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Empirical Equation for Pharmacokinetic Analysis of Drug Serum Levels After Oral Application

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The equation $\log(\text{concentration}) = a + b/\sqrt{T-\phi} + c\cdot\sqrt{T-\phi} + d\cdot(T-\phi)$ was used to calculate serum level curves from individual data sets of drug serum concentrations, obtained from experiments with orally administered drugs. These curves were subsequently used to calculate peak values, times for onset of peak, area, and other pharmacokinetic parameters that ought to be independent of any preconceived theory about the behavior of the drug in the system. A program is described by which parameters for individual data sets can be calculated and a mean curve with a peak value, time for onset of peak, and area equal to the arithmetic mean of the corresponding values for the participating subjects, is produced. The results of this method are compared to those of the "one-compartment model with lag time" and shown to be superior in all the test cases. In particular, the proposed method performs well with data from a highly protein-bound drug, for which the one-compartment model fails completely. Data sets of six to eight samples taken over the entire period of detectable serum levels, with 10% analytical error in the results, gave estimates of peak value and area with a coefficient of variation of 6 to 9%, whereas the variation in the estimates for different subjects in a treatment group amounted to 20 to 60%. This shows that the proposed method, although able to cope with a short series of imprecise measurements available in practical work, is still sufficiently sensitive to detect real differences between the individual subjects.

Teorell (7) in 1937 introduced the "one-compartment, open model" as a means of describing the time course of drug concentrations in serum after oral application of a fixed dose:

$$\text{conc}(T) = \frac{\text{dose}}{\text{vol}} \times \frac{\alpha}{\alpha-\beta} \times [\exp(-\beta \times T) - \exp(-\alpha \times T)] \quad (1)$$

where vol represents an apparent volume of distribution and α and β are absorption and elimination rate constants, respectively.

This model implies that the following conditions are true. (i) At the moment of application, ($T = 0$), the whole dose is instantaneously transferred to the sites of absorption. (ii) The absorption then takes place at a rate proportional to the remaining, unabsorbed part of the drug, all of which is gradually absorbed into the blood stream. Diffusion processes through membranes do not influence the absorption process, and drug loss by destruction in the stomach or excretion through the intestines can be ignored. (iii) Either no reversible exchange of drug takes place between serum and the various body organs or the equilibrium concentrations for such exchanges are established at a rate much greater than the absorption and elimination proper. Drug loss from these organs in ways other than through the blood stream is negligible. (iv) If alternative routes of elimination compete, e.g., metabolization and renal excretion, each of these processes must be of the first order, i.e., proceed at a rate proportional to the drug concentration in the serum. (v) If part of the drug is eliminated via the enterohepatic system, reabsorption in the intestines can be ignored.

Equation 1 should not be used for a drug that is suspected of violating one or more of the above-mentioned conditions. Many drugs may belong to this category, and many modifications of the basic model have been proposed to counteract the effects of such deviations. The simplest modification is the introduction of a lag time, ϕ, to account for the time lapse from the moment of application to the arrival of drug at the sites of absorption. This amounts to calculating all sampling times from $T = \phi$, instead of from $T = 0$. In my experience this generally leads to a better fit between model and actual data.

The problems of possible zero-order absorption, or a mixture of parallel zero- and first-order absorption have been discussed by Wagner and Nelson (8). They also mentioned cases of recycling via the enterohepatic cycle, accompanied by a detectable deformation of the curve in the form of a shoulder following the peak, or, in extreme cases, two local maxima.

Notari et al. (5), Perrier and Gibaldi (6), and Leeson and Weintraub (4) have explored the consequences of partial loss of unabsorbed drug in the gastrointestinal tract. Their results show that it is improper to use the basic model, or any modification thereof, which does not compensate for this potential loss in bioavailability comparisons between different drug formulations.

The effect of reversible exchange of drug between serum and various tissues may be taken into account by introducing one or more additional exponential terms into the basic model. Logically, one should use one additional term for each of the organs that must be treated as a separate entity.

With the limited knowledge available during the preliminary stages of investigation of new drugs it may be quite impossible to make an educated guess concerning which model to choose or to discriminate between alternative models. Westlake (9) sums up most of the work that has been done in this field and cites an illuminating example from an article by Lanczos (3). The problem treated was that of discriminating between models involving two or three exponential terms. The criterion for doing so was: which model would lead to the best fit when applied to a set of 24 simulated data points; these were calculated with two-decimal accuracy from one of the models. The best fit was obtained with a two-term model even though a three-term model had been used to furnish the data. The fit was extremely good, with the greatest difference between calculated and "experimental" values not exceeding 0.006.

One additional argument against the indiscriminate use of equation 1 merits some attention. Data sets from oral application of drugs do not, by themselves, contain sufficient information for unambiguous estimates of the parameter values for equation 1. For each set of parameter values (α, β, dose/vol) with α = a, β = b, and dose/vol = c, the alternative set with α = b, β = a, and dose/vol = $a \cdot c/b$ leads to exactly the same curve but quite different estimates of the pharmacokinetic parameters. If the values obtained for α and β happen to lie far apart, one of the alternative values for dose/vol may fall outside the range of reasonable values, thus solving the dichotomy. Otherwise, outside information, e.g., through intravenous experiments, must be supplied.

In many cases of practical interest, the main objective of pharmacokinetic investigations is not so much the elucidation of distribution patterns for a drug in the various organs, but rather the choice of an optimal dosage form. Typically, 6 to 12 subjects may participate in a crossover trial, and 6 to 12 blood samples taken from each subject at predetermined intervals of time may be analyzed, either immediately or sometimes after cold storage. The errors involved in the sampling and subsequent assay may well lead to a Karl Pearson coefficient of variation in the order of 10 to 15%. In such situations one may not feel inclined to accept the implications inherent in the use of equation 1 or one of its modifications, but may prefer to rely on whatever may be inferred from a smooth curve fitted to the data. This can provide estimates of area, peak value, and time for reaching the peak. Sums of exponential terms may, of course, be used for this purpose, but they are not necessarily the most convenient for this use. In this paper an alternative method is proposed.

MATERIALS AND METHODS

Curve-fitting program. The sampling values for each individual set of drug serum concentrations are first converted into the corresponding natural logarithms, except those having concentrations less than or equal to 0.10, the latter being omitted from the calculations. A curve is then fitted to the remaining data by means of the formula:

$$Y = a + b/x + c \cdot x + d \cdot x^2 \qquad (2)$$

where Y represents the logarithmic transform of concentration (conc); Y = ln(conc); x is a time metameter; $x = \sqrt{T - \phi}$, and ϕ, a, b, c, and d are all unknown constants that are to be estimated from the data.

If ϕ were known, then equation 2 would represent Y as a linear function of three independent variables, $1/x$, x, and x^2, and the coefficients a, b, c, and d could be estimated by linear regression techniques. This suggests an iterative scheme for finding the optimal value of ϕ for a particular data set: ϕ is first assigned a value equal to one-half of the earliest sampling time for the accepted data. A linear regression of Y on $1/x$, x, and x^2 then leads to least-squares estimates of the constants a, b, c, and d and a residual sum of squares. An increment of 10% of the initial value of ϕ is added to ϕ and the procedure is repeated. The new value for the residual sum of squares decides whether the iteration is to be continued in the same or reverse direction or, after the third iteration step, whether sufficient information is available for calculation of the optimal value of ϕ. The procedure is then repeated once more with this value of ϕ to obtain provisional

estimates of a, b, c, and d. Equation 2 is then used to calculate the deviations between the curve and each of the accepted data points, with the weighted square of these deviations being used in a deletion procedure to exclude obvious outliers. If this leads to the exclusion of a value, the whole procedure is repeated without this sample point.

There is always an arbitrary choice of a deletion criterion and of a suitable weight function for the regression. In this program the weight function chosen is of the form:

$$w = 100 \cdot \sqrt{\text{conc}/\max \text{conc}} \cdot [1 - (\phi/T)] \quad (3)$$

The square-root term in equation 3 favors the estimation of peak values and areas, whereas the last term, in brackets, softens the effect of small errors in the sampling times in the first, and sometimes steeply ascending, part of the curve.

The deletion criterion, expressed in logarithmic values, is a value of 4.0 for the product of w and the square of deviation for a particular data point. This corresponds to a deviation of approximately 22% in concentration units for values in the vicinity of the maximal value and of 42% for values one-tenth of this maximum.

The program imposes two restrictions on the allowable range of values for the coefficients of equation 2. The estimate of b is not allowed to equal or exceed zero. If this should occur during the computation, the value is arbitrarily set to -0.1. This convention forces the calculated concentration curve to pass through the value conc = 0 at $T = \phi$ even for data sets in which the first sampling point also happens to be associated with the highest value of conc.

The second restriction concerns the value of d. Positive values for this constant would lead to a curve that would ultimately increase without bounds. For d negative (or zero), the concentration curve will ultimately converge towards zero.

The program is designed to handle up to 12 samples per data set and a minimum of five sample points is required for the full use of equation 2. Sometimes small data sets of only four samples each are available, or the deletion procedure applied to a larger set results in four valid, remaining values. In such cases the program arbitrarily assigns a value of zero to the constant d and continues the computation by means of a modified version of equation 2 with the last term omitted. The resulting estimates of area, peak value, etc. are, of course, subject to higher variances than would otherwise be the case. Data sets containing only three valid values are not processed by the program; however, the experimental data are recorded.

The program is written in Basic FORTRAN IV for use on a small computer (IBM 360/22). It is designed to register all of the input data for each individual set, together with calculated values at the sampling times and the values of the following five parameters: area, peak value, time for peak, and the two time values, one on the ascending and one on the descending part of the curve, for which the concentration is half that of the peak. Finally, the calculated concentration curve is plotted on a line printer by using a 90 by 132 format of 8 lines per inch (2.54 cm) vertically. The observed sample values are superimposed on this curve.

The five aforementioned parameter values uniquely define the individual curve, given that it is to be of the general form of equation 2. They also contain information of pharmacokinetic interest and seem to be a reasonable choice for a parameter set on which to base the definition of a mean curve. In this program a mean curve is taken to be a curve of the general form resulting from the use of equation 2, with the stipulation that its area, peak value, time for peak, and times for concentration values one-half that of the peak are all equal to the arithmetic mean of the corresponding values for the subjects participating in the same treatment group. In some cases, especially if the individual values vary widely, it may not be possible to obtain an exact solution to the problem of computing a mean curve. The solution that minimizes the square of deviation between the mean of individual areas and the calculated area, while being exact with respect to the other four parameters, is then chosen.

The program stores all calculated parameter values for individuals, together with their corresponding experiment descriptions, in a data bank, thus greatly facilitating comparisons between experiments by different investigators.

To date, more than 1,400 individual records, taken from over 200 experiments dealing with a broad range of antibiotics, have thus been stored in an easily accessible form. This section of the program is somewhat machine dependent; however, only minor modifications would be necessary to adapt it to any computer having a FORTRAN compiler. Listings of the program are available upon request.

Data for performance test. To form a basis for a simulated experiment, three data sets were chosen, representing different types of drugs: (i) 500 mg of fusidic acid sodium salt (Fucidin, Leo Pharmaceutical Products), administered per os as two capsules to a healthy volunteer at Leo Pharmaceutical Products; (ii) 1,000 mg of ampicillin (Doktacillin, Astra), administered per os as two tablets, together with 1,000 mg of probenecid, to a healthy volunteer in another study conducted at the same location; and (iii) 1,400 mg of pivampicillin hydrochloride, an ester of ampicillin that is hydrolized immediately after absorption. This data set was taken from the results of Knothe et al. (2).

Fifteen additional sets were generated from each of the above data sets by adding 10% random error to each individual sample (there were seven, eight, and six samples per set, respectively). An additional 15 sets were generated with 15% random error. Equations 1 and 2 were both then applied to the basic and the simulated sets.

Data for comparative study. Knothe et al. (2) presented results of a crossover trial involving 12 healthy, male volunteers and three different ampicillin derivatives: amoxycillin (two capsules, 500 mg each), ampicillin (1 tablet, 1 g each), and pivampicillin hydrochloride (four capsules, 350 mg each, equimolar to 1 g of ampicillin).

Data for comparison between routes of administration. Data for comparison of administration routes were taken from those of Foltz et al. (1) and refer to a crossover trial with 311 mg of sodium ampicillin (intravenous), 616 mg of sodium ampicillin (intramuscular), and two capsules of pivampicillin hydrochloride (per os), equimolar to 500 mg of ampicillin.

RESULTS

Performance test. Figures 1, 2, and 3 show serum level curves obtained by applying equations 1 and 2, respectively, to the three basic data sets. The original measurements have been superimposed on the plots to indicate the best fit. In Fig. 1, the curve obtained with the one-compartment model completely ignores the existence of the two experimental values taken 24 and 48 h after the administration of the drug, whereas the curve computed by means of equation 2 passes through all the experimental points. (The maximal deviation being 1.6%.) In Fig. 2 and 3, the peak values lie 11 and 5% below the highest experimental value according to equation 1. For equation 2 the corresponding figures are 2% below and 1% above, respectively.

Table 1 shows the data deleted by the two programs before satisfactory adaptations could be obtained for the 2 × 3 × 16 individual data sets in the simulation experiment. The 40% deleted by equation 1 in experiment A include all the samples taken at 24 and 48 h. The 10% deleted by the same method in experiment B were randomly distributed over the sampling times. No deletions occurred at all when equation 2 was applied to the series with 10% random error. The few points deleted in the series with 15% error may well be attributable to the deletion criterion mentioned in the description of the program.

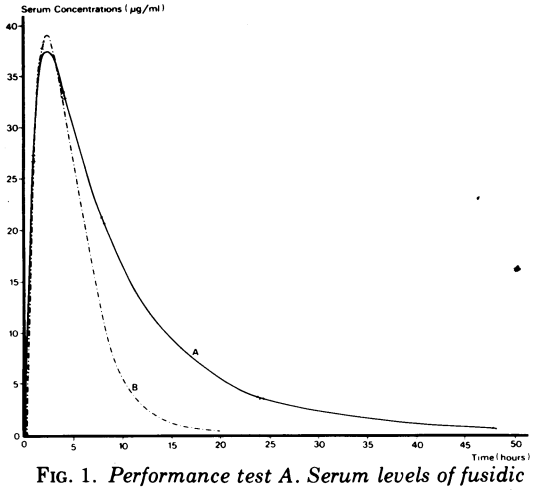

FIG. 1. *Performance test A. Serum levels of fusidic acid after administration of 500 mg of fusidic acid sodium salt per os. Experimental points* (O) *and curves calculated according to equation 2* (*A*) *and equation 1* (*B*).

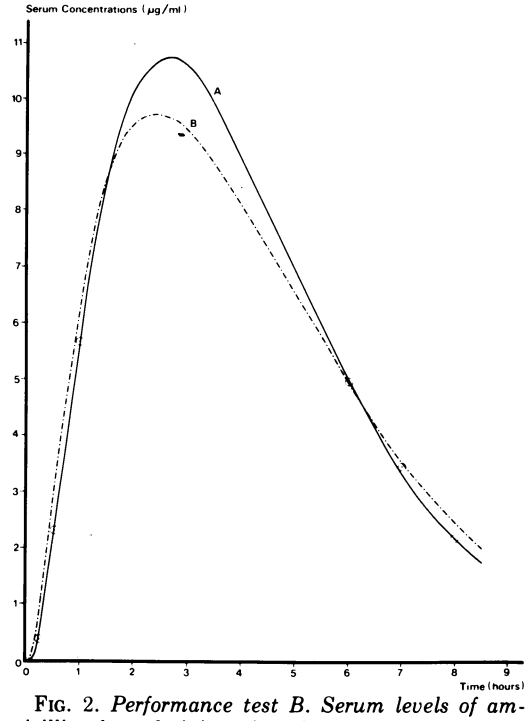

FIG. 2. *Performance test B. Serum levels of ampicillin after administration of 1,000 mg of ampicillin and 1,000 mg of probenecid per os. Experimental points* (O) *and curves calculated according to equation 2* (*A*) *and equation 1* (*B*).

Tables 2 and 3 list the mean values for areas and peak values calculated for the 16 individual data sets in each group of simulation experiments, in addition to giving the standard errors associated with estimates from a single set. The latter are expressed as Karl Pearson coefficients of variation. The mean area, calculated according to equation 1, is, of course, quite meaningless for experiment A. The peak values for experiments B and C substantiate the impression given by Fig. 2 and 3 that the values calculated by equation 1 are 5 to 10% lower than those calculated from equation 2, which, in turn, are approximately equal to the highest recorded sample value.

According to the figures for coefficients of variation, the proposed method, when applied to real data sets of six to eight samples each with 10% error in the sample values, should lead to estimates of areas and peak values with less than 10% error.

Comparative study. The results of applying

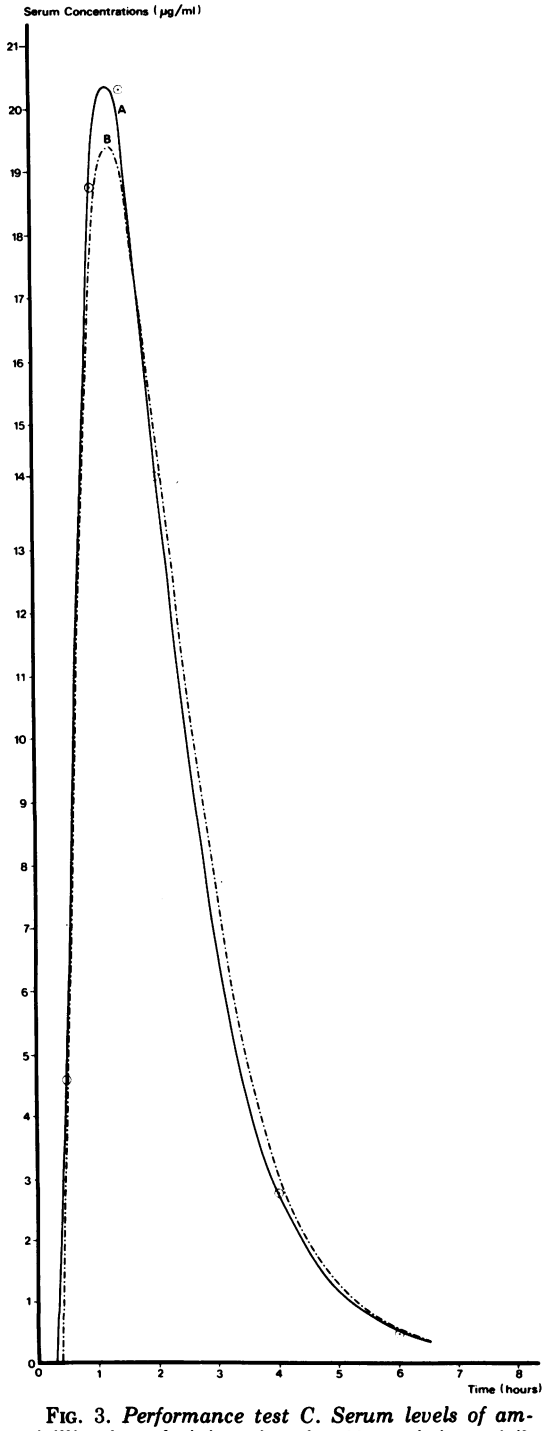

FIG. 3. *Performance test C. Serum levels of ampicillin after administration of 1,400 mg of pivampicillin hydrochloride per os. Experimental points* (O) *and curves calculated according to equation 2* (*A*) *and equation 1* (*B*).

equation 2 to the individual data sets from the crossover study of equivalent doses of ampicillin and two derivatives are presented in Table 4, and the mean curves are plotted together in Fig. 4. The bottom line of Table 4 shows the same trend for areas and peak values, the variation between subjects being the smallest for pivampicillin and decidedly greater for the poorly absorbed ampicillin.

Comparison of routes of administration. Table 5 gives the results of comparing, obtained by using equation 2, intravenous and intramuscular administration of ampicillin and peroral administration of pivampicillin. An overfill in the vials resulted in the administered doses not being equivalent. Therefore, to facilitate comparisons, a separate line has been added to the table. It contains the mean values for area and peak, adjusted to a common equimolar dose (500 mg of ampicillin). For four of the six subjects, the initial sample point in the intravenous experiment was deleted. This is reflected in the very high coefficient of variation given for this group.

DISCUSSION

The pharmacokinetic behavior of new drug formulations intended for peroral administrations is commonly evaluated by following the time course of drug in the serum after intake of a single dose. During the time interval of detectable drug levels, six to eight blood samples are usually taken. These samples are subsequently assayed, either immediately if available during normal working hours, or after cold storage. The analytical error may well amount to 10 to 15%. Under such circumstances, there is a need for a simple, yet powerful and not too sensitive, method of condensing the mass of data into a few parameter values.

The choice of parameters is somewhat arbitrary but should be limited to types for which the calculation of particular values does not depend upon prior knowledge of routes of absorption and elimination or the mechanism of these processes.

In this respect, the method proposed herein is superior to the one-compartment model, which is, at present, the most widely used procedure. It is evident (Fig. 1; Tables 1, 2, and 3) that drugs exist for which the one-compartment model fails completely. This is the case for highly protein-bound drugs, such as fusidic acid, that accumulate in tissues during the initial phase of absorption. The subsequent release from the tissue into the serum invali-

TABLE 1. *Performance test: number of deleted values*

Expt	Equation 1				Equation 2			
	No. deleted		% Deleted		No. deleted		% Deleted	
	10%[a]	15%	10%[a]	15%	10%	15%	10%	15%
A[b]	47	44	42.0	39.3	0	1	0.0	0.9
B[c]	10	17	7.8	13.3	0	3	0.0	2.3
C[d]	1	2	1.0	2.1	0	0	0.0	0.0

[a] Random error.
[b] 500 mg of fusidic acid sodium salt per os.
[c] 1,000 mg of ampicillin and 1,000 mg of probenecid per os.
[d] 1,400 mg of pivampicillin hydrochloride per os.

TABLE 2. *Performance test: means and coefficients of variation for area*

Expt	Equation 1				Equation 2			
	Mean (μg/ml × h)		Coefficient of variation (%)		Mean (μg/ml × h)		Coefficient of variation (%)	
	10%	15%	10%	15%	10%	15%	10%	15%
A[b]	271	282	18.8	18.4	415	435	5.8	8.5
B[c]	56.9	54.7	9.4	13.2	57.6	58.6	5.2	11.5
C[d]	43.2	42.7	5.6	10.1	43.1	43.2	5.7	8.3

[a] Random error
[b] 500 mg of fusidic acid sodium salt per os.
[c] 1,000 mg of ampicillin and 1,000 mg of probenecid per os.
[d] 1,400 mg of pivampicillin hydrochloride per os.

TABLE 3. *Performance test: means and coefficients of variation for peak values*

Expt	Equation 1				Equation 2			
	Peak (μg/ml)		Coefficient of variation (%)		Peak (μg/ml)		Coefficient of variation (%)	
	10%[a]	15%	10%	15%	10%	15%	10%	15%
A[b]	38.1	42.2	8.9	11.5	36.9	39.5	7.3	7.7
B[c]	10.1	9.6	13.8	10.8	11.0	11.4	8.4	20.3
C[d]	19.4	19.2	11.0	14.7	19.9	19.8	7.8	11.6

[a] Random error.
[b] 500 mg of fusidic acid sodium salt per os.
[c] 1,000 mg of ampicillin and 1,000 mg of probenecid per os.
[d] 1,400 mg of pivampicillin hydrochloride per os.

dates the suppositions necessary for a one-compartment model. The new method, on the other hand, is free of assumptions and simply fits a curve to the data. Figure 2 and the same tables illustrate another, however less obvious, example of the failure of the one-compartment model. The fitted curve possesses a peak 10% below the highest experimental value in the set, and 7 to 13% of all the sample values had to be deleted before a fit could be achieved. This considerable strain on the model could be caused by the poor absorption of ampicillin, only about 33% being recovered in the urine in this case. Here again, the new method is unaffected by drug loss through the intestinal tract.

The results of an experiment illustrated by Fig. 3 and recorded in Tables 1, 2, and 3 concerns a drug that is well absorbed, namely pivampicillin, with a urinary recovery of 76% in the form of ampicillin. The one-compartment model performs better in this case than in the previous example with ampicillin, although the

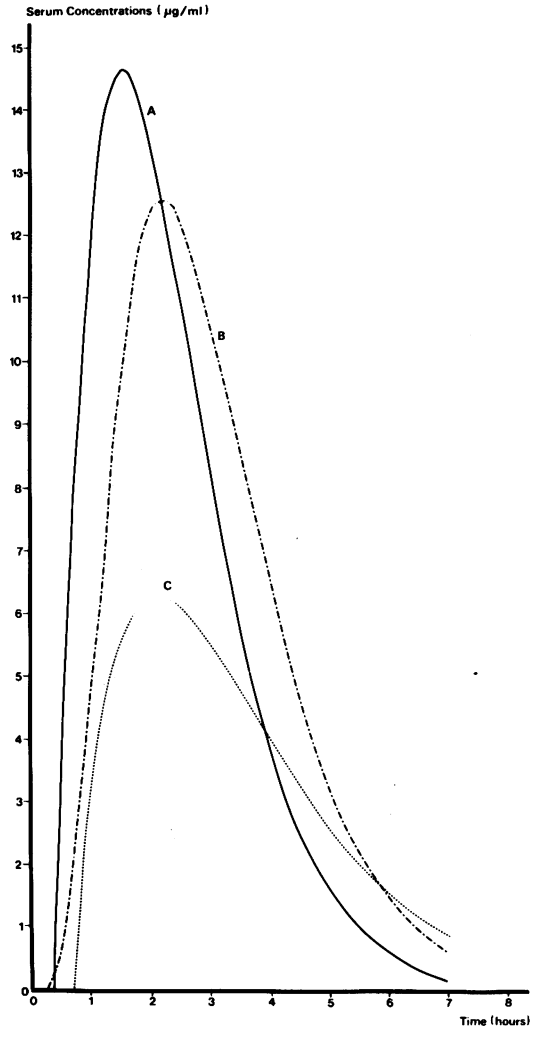

FIG. 4. *Comparative study. Mean serum level curves for 1,400 mg of pivampicillin hydrochloride administered per os (A), 1,000 mg of amoxycillin (B), and 1,000 mg of ampicillin (C).*

coefficients of variation are higher than those for the corresponding estimates obtained by the new method.

In Table 4 the coefficients of variation recorded on the bottom line include components that are due to differences between subjects, in addition to the components due to analytical error in the sample values. Estimates of the latter may be taken from Tables 2 and 3 and indicate that the differences between subjects in Table 4 are real. By the same argument, the differences between the coefficients of variation given in Table 4 for drugs B and C may reflect a greater variability in the absorption of ampicillin than in the absorption of pivampicillin. One limitation to the proposed method is illustrated in Table 5. The first sample taken after an intravenous injection is frequently deleted, resulting in unrealistically low peak values. On the other hand, the same is not true of data sets from intramuscular injections. The adjusted mean values for area given in Table 5 are practically identical for ampicillin applied intramuscularly and pivampicillin given per os, suggesting a nearly complete absorption of the latter. Foltz et al. (1), in a discussion of the results from the same experiment, arrived at an estimated absorption for pivampicillin of 88 to 95% based on peak values and areas, respectively. The derivation of these values was not specified, and the results seem to contradict their own figures for urinary recovery: 68.4% for the intramuscular dose of ampicillin and 77.0% for pivampicillin per os.

ACKNOWLEDGMENTS

Valuable advice and assistance was provided by T. Søndergaard in all matters pertaining to data processing techniques.

TABLE 4. *Comparative study: areas and peak values for equivalent doses*

Subject	Area (μg/ml)			Peak value (μg/ml)		
	A[a]	B[b]	C[c]	A	B	C
I	38.4	23.6	42.4	11.3	6.7	19.0
II	NS[d]	36.9	36.4	NS	9.8	10.7
III	40.5	11.2	31.9	9.5	2.5	8.6
IV	23.0	22.7	43.1	7.3	7.6	20.5
V	25.7	12.4	33.4	9.0	3.4	13.4
VI	NS	38.5	32.0	NS	3.5	11.2
VII	23.3	12.7	43.5	7.8	4.9	19.1
VIII	43.6	13.6	23.9	15.1	4.0	7.7
IX	24.5	38.9	46.3	8.3	7.8	17.7
X	41.4	14.9	49.8	13.2	4.7	21.7
XI	91.3	20.1	31.3	27.2	7.3	13.6
XII	44.1	35.4	41.4	17.1	15.3	13.1
Mean	39.6	23.4	38.0	12.6	6.5	14.7
Standard deviation (mean)	6.4	3.2	2.2	1.9	1.0	1.4
Coefficient of variation[e]	53.1	62.5	23.5	51.4	66.8	41.2

[a] 1,000 mg of amoxycillin.
[b] 1,000 mg of ampicillin.
[c] 1,400 mg of pivampicillin hydrochloride per os.
[d] NS, Data set deleted by the program.
[e] Karl Pearson coefficient of variation (percent) for individual data sets.

TABLE 5. *Comparison between routes of administration*

Subject	Area (μg/ml × h)			Peak value (μg/ml)		
	A[a]	B[b]	C[c]	A	B	C
1	12.0	34.7	21.2	9.9	18.8	7.3
2	14.7	23.8	17.0	25.6	12.7	8.9
3	8.5	31.6	23.7	9.2	22.0	9.4
4	11.2	33.5	28.4	9.2	14.8	11.6
5	18.0	32.3	27.8	20.0	13.0	9.9
6	15.5	23.4	28.3	28.8	11.4	13.9
Mean	13.3	29.9	24.4	17.1	15.5	10.2
Standard deviation (mean)	1.4	2.0	1.9	3.6	1.7	0.9
Mean[d]	21.4	24.3	24.4	27.5	12.6	10.2
Standard deviation (mean)[d]	2.2	2.0	1.9	5.8	1.4	0.9
Coefficient of variation[e]	30.5	19.2	22.9	71.2	28.8	24.9

[a] 311 mg of ampicillin intravenously.
[b] 616 mg of ampicillin intramuscularly.
[c] 712 mg of pivampicillin hydrochloride per os (500 mg of ampicillin).
[d] Adjusted to equivalent doses (500 mg of ampicillin).
[e] The Karl Pearson coefficient of variation (percent) for individual data sets.

LITERATURE CITED

1. Foltz, E. L., J. W. West, I. H. Breslow, and H. Wallick. 1971. Clinical pharmacology of pivampicillin, p. 442–454. Antimicrob. Ag. Chemother. 1970.
2. Knothe, H., B. Lauer, and K. Fabricius. 1974. Ampicillin, Pivampicillin und Amoxicillin. Arzneimittel-Forschung 24 Nr.6, p. 951–955.
3. Lanczos, C. 1956. Applied analysis. Prentice-Hall, Englewood Cliffs, N.J.
4. Leeson, L. J., and H. Weintraub. 1973. Calculating absorption rate constants for drugs with incomplete availability. J. Pharmacol. Sci. 62:1936–1941.
5. Notari, R. E., J. L. DeYoung, and R. Reuning. 1972. Effect of parallel first-order drug loss from site or administration on calculated values for absorption rate constants. J. Pharmacol. Sci. 62:225–228.
6. Perrier, D., and M. Gibaldi. 1973. Calculation of absorption rate constants for drugs with incomplete availability.

J. Pharmacol. Sci. 61:135–139.
7. Teorell, T. 1937. Kinetics of distribution of substances administered to the body. Arch. Int. Pharmacodyn. Ther. 57:205–224.
8. Wagner, J. G., and E. Nelson. 1964. Kinetic analysis of blood levels and urinary excretion in the absorptive phase after single doses of drug. J. Pharmacol. Sci. 53:1392–1403.
9. Westlake, W. J. 1973. Use of statistical methods in evaluation of in vivo performance of dosage forms. J. Pharmacol. Sci. 62:1579–1589.