Kinetic Analysis of Blood Levels and Urinary Excretion in the Absorptive Phase after Single Doses of Drug

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The use of per cent absorbed *versus* time plots to elucidate kinetic models for drug absorption is described. The following kinetic models, which are illustrated with experimental data, are considered: absorption by a zero-order process, by two zero-order processes operating in parallel, by a first-order process, by two parallel first-order processes, and by simultaneous zero-order and first-order processes.

THE MATHEMATICAL description of blood, serum, or plasma drug concentration and time data and data on amounts of drug excreted in various times is receiving increased attention by academic, clinical, and industrial researchers. The industrial phamacist, in particular, is faced with the task of devising methods which hopefully will allow him to predict from *in vitro* measurements the characteristic of a product with respect to the rate and extent it releases the active ingredient contained for absorption. This may require him to make measurements *in vivo* that allow him to describe absorption rate as a function of time and interpret these in a manner consistent with the physiological reality of the *in vivo* system studied. Although the intact animal may seem to be a system too complex for any interpretation of experimental data except gross ones, this is not necessarily the case. Once data are described in mathematical terms within the experimental error of the measurements, they become subject to interpretation which must be consistent with the physiological reality of the system and the physical-chemical, physical, and pharmaceutical characteristics of the product administered.

Several parameters have been used to estimate rate of drug absorption when a drug is administered in pharmaceutical dosage forms. Rate of absorption has been assessed by time of appearance of measurable blood level, time of appearance of maximum blood, serum, or plasma levels, amount of drug or drug metabolite excreted in the urine in a given time or time of appearance of maximum urinary excretion rate. All of these parameters give only qualitative indication of rate of drug absorption because they are only indirectly related to rate. Quantitative methods for estimating rate of absorption have been developed by Dominguez (1) and Nelson (2). The method of Dominguez is applicable to blood, serum, or plasma level *versus* time data and the method of Nelson to urinary excretion rate *versus* time data. Among other quantities, the method of Dominguez requires knowledge of the apparent volume of distribution; the method of Nelson requires knowledge of the fraction of a dose excreted as unchanged drug, the fraction of the dose absorbed, and the derivative of excretion rate *versus* time data. These parameters may be difficult to obtain with accuracy.

Recently (3), modifications of the methods of Dominguez (1) and of Nelson (2) have been described which greatly simplify calculation of drug absorption rate because values of per cent of total absorption are obtained. Use of these equations does not require a knowledge of a drug's volume of distribution, what fraction of a dose is absorbed, or the fraction of the dose absorbed that is excreted as unchanged drug.

It is the purpose of this paper to illustrate the applicability of these expressions in elucidating kinetic models that describe the various processes by which drugs may be absorbed. While it may not be possible always to determine the kinetics of the absorption process, sufficient data are available to illustrate the usefulness of the methods. Equation 1 is for blood, serum, or plasma level *versus* time data, and Eq. 2 is for urinary excretion data. The derivation of these expressions is given in the *Appendix*. In Eq. 1, A_T is the cumulative amount of drug absorbed from time zero to time T in any convenient units, A_∞ is the amount

$$\% \text{ absorbed} = \frac{A_T}{A_\infty} \times 100 = \frac{C_T + K\int_{t=\infty}^{t=T} C\,dt}{K\int_{t=0}^{T=\infty} C\,dt} \times 100 \quad \text{(Eq. 1)}$$

$$\% \text{ absorbed} = \frac{A_T}{A_\infty} \times 100 = \frac{(1/K)\cdot(dX_u/dt) + X_u}{(X_u)_\infty} \times 100 \quad \text{(Eq. 2)}$$

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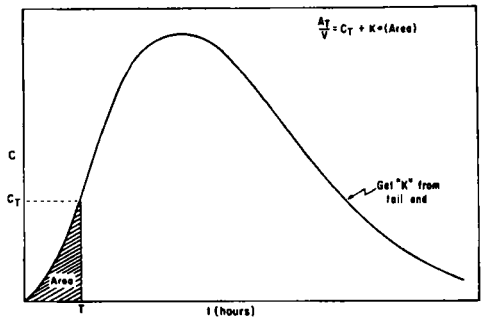


Fig. 1.—Illustrates graphically the operations necessary to obtain A_T/V (*i.e.*, the cumulative amount absorbed per unit volume of the apparent volume of distribution between time zero and time T) from blood level data.

eventually absorbed in the same units, K is the over-all rate constant for elimination from blood, etc., in reciprocal time, and C_T is blood, serum, or plasma concentration at time T. In Eq. 2, A_T, A_∞, and K have the same meanings as in Eq. 1; dX_u/dt is urinary excretion rate at time T, and X_u is the cumulative amount excreted in the same time. The method for using Eqs. 1 and 2 and the assumptions on which they are based have been described previously (3). However, their use is best illustrated by simulated blood level *versus* time curves and cumulative amount excreted *versus* time curves.

Figure 1 shows a hypothetical blood level *versus* time curve with various markings which will be used to illustrate the application of Eq. 1. The vertical line delineates an area under a blood level *versus* time curve from $t = 0$ to $t = T$ on the abscissa of the graph. These areas may be estimated by planimetry or by use of the trapezoidal rule. It is only necessary to multiply each of these cumulative areas by the value of K, as determined by well-known procedures (4), and add to each the value of blood concentration at corresponding times to obtain the cumulative amount absorbed per unit volume of the apparent volume of distribution. This is continued until a maximum or asymptotic value is obtained which is divided into the value obtained at earlier times to obtain per cent absorbed *versus* time data.

Figure 2 is a plot of cumulative amount of drug excreted *versus* time. Excretion rate values from curve in Fig. 2 are selected at various times (obtained from the slope of the curve as shown on the figure) and divided by K and added to the amount excreted in the same time as determined from the cumulative excretion curve. A maximum or asymptote will be obtained; when this quantity is obtained, division of it into the values of the quantities obtained at earlier times will give the per cent absorbed at various times in accord with Eq. 2.

Cases of Recycling via the Enterohepatic Cycle.—It is known that some drugs may be absorbed *via* the gastrointestinal tract, pass *via* the portal vein to the liver, and then be partially excreted *via* the bile back into the intestinal contents. Part or all of this drug may then be reabsorbed; some of it may be excreted in the feces.

In such cases the serum (or plasma) level–time plot may have a major maximum and a minor maximum or a major maximum and a shoulder rather than the usual exponential fall-off, beginning shortly following a single maximum in the plot. When the per cent absorbed time plot is derived from such a set of data, the cumulative per cent absorbed values may rise progressively, then decrease for a time, then increase again. At first glance this may appear to be inconsistent. However, we define rate of absorption as the rate of appearance of unchanged drug in the volume of distribution. This rate may be negative if the rate of efflux of drug from the blood back into the tract is greater than the rate of influx of drug from the tract to the blood. The latter can occur at certain times when recycling *via* the enterohepatic cycle takes place to a marked degree. In these cases it may be best to define the slope of the cumulative per cent absorbed–time plot calculated by the method of Wagner and Nelson (3) as the net flux across the gastrointestinal barrier, which is the result of influx from the tract to the blood and efflux from the blood and/or bile back into the tract. This takes care of the apparent inconsistency that the cumulative per cent absorbed can be less than it has been at earlier times, then gradually increase again.

Kinetic Models.—The kinetics of absorption, distribution, metabolism, and excretion of drugs can be adequately described by multicompartment models if unchanged drug is measured in the blood or in the urine, and measurements are made during the absorption phase. Differential equations and their solutions which depend upon the assumption that amount of drug, and not concentration of drug, is the

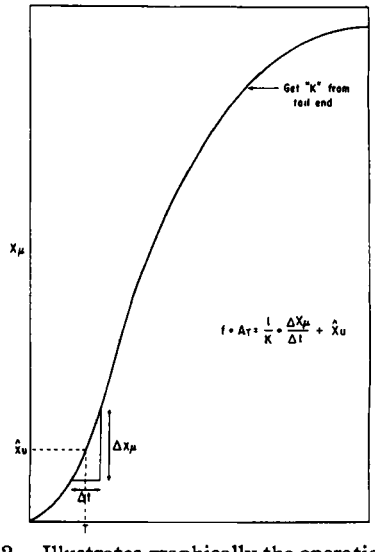


Fig. 2.—Illustrates graphically the operations necessary to obtain A_T/V (*i.e.*, the cumulative amount absorbed per unit volume of the apparent volume of distribution between time zero and time T) from a plot of cumulative amount of unchanged drug excreted in the urine against time.

driving force also are applicable to these kinetics. This is true since the assumption also is applicable to these kinetics. The assumption and definitions used herein include the following concepts: (*a*) only the volume of one compartment—namely, the apparent volume of distribution—is involved; (*b*) the rate of absorption is defined as the rate of appearance of ***unchanged*** drug in the apparent volume of distribution in amount/unit time, or per cent of total drug absorbed/unit time; hence, although the driving force may be the concentration in the intestinal contents, the volume of the intestinal content does not enter into the calculations and may be ignored; (*c*) the amount of unchanged drug excreted in the urine in a given time is the quantity measured and used in the kinetic calculations; hence, the volume of the urine is of importance only in the estimation of the amount of drug in the urine.

The apparent volume of distribution, V, is simply the number by which to multiply the plasma, serum, or whole blood concentration, so that there is material balance according to Eq. 3.

$$C_T V = A_T - E_T - M_T \qquad \text{(Eq. 3)}$$

where C_T is the plasma, serum, or whole blood concentration of unchanged drug at time T, A_T is the cumulative amount of unchanged drug absorbed to time T, E_T is the cumulative amount of unchanged drug which has been eliminated in the urine to time T, and M_T is the cumulative amount of drug metabolized to time T. No physical significance should be assigned to V since part of the drug in the volume, V, may be bound to protein or stored temporarily in one particular organ. Also, it is obvious that depending upon whether plasma, serum, or whole blood concentration is measured, the value of V will change even though everything else is held constant.

As previously explained, the method of calculation using blood (serum or plasma) unchanged drug concentration data involves estimation of A_T/V at various times after administration of the dose. The maximum or asymptotic value of A_T/V, $(A_T/V)_{max.}$ is FD/V, where F is the fraction of the dose absorbed and D is the dose. Hence, FD is the amount of drug absorbed and FD/V is the amount of drug absorbed per unit of apparent volume of distribution in concentration units. By the method of calculation one never knows the absolute values of F or V but the value of FD/V is obtained. This value is comparable to, but not the same as, the C_0 obtained by extrapolating a semilogarithmic plot of blood level against time. The C_0 obtained by such a method is an approximation (and frequently a poor one) for the desired value FD/V. Due to the relationship

$$FD = VK \int_{t=0}^{t=\infty} C dt \qquad \text{(Eq. 4)}$$

where K is the first-order rate constant for loss of drug from the volume of distribution, and the integral is the area under the blood level curve from time zero to time infinity, we have

$$\frac{FD}{V} = K \int_{t=0}^{t=\infty} C dt \qquad \text{(Eq. 5)}$$

Equation 5[1] provides a method of checking the value of FD/V obtained from the A_T/V *versus* time plot if sufficient blood samples are taken. Once the exponential fall-off of C with t is established, the area for the tail end of the C *versus* t plot can be estimated by

$$C = C_0 \exp[-Kt] \qquad \text{(Eq. 6)}$$

which describes this part of the blood concentration *versus* time curve. In Eq. 6, C is blood, etc.; concentration at time t and C_0 is defined below. If t' is the time when the exponential fall-off of blood concentration begins, and $C_{t'}$ is the blood concentration at this time, then the area under the blood concentration *versus* time curve from t' to t_∞ is given by

$$\int_{t=t'}^{t=\infty} C dt = \int_{t=t'}^{t=\infty} C_{t'} \exp[-K(t-t')] dt = \int_{t=\infty}^{t=t'} C_0 \exp(-Kt) dt = \frac{C_0}{K} \exp(-Kt') \qquad \text{(Eq. 7)}$$

where $\ln C_0 = \ln C_{t'} + Kt'$. This area must be added to the area under the C, t plot from $t = 0$ to t' to yield the area $\int_{t=0}^{t=\infty} C dt$.

Hence

$$\frac{FD}{V} = K \int_{t=0}^{t=\infty} C dt = K \left[\int_{t=0}^{t=t'} C dt + \int_{t=t'}^{t=\infty} C dt \right] \qquad \text{(Eq. 5a)}$$

If sufficient blood samples are taken during the interval $t = 0$ to $t = t'$, then the middle integral of Eq. 5a may be estimated with good accuracy using the trapezoidal rule. Also, as a consequence of the foregoing, the following theoretical relationship holds:

$$\frac{FD}{V} = \left(\frac{A_T}{V}\right)_{max.} = K \int_{t=0}^{t=\infty} C dt = C_{t'} + K \int_{t=0}^{t=t'} C dt \qquad \text{(Eq. 8)}$$

Variability of Blood Level and Urinary Excretion Data.—True variability of blood level and urinary excretion data may be attributed to the following factors: (*a*) assay error, (*b*) biological variation (*i.e.*, variation in V, f, F, and K) not only from subject to subject but also for a given subject from drug to drug or with a given drug, and (*c*) dosage form effects (*i.e.*, variation in F and dA/dt) not only from subject to subject tested with the same formulation of the same drug but also for a given subject from day to day with the same formulation.

Apparent variability of blood level and urinary excretion data may be attributed to (*a*) using a time interval too long for excretion rate measurement, (*b*) using the wrong mathematical method with a particular set of data (the mathematical method may be wrong since the method is based on certain assumptions which are invalid for the particular set of data being evaluated), (*c*) using the wrong criterion to estimate variability.

When comparing urinary excretion data with blood level data, blood (serum or plasma) levels must be measured at the midpoints of the urinary collection intervals to expect the proper equation to apply.

[1] Or its equivalent, Eq. 5a.

The correlation of excretion rate with blood levels must be done for each subject independently, since the theoretical relationship (4) indicates the slope of the straight line relating these variables will be KfV, and this will vary from subject to subject. Furthermore, this equation is true only where free unchanged drug is measured in the blood and the urine. Hence, if excretion rate does not correlate linearly with blood level when one measures, for example, a radioactive tracer such as tritium, etc., one should not blame the mathematical method. For example, the conclusion that, "The urinary excretion of both drugs varied widely among individuals, indicating this parameter is limited in value as a reflection of oral absorption," which has been made (5) was not justified on the basis of the evidence the authors presented. The authors measured tritium radioactivity in blood and urine; hence, one would expect that there may not be a quantitative relationship between urinary excretion rate and plasma level. Their first excretion interval of 0 to 4 hours was too large and probably covered all the absorption phase or even more, especially for phenylephrine hydrochloride. They could have compared the serum levels at 2 hours, with excretion in the 0 to 4-hour interval (since only in this instance were the serum levels at the midpoints of the excretion intervals); yet they failed to do so. They did not calculate per cent standard deviations—the most valid way to compare variability when the averages and dimensions of that which one is comparing are different. In fact, the per cent standard deviations calculated from their data (5) in Tables II and III were 49.7% for the plasma levels at 10 hours and 47.1% for the urinary excretion in the 8- to 12-hour interval for phenylephrine given as the hydrochloride, and 25.9% and 28.6%, respectively, for phenylephrine given as the tannate. In each pair, these are of the same order of magnitude. Another factor not recognized was that drug metabolites are usually eliminated more rapidly than they are formed. Hence, in the nonspecific assay used, no correlation between drug blood level and urinary excretion rate should be expected.

Correlation of excretion rate and serum level of tetracycline in three normal humans has been reported recently (6). The experimental design and mathematical methods need not be repeated here; the reader is referred to that paper for the details. In this particular set of experiments, it was necessary to carry out three assays on each serum sample to obtain about the same accuracy and precision as one obtains with a single urine assay.

Rate of urinary excretion of unchanged drug is given by (4)

$$\frac{dX_u}{dt} = KfVC \qquad \text{(Eq. 9)}$$

where dX_u/dt is urinary excretion rate, and f is the fraction of a dose eventually excreted unchanged in the urine, and the other terms have their usual meaning. Integration of Eq. 9 between the limits $t=0$ and $t=\infty$ and transposition of the f term gives

$$\frac{(X_u)_\infty}{f} = VK\int_{t=0}^{t=\infty} Cdt \qquad \text{(Eq. 10)}$$

Hence, another possible test of the variability of urinary excretion and blood levels is to compare the per cent standard deviation of $(X_u)_\infty$ and of $K\int_{t=0}^{t=\infty} Cdt$ obtained with a panel of known subjects in whom these quantities could be estimated at the same time. Experiments of this type were recently carried out at the organization with which one of the present authors (7) is affiliated using commercial capsules of tetracycline hydrochloride and a panel of eight male adults. The per cent standard deviation was 23.0% for $(X_u)_\infty$ based on 96-hour urinary excretion, 36.9% for the asymptotic value of $C_T + K\int_{t=0}^{t=T} Cdt$ (which is theoretically equivalent to $K\left(\int_{t=0}^{t=\infty} Cdt\right)$ in one experiment, 36.0% for $(X_u)_\infty$ based on 96-hour urinary excretion, and 24.3% for the asymptotic value of $C_T + K\int_{t=0}^{t=T} Cdt$ obtained in the second experiment. From these data one could *not* conclude that urinary excretion data were less reliable indices of physiological availability than blood level data.

Physiological Availability.—Oser and his associates (8) introduced the concept of physiological availability. They defined physiological availability as

$$\%\ \text{availability} = \frac{\%\ \text{of dose excreted in given time after test dose}}{\%\ \text{of dose excreted in same time after aqueous solution of drug is taken}} \times 100 \qquad \text{(Eq. 11)}$$

It is important to collect urine for a period long enough that essentially all drug excreted is collected. Otherwise, the estimated availability will be erroneous.

A more generalized equation for calculating physiological availability is

$$\%\ \text{availability} = \frac{\text{amount (or \%) absorbed after test dose}}{\text{amount (or \%) absorbed following the same dose in most readily available form}} \times 100 \qquad \text{(Eq. 12)}$$

Wagner *et al.* (9) showed that physiological availability could be estimated from blood level data as well as from urinary excretion data. Although the example utilized Eq. 8, the calculation was unnecessarily complicated by estimation of V in the individual subject by extrapolation of a plot of the logarithm of C against t.

If a crossover study is carried out in a panel of humans in which one or more test formulations of a given drug is compared with a readily available form of the drug, then the methods for estimating physiological availability are

Method 1:

$$\% \text{ availability} = \frac{\text{Average asymptotic value of } C_T + K\int_{t=0}^{t=T} Cdt \text{ for test preparation}}{\text{Average asymptotic value of } C_T + K\int_{t=0}^{t=T} Cdt \text{ for the readily available preparation}} \times 100 \quad \text{(Eq. 13)}$$

Method 2:

$$\% \text{ availability} = \frac{\text{Asymptotic value of } C_T + K\int_{t=0}^{t=T} Cdt \text{ calculated from average blood levels for test preparation}}{\text{Asymptotic value of } C_T + K\int_{t=0}^{t=T} Cdt \text{ calculated from average blood levels for readily available preparation}} \times 100 \quad \text{(Eq. 14)}$$

Method 3:

$$\% \text{ availability} = \frac{\text{Asymptotic value of } \frac{1}{K}\frac{dX_u}{dt} + X_u \text{ for test preparation}}{\text{Average asymptotic value of } \frac{1}{K}\frac{dX_u}{dt} + X_u \text{ for readily available preparation}} \times 100 \quad \text{(Eq. 15)}$$

Method 4:

$$\% \text{ availability} = \frac{\text{Asymptotic value of } \frac{1}{K}\frac{dX_u}{dt} + X_u \text{ calculated from average amounts excreted for test preparation}}{\text{Asymptotic value of } \frac{1}{K}\frac{dX_u}{dt} + X_u \text{ calculated from average amounts excreted for readily available preparation}} \times 100 \quad \text{(Eq. 16)}$$

Method 5:

$$\% \text{ availability} = \frac{\text{Average } (X_u)_\infty \text{ for test preparation}}{\text{Average } (X_u)_\infty \text{ for readily available preparation}} \times 100 \quad \text{(Eq. 17)}$$

Method 6:

$$\% \text{ availability} = \frac{\text{Average } \int_{t=0}^{t=\infty} Cdt \text{ for test preparation}}{\text{Average } \int_{t=0}^{t=\infty} Cdt \text{ for readily available preparation}} \times 100 \quad \text{(Eq. 18)}$$

Method 7:

$$\% \text{ availability} = \frac{\int_{t=0}^{t=\infty} Cdt \text{ calculated from average blood levels of test preparation}}{\int_{t=0}^{t=\infty} Cdt \text{ calculated from average blood levels of readily available preparation}} \times 100 \quad \text{(Eq. 19)}$$

Method 5, which is equivalent to the method of Oser and associates (8), requires collection of urine for approximately seven to ten biological half-lives of the particular drug involved. Urine must be collected for this interval of time to ensure collection of about 99% of the unchanged excreted drug. *Methods 6* and *7* require blood samples to be collected at intervals frequent enough and for a time long enough that there is obtained a good estimate of the area under the blood level–time curve from zero time to the time that the blood level is no longer measurable. *Methods 3* and *4* require that urine be collected only during the absorption phase, provided K is known. *Methods 1* and *2* require that blood samples be collected only during the absorption phase, provided K is known.

Usually, but not always, the asymptotic value of $C_T + K\int_{t=0}^{t=T} Cdt$ will be reached at, or shortly after, the peak of the *C versus t* plot. A pilot experiment will usually determine whether this is true for the particular formulation under study. If a pilot experiment is conducted first, one cannot only estimate K for the particular drug but also establish a reasonable blood and urine sampling scheme which is applicable to the particular drug and formulations. The most important blood and urine samples are those between the time of administration and the time when the maximum blood level is reached and those taken in the terminal part of the blood level–time plot or cumulative urinary excretion–time plot. The absorption phase is covered by the first group of samples and the value of K obtained from the latter group of samples. Hence, often a reduction or elimination of several blood or urine samples can be made between the time of the peak blood level and the time the blood or urine levels become essentially zero. Unfortunately, most blood level data reported in the literature were obtained with such sampling schedules that most of the results fall in the latter range.

If unchanged drug is measured in the blood and urine, then all seven methods above should give, within experimental error, the same estimate of physiological availability. Large deviations between the percentage obtained by different methods of calculations, say about 20%, should lead to the suspicion that one or more of the assumptions involved in making one or more of the estimates is invalid for the particular set of data.

Biological Examples.[2]—The first example in this

[2] Averaged data are used in fitting to various equations discussed. This may lead to errors in interpretation of the kinetic model which actually holds (11). This consideration is only important when wide variation in rate constants occurs in test subjects (12). Extremely large variations did not occur in the cases illustrated. However, the definitive test of the correctness of a given kinetic model lies in the demonstration that the individual rather than the average data obey the model.

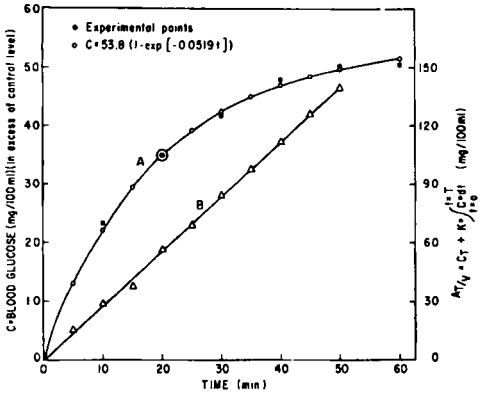


Fig. 3.—Curve A is a plot of blood glucose level against time taken from Jokipii and Turpeinen (10). The solid line is the one described by the equation A_T/V, and the solid dots are the experimentally observed values. Line B is a plot of A_T/V against time calculated according to the method described in the text.

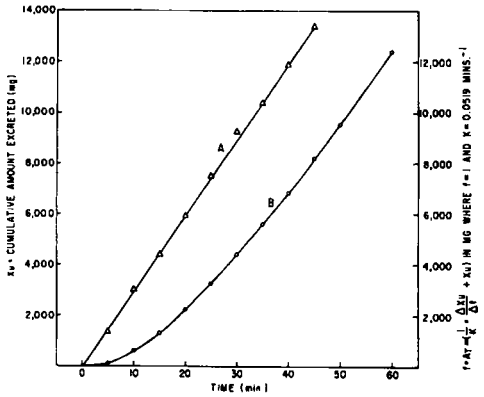


Fig. 4.—Agreement between theoretically predicted infusion rate of glucose calculated with the appropriate equation (right ordinate) and that known to be experimentally correct. Curve A is the least squares line, and the triangles are calculated values. Curve B represents hypothetical cumulative urinary excretion of glucose.

section will consider the case where the drug enters the fluids of distribution at a constant rate (zero-order process) and is eliminated from these fluids at a rate directly proportional to the existing concentration at a given time (first-order process). This sequence of processes is shown as *Model I* in the *Appendix*, and the expression which describes blood concentration as a function of time is Eq. 5A of the appendix.

The data used are the results of the experiments of Jokipii and Turpeinen (10). Glucose was infused as 5 to 6% isotonic solutions into the cubital vein at constant rates. The mean rate of infusion in 24 normal subjects was 297 mg./minute. The mean preinjection blood sugar was 84.9 mg./100 ml. This is the zero level at time zero shown on Fig. 3. The mean blood sugar level at 60 minutes is shown also in Fig. 3. The solid dots are the arithmetic values. The open circles are those obtained by the best fit—namely, $C = 53.8\,[1-\exp(-0.0519t)]$.

The triangles in Fig. 3 are values of $C_T + K\cdot$(area) calculated from these data. The slope of this line through these points is 2.794 ml./minute 100 ml. The line is straight, a reflection that the glucose was infused at a constant rate.

Since it is known that the actual infusion rate was 297 mg./minute, an estimate can be made of the apparent volume of distribution, V, from this rate and the slope of the A_T/V time plot. The calculated V is 10,600 ml. Exactly the same answer was obtained by Jokipii and Turpeinen (10) by assuming that the *Model 1* applied to these data.

Assume all the glucose in the blood was excreted unchanged in the urine, and urine was assayed for glucose. Figure 4 shows a hypothetical cumulative excretion curve for this case.

It should be noted that the cumulative excretion curve, X_u *versus* t, is curved throughout the 60-minute infusion period. It appears linear from 40 to 60 minutes, but the rate calculated in this interval is 274 mg./hour, which is 7.7% lower than the actual rate of 297 mg./minute.

By the method previously outlined, values of $1/K\cdot(\Delta X_u/\Delta t) + X_u$ (see Eq. 42A of the *Appendix*) were calculated and are shown as the triangles here. The slope of the line drawn through these points is 297 mg./minute, which is exactly the known infusion rate. These results are supporting evidence that the simple graphical method is highly accurate. The apparent linearity of the hypothetical cumulative excretion plot in the 40 to 60-minute interval is shown to be only apparent in Fig. 4 when the excretion rate is plotted against time (*cf.* Fig. 5). A cumulative excretion plot is very "insensitive" compared with the derivative plot.

If a loading dose, exactly equal to k_0/K, is injected rapidly intravenously and at the same time the constant rate infusion is started, then the blood level will remain constant,[3] and a plot of cumulative amount of unchanged drug in the urine against time will be linear as long as the constant infusion rate is maintained.

It may be that absorption proceeds into the fluids of distribution by two parallel zero-order processes (*Model 2* of the *Appendix*). Data are available with which this can be shown. Tanaka *et al.* (13) reported blood levels of sulfanilamide in five dogs administered in two different formulations of sulfanilamide orally. Sample I was a micropellet formulation containing 33.2% of sulfanilamide in gelled gelatin. Sample II was a similar micropellet formulation which had been treated with 10% formalin-isopropanol at 2 to 5° for 24 hours, then dried; it contained 19.0% sulfanilamide. Both preparations were administered orally to the dogs at a dose of 250 mg. of sulfanilamide per kilogram of body weight. The results obtained with the second preparation were interpreted in terms of the model just discussed after computing per cent absorbed *versus* time plots. The results are summarized in Fig. 6. As may be seen, two zero-order processes were in operation during absorption. The values of the constants and material balance are summarized in Table I.

In a study in which 200-mg. doses of lincomycin were injected intramuscularly, data (7) were obtained which could be interpreted as consistent with *Model 3* of the *Appendix*. Nearly 70% of the dose was absorbed rapidly, comparable to a rapid intra-

[3] Actually, in the usual medical experiment the loading dose is less than or greater than k_0/K, and the constant rate infusion is continued until the measured blood level becomes apparently constant.

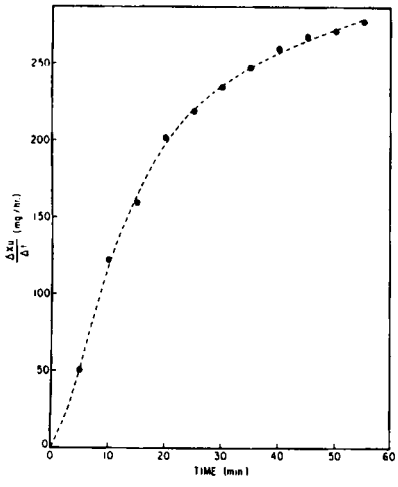


Fig. 5.—Hypothetical urinary excretion rate of glucose *versus* time. (See text regarding this curve.)

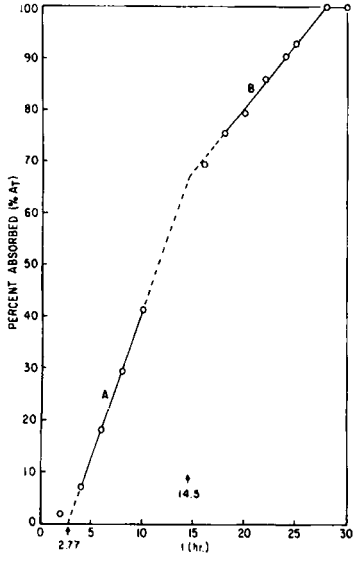


Fig. 6.—Per cent absorbed *versus* time plot calculated from blood level *versus* time data obtained following the administration of sulfanilamide in sustained-release form (see text for reference). Two zero-order processes were apparently in operation. The equation describing segment A is $\% A_T = 5.67t - 15.7$, and the equation for segment B is $\% A_T = 2.48t + 30.5$. The arrow on the figure indicates the time in hours when the first process ceased.

venous injection, and about 30% by a first-order process (see Fig. 7). Hence, data were fitted to the sum of Eqs. 7A and 20A of the *Appendix*. The correlation between experimentally observed and theoretically predicted values of serum level *versus* time by the resulting equation is shown in Table II. It will be seen from data in this table that the correlation was excellent.

It may also be the case that drug is absorbed by two first-order processes operating in parallel, as in the scheme shown as *Model 4* in the *Appendix*.

Data in the literature (14) on blood levels of sulfaethylthiadiazole as a function of time after the administration of a sustained-release suspension of this substance have been interpreted in terms of this model.

Per cent absorbed *versus* time values were calculated using Eq. 1. When plotted (Fig. 8), it appeared that the line connecting the points might be one delineating a cumulative first-order process.

TABLE I.—SUMMARY OF DATA FOR A CASE OF ABSORPTION AND ELIMINATION CONFORMING TO *Model 2*

Clock Time, Hr.	Time Interval, Hr.	% of Dose Absorbed/ Hr.[a,b]	Total % of Dose Absorbed
2.8–14.5	11.7	3.19	37.3
2.8–28	25.2	2.48	62.5
		Total	99.8

[a] The value shown for the first interval is that calculated by subtracting the value for the second interval from the slope of the first linear segment of the two shown in Fig. 6. The slope of the latter mentioned line was 5.67% per hour. [b] The true dimensions of a zero-order rate constant are amount/unit time. Therefore, because of the method of calculation, *viz.*, per cent absorbed *versus* time, the values in this column should be thought of as multiplying the amount eventually absorbed.

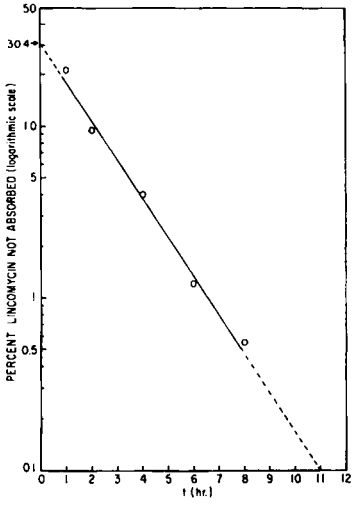


Fig. 7.—Apparent first-order absorption of part of the dose of lincomycin (hydrochloride) following intramuscular injection. The arrow on the ordinate indicates the percentage absorbed by this process. The initial part of the dose was absorbed at a rate comparable to that observed following intravenous injection. The line shown on the graph would be described by $100 - A_T/A_\infty = 30.4 \exp(-0.515t)$ on Cartesian coordinate paper. The open circles are values calculated from serum level data using Eq. 1 and after subtraction of these from 100.

TABLE II.—COMPARISON BETWEEN OBSERVED AND THEORETICALLY PREDICTED LINCOMYCIN SERUM LEVELS AT VARIOUS TIMES[a]

Time, Hr.	Observed Serum Levels, mcg./ml.	Theoretically Predicted Serum Levels, mcg./ml.
1	3.8	3.5
2	3.8	3.8
4	3.0	2.8
6	2.3	2.3
8	1.7	1.7
12	0.9	0.9

[a] Following a 200-mg. intramuscular dose.

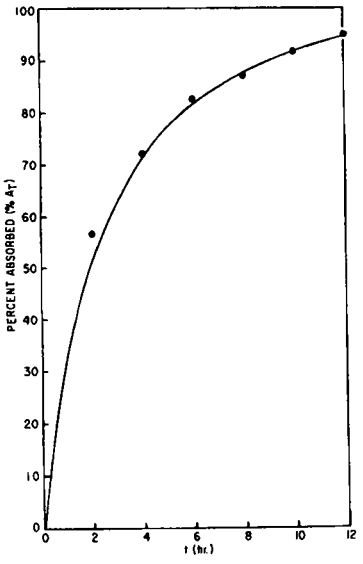


Fig. 8.—Per cent absorbed *versus* time plot calculated from blood level *versus* time data obtained following oral administration of sulfaethylthiadiazole in sustained-release form (14). The solid circles are values directly calculated from average serum levels. The line is based on the analysis shown in Fig. 9.

Therefore, per cent drug unabsorbed was plotted *versus* time on semilogarithmic paper. (The procedure was the same as in the preceding case.) This plot is shown in Fig. 9. If the differences between line B and extrapolated line C are plotted as a function time, another straight line, A, results. This could be interpreted as an indication that absorption occurred by two parallel apparent first-order processes.[4]

The appropriate equation to estimate the blood levels of sulfaethylthiadiazole is Eq. 28A in the *Appendix*. For this particular example, the value FD/V = 20 mg.% was obtained by extrapolating a plot of A_T/V *versus* time (analogous to extrapolating Fig. 8 to 100%). The other constants were obtained as follows: f_i = 0.334 from the intercept of line A and f_s = 0.666 from the intercept of line C of Fig. 9; k_a = 1.074 hr.$^{-1}$ from the slope of line A and k_a' = 0.219 hr.$^{-1}$ from the slope of line C of Fig. 9; K = 0.0928 hr.$^{-1}$ was obtained from data in the same paper (14) obtained following administration of crystalline (noncoated) sulfaethylthiadiazole. Figure 10 compares the estimated blood levels (dotted line) with the observed blood levels (solid dots). The estimated blood levels agree to within 0.3 to 5% (average 2.1%) of the observed blood levels. Even better agreement of estimated and observed blood levels could have been obtained with a computer using the blood level and time values themselves rather than the logarithms of the blood level values.

Hypothetical Example.—A hypothetical example of *Model 5* of the *Appendix* illustrates the accuracy of the method when absorption occurs by simultaneous zero-order and first-order processes. The parameters chosen (Eq. 32A) were as follows: FD = 100%, f_s = 0.70, k_0 = 7%/hour (hence, 10 hours were required to release all the "drug" from compartment A at a constant rate), f_i = 0.30, k_a = 0.693 hour^{-1}, and K = 0.1386 hour^{-1} corresponding to a biological half-life of 5 hours. Figure 11 is a plot of the per cent of drug in compartment C

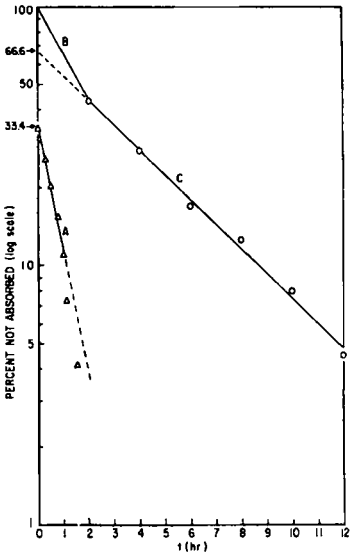


Fig. 9.—A plot of per cent sulfaethylthiadiazole unabsorbed (logarithmic scale) *versus* time showing two components in the absorption phase. The open circles delineate a line described by 100 − A_T = 66.6 exp (−0.219t) on linear coordinate paper. The points for the line delineated by triangles were obtained by subtracting values given by the extrapolated portion of the other line and those given by the line connecting the last open circle and the 100% value. The equation of this line on linear coordinate paper is described by 100 − A_T = 33.4 exp (−1.074 t). The arrows on the ordinate indicate the percentages not absorbed by the two parallel first-order process. (Additional explanation is given in the text.)

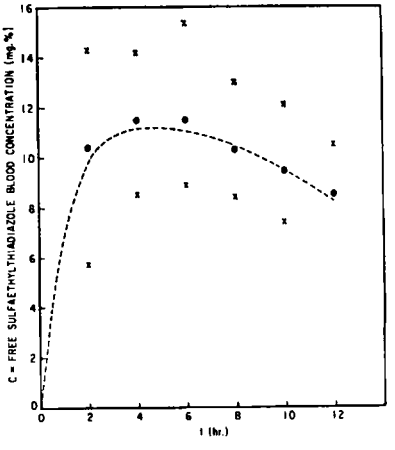


Fig. 10.—Agreement between theoretically predicted sulfaethylthiadiazole blood levels and time (line) and experimentally observed levels (solid circles). The X's represent range of individual subject experimental values observed. Mean values were used to obtain the plotted solid circles and the theoretical line.

[4] It also could be the case that two consecutive processes were involved. However, this was shown not to be the case by further mathematical analysis.

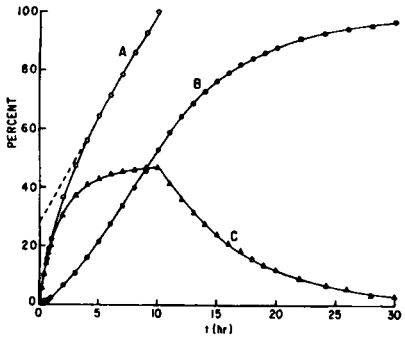


Fig. 11.—Hypothetical percentages of drug in various compartments of distribution for a specific case when drug is absorbed by parallel zero and first-order processes. This is *Model 5* of the *Appendix*. (See text under *Hypothetical Example* for explanation of curves.)

(analogous to the blood level) and the cumulative amount of drug in compartment D (analogous to unchanged drug excreted in the urine plus metabolites). The amounts remaining in compartments A and B at times t—namely, X_a and X_b, respectively—were directly calculated and used to produce the third line, $\%\ A_T = 100-(X_a + X_b)$, shown in Fig. 11. From 5 to 10 hours the latter line is essentially linear. However, it is not exactly linear, since at 5 hours 6.25% of the original 30% of the drug in compartment A is still there and being released at a first-order rate. However, this is a relatively small amount compared with the 35% being released at a rate of 7%/hour which is in compartment B at the same time. By assuming linearity of the $\%\ A_T$, t plot in the 5- to 10-hour interval, some error is introduced. The magnitude of this error is shown in Table III in the first row. The second row in the table gives the constants back-calculated from the compartment C data using Eq. 1; the third row in Table III gives the constants back-calculated from the compartment D data using Eq. 2. It may be seen that the new methods introduce little or no more error than is caused by the assumption that the $\%\ A_T$, t plot is linear in the 5- to 10-hour period. These results were achieved simply with a pencil and paper using the trapezoidal rule to estimate the areas and reading the X_d values directly off the original graph. Both analog and digital computers yielded the same results.

This model illustrates another important point. Even when 70% of the dose was released at a constant rate, the blood level (amount in compartment C) never became flat or constant, and the cumulative excretion curve (amount in compartment D) never became linear. Even if the proper loading dose—namely, $k_0/K = 7\%/0.1386 = 50.5\%$—had been placed in compartment B initially and the remaining 49.5% put in compartment A and released over 10 hours at a constant rate of 4.95%/hour, the resulting compartment C plot would be nearly, but not exactly, parallel to the time axis for only a short interval of time.

Equations to Estimate Blood Levels.—The equation to provide estimated blood levels at any time t after administration of a single dose of a drug may also be derived by using only the numerator of Eq. 1 and by using Eq. 8. In this case, the total initial amount in compartments A and B of the models in the *Appendix* becomes FD/V and is in the same concentration units as the measured blood levels. In this case, the per cent absorbed *versus* time plot is replaced by an A_T/V *versus* time plot, where A_T/V is in the units of the measured blood levels. This procedure results in considerable time saving since the conversion to percentages is eliminated.

APPENDIX

This appendix considers various models to describe drug absorption, metabolism, and excretion with which new data and data in the literature may be interpreted (in most cases). Also contained is the derivation of the mathematical expressions which describe blood, serum, or plasma level and in some cases, urinary excretion of drug in the models presented.

Model 1.—The first model to be considered is

$$A \xrightarrow{k_0} C \xrightarrow{K} D$$

In *Model 1*, A represents drug at an absorption site or in an infusion apparatus being transferred to a compartment C (drug in blood and the other fluids of distribution in apparent equilibrium) by a process whose rate is constant (zero-order process) and from which it is removed from the body by metabolism

TABLE III.—CONSTANTS OF *Model 5* BACK-CALCULATED BY VARIOUS METHODS AND THE PERCENTAGE ERROR OF THE CALCULATED VALUES FROM THE ACTUAL VALUES USED TO GENERATE THE MODEL CURVES

	Constant Involved							
	100 f_b, %		100 f_s, %		k_1, Hr.$^{-1}$[a]		k_0, %/Hr.	
Method of Calculation	Calcd. Value	% Error	Calcd. Value	% Error	Calcd. Value	% Error	Calcd. Value	% Error
Graphically from actual X_a and X_b values from 5 to 10 hr.	28	−6.67	72	+2.86	0.717[a]	+3.46	7.18	+ 2.6
From X_c, t values using $X_c + K\int_{t=0}^{t=T} X_c dt$	28.1	−6.33	71.9	+2.71	Not estimated		7.17	+ 2.4
From X_d, t values using $\frac{1}{K}\frac{\Delta X_d}{\Delta t} + X_d$	28.2	−6.00	71.8	+2.57	Not estimated		7.19	+ 2.7
From actual X_d, t values from 5 to 10 hr., *assuming* excretion rate is constant	These values indeterminate by this method						6.27	−10

[a] $k_1 = \frac{-2.303}{t}\log_{10}\left[\frac{100 - \%\ A_T - (100\ f_s - k_0 t)}{100\ f_b}\right]$. Values of k_1 were calculated for t = 0.2, 0.4, 0.6, 0.8; 1, 2, 3, and 4 hr. then averaged.

and/or excretion of unchanged drug at a rate directly proportional to the concentration present in compartment C (first-order process) to compartment(s) D. The quantities k_0 and K are the zero and first-order rate constants, respectively, with dimensions of amount per unit time and reciprocal time, respectively. The rate of change of concentration C in compartment C with time in *Model 1* will be equal to

$$\frac{dC}{dt} = \frac{k_0}{V} - KC \qquad \text{(Eq. 1A)}$$

where V is the apparent volume in which drug becomes distributed (*i.e.*, the volume of compartment C). Rearranging Eq. 1A and integrating gives

$$-\frac{1}{K} \ln \left(\frac{k_0}{V} - KC\right) = t + \text{constant} \quad \text{(Eq. 2A)}$$

If at zero time no drug is absorbed, the value of the constant is

$$-\frac{1}{K} \ln (k_0/V) = \text{constant} \quad \text{(Eq. 3A)}$$

Inserting Eq. 3A in Eq. 2A and rearranging gives

$$\ln \frac{k_0/V - KC}{k_0/V} = -Kt \qquad \text{(Eq. 4A)}$$

If Eq. 4A is raised to power of the natural logarithm and rearranged, the following expression results which gives blood, serum, or plasma concentration as a function of time:

$$C = \frac{k_0}{KV} [1 - \exp(-Kt)] \quad \text{(Eq. 5A)}$$

If the constant of integration in Eq. 2A is evaluated under the condition that at zero time $C = C^0$, then the expression becomes after rearranging and raising it to powers of the natural logarithm

$$C = \frac{k_0}{KV} + \left(\frac{k_0}{KV} - C^0\right) \exp(-Kt) \quad \text{(Eq. 6A)}$$

If C^0 is selected to equal k_0/KV, then Eq. 6A reduces to

$$C = \frac{k_0}{KV} \qquad \text{(Eq. 7A)}$$

and blood, etc., concentration would be constant for as long as drug is absorbed or introduced at a constant rate. This is the case when an appropriately calculated initial loading dose is given by rapid intravenous injection, and drug infusion starts immediately at a constant rate by the intravenous route.

If accumulation of unchanged drug is followed in compartment D, assuming that some part of the dose is excreted unchanged in the urine, an expression can be developed to describe this accumulation. Urinary excretion rate will be given by (4)

$$\frac{dX_u}{dt} = k_1 VC \qquad \text{(Eq. 8A)}$$

where k_1 is the first-order urinary excretion rate constant. Substituting for C by its value as given in Eq. 5A yields

$$\frac{dX_u}{dt} = \frac{k_1 k_0}{K} [1 - \exp(-Kt)] \quad \text{(Eq. 9A)}$$

Integrating Eq. 9A gives

$$X_u = \frac{k_1 k_0 t}{K} + \frac{k_1 k_0 \exp(-Kt)}{K^2} + \text{constant} \quad \text{(Eq. 10A)}$$

If at zero time no drug has been excreted, the constant of integration has the following value:

$$\text{constant} = -\frac{k_1 k_0}{K^2} \qquad \text{(Eq. 11A)}$$

Inserting this expression in Eq. 10A and rearranging gives

$$X_u = \frac{k_1 k_0 t}{K} - \frac{k_1 k_0}{K^2} [1 - \exp(-Kt)] \quad \text{(Eq. 12A)}$$

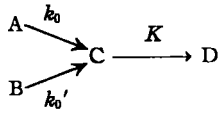
as the expression desired. After a sufficiently long time (seven to ten half-lives), the term containing the exponential in Eq. 12A becomes negligible and the equation reduces to

$$X_u = \frac{k_1 k_0 t}{K} - \frac{k_1 k_0}{K^2} \qquad \text{(Eq. 13A)}$$

and a plot of cumulative amount of unchanged drug excreted would become linear.

In Eq. 13A the ratio, k_1/K, is the fraction of a dose, f, eventually excreted unchanged.

Model 2.—Another model in which the drug absorption part would conceivably be found in practice is



The constants k_0 and K have the same meaning as previously. The constant, k_0', is a zero-order rate constant for an absorption or infusion process which operates simultaneously with the other zero-order process. In *Model 2* rate of change of blood, etc. (compartment C) concentration with time is given by

$$\frac{dC}{dt} = \frac{k_0 + k_0'}{KV} - KC \qquad \text{(Eq. 14A)}$$

By the procedure identical to that used to obtain Eq. 5A, blood concentration as a function of time in *Model 2* will be given by

$$C = \frac{k_0 + k_0'}{KV} [1 - \exp(-Kt)] \quad \text{(Eq. 15A)}$$

Model 3.—It could be the case that absorption proceeds by a single first-order process and the situation may be depicted as

$$FD \text{ at } t = 0\} \quad A \xrightarrow{k_a} C \xrightarrow{K} D$$

In *Model 3*, k_a is the first-order rate constant for the absorption process. The rate of change of blood, etc., concentration is given by

$$\frac{dC}{dt} = \frac{k_a X_a}{V} - KC \qquad \text{(Eq. 16A)}$$

In Eq. 16A, X_a is the amount of the drug at the absorption site at any time, t, and the other terms have the same meaning as previously described.

If the drug disappears by a first-order absorption process, then X_a will be given by

$$X_a = FD \exp(-k_a t) \quad \text{(Eq. 17A)}$$

where D is the dose and F the fraction of it eventually absorbed by the first-order process. Inserting the value of X_a as given above in Eq. 16A and integrating the resulting expression gives

$$C = (\text{constant}) \exp(-Kt) + \frac{k_a FD}{V(K - k_a)} [\exp(-K_a t) \quad \text{(Eq. 18A)}$$

If at zero time no drug is in the blood, the constant of integration has the following value

$$\text{constant} = -\frac{k_a FD}{V(K - k_a)} \quad \text{(Eq. 19A)}$$

Inserting the value of this constant in Eq. 18A and rearranging the resulting expression gives

$$C = \frac{F \cdot D}{V} \frac{k_a}{K - k_a} [\exp(-k_a t) - \exp(-Kt)] \quad \text{(Eq. 20A)}$$

Using Eq. 8A, urinary excretion rate of unchanged drug (if any) will be described by

$$\frac{dX_u}{dt} = \frac{k_1 k_a FD}{K - k_a} [\exp(-k_a t) - \exp(-Kt)] \quad \text{(Eq. 21A)}$$

Equation 21A may be integrated to obtain

$$X_u = \frac{k_1 k_a FD}{K - k_a} \left[\frac{\exp(-Kt)}{K} - \frac{\exp(-k_a t)}{k_a}\right] + \text{constant} \quad \text{(Eq. 22A)}$$

If at zero time no drug has been excreted, the constant of integration has the following value:

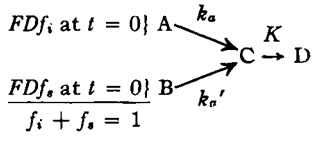
$$\text{constant} = -\frac{k_1 FD}{K - k_a} \left(\frac{k_a - K}{K}\right) \quad \text{(Eq. 23A)}$$

If Eq. 23A is substituted in Eq. 22A and resulting expression rearranged, the following equation may be obtained:

$$X_u = \frac{k_1 FD}{(K - k_a)} [1 - \exp(-k_a t)] - \frac{k_1 k_a FD}{(K - k_a)} [1 - \exp(-Kt)] \quad \text{(Eq. 24A)}$$

Equation 24A describes cumulative amount of unchanged drug excreted, and again the ratio, k_1/K, is equal to the fraction of a dose excreted in this form.

Model 4.—Absorption may also precede by two parallel first-order processes as shown:



In *Model 4* f_i and f_s are, respectively, the fractions of the dose absorbed by the indicated processes. In this model, drug blood, etc., level will be described by the following expression, where A and B are the two sources of drug, and k_a and k_a' are the first-order rate constants for the indicated processes.

$$\frac{dC}{dt} = \frac{FD}{V}(k_a X_a + k_a' X_b) - KC \quad \text{(Eq. 25A)}$$

Equation 25A may, after substituting for X_a and X_b as given in Eq. 17A, be rearranged and integrated to give

$$C = (\text{constant}) \exp(-Kt) + \frac{k_a FDf_i}{V(K - k_a)} \exp(-k_a t) + \frac{k_a' FDf_s}{V(K - k_a')} \exp(-k_a' t) \quad \text{(Eq. 26A)}$$

If no drug is in circulation at zero time, then the constant of integration has the value

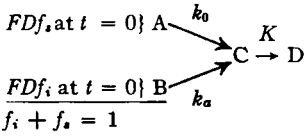
$$\text{constant} = -\frac{k_a FDf_i}{V(K - k_a)} - \frac{k_a FDf_s}{V(K - k_a')} \quad \text{(Eq. 27A)}$$

Inserting Eq. 27A in Eq. 26A gives, on rearrangement

$$C = \frac{FD}{V}\left\{\left[\frac{f_i k_a}{(K - k_a)}\right][\exp(-k_a t) - \exp(-Kt)] + \left[\frac{f_s k_a'}{(K - k_a')}\right][\exp(-k_a' t) - \exp(-Kt)]\right\} \quad \text{(Eq. 28A)}$$

to describe blood (compartment C) level as a function of time.

Model 5.—In the preceding model two first-order absorption processes were assumed to be in operation simultaneously. It may also be that both a zero and first-order process operate simultaneously as shown in the following model:



Rate of change of blood (compartment C) concentration with time in the *Model 5* above is given by

$$\frac{dC}{dt} = \frac{k_0}{V} + \frac{k_a X_a}{V} - KC \quad \text{(Eq. 29A)}$$

After substituting for X_a in Eq. 29A, as given by Eq. 17A, rearranging, and integrating, the following expression is obtained:

$$C = (\text{constant}) \exp(-Kt) + \frac{k_0}{KV} + \frac{k_a FDf_i}{V(K - k_a)} \exp(-k_a t) \quad \text{(Eq. 30A)}$$

If at zero time no drug is present in the blood, the constant of integration in Eq. 30A has the value

$$\text{constant} = -\left[\frac{k_0}{KV} + \frac{k_a FDf_i}{V(K - k_a)}\right] \quad \text{(Eq. 31A)}$$

Substituting for the constant in Eq. 30A by its value as given by Eq. 31A gives

$$C = \left\{\left(\frac{FD}{V}\right)\left(\frac{f_i k_a}{K - k_a}\right)[\exp(-k_a t) - \exp(-Kt)]\right\} + \left\{\frac{k_0}{VK}[1 - \exp(-Kt)]\right\} \quad \text{(Eq. 32A)}$$

as the expression which describes blood level as a function of time. This equation is valid during the time zero-order absorption is occurring.

The derivation of the expressions given in the text to calculate per cent of the absorbed dose of a drug as a function of time begins with a material balance accounting for the dose absorbed at all times. This material balance is

$$FD = X_{a+b} + X_c + X_d \quad \text{(Eq. 33A)}$$

where X_{a+b} is the amount at absorption site at any time, X_c is the amount in the body at the same time, and X_d is the amount eliminated from the body also in the same time. Another material balance is

$$A_T = X_c + X_d \quad \text{(Eq. 34A)}$$

Hence,

$$\frac{dA}{dt} = \frac{dX_c}{dt} + \frac{dX_d}{dt} \quad \text{(Eq. 35A)}$$

Furthermore, since $X_c = VC$ and $dX_c/dt = V \cdot dC/dt$ and since $dX_d/dt = KVC$ (loss from V is assumed to be first order), Eq. 35A may be written

$$\frac{dA}{dt} = V\frac{dC}{dt} + KVC \quad \text{(Eq. 36A)}$$

Integration of Eq. 36A between the limits $t=0$ and $t=T$ yields

$$A_T = V\left(C_T + K\int_{t=0}^{t=T} Cdt\right) \quad \text{(Eq. 37A)}$$

Integration of Eq. 36A between the limits $t=0$ and $t=\infty$ yields

$$A_\infty = V \cdot K \cdot \int_{t=0}^{t=\infty} Cdt \quad \text{(Eq. 38A)}$$

By definition, we have

$$\%\ \text{absorbed} = \frac{A_T}{A_\infty} \times 100 \quad \text{(Eq. 39A)}$$

Hence,

$$\%\ \text{absorbed} = \frac{C_T + K\int_{t=0}^{t=T} Cdt}{K\int_{t=0}^{t=\infty} Cdt} \times 100 \quad \text{(Eq. 40A)}$$

The denominator of Eq. 40A is the maximum or asymptotic value of the numerator.

If urinary excretion of unchanged drug is followed, Eq. 40A may be modified. Urinary excretion rate of unchanged drug is given by (4):

$$\frac{dX_u}{dt} = fVKC \quad \text{(Eq. 41A)}$$

Solving Eq. 41A for C, substituting into Eq. 40A, and simplifying yields

$$\%\ \text{absorbed} = \frac{(1/K)\cdot[(dX_u/dt) + X_u]}{(X_u)_\infty} \times 100 \quad \text{(Eq. 42A)}$$

GLOSSARY

dA/dt, instantaneous absorption rate (units of amounts per unit time).
A_T, amount absorbed from time zero to time T (weight units).
A_∞, amount eventually absorbed, $A_\infty = FD$ (weight units).
C, the blood (serum or plasma) concentration (concentration units) assumed to be representative of compartment C in the models.
C_T, the blood (serum or plasma) concentration at time T (concentration units).
V, the apparent volume of distribution (volume units). See *Introduction* for definition.
K, the first-order rate constant for loss of drug from V units (units of reciprocal time).
D, the dose of drug administered (weight units).
F, the fraction of the drug absorbed (*i.e.*, the fraction of the dose which reaches V). This is a dimensionless number and $0 \leq F \leq 1$.
f, the fraction of the drug reaching the circulation (*i.e.*, V) which is excreted unchanged in the urine. This is a dimensionless number and $0 \leq f \leq 1$.
X_c, amount of unchanged drug retained in V at a given time (weight units).
X_d, amount of drug eliminated from V by all processes in a given time (weight units).
X_u, amount of unchanged drug eliminated in the urine to a given time (weight units) and $X_u = f \cdot X_d$.
dX_u/dt, the instantaneous rate of urinary excretion of unchanged drug at time t. This is the first derivative of a plot of cumulative amount of unchanged drug excreted in the urine against time (units of weight per unit time).
d^2X_u/dt^2, the rate of change of urinary excretion rate. This is the second derivative of a plot of cumulative amount of unchanged drug excreted in the urine against time.
$(X_u)_\infty$, the amount of unchanged drug excreted in the urine in infinite time (weight units).
% A_T, the amount of drug absorbed to time T expressed as a percentage of the total amount absorbed [*i.e.*, % $A_T = (A_T/A_\infty) \times 100$].
$\int_{t=0}^{t=T} Cdt$, the area under a plot of blood (serum or plasma) concentration against time between time zero and time T (units of concentration × time).
$\int_{t=0}^{t=\infty} Cdt$, the area under a plot of blood (serum or plasma) concentration against time between time zero and infinite time (units of concentration × time).

Interpretation of the Models

A and/or B, drug in the dosage form and/or gastrointestinal tract or site of injection (*i.e.*, drug in A and/or B is unabsorbed).
C, drug in V of which blood (serum or plasma) is a part. In the models C is the concentration of compartment C, whose volume is V. Hence, $C = X_c/V$.
D, drug in the urine and/or metabolites.
k_0, a zero-order rate constant (amount/unit time).
k_1 and k_2, first-order rate constants (units of reciprocal time).
X_a, X_b, X_c, and X_d, amounts of drug in the compartments A, B, C, and D at time t, respectively.
fi, that fraction of the drug absorbed which is absorbed at rapid rates from compartment A.
fs, that fraction of the drug absorbed which is absorbed slowly from compartment B.
k_a and k_a', first-order absorption rate constants (units of reciprocal time).

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