Br. J. Pharmac. Chemother. (1967), **29**, 181–193.

DRUG URINARY EXCRETION DATA—SOME ASPECTS CONCERNING THE INTERPRETATION

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(*Received August* 16, 1966)

The study of the excretion of a drug and its metabolites in urine after drug administration can provide valuable information concerning drug absorption, distribution and elimination. The maximum value of these studies is, however, only obtained by a detailed kinetic analysis of the experimental results. While certain procedures may be preferable for a specific purpose, two methods of treating the experimental results are capable of general application and are suitable for mathematical interpretation. The first is derived from the classical method of chemical kinetics. In principle it seeks to calculate the amount of drug in the body from a knowledge of the amount of drug excreted at that time and the total amount finally excreted. Its application to drug urinary excretion data will here be termed the " Sigma-minus " method. The second is the " Rate " method. This is based on a study of the decline in the rate of excretion of drug in the urine.

These methods cannot, however, be regarded simply as alternative procedures. They do not necessarily provide identical information, and each method can on certain occasions yield information which is not available from the other (Martin, 1965, 1967). Apart from a contribution by Wagner (1963) relating to some of the errors which may arise in the plotting and interpretation of urinary excretion data, no critical evaluation of these methods appears in the literature. This communication records the results of a theoretical appraisal of the value and application of these methods to the excretion of drug and drug metabolites in urine.

THEORETICAL CONSIDERATIONS

Application to the excretion of drug in urine

(i) *The " Sigma-minus " method*

This method was used by Bray, Thorpe & White (1951). When applied to the excretion of unchanged drug in urine the " Sigma-minus " method consists of plotting log $(D_{U\infty}-D_U)$ against time, where $(D_{U\infty}-D_U)$ represents the sum (*Sigma*) of the amounts of drug excreted until such time as excretion may be considered to be complete $(D_{U\infty})$ *minus* the cumulative amount of drug excreted to a time t, (D_U). When drug elimination is first order, this is based on the equation:

$$\ln (D_{U\infty}-D_U) = \ln \frac{k_d}{K} D'_o - Kt \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (1)$$

where k_d is the rate constant governing the urinary excretion of unchanged drug, K is the rate constant for the elimination of drug by all routes, and D'_o is a constant which may be interpreted as that amount of drug which if present in the body at t=o would ultimately give rise to a pattern of drug decline identical to that observed on this occasion after the administration of the dose D_o. The slope of the plot is equal to $-K$.

After the oral administration of a drug there is an initial period when absorption is in progress. Any drug which is subsequently absorbed but which at that time is in the gastro-intestinal tract is interpreted in this plot as present in the body, so that in the present context the meaning of the plot during this period is fictional. Subsequently, when absorption of drug has ceased or has become negligible, a plot which is based on the unchanged drug in urine represents the decline of that fraction of the total drug in the body which ultimately appears in the urine as unchanged drug (equation (1)). When drug elimination is first order, K may be determined from the slope of the terminal, linear section of the log " Sigma-minus " plot.

Reference to this method as a plot of the log " amount of drug in the body " or log " amount not yet excreted " can for the above reasons be misleading, and it will be shown to be particularly so when applied to a metabolite (equation (8)). The nomenclature " Sigma-minus " provides a simple description which avoids these implications and describes the method in terms only of the method of calculation.

The " Sigma-minus " method requires knowledge of $D_{U\infty}$ and in theory therefore requires the collection of urine until such time as excretion is complete. In practice, urine is collected over a number of consecutive short intervals of time and then over one or more longer periods until the drug can no longer be estimated. Wagner (1963) has suggested that the collection of urine for a period corresponding to 10 half-lives of the drug is usually adequate for this purpose. He also emphasized that failure to determine or use the true recovery value can give rise to curvature in the plot. The examination of a number of theoretical plots shows, however, that a small error in the assessment of $D_{U\infty}$ can give rise to plots which could well be interpreted as linear over a considerable period, but that the slope of the apparently linear section then shows an appreciable departure from the true slope. In practice, such an interpretation is even more likely, for analytical errors frequently accompanied by actual fluctuations in the rate of drug elimination, will also operate to give departure from perfect linearity.

A minor error in the assessment of $D_{U\infty}$ introduces an error in every value plotted, but recognition of these errors in terms of curvature developing in the plot only becomes apparent at high values of t. If curvature is to be detected and the potential error in the slope of the "linear" section acknowledged, the collection of urine at short intervals of time must continue for as long as possible, before finally resorting to collection over a longer terminal period. This aspect is illustrated in Fig. 1, which shows the true plot and two plots which are constructed on the basis that a small error in the assessment of $D_{U\infty}$ has occurred in the terminal period of urine collection. Curvature of the log " Sigma-minus " plot arising from an underestimate of the amount of drug recovered in the urine gives the false impression that drug elimination becomes relatively more rapid as it proceeds (Fig. 1, curve C). This could, however, be a true observation if drug elimination takes place by simultaneous first order and zero order processes. Conversely, an estimation of $D_{U\infty}$ which is in excess

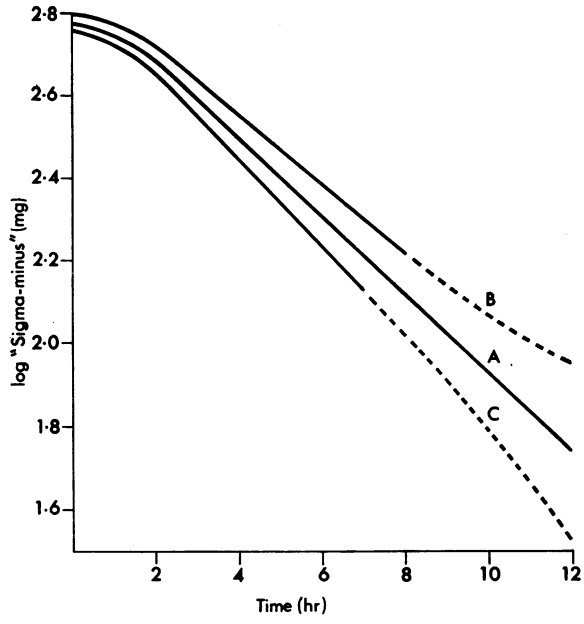

Fig. 1. The correct " Sigma-minus " plot (A) and two plots (B and C) which are constructed from erroneous values of $D_{U\infty}$. A small error in the assessment of $D_{U\infty}$ can give rise to a plot which might well be interpreted as linear over a considerable period, but its slope shows an appreciable departure from the true value. Curvature in (B) and (C) becomes apparent only at high values of t. The value of $D_{U\infty}$ is assessed in (B) as 105% and in (C) as 95% of the true theoretical value, the error being introduced in the terminal period of urine collection. Calculation of K from the apparent linear section of these plots causes an error of 13%.

of the true value will give the false impression that drug elimination becomes relatively slower in the final phase (Fig. 1, curve B). This could also be a true effect if a drug is extensively bound to the plasma or tissue proteins. On the evidence of the log " Sigma-minus " plot, it is therefore often uncertain whether the curvature of the plot is a true feature of drug elimination or arises as an artefact.

Certain special features arise as a result of the method used in calculating the " Sigma-minus " values. Let the amount of drug excreted in successive periods of time after drug administration be d_{U_1}, d_{U_2}, d_{U_3}, - - -, followed by a terminal period in which an amount d_{U_n} is excreted. If the experimentally determined figures are $(d_{U_1}+a_1)$, $(d_{U_2}+a_2)$, $(d_{U_3}+a_3)$, $(d_{U_4}+a_4)$ - - - $(d_{U_n}+a_n)$, where a_1, a_2, a_3 - - a_n are errors introduced in the collection or analysis of the respective urines, then the values of $(D_{U\infty}-D_U)$ which are plotted are:

At t = o: $(d_{U_1}+a_1) + (d_{U_2}+a_2) + (d_{U_3}+a_3) + - - - (d_{U_n}+a_n)$
At t = 1: $(d_{U_2}+a_2) + (d_{U_3}+a_3) + (d_{U_4}+a_4) + - - - (d_{U_n}+a_n)$
At t = 2: $(d_{U_3}+a_3) + (d_{U_4}+a_4) + - - - (d_{U_n}+a_n)$
At t = 3: $(d_{U_4}+a_4) + - - - - - - - - - - (d_{U_n}+a_n)$

Several analytical determinations contribute to each value of $(D_{U\infty}-D_U)$, but all values include $(D_{U_n}+a_n)$ and the accuracy of each term and hence that of the entire plot is

dependent on the accuracy of $D_{U\infty}$. The value of any term is independent of all measurements up to and including that made at time t, thus the value of $(D_{U\infty}-D_U)$ at the third hour does not contain the term $(D_{U_3}+a_3)$ and a major error arising at time t does not invalidate that result or any subsequent results, but it does affect all results before time t.

(ii) *The "Rate" method*

This method was introduced by Swintosky (1957). When drug elimination is first order and the process of drug absorption has ceased, a log plot of the rate of excretion of drug against time exhibits a terminal linear section of slope equal to $-K$, according to the equation:

$$\ln\left(\frac{dD_U}{dt}\right) = \ln k_a D'_o - Kt \quad \ldots\ldots (2)$$

It is not possible to determine the instantaneous rate of excretion of drug in urine $\left(\frac{dD_U}{dt}\right)$ and it is necessary to make use of the average rate of excretion over a short period of time. In practice, the log of the amount of drug excreted (ΔD_U) in a series of equal intervals (Δt) is plotted against time, at the mid-point of each time interval. If a factor λ is introduced to account for this departure, so that,

$\frac{\Delta D_U}{\Delta t} = \lambda \frac{dD_U}{dt}$, then, this plot is based on the equation:

$$\ln\left(\frac{\Delta D_U}{\Delta t}\right) = \ln k_a D'_o \lambda - Kt \quad \ldots\ldots (3)$$

In seeking to base any calculations on the plot of $\log\left(\frac{\Delta D_U}{\Delta t}\right)$ instead of the true value $\log \frac{dD_U}{dt}$, it is necessary to consider the magnitude of the displacement of this plot from the true position.

When the decline of $\frac{dD_U}{dt}$ is first order, then:

$$\frac{dD_U}{dt} = k_a D \quad \ldots\ldots (4)$$

where D is the amount of drug in the body at a time t which is the mid-point of a time interval.

The amount of drug excreted (ΔD_U) in the interval Δt is related to the difference in the amount of drug in the body (ΔD) at time $(t-\frac{1}{2}\Delta t)$ and that at $(t+\frac{1}{2}\Delta t)$ by the expression $\Delta D_U = \frac{k_a}{K}\Delta D$. Then, since $D = D_o e^{-Kt}$:

$$\frac{\Delta D_U}{\Delta t} = \frac{k_a}{K\Delta t}\left(D e^{\frac{1}{2}\Delta tK} - D e^{-\frac{1}{2}\Delta tK}\right) \quad \ldots\ldots (5)$$

$$\text{and } \lambda = \frac{\Delta D_U}{\Delta t} \Big/ \frac{dD_U}{dt} = \frac{e^{\frac{1}{2}\Delta tK} - e^{-\frac{1}{2}\Delta tK}}{K\,\Delta t} \quad \ldots\ldots (6)$$

Under the conditions specified, λ is therefore a constant which depends only on the value of K and Δt. The plot of $\log \frac{\Delta D_U}{\Delta t}$ against time (equation (3)) is therefore linear and parallel to that of $\log \frac{dD_U}{dt}$ (equation (2)), consequently no error arises in the use of its slope for the calculation of K.

If Δt is expressed in terms of the drug's half-life ($t_{0\cdot5}$), so that, $\Delta t = \theta t_{0\cdot5}$, then, since $t_{0\cdot5} = \frac{\ln 2}{K}$,

$$\lambda = \frac{e^{\frac{1}{2}\theta \ln 2} - e^{-\frac{1}{2}\theta \ln 2}}{\theta \ln 2} = \frac{2^{\frac{1}{2}\theta} - 2^{-\frac{1}{2}\theta}}{\theta \ln 2} \quad \ldots\ldots (7)$$

Values of λ corresponding to selected values of θ are given in Table 1.

TABLE 1

THE RELATIONSHIP BETWEEN THE AVERAGE RATE OF EXCRETION OF DRUG $\frac{\Delta D_U}{\Delta t}$ AS DETERMINED OVER DIFFERENT INTERVALS OF TIME (Δt) AND THE RATE OF EXCRETION $\frac{dD_U}{dt}$ AT THE MID-POINT OF THE TIME INTERVAL, WHEN THE DECLINE IN THE RATE OF EXCRETION IS LOG-LINEAR

Calculated from equation 7

ΔT (expressed in terms of drug half-life)	$\frac{\Delta D_U}{\Delta t} \Big/ \frac{dD_U}{dt}$
3·0	1·19
2·0	1·08
1·0	1·02
0·67	1·009
0·5	1·005
0·33	1·0001

Relative to the plot of $\log \frac{dD_U}{dt}$, the linear section of the plot of $\log \frac{\Delta D_U}{\Delta t}$ is displaced to higher values ($\lambda > 1$), but, if urine is collected at intervals which are not larger than one half-life of the drug, the error is not greater than +2% ($\lambda = 1.02$, Table 1). When the decline in the rate of excretion is not first order, λ is not constant and at certain times $\frac{\Delta D_U}{\Delta t}$ will underestimate the true rate of excretion ($\lambda < 1$). This is illustrated in Fig. 2. Provided, however, that Δt is small, it would appear that the error involved in the substitution of $\frac{\Delta D_U}{\Delta t}$ for $\frac{dD_U}{dt}$ in equation (2) is less than the normal experimental error.

Application to the excretion of a metabolite in urine

In addition to those factors which govern its formation, the excretion of a metabolite in urine is governed by an elimination rate constant which consists of a rate constant for its

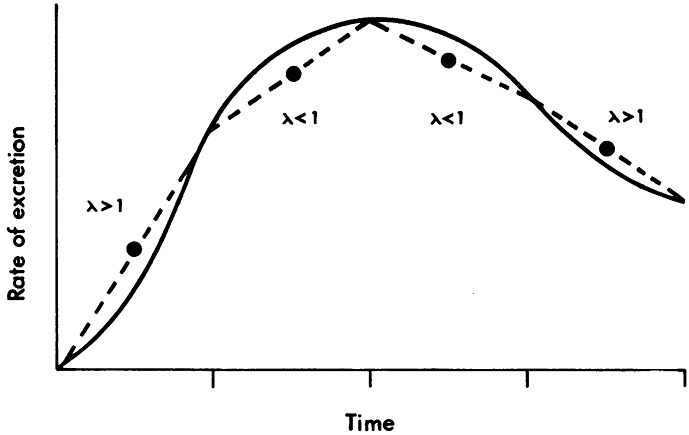

Fig. 2. A diagrammatic representation of the rate of excretion of drug $\left(\frac{dD_U}{dt}\right)$ against time (solid line) and the average rate of excretion $\left(\frac{\Delta D_U}{\Delta t}\right)$ determined over a short interval of time and plotted at the mid-point of the interval (– – ● – –) during four phases of drug elimination.

$$\lambda = \frac{\Delta D_U}{\Delta t} \Big/ \frac{dD_U}{dt}$$

urinary excretion and the rate constants for its elimination by other routes—for example, by further metabolism. The following considerations relate to a metabolite which is eliminated only by urinary excretion, in this instance therefore its rate of elimination is governed only by an excretion rate constant, k_u.

(i) *The " Sigma-minus " method*

The application of the " Sigma-minus " method to a metabolite differs in one respect from that of the drug. Let

$M_{U\infty}$ = Amount of metabolite in the urine when excretion is complete,
M_U = Amount of metabolite in the urine at time t,
M_B = Amount of metabolite in the body at time t, and
k_f = first order rate constant governing the formation of this metabolite.

It has been shown (Cummings, Martin & Park, 1967) that

$$(M_{U\infty} - M_U) = \frac{k_f}{K} D + M_B \quad \ldots\ldots (8)$$

and a plot of $(M_{U\infty} - M_U)$ against time therefore relates not only to that fraction of the drug in the body which is ultimately eliminated as metabolite, but includes also the amount of the metabolite in the body.

The log " Sigma-minus " plot for a metabolite can give rise to a terminal linear section and its slope will depend on whether the excretion rate constant of the metabolite (k_u) is greater or smaller than the elimination rate constant of the drug (K), according to one or other of the following equations (Cummings, Martin & Park, 1967).

When $k_u > K$, and at high values of t:

$$\ln (M_{U\infty} - M_U) = \ln \frac{k_u k_f D'_o}{K(k_u - K)} - Kt \quad \ldots\ldots (9)$$

When $K > k_u$, and at high values of t:

$$\ln (M_{U\infty} - M_U) = \ln M'_o - k_u t \quad \ldots\ldots (10)$$

where M'_o is a constant which may be interpreted as that amount of metabolite which if present in the body at t=o would give rise to a metabolite excretion pattern identical to that observed in the terminal phase on this occasion after administration of the dose of drug, D_o.

If a terminal linear section is observed in these plots, then either K, or k_u may be calculated from its slope.

A knowledge of $D_{U\infty}$ and $M_{U\infty}$ is required not only for the construction of the respective " Sigma-minus " plots, but also for the assessment of the extent of drug absorption and for the calculation of the specific rate constants which govern drug excretion and metabolite formation.

The rate constants governing metabolite formation also constitute the only valid basis for the comparison of the rate of metabolism of drugs. For example, when two drugs, A and B, are excreted in the form of their acetyl derivatives to the extent of 50% and 25% of the dose respectively, it might be erroneously concluded on evidence of this nature that drug A is acetylated at twice the rate of drug B. Such a conclusion cannot be made on this evidence alone. The fraction of the dose excreted as metabolite M is governed by the relationship:

$$\frac{M_{U\infty}}{D_{U\infty} + M_{U\infty}} = \frac{k_f}{k_d + k_f}$$

where $k_d + k_f = K$. The amount of drug excreted as metabolite depends therefore not only on k_f but also on k_d. If k_d for drug A is 0.05 hr^{-1} and k_d for drug B is 0.3 hr^{-1}, calculation then shows that drug B (k_f=0.2 hr^{-1}) is in fact acetylated twice as fast as drug A (k_f= 0.1 hr^{-1}).

(ii) *The " Rate " method*

A log " Rate " plot relating to the excretion of a metabolite in the urine can also give rise to a terminal linear section and its slope will depend on which of the rate constants, k_u or K, is the greater (Cummings, Martin & Park, 1967).

When $k_u > K$, then at high values of t:

$$\ln \frac{dM_U}{dt} = \ln \frac{k_u k_f D'_o}{k_u - K} - Kt \quad \ldots\ldots (11)$$

When $K > k_u$, then at high values of t:

$$\ln \frac{dM_U}{dt} = \ln k_u M'_o - k_u t \quad \ldots\ldots (12)$$

Under these conditions, either K (equation (11)) or k_u (equation (12)) can be calculated from the slope of the plot of log $\frac{\Delta M_U}{\Delta t}$ against time.

Two methods, the " Rate *v* Amount " method (Martin, 1967) and the " Terminal-ratio " method (Cummings, Martin & Park, 1967) have recently been proposed for the determination of the excretion rate constant of a metabolite from urinary excretion data. Their application has been exemplified by Cummings, King & Martin (1967). Both methods involve the use of " Rate " data, but they also require knowledge of k_d and k_f, and hence of $D_{U\infty}$ and $M_{U\infty}$.

Subject to certain limitations, it is possible to obtain calculated values for $D_{U\infty}$ and $M_{U\infty}$ by the extrapolation and summation of " Rate " data. These values can frequently serve as suitable approximations which may be used for the calculation of the specific rate constants which govern drug elimination. When the log " Rate " plot shows a well-defined terminal linear section, a value of $D_{U\infty}$ may be calculated as the sum of the amounts of drug excreted until such time as the log " Rate " plot is linear, plus the sum to infinity of a series of excretion terms which are assumed to continue to decline exponentially. The latter is the sum to infinity (S_∞) of a geometric series $\left(S_\infty = \frac{a}{1-r}\right)$ with the ratio (r) equal to e^{-K}. Thus:

$$D_{U\infty} \text{ calc.} = (d_{U_1} + d_{U_2} + \cdots d_{U_{T-1}}) + \left(\frac{d_{U_T}}{1 - e^{-K}}\right) \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots (13)$$

where d_{U_T} is the amount of drug excreted in the hr ending at time T when the decline in the rate of excretion is log-linear, and K (hr^{-1}) is calculated from the slope of the log " Rate " plot.

Comparative features of the " Rate " and the " Sigma-minus " methods

Theoretical consideration of the " Sigma-minus " method has emphasized that the asymptotic amount of drug or metabolite excreted in urine must be assessed with considerable accuracy, but this is frequently difficult in practice. The collection of urine must continue without interruption and without loss, this can impose the inconvenience and the inaccuracies associated with the collection of urine for periods of time as long as one week when the half-life of the drug exceeds 17 hr.

The " Rate " method does not require knowledge of $D_{U\infty}$ or $M_{U\infty}$ (Swintosky, 1957) and the loss of one urine specimen does not invalidate the entire experiment. An unacknowledged error in the time of one urine collection or the incomplete emptying of the bladder on one occasion, gives rise, however, to two erroneous " Rate " values, whereas these features give rise to only one erroneous " Sigma-minus " value. In the " Rate " method the collection of urine can be discontinuous; it can be abandoned overnight and recommenced the following day. The " Rate " method is therefore particularly applicable to the investigation of any progressive change in the rate of drug elimination which may occur during a course of drug therapy, for the rate of excretion of drug or metabolite can be studied for a selected number of hours on successive days.

Fluctuations in the rate of drug elimination and experimental errors both cause appreciable departures from linearity in the log " Rate " plot, whereas these are usually reflected to a much smaller extent in the log " Sigma-minus " plot and depend on the value of K. This is illustrated in Fig. 3. An increase of 10% in the amount of drug excreted in any one period would appear as a 10% deviation in the " Rate " plot, but when $K<1$ the same

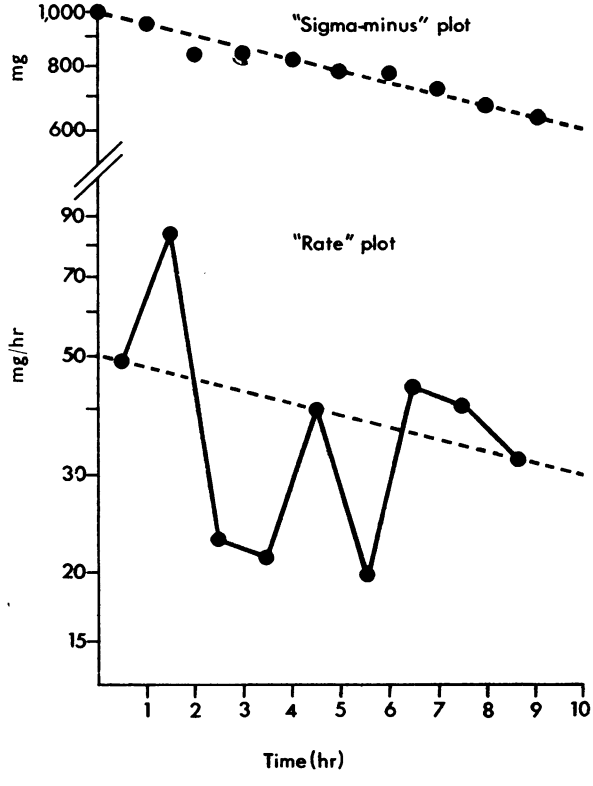

Fig. 3. The log " Sigma-minus " plot and the corresponding log " Rate " plot relating to data for the excretion of drug in urine. The dotted line represents a theoretical decline corresponding to $K = 0.05\ hr^{-1}$. Fluctuations in the rate of drug elimination are reflected to a much greater extent in the " Rate " plot.

increase represents a much smaller percentage decrease in the " Sigma-minus " value when it is related to the fraction remaining in the body. An error of $+x\%$ in a " Rate " value gives a corresponding error of $-Kx\%$ in the " Sigma-minus " value. The " Rate " method provides, therefore, a far more sensitive indication of changes in the rate of drug elimination which may be the result, for example, of changes in urine volume or pH, of enterohepatic recycling of drug, or of the administration of a second drug.

The application of the " Rate " method and the " Sigma-minus " method to the urinary excretion of a metabolite in a model system when $k_u>K$, is illustrated in Fig. 4. The " Sigma-minus " plot gives no direct indication of the extent of metabolite accrual, whereas the log " Rate " plot for a metabolite rises from zero to a maximum value and it is at this

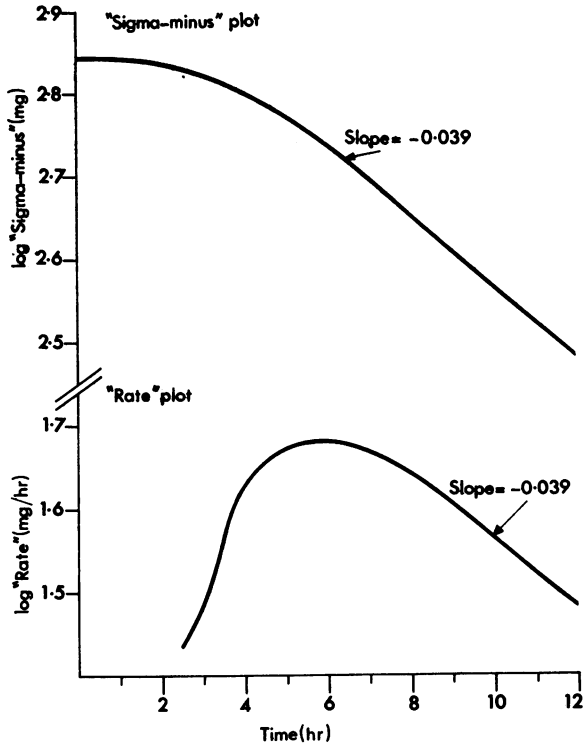

Fig. 4. The log " Sigma-minus " plot and the log " Rate " plot are constructed from theoretical data which relate to the excretion of a metabolite in urine. The value of K ($k_u > K$) can in this instance be determined from the slope of the terminal, linear section of either plot ($K = -2.303 \times$ slope). The slope of the log " Sigma-minus " plot in the period 6–7 hr is −0.039 and is within 10% of the terminal slope (−0.043), whereas the corresponding log " Rate " plot exhibits a maximum at that time and it is not until the 9½–10½ hr period that its slope is within 10% of the terminal slope.

time that the amount of metabolite in the body is also at its maximum. Both log plots exhibit a terminal section which can be interpreted as linear, they are then parallel and K can be calculated from the slope. When the difference between k_u and K is small, it may not always prove possible to obtain " Rate " data over a period which is long enough to establish that the log plot has closely approached its terminal linear rate of decline, and calculations based on the slope of the plot would then tend to underestimate the value of K. The slope of the log " Sigma-minus " plot at all times shows a smaller departure from the terminal slope than the corresponding log " Rate " plot and for this reason it may on occasions offer a more reliable assessment of K. This feature is exemplified in Fig. 4.

The theoretical relationship which exists between the linear sections of the log " Rate " plot and the log " Sigma-minus " plot for a drug is shown by subtracting equation (1) from equation (2):

$$\frac{dD_U}{dt} = K(D_{U\infty} - D_U) \quad \ldots\ldots (14)$$

When the plots relate to metabolites, the relationship depends on the relative value of k_u and K. When $k_u > K$ and when both plots are linear and parallel, subtraction of equation (9) from equation (11) gives:

$$\frac{dM_U}{dt} = K(M_{U\infty} - M_U) \quad \ldots\ldots (15)$$

Under similar conditions, when $K > k_u$, subtraction of equation (10) from equation (12) gives:

$$\frac{dM_U}{dt} = k_u(M_{U\infty} - M_U) \quad \ldots\ldots (16)$$

Equations (14), (15) and (16) form the basis of " Rate " *v* " Sigma-minus " plots (Martin, 1967). A further extension of this type of plot is the " Rate *v* Amount " method for the determination of the excretion rate constant of a metabolite (Martin, 1967). Whereas the experimental " Rate " values relate to the time at the mid-point of each period in which urine is collected, the " Sigma-minus " values relate to the time at the end of each period and it is therefore necessary for the present purpose to obtain the interpolated values from one or other of these plots so that they can be related at identical times.

It has been suggested (Martin, 1965) that the " Rate " method and the " Sigma-minus " method can give entirely different information when applied to a drug which has a very high affinity for the plasma proteins. Under these conditions the " Rate " plot based on the excretion of drug then reflects the decline of the free drug in the body, and the " Sigma-minus " plot reflects the decline of total drug. Both methods therefore provide valid information.

The two methods also differ when applied to a drug which is eliminated by simultaneous zero order and first order processes. When one metabolite of a drug is formed in a zero order process, a log " Rate " plot based on the excretion of drug in urine is a curve and this provides a true indication of the rate of drug elimination (Fig. 5). This follows from the relationship $\frac{dD_U}{dt} = k_d D$. The curvature of the log " Rate " plot shows an increasing slope and signifies that drug elimination becomes relatively more rapid and K progressively larger as elimination proceeds. The effective value of K which applies at a particular time may be obtained from the slope of the log " Rate " plot at that time. Under these conditions the " Sigma-minus " plot based on the excretion of drug in urine gives a false interpretation and does not reflect the rate of drug elimination. This arises from the fact that the " Sigma-minus " plot relates to the decline of that fraction of drug in the body which is eliminated unchanged (equation (1)), and under these circumstances this is not constant.

Wagner (1963) advocated that drug urinary excretion data should be interpreted by both the " Rate " and the " Sigma-minus " method. This procedure is desirable, but there are few examples of its application (Swintosky, Robinson & Foltz, 1957; Swintosky, Foltz, Bondi & Robinson, 1958; Chulski, Johnson, Schlagel & Wagner, 1963; Bleidner, Harmon, Hewes, Lynes & Hermann, 1965; Cummings *et al.*, 1967). The majority of studies have been interpreted by the " Sigma-minus " method, whereas relatively few

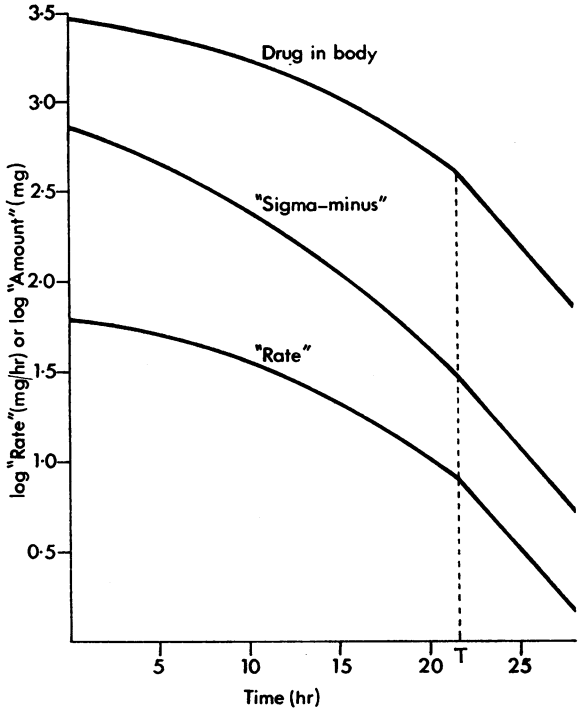

Fig. 5. The log " Rate " plot based on the excretion of drug in urine gives a true indication of the rate of drug elimination when this takes place by simultaneous zero order and first order processes, whereas the corresponding log " Sigma-minus " plot fails in this respect. In this model, the excretion of drug takes place by a first order process, and a metabolite is formed in a zero order process until the drug in the body is less than a critical amount ($D_{crit.}$). This occurs at time T and metabolite formation then takes place by a first order process. Data calculated from the equation of Cummings, Martin & Park (1964), $D = \left(\frac{k_o}{k_d} + D_o \right) e^{-k_d t} - \frac{k_o}{k_d}$. First order rate constant for drug excretion (k_d) = 0.020 hr^{-1}. First order rate constant for metabolite formation (k_1) = 0.2375 hr^{-1}. Zero order rate constant for metabolite formation (k_o) = 90 mg/hr. D_o = 3,000 mg $D_{crit.}$ = 379 mg.

workers have employed the " Rate " method. The present considerations serve to emphasize the value of the " Rate " method in terms of its theoretical significance and simple application in practice.

SUMMARY

1. The " Rate " and " Sigma-minus " methods for the interpretation of drug and metabolite urinary excretion data have been studied in terms of their theoretical significance and practical application.

2. The " Sigma-minus " method necessitates an accurate assessment of the total amount of drug (or metabolite) excreted in urine. This can be impracticable when drug elimination is slow or when the study relates to multiple dose therapy.

3. The average rate of urinary excretion determined over a short interval of time corresponds very closely to the rate of excretion at the mid-point of that time interval.

4. Subject to certain limitations, calculated values of the total amount of drug and metabolite excreted in urine may be obtained by the extrapolation and summation of " Rate " data.

5. The " Rate " method can be applied to study any change in the elimination rate constants when drug administration continues over long periods.

6. The " Rate " method directly indicates when the rate of excretion of drug and metabolite are maximum and emphasizes the extent of metabolite accrual.

7. The rate of metabolism of drugs can only be compared on the basis of the respective rate constants which govern metabolite formation.

8. The " Rate " method is applicable to drug elimination involving a zero order process, whereas the " Sigma-minus " method is not valid under these conditions.

9. A simple relationship exists between the " Rate " method and the " Sigma-minus " method and this can form the basis of " Rate " *v* " Sigma-minus " plots.

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