of the decrease in pH. The term "apparent equilibration" with reference to the pH data is used advisedly since the data clearly show that the true equilibrium with the original plastic will never be reached. Since the plastic is leaching one or more constituents into the solution, the material is continually being altered and it is improbable that a true equilibrium is attained.

Although the adsorption of acids and bases has been found in some cases to be proportional to the concentration of undissociated molecules, many highly ionized surface-active substances are known so that the extent of ionization itself cannot be a sole controlling factor. As a matter of fact, the experiments conducted with hydroalcoholic solvents have demonstrated the maximum sorbic acid adsorption from the solution containing about 10% (v/v) of ethyl alcohol. This finding had not been anticipated. Autian and Shaikh, in their study on adsorption of sorbic acid by nylon (13), noted that as the water is replaced with a less polar solvent, the binding of sorbic acid decreased. The experiments described, which were carried out three times, show that plastic cellulose acetate behaves differently with respect to sorbic acid. No explanation can be given by this author for the reason or reasons why the adsorption increases and then sharply decreases with increase in alcohol concentration.

The effect of temperature has not been studied because of the instability of sorbic acid at somewhat elevated temperatures (14).

SUMMARY AND CONCLUSIONS

The adsorption of sorbic acid by plastic cellulose acetate and cellulose triacetate has been studied and a method for its determination has been developed. Langmuir adsorption isotherms were determined and the constants calculated. The main significance of this paper is that the applicability of the Langmuir equation to the comparative study of different plastic materials with respect to adsorption has been demonstrated. The method suggested is just one parameter which may be helpful in studying drug–plastic interactions but many other tests and procedures might be necessary to establish useful standards for a particular plastic.

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Multiple Dose Excretion Kinetics

By R. G. WIEGAND, J. D. BUDDENHAGEN, and C. J. ENDICOTT

General mathematical equations describing expected blood and urine drug concentrations were derived to analyze riboflavin excretion data after a single large oral dose followed by multiple smaller but equal doses at equal time intervals. The urinary excretion equation was applied to the riboflavin data to obtain the least squares fit using the IBM digital computer, and by this means the absorption and excretion rates were determined. Such calculations can be applied to find the optimum dosage regimen of other drugs for which the kinetic constants are known. The general expressions reduce to all simpler cases already reported in the literature.

THE FITTING of equations to experimental data on blood and urine concentrations of drug has found wide application in determining the kinetics of the processes involved and in measuring the rates of these processes. Considering absorption and elimination of drug to be apparent first order processes, equations describing blood drug levels (1–4) and urine levels (2, 5) after a single oral dose of drug have been reported. The general equation for blood levels after multiple oral administration of drug at equal doses and time intervals was derived by Dost (4). Boxer, *et al.* (6), had earlier used a simplified form of this equation to obtain the expected maximum and minimum blood levels

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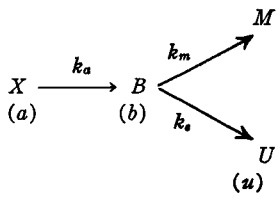
after intravenous administration. For the dosage regimen of an initial large dose and subsequent smaller equal doses at equal time intervals Swintosky, *et al.* (7), have given an approximation for the maximum and minimum blood levels expected, and Krüger-Thiemer (8, 9) has derived the equation giving the ratio of initial to sustaining doses such that the blood level at the time of the first sustaining dose will be maintained.

The general equations describing blood or urine drug levels after administration of an initial dose different in size from successive equal doses at equal time intervals have not been published. Such an equation for blood levels should reduce as time approaches infinity to the expression given by Swintosky, *et al.* (7), for maximum and minimum blood levels, and by appropriate substitutions the dose ratio should be obtained. It should also reduce to the general equations for blood concentration after multiple equal doses or after a single dose. Similarly, the equation for urine levels should reduce to the expression for use with data collected after all equal doses as well as to the equation describing urine drug levels after a single dose. In the process of reducing the general expressions to the simpler forms the assumptions on which the simpler equations are based become apparent and the expected errors resulting from their use can be calculated.

After a large dose and successive smaller doses, the general form of the equations will also make possible calculation of the complete curves for blood or urine levels. This will allow fitting the curves to actual data collected after this dosage regimen, confirming the kinetic order and obtaining a measure of the rates involved. The work with riboflavin reported here was started to find the amount of vitamin necessary in divided doses to maintain the circulating level. The equations were derived to analyze the urinary riboflavin data in terms of the rates of absorption and excretion plus the parameters of dosage.

MATHEMATICAL DERIVATION

After oral administration of a drug, it and its metabolites will pass through a series of compartments according to the flow diagram



where X is the gastrointestinal tract, B is the body exclusive of the gastrointestinal tract and urine, U is the urine, and M indicates the metabolite pool. Apparent first order rate constants are assigned for absorption, k_a, metabolism, k_m, and excretion, k_e. Since when working with blood levels of drug the relative contribution to disappearance of drug by metabolism or excretion is usually not known, the apparent first order disappearance constant, k_d, is defined as the sum of k_e and k_m. The fractional amounts of the total dose in a compartment at any time will be given by the lower case letters in parentheses in the diagram.

Following an initial dose A_o, the amount of drug in the gastrointestinal tract, body, and urine at time τ is given by substitution of $t = \tau$ in previously published equations (5) as

$$a = A_o e^{-k_a \tau} \qquad \text{(Eq. 1)}$$

$$b = \frac{A_o k_a}{k_d - k_a} (e^{-k_a \tau} - e^{-k_d \tau}) \qquad \text{(Eq. 2)}$$

$$u = A_o \frac{k_e}{k_d} \left(1 - \frac{(k_d e^{-k_a \tau} - k_a e^{-k_d \tau})}{(k_d - k_a)}\right) \qquad \text{(Eq. 3)}$$

If a second oral dose, a_o, (different in size from the initial dose) is administered at time τ, the amounts of drug in the compartments a, b, and u can be derived by solving the differential equations

$$-\frac{da}{dt} = k_a a \qquad \text{(Eq. 4)}$$

$$\frac{db}{dt} = k_a a - k_d b \qquad \text{(Eq. 5)}$$

$$\frac{du}{dt} = k_e b \qquad \text{(Eq. 6)}$$

where time, t, is calculated from the time of administration of the last dose. Using Eqs. 1, 2, and 3 for the values of a, b, and u at $t = O$, the equations giving the amount of drug in each compartment as a function of time are

$$a = (a_o + A_o e^{-k_a \tau}) e^{-k_a t} \qquad \text{(Eq. 7)}$$

$$b = \frac{k_a}{k_d - k_a} [(a_o + A_o e^{-k_a \tau}) e^{-k_a t} - (a_o + A_o e^{-k_d \tau}) e^{-k_d t}] \qquad \text{(Eq. 8)}$$

$$u = \frac{k_e}{k_d} \left[A_o + a_o - \frac{k_d(a_o + A_o e^{-k_a \tau})}{k_d - k_a} e^{-k_a t} + \frac{k_a(a_o + A_o e^{-k_d \tau})}{k_d - k_a} e^{-k_d t}\right] \qquad \text{(Eq. 9)}$$

Similar extension of Eqs. 7, 8, and 9 can be made for successive oral doses equal to the second (a_o), administered at the same time interval τ. Under these conditions the term within the parentheses in Eq. 7 becomes $(a_o + a_o e^{-k_a \tau} + a_o e^{-2k_a \tau} + \ldots + a_o e^{-(n-1)k_a \tau} + A_o e^{-nk_a \tau})$. Because the sum of all but the last term in this expression equals $a_o(1 - e^{-nk_a \tau})/(1 - e^{-k_a \tau})$, the expression for a after an initial dose A_o and successive doses a_o given at time intervals τ becomes

$$a = \left(A_o e^{-nk_a \tau} + a_o \frac{1 - e^{-nk_a \tau}}{1 - e^{-k_a \tau}}\right) e^{-k_a t} \qquad \text{(Eq. 10)}$$

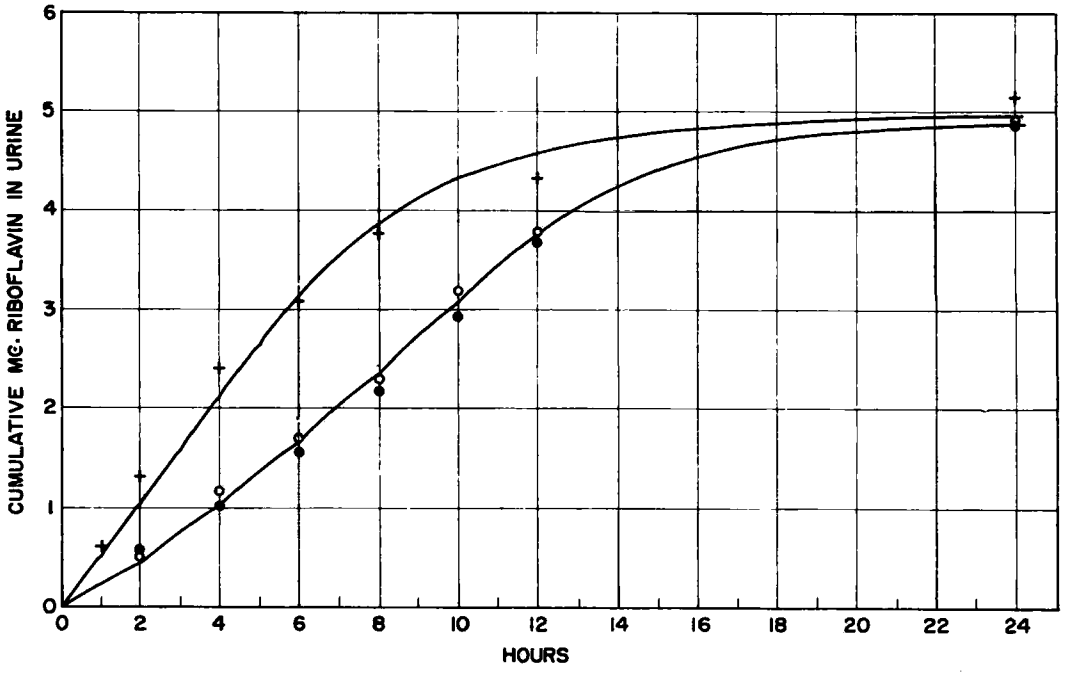


Fig. 1.—Mean cumulative riboflavin urine levels from 10 adults after 5 mg. riboflavin orally at zero time and 5 doses of 1 mg. every hour (+, experiment 800) or after 2.4 mg. at zero time and 5 doses of 1.5 mg. every 2 hours, (○, experiment 801; ●, experiment 996). Curves are calculated according to equation 12 with $k_e = .123$ hr.$^{-1}$, $k_d = .246$ hr.$^{-1}$, $k_a = 30$ hr.$^{-1}$, and appropriate values of A_0, a_0, τ, n, and t.

where n is the number of doses of size a_o. By similar derivations the equations describing b and u in this general case become

$$b = \frac{k_a}{k_d - k_a}\left[\left(A_o e^{-nk_a\tau} + a_o\frac{1 - e^{-nk_a\tau}}{1 - e^{-k_a\tau}}\right)e^{-k_a t} - \left(A_o e^{-nk_d\tau} + a_o\frac{1 - e^{-nk_d\tau}}{1 - e^{-k_d\tau}}\right)e^{-k_d t}\right] \quad \text{(Eq. 11)}$$

$$u = \frac{k_e}{k_d}\left[A_o + na_o - \frac{k_d}{k_d - k_a}\left(A_o e^{-nk_a\tau} + a_o\frac{1 - e^{-nk_a\tau}}{1 - e^{-k_a\tau}}\right)e^{-k_a t} + \frac{k_a}{k_d - k_a}\left(A_o e^{-nk_d\tau} + a_o\frac{1 - e^{-nk_d\tau}}{1 - e^{-k_d\tau}}\right)e^{-k_d t}\right] \quad \text{(Eq. 12)}$$

If the initial dose was the same as all successive doses ($A_o = a_o$) Eq. 11 reduces to the form given by Dost (4) for the case of equal doses administered at equal time intervals

$$b = \frac{a_o k_a}{k_d - k_a}\left[\left(\frac{1 - e^{-n'k_a\tau}}{1 - e^{-k_a\tau}}\right)e^{-k_a t} - \left(\frac{1 - e^{-n'k_d\tau}}{1 - e^{-k_d\tau}}\right)e^{-k_d t}\right] \quad \text{(Eq. 13)}$$

where n' is the number of doses given ($n' = n + 1$). Similar reduction of Eq. 12 can be made, giving

Equation 11 reduces to $b = 0$ at infinite time, which would be expected since the drug is no longer in the body. Equation 12 reduces at infinite time to $u = \frac{k_e}{k_d}(A_o + na_o)$, which indicates that the fraction of the total dosage administered which appears in the urine is a function of the rate of excretion compared to the sum of the excretion and metabolism rates.

According to the nomenclature used above, the fraction of drug in compartment b at the time of administration of the first dose of size a_o is given by substitution of $n = 0, t = \tau$ in Eq. 11. Substitution of $n = \infty, t = \tau$ in the same equation gives the minimum value of b after sufficient doses of size a_o such that the effect of the initial dose A_o is negligible. From these two equations the ratio A_o/a_o can be obtained as

$$\frac{A_o}{a_o} = \frac{1}{(1 - e^{-k_a\tau})(1 - e^{-k_d\tau})} \quad \text{(Eq. 15)}$$

This is the same form as given by Krüger-Thiemer (8) for the ratio of initial dose to supporting dose such that the blood drug levels obtained at time τ after the initial dose will be maintained. The blood levels at any time can be calculated from the expression $c = b/V_d'$, where c = drug concentration in blood (mg./L.) and V_d' = specific volume of distribution (L./Kg.) if dose is in units of mg./Kg., and substituting b from Eq. 11 to give

$$u = a_o\frac{k_e}{k_d}\left[n' - \frac{\{k_d[(1 - e^{-n'k_a\tau})/(1 - e^{-k_a\tau})]e^{-k_a t} - k_a[(1 - e^{-n'k_d\tau})/(1 - e^{-k_d\tau})]e^{-k_d t}\}}{k_d - k_a}\right] \quad \text{(Eq. 14)}$$

$$c = \frac{k_a}{V_d'(k_d - k_a)}\left[\left(A_o e^{-nk_a\tau} + a_o\frac{1 - e^{-nk_a\tau}}{1 - e^{-k_a\tau}}\right)e^{-k_a t} - \left(A_o e^{-nk_d\tau} + a_o\frac{1 - e^{-nk_d\tau}}{1 - e^{-k_d\tau}}\right)e^{-k_d t}\right] \quad \text{(Eq. 16)}$$

METHODS AND RESULTS

Riboflavin U.S.P. in finely divided form was used in this study. Suspensions were freshly prepared in deionized water at a concentration of 10 mg. riboflavin per 50 ml. Each subject drank the appropriate amount of suspension at the indicated interval, rinsing the container with several smaller portions of water to insure consumption of the total dose.

Ten apparently healthy adults were used as subjects. The subjects were placed on a semi-restricted diet, refraining from eggs, liver, and vitamin supplements for one day preceding the test and the two-day test period. On test 996 the diet was more closely controlled. No food, other than a 200-ml. portion of vegetable puree at 2-hour intervals, was consumed during the critical 12-hour Wednesday test period. This test was included to check the effect of diet in the first two experiments where the subjects were allowed to consume the foods of their choice with the exceptions previously mentioned. A 9.9-mg. or 10-mg. dose of riboflavin, divided as outlined in Table I, was used in the study.

The test periods began Tuesday morning at 8:15 and lasted through 8:15 on Thursday morning. On the first day, all the urine accumulated up to 8 hours and from 8 to 24 hours after the start of the test was collected and used to obtain the base riboflavin excretion level for each individual. Wednesday morning at 8:15 a.m. the first dose of the test series was taken. Subsequent doses were taken as indicated in Table I. Urine was collected at the time intervals shown in Table I during each experiment. The urine was collected in amber glass bottles, the volume measured, and aliquots stored at 4° until assayed.

The urine was assayed for riboflavin by the U.S.P. fluorometric method (10). The base value for each individual was subtracted from the riboflavin levels obtained after the ingestion of the test preparation to determine the net amount of riboflavin excreted. The excretion data obtained are presented in Table I.

The data in Table I were analyzed using Eq. 12. In this equation for total amount of drug in urine the parameters A_o, a_o, n, τ, and t are known for any single value of u reported. Because the average fraction of the total dose excreted within 24 hours in the three experiments was 0.50, this value of the ratio k_e/k_d was used. Thus, only k_a and k_e remained to be determined. This was done by assuming values for these constants and evaluating Eq. 12 at each time a urine sample was collected. The sum of the squares of the differences between the observed and calculated values of u was obtained. An IBM 1620 digital computer was used for the calculations. The constants k_a and k_e which minimized this sum of squares were $k_e = 0.123$ hr.$^{-1}$ and $k_a > 30$ hr.$^{-1}$. Values of k_a as great or greater than 30 hr.$^{-1}$ are not meaningful in this application because they indicate that absorption is 95% complete in a tenth of an hour or less.

The mean cumulative urinary riboflavin levels are shown in Fig. 1 for each of the three experiments with the curves calculated according to Eq. 12 with $k_a = 30$ hr.$^{-1}$, $k_e = 0.123$ hr.$^{-1}$, $k_d = 0.246$ hr.$^{-1}$ and other constants as given by Table I.

The theoretical levels of drug in compartment b during the 24-hour duration of the experiment can be calculated from Eq. 11 without further assumptions, and are shown in Fig. 2.

DISCUSSION

The applicability of Eq. 12 to the riboflavin excretion data depends primarily on the assumption of apparent first order kinetics of riboflavin excretion. This kinetic order is substantiated by the riboflavin excretion data of Axelrod, *et al.* (11), and Najjar and Holt (12), obtained after single doses of the drug. First order excretion is also consistent with the finding of Morrison and Campbell (13) that the per cent of dose excreted is constant over the 1 to 20 mg. range of oral doses.

The fraction of the total dose excreted appears from our data to be independent of how the total dose is divided or at what interval the individual doses are administered. This is similar to the findings of Chapman and Campbell (14) and Morrison and Campbell (13), who reported equal recovery of riboflavin in urine after single or divided oral dosage.

TABLE I.—URINARY RIBOFLAVIN EXCRETION IN HUMAN SUBJECTS

Time Interval, hr.	Total Riboflavin (mg.) Excreted During Indicated Interval (Mean ± S.D.)[a] Test 800: 5.0 mg. at $t = o$ and 1.0 mg. every hour for 5 doses	Test 801: 2.4 mg. at $t = o$ and 1.5 mg. every 2 hours for 5 doses	Test 996: 2.4 mg. at $t = o$ and 1.5 mg. every 2 hours for 5 doses
0–1	0.62 ± 0.34		
1–2	0.68 ± 0.20		
0–2		0.53 ± 0.13	0.58 ± 0.13
2–4	1.11 ± 0.31	0.66 ± 0.17	0.45 ± 0.07
4–6	0.70 ± 0.32	0.51 ± 0.19	0.53 ± 0.19
6–8	0.68 ± 0.28	0.61 ± 0.12	0.61 ± 0.14
8–10		0.89 ± 0.18	0.77 ± 0.16
10–12		0.65 ± 0.29	0.73 ± 0.18
8–12	0.56 ± 0.18		
12–24	0.60 ± 0.11	1.13 ± 0.36	1.23 ± 0.33

[a] Each value is based on the mean of 10 subjects.

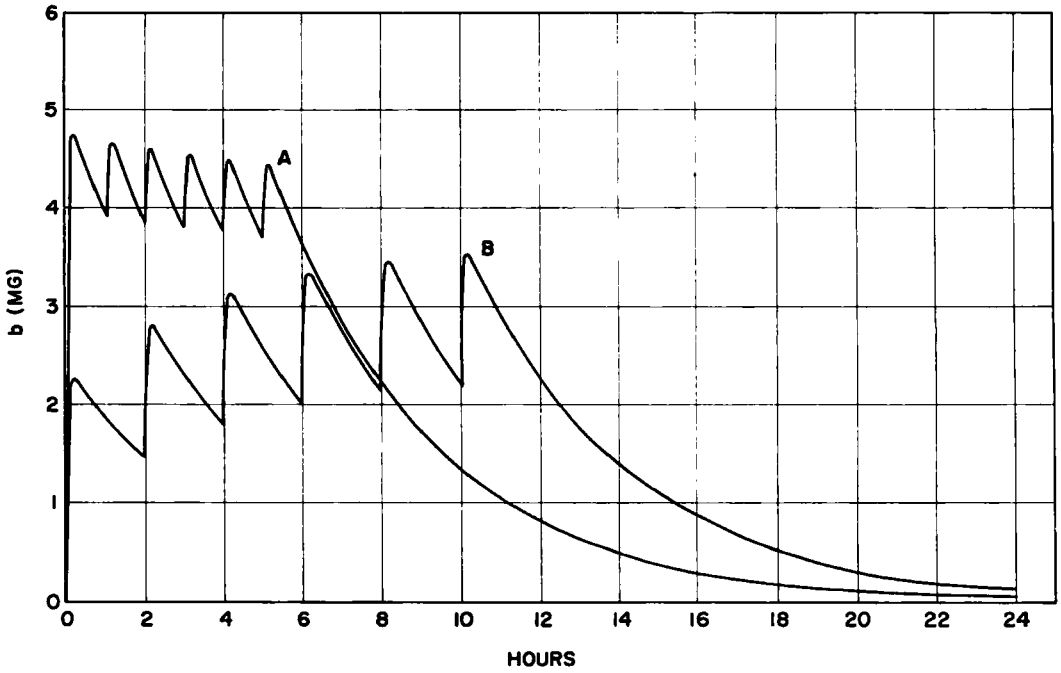


Fig. 2.—Amount of riboflavin in the body (b) as calculated from Eq. 11 with k_d = .246 hr.$^{-1}$ and k_a = 30 hr.$^{-1}$. In curve A, A_0 = 5 mg., a_0 = 1 mg., τ = 1 hr., and $n_{max.}$ = 5. In curve B, A_0 = 2.4 mg., a_0 = 1.5 mg., τ = 2 hr., and $n_{max.}$ = 5.

The shape of the excretion curve calculated from Eq. 12 during any time period τ is convex, rising more rapidly during the first part of the period than later. This is because riboflavin appears to be rapidly absorbed, causing higher blood levels early in the period (see Fig. 2), and thus more rapid excretion than occurs toward the end of the interval. For drugs which are slowly absorbed the shape of the excretion curve would be sigmoid, with the inflection occurring at the time of peak blood concentration.

More apparent in this type experiment than the shape of the excretion curve in the interval τ is the shape over the period of the whole experiment. If blood levels of drug are higher after each successive dose (due to a low dose ratio, A_0/a_0) the general shape of the excretion curve will be concave, rising more steeply during each successive interval. This is the shape of the lower curve in Fig. 1 where the dose ratio was 1.6. If blood levels of drug are lower after each successive dose due to a high dose ratio, a generally convex excretion curve will result. This is the case in test 800 in which the dose ratio was 5.0.

Absorption rate, as well as kinetic order, is best determined by the shape of the curve in the time period in which absorption is occurring. In these experiments urine samples over the period of drug administration were emphasized rather than consecutive samples after a single administration. Thus, the shape of the curves obtained from the data in Table I are primarily determined by the dose ratio and the time interval between doses. This does not mean that absorption rate cannot be calculated from this type experiment. In theory it can be calculated under any combination of dosage variables, but in practice a precise measure is best obtained using Eq. 12 when absorption is not essentially complete in the interval between doses.

The equations derived for blood and urine drug levels after an initial dose different from the remaining doses reduce to the forms given in the literature for more specific cases. Equation 13, which gives the values of b after all equal doses at equal time intervals, is the same as that of Dost (4) except for nomenclature. This equation, for the case of intravenous administration ($k_a = \infty$) considered by Boxer, *et al.* (6), simplifies to $b = a_0(1 - e^{-n'k_d\tau})\, e^{-k_d t}/(1 - e^{-k_d\tau})$. Neglecting distribution of drug immediately after injection, the ratio of the value of b when equilibrium is established, b_∞, ($n' = \infty$), to its value in the first period, b_1, ($n' = 1$), is $b_\infty/b_1 = 1/(1 - e^{-k_d\tau})$. This is the expression given by Boxer, *et al.*

Considering the more cymplicated case in which the initial dose is different than successive doses and in which drug is administered orally, the blood levels (c in Eq. 16) or fraction of drug in the body (b in Eq. 11) after a large number of doses such that equilibrium is established can be calculated from the equations after substitution on $n = \infty$ and simplifying. Thus, Eq. 16 simplifies to the form of Eq. 13 and is similar to the treatment of Boxer, *et al.* (6), except that k_a is not large enough to make the exponential terms containing it zero. Maximum and minimum values of blood concentration are then given by the equations

$$c_{max.} = \frac{a_0 k_a}{V_d'(k_d - k_a)} \left[\frac{e^{-k_a t_{max.}}}{1 - e^{-k_a\tau}} - \frac{e^{-k_d t_{max.}}}{1 - e^{-k_d\tau}} \right] \quad \text{(Eq. 17)}$$

where

$$t_{max.} = ln \frac{\left[\frac{k_d(1 - e^{-k_a\tau})}{k_a(1 - e^{-k_d\tau})}\right]}{k_d - k_a} \quad \text{(Eq. 18)}$$

and

$$c_{min.} = \frac{a_o k_a}{V_d'(k_d - k_a)} \left[\frac{e^{-k_a\tau}}{1 - e^{-k_a\tau}} - \frac{e^{-k_d\tau}}{1 - e^{-k_d\tau}}\right] \quad \text{(Eq. 19)}$$

Equations 17 and 18 are identical to the equations derived by Dost (4) for all equal doses because as n approaches infinity the effect of the initial dose on equilibrium blood levels disappears. Equation 19 differs from the equation given by Dost for minimum blood levels only by the exponential factors in the numerators, and reduces directly to the form given by Dost. Equation 19 also reduces to a form similar to the expression given by Swintosky, *et al.* (7), for minimum blood levels when k_a is large. However, Swintosky uses one extrapolated value for $a_o k_a / V_d'(k_d - k_a)$ into which he also combines the absorption terms. Swintosky arrives at his equation for $c_{max.}$ by similar means.

The dose ratio, A_o/a_o, which will maintain a minimum blood level equal to that existing at time τ after the first dose, A_o, is given in Eq. 15. This has been given by a different derivation by Krüger-Thiemer (8), who suggested its clinical application for cases in which k_a is large and $\tau = t_{1/2}$, the half-life of drug disappearance, whereby the dose ratio becomes 2. When k_a is large such that absorption is complete in the interval τ, the equilibrium minimum blood level obtained after many doses is also obtained after the first dose, resulting in a plateau effect (15). From Eq. 16 the effect of repeated doses before absorption of the previous dose is complete is found to be an increase in both maximum and minimum blood levels above the equilibrium values. These higher blood concentrations decrease to the equilibrium values when n becomes large. Thus the dose ratio given by Krüger-Thiemer will not give the plateau effect desired if the product $k_a\tau$ is not large, although minimum drug concentrations will be maintained.

The equations given above should be useful in the interpretation of blood drug concentration or cumulative drug urine level data obtained after the common dosage regimen of one large dose and subsequent equal smaller doses at equal time intervals. Such experiments are useful in determining that the calculated dosage regimen is optimal, and the analysis of the results according to the appropriate equation should allow an assessment of what actually occurred. The equations in their general form are also useful for the derivation of simpler forms by substitution of the appropriate limiting assumptions.

SUMMARY

1. General mathematical equations have been derived to analyze plasma concentration or urinary excretion data obtained when a drug is given as one large dose followed by successive equal small doses at equal time intervals.

2. The validity of the urinary excretion equation has been demonstrated by fitting the equation to urinary excretion data from human subjects. Assuming first-order kinetics, the absorption, disappearance, and excretion constants of riboflavin were found to be: $k_a = 30$ hr.$^{-1}$, $k_d = 0.25$ hr.$^{-1}$, and $k_e = 0.12$ hr.$^{-1}$.

3. The disappearance rate was found to be the controlling factor for sustaining riboflavin levels. In the case of riboflavin, absorption is almost immediate and an accurate measure of the absorption rate was not made.

4. Expected maximum and minimum blood levels can be calculated when the necessary rate constants and volume of distribution are known.

5. The equations presented reduce to simpler expressions found in the literature by substituting appropriate limiting functions.

6. These equations allow calculation of the ratio of the initial dose to subsequent smaller doses given at equal time intervals which will maintain a relatively constant blood level. Such calculations can be applied to find the optimum dosage regimen of any drug for which the absorption, excretion, and disappearance constants are known.

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