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KINETIC CONSIDERATIONS RELATING TO THE ACCRUAL AND ELIMINATION OF DRUG METABOLITES

BY

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Consideration of the therapeutic effect or toxic action of a drug must also include consideration of the potential effect of its metabolites. Therefore regard should be given not only to the qualitative aspects of drug metabolism, but also to the kinetics of metabolite formation and metabolite elimination.

The following considerations relate to the application of kinetic equations to the processes of elimination of a drug and its metabolites and their use for the evaluation of rate constants for these processes from urinary excretion data.

Drugs are eliminated from the body by excretion and by transformation to metabolites. These processes occur simultaneously but the extent of each varies from one drug to another. The metabolites of the drug are then also eliminated by excretion and further metabolism. The amount of drug in the body at any time depends both on its rate of absorption and its rate of elimination. Similarly the amount of a metabolite in the body will depend on its rate of formation and its rate of elimination and will increase until these rates are equal; this growth in the amount of metabolite has been referred to by Cummings & Martin (1963) as metabolite accrual. It is well recognized that when a drug is rapidly metabolized to a metabolite which is slowly eliminated, the amount of metabolite in the body may eventually exceed the amount of drug. Little consideration has been given, however, to the amount of metabolite in the body when the metabolite is rapidly eliminated, and it has sometimes been incorrectly assumed that the rate of elimination of a metabolite can then be equated to its rate of formation. Drug excretion, drug metabolism and metabolite elimination can be treated as a number of consecutive and parallel processes for which it is frequently possible to obtain overall rate constants and in certain instances specific rate constants. The magnitude and duration of metabolite accrual is governed by the value of these rate constants.

Kinetic equations for the elimination of a model drug and its metabolites

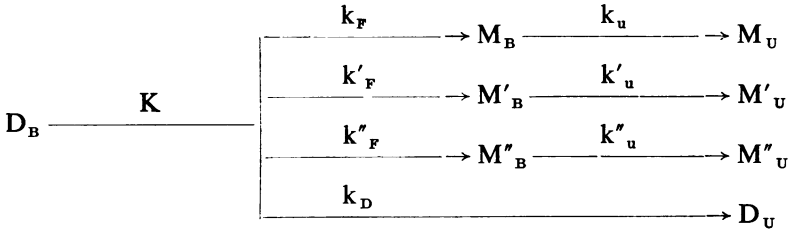
The elimination of a drug by excretion and metabolism and the subsequent elimination of the metabolites, is considered in respect of a model drug. In the first instance this drug is postulated to be instantaneously absorbed and equilibrated in the body water, so that the amount of drug in the body at zero time is equated to the amount administered. The

consequences of departure from this idealized treatment will be assessed in the sequel. A first order rate law will be assumed for all the processes involved in the elimination of the drug and of its metabolites. The drug is considered to undergo elimination by excretion of unchanged drug with the rate constant, k_D, and by the simultaneous formation of a number of metabolites M, M′, M″ . . . , with the rate constants k_F, k'_F, k''_F . . . , respectively. The overall rate constant for the elimination of drug by all routes is K, where:

$$K = k_D + k_F + k'_F + k''_F + \quad \ldots\ldots (1)$$

The metabolites are considered to be instantaneously equilibrated in the body water and to undergo no further metabolism. They are excreted unchanged with the rate constants k_u, k'_u, k''_u, . . . , respectively.

The elimination of the drug and the excretion of its metabolites may be represented as follows:



The following equations for these processes are presented in respect of one metabolite, but they may also be applied to the other metabolites when the appropriate rate constants are substituted. In these equations:

D_o = Amount of drug in the body at zero time.

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

D_U = Amount of drug excreted in the urine at time t,

M_F = Amount of metabolite formed at time t,

M_B = Amount of metabolite in the body at time t,

M_U = Amount of metabolite excreted in the urine at time t,

so that, $D_o = D_B + D_U + M_F$ and $M_F = M_B + M_U$, when expressed in molar quantities.

Thus, $\frac{dD_B}{dt} = -KD_B$ ..... (2)

so, $D_B = D_o e^{-Kt}$ ..... (3)

Also, $\frac{dD_U}{dt} = k_D D_B = k_D D_o e^{-Kt}$ ..... (4)

so, $D_U = \frac{k_D D_o}{K}(1-e^{-Kt})$ ..... (5)

Similarly, $\frac{dM_F}{dt} = k_F D_o e^{-Kt}$ ..... (6)

so, $M_F = \frac{k_F D_o}{K}(1-e^{-Kt})$ ..... (7)

The rate of change of the amount of metabolite in the body is equal to the rate of metabolite formation minus its rate of excretion, and so:

$$\frac{dM_B}{dt} = k_F D_o e^{-Kt} - k_u M_B \quad \ldots\ldots (8)$$

and by integration with the condition that at $t=0$, $M_B=0$,

$$M_B = \frac{k_F D_o}{k_u - K}(e^{-Kt} - e^{-k_u t}) \quad \ldots\ldots (9)$$

$$\text{Then, } \frac{dM_U}{dt} = k_u M_B = \frac{k_u k_F D_o}{k_u - K}(e^{-Kt} - e^{-k_u t}) \quad \ldots\ldots (10)$$

$$\text{and } M_U = \frac{k_F D_o}{K(k_u - K)}[k_u(1 - e^{-Kt}) - K(1 - e^{-k_u t})] \quad \ldots\ldots (11)$$

Similar equations have been used by Gehlen (1933); Teorell (1937); Bray, Thorpe & White (1951); Dost (1953) and others in theoretical studies of drug elimination.

These equations have been expressed in terms of the amount of drug participating in each process or reaction, whereas the rate equations more accurately relate to the concentration of drug. During the course of drug elimination, the volume changes in the various compartments of the body are considered to be small and the use of amounts instead of concentration terms therefore gives rise to little error. It is, however, frequently necessary in a detailed study to define the system not in terms of total drug concentration, but in terms of the concentration of free (not bound) drug, and often in terms of a particular molecular form of the drug—for example, ion or undissociated molecule.

Metabolite accrual

Under the conditions specified, the amount of drug in the body declines from a maximum value at zero time in a manner described by equation (3). The total amount of metabolite formed is zero at zero time, but will be seen from equation (7) to increase to approach asymptotically a value of $D_o k_F/K$. The amount of metabolite in the body will depend, in addition, upon the value of the rate constant for the excretion of the metabolite, k_u, as shown by equation (9). This is exemplified in Fig. 1.

The rate of change of the amount of metabolite in the body is obtained by subtracting the rate of metabolite excretion from the rate of metabolite formation, or by differentiating equation (9), then:

$$\frac{dM_B}{dt} = \frac{dM_F}{dt} - \frac{dM_U}{dt} = \frac{k_F D_o}{k_u - K}(k_u e^{-k_u t} - K e^{-Kt}) \quad \ldots\ldots (12)$$

This relationship provides an assessment of metabolite accrual, for the amount of metabolite in the body, M_B, will increase while $\frac{dM_F}{dt} > \frac{dM_U}{dt}$, will be at its maximum value when $\frac{dM_F}{dt} = \frac{dM_U}{dt}$, and will decrease when $\frac{dM_F}{dt} < \frac{dM_U}{dt}$. Thus, initially the rate of metabolite formation exceeds its rate of excretion. There is one point in time when the two rates are equal and thereafter the rate of metabolite excretion exceeds its rate of formation. A plot of $\frac{dM_F}{dt}$ would therefore intersect a plot of $\frac{dM_U}{dt}$ when $\frac{dM_B}{dt}=0$,

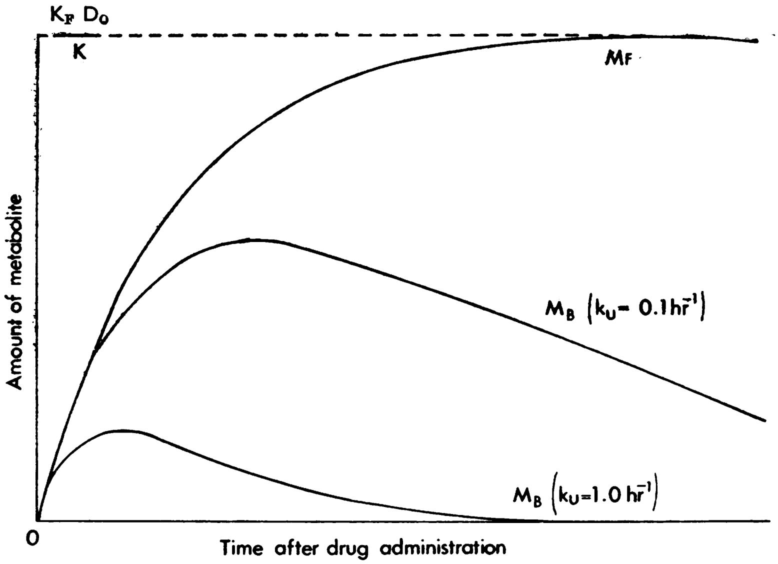


Fig. 1. The relationship between the amount of metabolite formed, M_F, and the amount of metabolite in the body, M_B, when the excretion rate constant, k_u, is assigned a value of 0.1 hr^{-1}, and of 1.0 hr^{-1}. (The elimination rate constant for the drug, K=0.3 hr^{-1}, and the rate constant for the formation of the metabolite, k_F=0.15 hr^{-1}).

that is, when M_B and $\frac{dM_U}{dt}$ are both at their maximum values; this was deduced by Cummings & Martin (1963) and is illustrated in Fig. 2. (The rate of formation of a metabolite is of theoretical importance although it cannot usually be determined experimentally.)

The maximum value of M_B is attained when $\frac{dM_B}{dt} = 0$ and the time after dosage when this is achieved, t(M_B max), may therefore be obtained by setting equation (12) equal to zero, then:

$$k_u e^{-k_u t} = K\, e^{-Kt}$$

$$\text{so, } t(M_B \max) = \frac{\ln\left(\frac{k_u}{K}\right)}{k_u - K} \quad \text{(13)}$$

The maximum amount of metabolite attained in the body may be obtained putting $t = t(M_B \max)$ in equation (9)—that is:

$$M_B \max = \frac{k_F D_o}{k_u - K}\left[\left(\frac{K}{k_u}\right)^{\frac{K}{k_u - K}} - \left(\frac{K}{k_u}\right)^{\frac{k_u}{k_u - K}}\right] \quad \text{(14)}$$

The effect of the value of k_u upon the maximum amount of metabolite attained in the body and the time of its attainment when a specific value is assigned to K and to k_F is exemplified in Table 1. It may be seen from Table 1 and Fig. 1 that, when the excretion rate constant for the metabolite, k_u, is small, there is considerable accrual of the metabolite

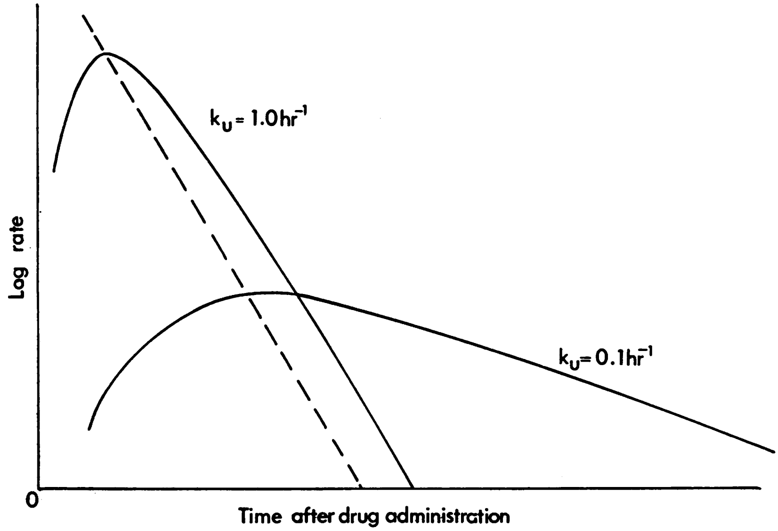


Fig. 2. A plot of the log rate of metabolite formation (- - -) and of the log rate of metabolite excretion (——) when $k_u > K (k_u = 1.0\ hr^{-1})$ and when $k_u < (k_u = 0.1\ hr^{-1})$. ($K = 0.3\ hr^{-1}$, $k_F = 0.15\ hr^{-1}$).

TABLE 1

THE MAXIMUM AMOUNT OF METABOLITE IN THE BODY, M_B MAX, AND THE TIME AT WHICH THIS IS ATTAINED, $t(M_B$ MAX), FOR A MODEL DRUG WHICH IS INSTANTANEOUSLY ABSORBED, WHEN DIFFERENT VALUES ARE ASSIGNED TO THE EXCRETION RATE CONSTANT FOR THE METABOLITE, k_u

(The drug elimination rate constant, $K = 0.3\ hr^{-1}$, the metabolite formation rate constant, $k_F = 0.1\ hr^{-1}$, and the dose of drug administered, $D_o = 1$)

k_u (hr^{-1})	$\frac{M_B \max}{D_0}$	$t(M_B \max)$ (hr)	$\frac{t(M_B \max)}{t_{0 \cdot 5}}$
0	0·33	∞	∞
0·05	0·23	7·16	3·10
0·10	0·19	5·50	2·38
0·50	0·09	2·55	1·10
1·00	0·06	1·72	0·74
1·50	0·04	1·34	0·58
3·0	0·03	0·85	0·37

and $t(M_B \max)$ is relatively large. When the excretion rate constant is large, accrual of the metabolite still occurs, but to a smaller extent, and $t(M_B \max)$ is relatively small.

While the value of $t(M_B \max)$ depends upon the absolute values of K and k_u, an expression can be obtained for the ratio of $t(M_B \max)$ to the half-life of the drug, $t_{0 \cdot 5}$, which is a function of k_u/K only and which is independent of the absolute values of the rate constants:

$$\frac{t(M_B \max)}{t_{0 \cdot 5}} = \frac{\ln \left(\frac{k_u}{K}\right)}{\left(\frac{k_u}{K} - 1\right) \ln 2} \qquad (15)$$

This expression is derived from equation (13) and the relationship, $t_{0 \cdot 5} = \ln 2/K$.

Cummings & Martin (1963) have advanced theoretical considerations suggesting that k_u will not exceed 3 hr^{-1} and that it will more probably not exceed 1 hr^{-1} even if the metabolite exhibits the maximum renal clearance. Many drugs have a half-life within the range 1 to 7 hr and, on the basis of the higher figure ($K = 0.1$ hr^{-1}), $\frac{k_u}{K}$ will therefore not exceed 30, and 10 is a more probable ratio. Equation (15) indicated that when $\frac{k_u}{K} = 10$, the amount of metabolite in the body reaches its maximum after the elapse of 0.37 of the drug's half-life (Table 1), which for a drug with a half-life of 7 hr means that metabolite accrual continues over a period of about 2.5 hr.

The rate of excretion of the model drug and its metabolites

When the logarithm of the rate of excretion of the drug is plotted against time, the straight line which is obtained is described by:

$$\ln \frac{dD_U}{dt} = \ln k_D D_o - Kt \quad \ldots\ldots (16)$$

This is the logarithmic form of equation (4); it has an intercept on the ordinate equal to $\ln k_D D_o$ and a slope equal to $-K$.

Equations of the same form as (16) are also obtained for the metabolites, but only when t is large. Then, when k_u is greater than K, equation (10) reduces to:

$$\ln \frac{dM_U}{dt} = \ln \frac{k_u k_F D_o}{k_u - K} - Kt \quad \ldots\ldots (17)$$

and when $k_u < K$ to:

$$\ln \frac{dM_U}{dt} = \ln \frac{k_u k_F D_o}{K - k_u} - k_u t \quad \ldots\ldots (18)$$

After the administration of a drug, the rate of excretion of a metabolite, in parallel with the amount of metabolite in the body, will increase to attain a maximum value at a time given by equation (13). It will thereafter decline, and a plot of the logarithm of the rate of excretion of the metabolite against time will eventually become linear. The slope of the linear portion of the plot will depend upon which of the rate constants, k_u or K, is the greater, as shown by equations (17) and (18) and Fig. 2. The slope of the plot of $\ln \frac{dM_U}{dt}$ against time will be equal to K, when k_u is greater than K, and will be equal to k_u when K is greater than k_u. When k_u and K are very different in magnitude a linear plot is obtained after a short time, but, when k_u and K are nearly equal, the plot will only approach linearity after a very long time.

When k_u is equal to K, equations (9), (10) and (11) cannot be used in the form given, but alternative expressions can be obtained from these equations which may be used under this condition. For example, equation (10) may be written:

$$\frac{dM_U}{dt} = \frac{k_u k_F D_o e^{-Kt}}{k_u - K} (1 - e^{(K-k_u)t}$$

This on expansion of $(1 - e^{(K-k_u)t}$ and division by $-(K - k_u)$ gives:

$$\frac{dM_U}{dt} = k_u k_F D_o e^{-Kt} \left[t + \frac{K - k_u}{2!} t^2 + \frac{(K-k_u)^2}{3!} t^3 + \right]$$

which when $k_u = K$ reduces to:

$$\frac{dM_U}{dt} = K\,k_F\,D_o\,t\,e^{-Kt} \quad \ldots\ldots (19)$$

Thus,

$$\ln\frac{dM_U}{dt} = \ln K\,k_F\,D_o + \ln t - Kt \quad \ldots\ldots (20)$$

$$\text{or } \ln\left(\frac{1}{t}\frac{dM_U}{dt}\right) = \ln K\,k_F D_o - Kt \quad \ldots\ldots (21)$$

Therefore, when $K=k_u$, a plot of $\ln\left(\frac{1}{t}\frac{dM_U}{dt}\right)$, but not of $\ln\frac{dM_U}{dt}$, against time will give a straight line with a slope equal to $-K$. Similarly equations 9 and 11 must be replaced by:

$$M_B = k_F\,D_o\,t\,e^{-Kt} \quad \ldots\ldots (22)$$

$$M_U = \frac{k_F D_o}{K}\left[1-e^{-Kt}-Kt\,e^{-Kt}\right] \quad \ldots\ldots (23)$$

Only when the value of k_u for each metabolite is greater than K will plots of the logarithm of the rate of excretion of all the metabolites eventually become parallel to each other and also parallel to a plot of the rate of excretion of unchanged drug. This is apparent from equations (16) and (17) and is illustrated in Fig. 3.

It frequently happens that the individual metabolites and free drug cannot be estimated separately, but may all be determined together to give results which may be expressed as "total drug." This total excretion rate, $\frac{d(D_U+M_U)}{dt}$, is given by summing the individual

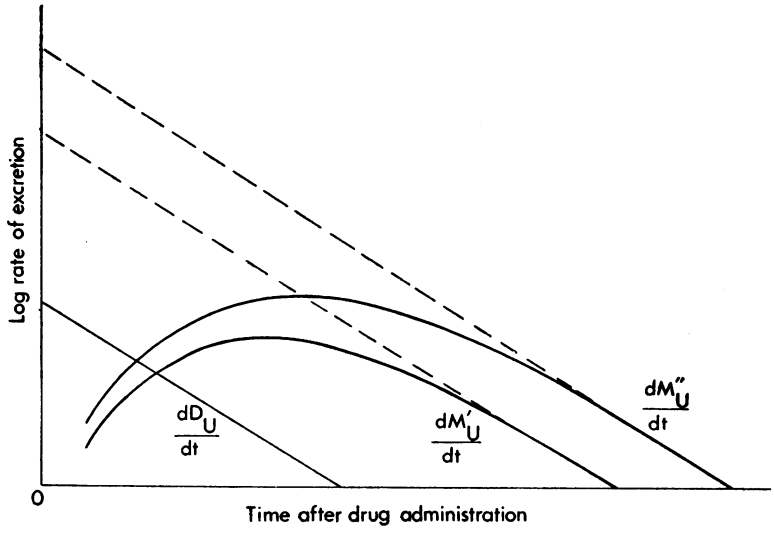


Fig. 3. Plots of the log rate of excretion of the drug, $\frac{dD_U}{dt}$, and the log rate of excretion of two metabolites, $\frac{dM'_U}{dt}$, $\frac{dM''_U}{dt}$, when k'_u and k''_u are larger than K and drug absorption is instantaneous.

rates of excretion for all metabolites and for the unchanged drug, and so:

$$\frac{d(D_U+M_U)}{dt} = \frac{dD_U}{dt} + \sum_{All\ M_U} \frac{dM_U}{dt} = D_o\left[k_D e^{-Kt} + \sum_{All\ k_F,\ k_u} \frac{k_F k_u (e^{-Kt}-e^{-k_u t})}{k_u - K}\right]$$

Then, provided that all the k_u values are greater than K, this leads at large values of **t** to:

$$\ln \frac{d(D_U + M_U)}{dt} = \ln D_o\left[k_D + \sum_{All\ k_F,\ k_u} \frac{k_u k_F}{k_u - K}\right] - Kt \quad \ldots\ldots (24)$$

which is the equation of a straight line of slope equal to $-K$.

Under these conditions, therefore, a plot of the logarithm of the rate of excretion of " total drug " will ultimately become a straight line of slope equal to $-K$, but the plot may present an irregular pattern until such time as all the metabolites are excreted in a constant ratio.

Treatment of excretion data by the " Sigma-minus " method

The above considerations have related to the treatment of excretion data by the " Rate " method, which was first used by Swintosky (1957). An alternative procedure, which has been more extensively used, makes use of the total amount of drug excreted instead of the rate of drug excretion: it may be conveniently termed the " Sigma-minus " method (Martin, 1967) and enables rate constants to be obtained in a similar way to the " Rate " method.

In respect of the excretion of unchanged drug, the " Sigma-minus " method consists of plotting the amount of drug which is ultimately excreted ($D_{U\infty}$) minus the cumulative amount of drug (D_U) excreted in time t, against time after drug administration; from equation (5):

$$(D_{U\infty} - D_U) = \frac{k_D D_o e^{-Kt}}{K} \quad \ldots\ldots (25)$$

$$\text{so, } \ln (D_{U\infty} - D_U) = \ln \frac{k_D D_o}{K} - Kt \quad \ldots\ldots (26)$$

and this method is based on equations of this type. Thus, the " Sigma-minus " method when applied to the excretion of drug in urine gives the decline of that fraction of the dose which is excreted unchanged.

The application of the " Sigma-minus " method to the excretion of a metabolite in urine is more complex, but equations of the same form as equation (25) may be obtained. If the total amount of the metabolite ultimately excreted is $M_{U\infty}$, then since $M_F = M_B + M_U$, $(M_{U\infty} - M_U) = M_{U\infty} - M_F + M_B$ and substitution of the value for $(M_{U\infty} - M_F)$ from equations (7) and (11) gives:

$$(M_{U\infty} - M_U) = \frac{k_F D_o e^{-Kt}}{K} + M_B \quad \ldots\ldots (27)$$

The " Sigma-minus " plot with respect to the metabolite, therefore, relates not only to the decline of that fraction of the drug ultimately eliminated as metabolite, but also to the decline of the amount of the metabolite present in the body.

Substituting for M_B from equation (9) gives:

$$(M_{U\infty} - M_U) = \frac{k_F D_o e^{-Kt}}{K} + \frac{k_F D_o (e^{-Kt} - e^{-k_u t})}{k_u - K}$$

which, when k_u is greater than K and t is large, reduces to:

$$(M_{U\infty} - M_U) = \frac{k_u k_F D_o}{K(k_u - K)} e^{-Kt} \quad \ldots\ldots (28)$$

$$\text{or } \ln (M_{U\infty} - M_U) = \ln \frac{k_u k_F D_o}{K(k_u - K)} - Kt \quad \ldots\ldots (29)$$

thus giving equations of the same form as equations (25) and (26). Under these conditions a plot of $\ln (M_{U\infty} - M_U)$ against time ultimately becomes linear with a slope equal to $-K$. Also, extrapolation of the linear section of this plot provides an intercept equal to $\ln \frac{k_u k_F D_o}{K(k_u - K)}$ at $t = 0$.

Comparison of equations (16) and (26) and of equations (17) and (29) shows that when t is large the plots of urinary excretion data which are obtained by the " Rate " method and by the " Sigma-minus " method are described by equations of the same type. All the plots have a slope equal to $-K$, but the intercepts of the " Rate " plots differ from those of the " Sigma-minus " plots, by ln K (Martin, 1967).

The effect of the rate of absorption

Considerations have so far been concerned with a model drug which was instantaneously absorbed. In practice, however, the rate of absorption of a drug will always have an effect on its rate of elimination. Consideration will now be given to the elimination of a model drug which is not instantaneously absorbed.

After the oral administration of a dose of drug, D_o, the amount of drug in the body will change at a rate given by:

$$\frac{dD_B}{dt} = \text{Rate of absorption} - K D_B \quad \ldots\ldots (30)$$

and will build up to a maximum value, max D_B. The value max D_B will be less than D_o, because some of the absorbed drug is eliminated while absorption is proceeding.

It is seldom possible to ascribe a single rate constant to the process of drug absorption from the gastrointestinal tract because this depends on many factors. However, from the time when the rate of absorption becomes negligible, equation (30) will reduce to:

$$\frac{dD_B}{dt} = -KD_B \quad \ldots\ldots (31)$$

Integration then gives:

$$\ln D_B = \text{Constant} - Kt \quad \ldots\ldots (32)$$

The constant of integration can be equated with D'_o, where D'_o is the theoretical amount of drug which, if instantaneously absorbed and distributed, would give a pattern of decline identical with that observed in the final phase after the oral administration of an amount of drug D_o at $t = 0$. Equation (32) then becomes:

$$\ln D_B = \ln D'_o - Kt \quad \ldots\ldots (33)$$

The amount of drug in the body, D_B, will increase while its rate of absorption is greater than its rate of excretion, will reach a maximum when the two rates are equal (equation (30)) and will then decline, and a plot of $\ln D_B$ against time will become linear when the rate of absorption has become negligible (equation (33)). The linear part of this plot will have a

slope equal to $-K$ and, by extrapolation to zero time, an intercept on the ordinate equal to $\ln D'_o$.

The same considerations can also be applied to the rate of excretion of the drug in urine and equation (16) can be written:

$$\ln \frac{dD_U}{dt} = \ln k_D D'_o - Kt \quad \ldots\ldots (34)$$

Similarly, an equation of the same form can be obtained for the rate of excretion of a metabolite in urine when k_u is greater than K and t is large, then equation (17) can be written:

$$\text{and } \ln \frac{dM_U}{dt} = \ln \frac{k_u k_F D'_o}{k_u - K} - Kt \quad \ldots\ldots (35)$$

The ultimate slope of the plots of $\ln \frac{dD_U}{dt}$ and of $\ln \frac{dM_U}{dt}$ against time are the same as when absorption is considered to be instantaneous, but the intercepts obtained by extrapolating the linear part of these plots to zero time are now $\ln k_D D'_o$ and $\ln \frac{k_u k_F D'_o}{k_u - K}$ respectively (Fig. 4). These intercepts both contain D'_o and their value therefore depends

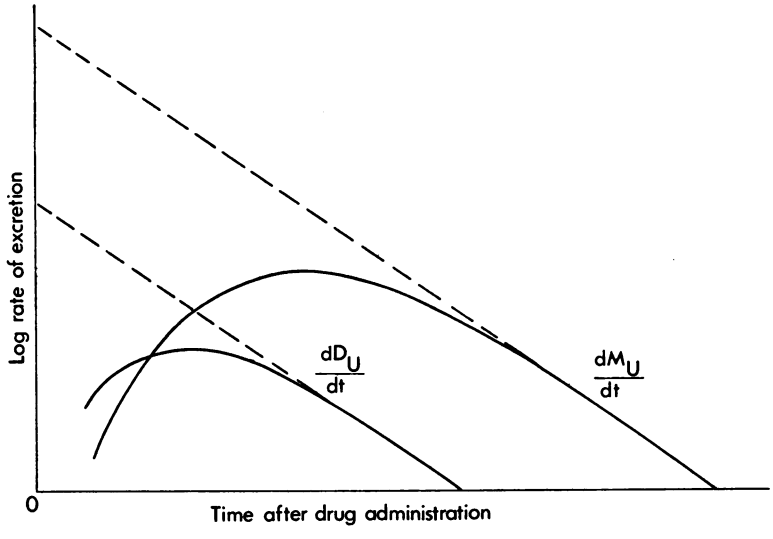


Fig. 4. A log plot of the rate of excretion of drug, $\frac{dD_U}{dt}$ and of the rate of excretion of a metabolite, $\frac{dM_U}{dt}$, when k_u is larger than K and the drug is administered orally.

upon the amount of drug administered and on the rate of its absorption. The difference in their values:

$$\ln \frac{k_u k_F D'_o}{k_u - K} - \ln k_D D'_o = \ln \frac{k_u k_F}{k_D (k_u - K)} \quad \ldots\ldots (36)$$

is independent of D'_o, and is therefore independent of the rate of absorption and of the

amount of drug administered and will thus have the same value as when absorption is considered to be instantaneous.

The difference in the value of these two intercepts also represents the logarithm of the ratio of the rate of excretion of metabolite to the rate of excretion of the drug in the urine in the final phase when both plots are linear and parallel.

An evaluation of D'_o can be obtained by an alternative treatment in which the absorption of the drug is considered to occur in small increments. Thus, when the amount of drug D_o is administered orally at time t_o, an amount of drug D_1, D_2, . . . D_i . . . D_n is absorbed at a time t_1, t_2, . . . t_i . . . t_n respectively, so that

$$D_o = D_1 + D_2 + \ldots + D_i + \ldots = \sum_{\substack{\text{All values} \\ \text{of i}}} D_i$$

Then, since all subsequent processes are first order, the rate of elimination can be considered separately for each increment and the net effect is obtained by summation. Equation (3) now becomes:

$$D_B = D_1 e^{-K(t-t_1)} + D_2 e^{-K(t-t_2)} \ldots + D_i e^{-K(t-t_i)} = e^{-Kt} \sum_{t_i < t} D_i e^{Kt_i}$$

The value of $\sum D_i e^{Kt_i}$ changes until absorption of the drug is complete, when it becomes constant and can be identified with the constant D'_o in equation (33)—that is:

$$\sum_{\substack{\text{All values} \\ \text{of i}}} D_i e^{-Kt_i} = D'_o$$

The plot of $\ln \frac{dD_U}{dt}$ and of $\ln \frac{dM_U}{dt}$ (equations (37) and (38)) can therefore only become linear when the term $\sum D_i e^{Kt_i}$ is constant—that is, when the process of absorption has ended.

The intercepts obtained by extrapolating the linear parts of plots $\ln \frac{dD_U}{dt}$ and $\ln \frac{dM_U}{dt}$ to zero time are $\ln k_D \sum_{\text{All i}} D_i e^{Kt_i}$ and $\ln \frac{k_u k_F}{k_u - K} \sum_{\text{All i}} D_i e^{Kt_i}$, respectively. Since $\sum_{\text{All i}} D_i$ is equal to D_o it follows that $\sum_{\text{All i}} D_i e^{Kt_i}$ which is identified with D'_o, is greater than D_o and the intercepts are displaced to higher values compared with when drug absorption is instantaneous.

The above considerations relate to those cases in which the effective rate constant governing drug absorption is considerably greater than the rate constant governing drug elimination. When this is not so, the term for absorption in the equations for the elimination of the drug and its metabolites will become negligible only after a very long time. This will be reflected in the $\ln \frac{dD_U}{dt}$ and $\ln \frac{dM_U}{dt}$ plots which may as a consequence become linear only when t is very large.

The determination of the excretion rate constants of metabolites

If certain conditions are fulfilled, the excretion rate constant of a metabolite (k_u) can be determined from a study of the drug and metabolite urinary excretion data.

Whilst many parameters are influenced by the fact that the absorption of a drug from the gastrointestinal tract may be highly variable, it has been shown that the ratio of certain parameters is independent of this factor. The following considerations do not involve the assumption that the whole of dose is absorbed, but it is, however, necessary to specify that drug absorption is relatively rapid, so that in effect there is a time when the process of absorption has become negligible. It must also be assumed that both the drug and metabolite rapidly attain a state of equilibrium distribution in the body. Then the following two methods may be used for the evaluation of k_u.

(i) " *Rate* v. *Amount* " *method*

This method is independent of the relative or absolute values of k_u and K, but it is dependent on the excretion of sufficient unchanged drug in urine for its pattern of excretion to be determined. This method (Martin, 1967) is based on the construction of a " Rate *v.* Amount," $\left(\frac{dM_U}{dt} \textit{ v. } M_B\right)$, plot for the metabolite, according to equation (37), and the determination of k_u from its slope.

$$\frac{dM_U}{dt} = k_u M_B \quad \ldots\ldots (37)$$

When drug elimination is a first order process:

$$\frac{M_F}{D_U} = \frac{k_F}{k_D} = \frac{M_{U\infty}}{D_{U\infty}}$$

and the value of M_B can be calculated from the relationship $M_B = M_F - M_U$, for then:

$$M_B = \frac{M_{U\infty}}{D_{U\infty}} D_U - M_U \quad \ldots\ldots (38)$$

The experimental procedure consists of determining the amount of drug and metabolite excreted in the urine at a number of equal time intervals, to yield values of $\frac{dM_U}{dt}$ and also of D_U, M_U, $D_{U\infty}$, $M_{U\infty}$.

(ii) *The* " *Terminal Ratio* " *method*

This method is based on the ratio of the rate of excretion of metabolite to the rate of excretion of drug when this has become constant, that is, on the difference in the values of equations (35) and (34):

$$\ln\left(\frac{dM_U/dt}{dD_U/dt}\right) = \ln\left(\frac{k_F}{k_D}\frac{k_u}{k_u - K}\right) \quad \ldots\ldots (39)$$

The value of $\frac{dM_U/dt}{dD_U/dt}$ can be obtained from the difference in the value of the intercepts on the ordinate when the linear parts of the plots of $\ln \frac{dM_U}{dt}$ and $\ln \frac{dD_U}{dt}$ are extra-

polated to zero time. Then, if the terminal ratio $\frac{dM_U/dt}{dD_U/dt} = r$, re-arrangement of equation (39) gives:

$$k_u = \frac{rK}{r - k_F/k_D} \quad \ldots\ldots (40)$$

and, since K can be determined from the slope of these plots and $k_F/k_D = M_{U\infty}/D_{U\infty}$ (equations (5) and (11)), the value of k_u may be calculated from equation (40). The practical application of this method requires the plots of $\ln \frac{dD_U}{dt}$ and $\ln \frac{dM_U}{dt}$ to become linear and parallel.

When k_u and K are nearly equal the plot of $\ln \frac{dM_U}{dt}$ will probably not attain a true linear decline within the duration of the study. If the plots of $\ln \frac{dD_U}{dt}$ and $\ln \frac{dM_U}{dt}$ against time become linear but not parallel (Fig. 5) this indicates that K is greater than k_u and the slope of the linear part of the $\ln \frac{dM_U}{dt}$ plot is then equal to $-k_u$. In this instance the difference between the intercepts cannot be used for the evaluation of any rate constant.

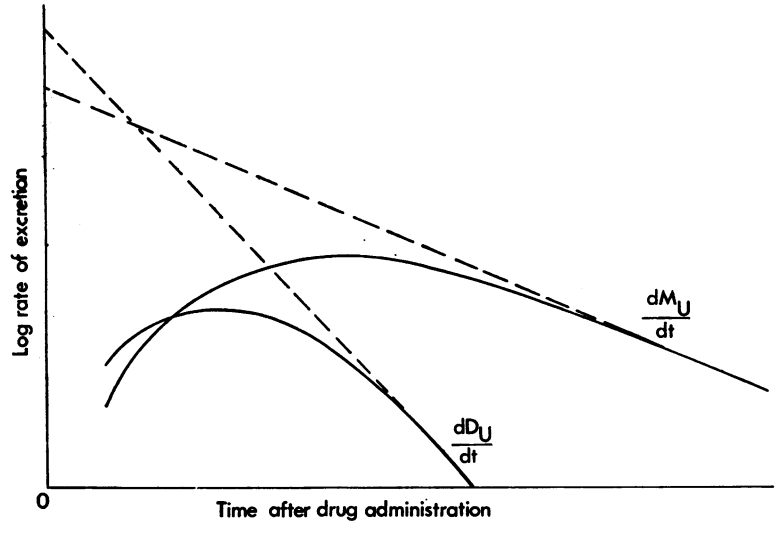


Fig. 5. A log plot of the rate of excretion of drug and rate of excretion of a metabolite when k_u is smaller than K and the drug is administered orally.

SUMMARY

1. The kinetics of the process of elimination of a drug by excretion and by metabolism and the subsequent excretion of the metabolites has been considered in respect of a model drug.

2. Metabolite accrual has been defined in terms of differential equations, and the extent of accrual has been shown to depend upon the relative values of the elimination rate constant of the drug (K) and the excretion rate constant of the metabolite (k_u).

3. A plot of log rate of metabolite excretion against time can have a terminal linear section of slope equal to $-K$ when $k_u > K$, or to $-k_u$ when $k_u < K$.

4. The effect of the rate of absorption on the terminal section of the above plots has been assessed by considering drug absorption to occur in small increments.

5. It has been shown that while the size of the dose administered and its rate of absorption alter the value of many parameters, the ratio of certain parameters is not changed.

6. Consideration has been given to two methods for the determination of the excretion rate constant of a metabolite.

REFERENCES

BRAY, H. G., THORPE, W. V. & WHITE, K. (1951). Kinetic studies of the metabolism of foreign organic compounds. 1. The formation of benzoic acid from benzamide, toluene, benzyl alcohol and benzaldehyde and its conjugation with glycine and glucuronic acid in the rabbit. *Biochem. J.*, **48**, 88–96.

CUMMINGS, A. J. & MARTIN, B. K. (1963). Excretion and the accrual of drug metabolites. *Nature, Lond.*, **200**, 1296–1297.

DOST, F. H. (1953). *Der Blutspiegel: Kinetik der Konzentrationsabläufe in der Kreislauffüssigkeit.* Georg Thieme, Leipzig.

GEHLEN, W. (1933). Wirkungsstärke intravenös verabreichter arzneimittel als Zeitfunktion. *Naunyn-Schmiedebergs Arch. exp. Path. Pharmak.*, **171**, 541–554.

MARTIN, B. K. (1967). Drug urinary excretion studies—A new method of treating the data. *Nature, Lond.* (in press).

SWINTOSKY, J. V. (1957). Excretion equations and interpretation for digitoxin. *Nature, Lond.*, **179**, 98–99.

TEORELL, T. (1937). Kinetics of distribution of substances administered to the body. I. The extravascular modes of administration. *Archs. int. Pharmacodyn. Ther.*, **57**, 205–225. II. The intravascular modes of administration. *Archs. int. Pharmacodyn. Ther.*, **57**, 226–240.