than that calculated. For example, if absorption of drug occurs by a first order process with a rate constant equal to 1·386 hr^{-1}, so that absorption is almost complete in 2 hr, a dose of 1·14 m-mole of drug every 4 hr would provide the required drug level (0·5 m-mole) with a maximum value of 1·05 m-mole.

Similar considerations apply to the oral administration of precursor, but to a much smaller extent. When the drug is rapidly eliminated (half-life, 2 hr) the rate of drug absorption has an appreciable effect on the drug level plateau. The model precursors are slowly eliminated and the effect of large variations in their rate of absorption causes only a relatively small change in the drug level plateau and the values obtained will differ very little from those calculated on the basis of instantaneous absorption.

The process of absorption will therefore tend to operate to the advantage of the drug, a smaller dose of drug being necessary, whereas the incomplete conversion of precursor to drug ($k_f < K_P$) will necessitate the use of a larger dose of precursor. No attempt has been made to adjust the data in Table 2 in either of these respects, accordingly the data must be interpreted with these limitations in mind. In practice, both of these features will be elucidated in the course of studies relating to the administration of single doses and this data would then be used to predict the plateau level obtained with multiple doses.

The performance of a particular dosage schedule of drug or precursor can be assessed in terms of:

1. Size of the dose.
2. Dosage interval.
3. Fluctuation of the drug level plateau above the minimum required value.
4. Number of doses required to approach the plateau level of drug.

The efficiency or economy provided by any particular dosage regimen can also be assessed by comparing the total daily dose of drug or precursor with that amount of drug which, if administered continuously over 24 hr at a constant rate—for example, by continuous infusion—would maintain the drug level at exactly 0·5 m-mole. The amount of drug necessary for this purpose can be calculated from the expression, $24\ K\ minD^n$, which in the present instance shows a minimum requirement of 4·16 m-mole of drug daily.

Examination of the results in Table 2 suggests that an 8-hourly dosage schedule of the drug may well be impracticable and that it may be necessary to accept the inconvenience of 4-hourly dosage. An 8-hourly dosage schedule becomes possible with the use of a precursor of half-life 8 hr ($K_P = \cdot 0867\ hr^{-1}$), and, when administered in doses of 1·6 m-mole, it gives a drug plateau level which varies only between 0·5 and 0·625 m-mole. It does, however, require four such doses to approach 90 % of these values (Table 2).

The administration at 8-hourly intervals of suitable doses of the two precursors of half-life 12 hr and 25·8 hr, respectively, can also be considered. They give rise to a very steady drug level, which probably exceeds the limitations imposed in practice by other factors, but their main disadvantage when used in this manner is the number of doses which is required to approach the plateau level. These precursors are used to greater advantage if they are administered at intervals which correspond to their respective half-lives and in this manner, a 12-hourly and 24-hourly dosage schedule becomes a possibility (Table 2).

Whereas the use of a precursor can obviate the high drug concentrations which lead to an excessive response or toxic effect, this is nevertheless achieved only at the cost of high levels of precursor (Table 2). It is essential, therefore, that the drug precursor possesses no undesired or toxic effect even at high dosage. This introduces a further limitation in the use of precursors.

A further consideration which arises from the use of a precursor is that a larger number of doses may be required before the drug level approaches the desired plateau. This delay can be partly overcome by administering an initial dose of precursor which is larger than that of the standard maintenance dose, or by administering a dose of the drug with the initial dose of precursor.

When the objective is to overcome the incomplete absorption of the drug or to avoid the irritant effect or instability of the drug in the gut, a precursor which is free from these defects and which is very rapidly metabolized to the drug ($K_P > K$) can well satisfy these requirements. When the main objective is to obviate the frequent dosage which is necessary when the drug has a very short half-life, this can be achieved by the use of a precursor which has a longer half-life than that of the drug ($K_P < K$). The use of a precursor under these conditions can also provide a more uniform drug level, and this aspect can well constitute the major objective when the margin between effective and toxic levels of drug is small.

SUMMARY

1. The rate of growth and of decline of drug in the body after the administration of a precursor can differ considerably from that obtained after drug administration and this is governed by the elimination rate constant of the precursor (K_P).

2. The rate constant which governs the formation of drug (k_f) determines the fraction (k_f/K_P) of the precursor which is effectively utilized in drug formation.

3. When the elimination rate constant of the precursor (K_P) is less than that of the drug (K), the precursor gives a drug level which declines relatively more slowly and at a rate which is never greater than that of the precursor.

4. Equations have been presented which describe the amount of drug in the body after the administration of multiple doses of a model precursor. These equations have been used to calculate the minimum and maximum values of the drug level plateau and to devise dosage schedules for the precursor.

5. It is expedient to perform the initial calculations on the basis that the precursor is completely converted to drug ($k_f = K_P$), so as to provide a general solution which can then readily be adjusted for any value of k_f.

6. The use of a precursor which is slowly converted to the drug, relative to the rate of drug elimination ($K_P < K$), can serve to extend the dosage interval and to maintain a more uniform drug level.

7. Slow absorption of drug from the gut has the effect of reducing the dosage requirement of drug, whereas the rate of absorption of precursor has only a small effect on the dosage requirements of precursor when K_P is $< K$.

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