Computer Program for a Double Exponential Equation to Determine Biological Constants

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A new computer program in Fortran II (with Format) for the equation, $C = \frac{a_0 k_a}{V_d(k_a - k_d)} \cdot (e^{-k_d t} - e^{-k_a t})$, has been written. This program overcomes the problems of the previous programs published. A grid method was used to search for the constants and a method to handle exponential overflow was included. Applicability of the equation and the computer program was demonstrated on the IBM 1410 computer system with eight different sets of data from the literature. The data represented a variety of drugs, *i.e.*, sulfaethylthiadiazole, aspirin alone or with additives, oxazepam, penicillin salts, and trimeprazine, in a variety of dosage forms. The conclusions of the authors were verified by the calculated constants. In some instances the conclusions of the originators of the data could be expanded by the use of the calculated constants.

As our techniques become more sophisticated and our understanding of biological systems becomes greater, the mathematical interpretation of the data can become more refined.

Teorell's work (1) stands as a landmark in the field of kinetics of drug absorption, distribution, and excretion. Teorell's equation 25 is a simplification of the kinetics of drug absorption, distribution, and excretion. It describes the kinetics of drug appearance in the blood and its disappearance from the blood when the drug is administered by any route other than i.v. The constant k_d is a combination of various rate constants due to tissue absorption, drug release from tissues, metabolism, and excretion by all organs.

$$C = \frac{k_a a_0}{V_d(k_a - k_d)} (e^{-k_d t} - e^{-k_a t}) \quad \text{(Eq. 1)}$$

a_0 = drug dose in mg./Kg.,
C = blood drug concentration in mcg./ml.,
t = time in hours,
k_a = the apparent first-order absorption rate constant in hr.$^{-1}$,
k_d = the apparent first-order drug disappearance rate constant from the blood in hr.$^{-1}$,
V_d = the specific apparent volume of drug distribution in L./Kg.

Equation 1 also neglects any effect due to excretion of the drug in the bile and reabsorption by the intestine. Teorell assumed apparent first-order kinetics for drug appearance and disappearance in the blood, which has been shown many times before to be a valid assumption. The absorption and excretion of certain drugs and dosage forms may not follow apparent first-order kinetics, *e.g.*, some sustained-release dosage forms or when metabolism of the drug is the slowest step.

In spite of the limitations of this equation, it may yield useful information about the rate of drug absorption, indirectly about the process of absorption, and the rate of drug disappearance from the blood.

It is the purpose of this paper to describe a new computer program used to solve Eq. 1, and to illustrate the application of this equation and computer program.

This program is different from the one previously reported (2) because a simpler, more rugged search routine is used to determine the constants, a method is included to handle exponential overflow, and the number of search grids is not limited. In addition, one less parameter is calculated, increasing speed and accuracy. A value for a_0/V_d is determined rather than for V_d only.

COMPUTER PROGRAM

Using the following:

$$\frac{a_0}{V_d} = \gamma, \text{ and } k_a - k_d = \delta$$

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The flow diagram for the program shown in Fig. 2 is available from the authors on request.

Eq. 1 may be rewritten as:

$$C = \frac{\gamma k_a}{\delta} (e^{-k_d t} - e^{-k_a t}) \qquad \text{(Eq. 2)}$$

Rearranging

$$C = \frac{\gamma}{\delta} k_a e^{-k_a t} (e^{\delta t} - 1) \qquad \text{(Eq. 3)}$$

Taking natural logs

$$\ln C - \ln(e^{\delta t} - 1) = \ln \left(\frac{\gamma}{\delta} k_a\right) - k_a t \quad \text{(Eq. 4)}$$

Equation 4 may be calculated by means of the least squares procedure. The program calculates the best values for the constants by finding the curve with the minimum variance.

The program in Fortran II (with Format) is divided into three main parts: (*a*) the data input statements 1–70, (*b*) the search for minimum variance, statements 75–360, and (*c*) the printing of the final results, statements 360–480.

The first card of the input data contains the title of the data (up to 80 positions). The second card is the number of observations (N) and the print control k_1. If the value of the print control k_1 is anything other than a zero or blank, the minimum variance and corresponding k_a, k_d, and k_d/k_a will be printed after each grid search. This was included in the program to give greater versatility if one is interested in seeing the results of each search. The third card contains the estimated values of k_a and for the ratio k_d/k_a. These estimates were made from literature values for similar drugs or just estimated. These estimates could vary by a factor of 10 or more and still obtain a proper solution to the equation. If the initial estimates of k_a and k_d differ from the final calculated values by a factor greater than 10, the computations would take about 45 min. The computer will continue to compute until it has calculated the best values. The fourth card begins the observations, one time value, and the corresponding concentration per card.

The second portion of the program begins using the input to obtain a variance. The initial estimates of k_a and k_d/k_a become the center for a 2^3 factorial ($\times$ in Fig. 1). The initial incrementing value of 0.1 is added or subtracted from the estimates of k_a and k_d/k_a giving eight new estimates for which variances are computed. A new factorial is built around the minimum variance of the eight computed. The current estimates of k_a and k_d/k_a are incremented and decremented in steps of 0.1 until the current minimum variance computed is larger than the previous one, or until k_a or k_d/k_a become zero or less than zero by subtraction of 0.1. The 0.1 incrementing value is then reduced to 0.05. The grid search routine continues alternately reducing the increment values by 0.005 each time the currently computed minimum variance exceeds the previous minimum variance, until the value of k_a increment reaches zero. The values for k_a and k_d/k_a are essentially incremented and decremented independently.

In this manner, the program converges on the minimum variance, which is assumed when the k_a increment reaches zero.

A simplified grid search routine is presented in Fig. 1.

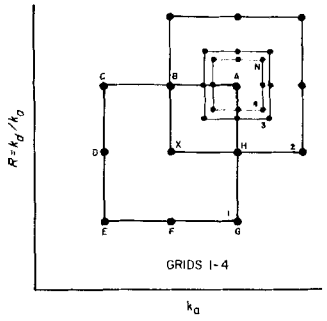

Fig. 1.—Grid search routine. Key: $\times$, initial intersection, the first estimates of k_a and k_d/k_a; A–H, first eight values to calculate variances. First minimum variance at A. The eight variances in grid 2 were greater than the one at A, so that the increments were reduced to 0.05 giving grid 3. For the purpose of this example both k_a and k_d/k_a were reduced simultaneously. In the program they are incremented and decremented independently. In grid 3 the new values of k_a and k_d/k_a gave larger variances than in A, so that the 0.05 increments were reduced by 0.005 (new increment = 0.045), giving grid 4. Again for simplification both constants were reduced simultaneously. A new minimum variance was found at N. The eight values in a grid using grid 1 as an example are: A: R + increment, k_a + increment; B: R + increment, k_a; C: R + increment, k_a − increment; D: R, k_a − increment; E: R − increment, k_a − increment; F: R − increment, k_a; G: R − increment, k_a + increment; and H: R, k_a + increment.

The final portion of the program computes and prints calculated concentrations at 15-min. intervals through the maximum time of the observed data. Following this, the values for δ, a_0/V_d, k_a, k_d, k_d/k_a, and the variance are printed.

A routine is set up in the program to avoid exponential overflow. This is done by checking the value of $-k_a t$. The exponential value ($e^{-k_a t}$) approaches zero as time increases. Absorption should be complete after many hours (*e.g.*, 24 hr.), so that if the value of $k_a t$ is greater than 50, the rate of absorption into the blood is negligible and the effect due to absorption is set to zero.

The approach using input of k_d/k_a is taken rather than using a constant for k_d because it is more accurate to work with this ratio.

The program was written for an IBM 1410 computer system, and due to the small core usage, it may be adopted to almost any computer system using Fortran. This program is fairly lengthy, dependent in part on the accuracy of the initial estimates for k_a and k_d/k_a and in part due to running the program concurrently with an interruptible telecommunications monitor. The procedure takes from 5 min. to 45 min. per set of data.

The complete program for Fortran II (with Format) is presented in Fig. 2.

RESULTS AND DISCUSSION

Most blood concentration *versus* time data in the literature could not be fitted by this equation because of: (*a*) poor spacing of time intervals, (*b*)

insufficient number of data, and (*c*) data were not collected over a sufficiently long period of time. These shortcomings of the data usually meant that the experiments were not designed for kinetic studies. Most of the usable data were found in the pharmaceutical literature where experiments were often designed for rate studies.

If the data showed an initial "lag phase" and only two points on the ascending portion of the curve, then the program may fail. Dropping the data for the lag phase and solving the equation would reduce the variance but may still give a poor fit due to lack of data. If the observed data give a high, sharp peak, the program would calculate a line below the peak and give a relatively poor estimate of the concentrations representing the peak.

Obviously, if the data do not follow apparent first-order kinetics, the equation would not fit the

```
C
C     CALCULATION OF KINETIC CONSTANTS FROM BLOOD LEVELS OF DRUGS
C     SEARCH ROUTINE FOR BEST REGRESSION FIT
C
C           DATA INPUT
C     THE FIRST CARD CONTAINS AN EIGHTY POSITION TITLE
C     THE SECOND CARD CONTAINS THE NUMBER OF OBSERVATIONS TO FOLLOW AND
C     THE PRINT CONTROL
C     THE THIRD CARD CONTAINS THE ESTIMATED VALUE FOR KA AND THE VALUE
C     FOR R, WHERE R= KD/KA
C     FOLLOWING THIS ARE THE VALUES FOR THE EXPERIMENTAL DATA.  ONE TIME
C     VALUE AND THE CORRESPONDING OBSERVED CONCENTRATION PER CARD
C
      DIMENSION COBS(25),TIME(25),TRY(8),SKA(8),SR(8),TITLE(8),SGAM(8)
    1 READ 10, ((TITLE(I), I=1,8)
   10 FORMAT(8A10)
      READ 20, N, K1
   20 FORMAT(2I2)
      XN=N
      READ 30, XKA, R
   30 FORMAT(2F10.0)
C
C     N= NUMBER OF OBSERVATIONS.  K1 = PRINT CONTROL.  IF K1 IS ANYTHING
C     THAN ZERO OR BLANK, THE MINIMUM VARIANCE AND CORRESPONDING KA AND
C     KD WILL BE PRINTED AFTER EACH GRID SEARCH
C     KA = FIRST ORDER ABSORPTION CONSTANT.     R = KD/KA, WHERE KD IS
C     THE APPARENT FIRST ORDER DISAPPEARANCE CONSTANT
C
      NCOUNT =0
      TKA=XKA
      TR=R
      JN=1
      XINC=0.1
      RINC=0.1
      DEC=0.05
      RDEC=0.05
      SUMX=0.
      J9=0
      NPAGE=0
C
C     SET INITIAL CONDITIONS INTO TEMPORARY MINIMUM POSITION
C     SET UP VALUES FOR INCREMENTS AND SET UP J9 AS CONTROL FOR WHICH
C     INCREMENT IS TO BE CHANGED FIRST
C
      NPAGE=NPAGE+1
      PRINT 40,(TITLE(I), I=1,8),NPAGE
   40 FORMAT(1H1,5X,70HSEARCH FOR CALCULATION OF KINETIC CONSTANTS FROM
     1BLOOD LEVELS OF DRUGS,5X,4HPAGE,I3//7X,8A10)
      PRINT 50
   50 FORMAT(//32X,17HEXPERIMENTAL DATA//29X,10HOBSERVED C,8X,4HTIME//)
      DO 70 J= 1,N
      READ 30, TIME(J),COBS(J)
      PRINT 60, COBS(J),TIME(J)
   60 FORMAT(27X,F12.5,6X,F8.3/)
   70 SUMX=SUMX+TIME(J)


  270 XSIG = TRY(1)
      XKA = SKA(1)
      R = SR(1)
      GAMMA = SGAM(1)
  280 CONTINUE
C
C     TEST PRINT CONTROL.  IF SET, PRINT MINIMUM VARIANCE AND
C     CORRESPONDING CONSTANTS ON GRID
C
      IF(K1)281,289,281
  281 XKA=XKA*R
      NCOUNT=NCOUNT-1
      IF(NCOUNT)282,282,283
  282 NPAGE =NPAGE +1
      PRINT 40,(TITLE(I),I=1,8),NPAGE
      NCOUNT = 41
  283 PRINT 285,XSIG,XKA,XKD,R
  285 FORMAT(/5X,5HVAR =,F12.5,5H KA= ,F12.5,5H KD= ,F12.5,4H R= ,F12.5)
C
C     IS THIS MINIMUM LESS THAN PREVIOUS MINIMUM?
C     IF SO, CONTINUE SEARCH AROUND CURRENT POINT
C     IF NOT, REDUCE INCREMENT AND CONTINUE SEARCH AROUND TEMPORARY
C     MINIMUM
C
  289 IF(XSIG-TEMP)290,335,335
  290 TEMP = XSIG
      TGAM=GAMMA
      TKA =XKA
      TR = R
C
C     R CAN NEVER BE ZERO, KA CAN NEVER BE LESS THAN OR EQUAL TO ZERO
C
  300 IF(R-RINC)310,335,310
  310 IF(XKA-XINC)335,335,320
  320 XKA = XKA + XINC
      GO TO 75
C
C     FOR FIRST POINT OF KA AND R
C
  330 TEMP = SIGMA
      TGAM = GAMMA
      IN = 8
      GO TO 300
C
C     REDUCE THE VALUE OF THE INCREMENTS ALTERNATELY
C
  335 IF(J9-1)340,350,340
  340 XINC = XINC - DEC
      DEC =0.005
      XKA = TKA
      R = TR
      J9 =1
C
C     IF KA INCREMENT IS ZERO ASSUME MINIMUM VARIANCE HAS BEEN FOUND
C


   75 DO 240 I=1,IN
      XKD=XKA*R
      DELTA=XKA-XKD
C
C     KD MAY NEVER BE = OR GREATER THAN KA
C
      IF(DELTA)190,190,80
   80 SUMY=0.
      DO 90 J=1,N
   90 SUMY=SUMY + LOGF(COBS(J)/(EXPF(DELTA*TIME(J))-1.))
      IF ACCUMULATOR OVERFLOW, 190, 100
  100 GAMMA = EXPF(SUMY/XN + XKA*SUMX/XN)*DELTA/XKA
C
C     GAMMA= AO/VD
C
      VAR=0.
      DO 160 J= 1,N
C
C     ROUTINE TO AVOID EXPONENTIAL OVERFLOW
C
      IF(-XKA*TIME(J) + 50.)110,110,150
  110 CALC=(GAMMA*XKA/DELTA)*(EXPF(-XKD*TIME(J)))
      GO TO 160
  150 CALC= (GAMMA*XKA/DELTA)*(EXPF(-XKA*TIME(J)))*(EXPF(DELTA*TIME(J))-
         1.)
  160 VAR=VAR + (COBS(J)-CALC)**2
      IF(IN-1)180,170,180
  170 SIGMA = VAR/(XN-3.)
      GO TO 330
  180 TRY(I) = VAR/(XN-3.)
      SKA(I)=XKA
      SR(I) = R
      SGAM(I) = GAMMA
  190 GO TO (200,210,210,220,220,230,230,240),I
C
C     SIGMA = INITIAL AND FINAL VARIANCES
C     STATEMENT 190 CAUSES COMPUTATION OF THE EIGHT POINTS ON THE GRID
C
  200 R = R-RINC
      GO TO 240
  210 XKA = XKA-XINC
      GO TO 240
  220 R = R + RINC
      GO TO 240
  230 XKA = XKA + XINC
  240 CONTINUE
C
C     SEARCH FOR MINIMUM VARIANCE ON GRID
C
      XSIG = TRY(1)
      XKA = SKA(1)
      R = SR(1)
      GAMMA = SGAM(1)
      DO 280 I = 2,8
      IF(XSIG-TRY(I))280,280,270



      IF(XINC)360,360,300
  350 RINC = RINC -RDEC
      RDEC = 0.005
      XKA = TKA
      R = TR
      J9 = 0
      GO TO 300
C
C     MINIMUM VARIANCE HAS BEEN FOUND.  PRINT FINAL RESULTS
C
  360 GAMMA = TGAM
      XKA = TKA
      R = TR
      SIGMA = TEMP
      XKD = XKA*R
      DELTA = XKA-XKD
      NPAGE = NPAGE +1
      PRINT 40,(TITLE(I),I = 1,8),NPAGE
      PRINT 370
  370 FORMAT(///32X,8HBEST FIT///15X,12HCALCULATED C,8X,4HTIME//)
      NCOUNT = 41
      JN=TIME(N)+4.
C
C     CALCULATE CONCENTRATION AT FIFTEEN MINUTE INTERVALS
C
      XTIME=0.
      DO 450 J=1,JN
      XTIME=XTIME+.25
C
C     ROUTINE TO AVOID EXPONENTIAL OVERFLOW
C
      IF(-XKA*XTIME+50.)380,380,420
  380 CALC=(GAMMA*XKA/DELTA)*(EXPF(-XKA*XTIME))*(EXPF(-XKD*XTIME))
      GO TO 430
  420 CALC=(GAMMA*XKA/DELTA)*(EXPF(-XKA*XTIME))*(EXPF(DELTA*XTIME)-1.)
  430 NCOUNT = NCOUNT - 1
      IF(NCOUNT)440,440,450
  440 NAPGE = NPAGE +1
      PRINT 40,(TITLE(I),I=1,8), NPAGE
      PRINT 370
      NCOUNT = 41
  450 PRINT 460,CALC,XTIME
  460 FORMAT(15X,F12.5,4X,F8.3/)
      IF(NCOUNT-18)470,470,480
  470 NPAGE = NPAGE +1
      PRINT 40,(TITLE(I),I=1,8),NPAGE
  480 PRINT 490,DELTA,GAMMA,XKA,XKD,R,SIGMA
  490 FORMAT(//20X,7HDELTA =,4X,F12.5//20X,7HAO/VD =,4X,F12.5//20X,4HKA
     1=,7X,F12.5//20X,4HKD =,7X,F12.5//20X,7HKD/KA =,4X,F12.5//20X,11HVA
     2RIANCE = ,F12.5)
      PAUSE
      GO TO 1
      END
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Fig. 2.– Computer program in Fortran II (with Format) for double exponential equation.

observed data. Symmetrical curves on rectangular coordinates are an indication of non-first-order rates.

If the data for each subject were used instead of averages, then additional steps may be added to the program to calculate the variation about each point on the observed curve. With the present program separate tests must be made to determine the goodness of fit of the calculated curve. The χ^2 test,

$$\chi^2 = \frac{(C_{obs.} - C_{calcd.})^2}{C_{calcd.}}$$

can be used. The χ^2 values obtained are compared with the table of χ^2 values. It was found that the computer calculated variance was just as good an indicator of goodness of fit as the χ^2 test.

The following is a brief discussion of several sets of data obtained from the literature. The constants are presented in Table I.

The disappearance rate constant for sulfaethylthiadiazole (SETD) calculated by Swintosky *et al.* (3) was verified. Using averages of the published data, the k_d calculated by the computer is 0.0856 hr.$^{-1}$ and that reported was 0.073 hr.$^{-1}$ (average of four values). The k_a calculated is 2.68 hr.$^{-1}$, indicating a much more rapid absorption than disappearance from the blood. The a_0 was calculated from the 2.0-Gm. dose divided by the average weight of the subjects.

Table I.—Computer Calculated Constants from Literature Data

Ref.	k_a hr.$^{-1}$	k_d hr.$^{-1}$	V_d L./Kg.
(3)	2.675	0.0856[a]	0.62
(4)			
1.0 Gm.	0.500	0.438	0.0718
2.0 Gm.	0.455	0.417	0.0895
3.0 Gm.	0.285	0.221	0.120
4.0 Gm.	0.495	0.370	0.117
(5)			
Plain tablet	0.970	0.0909[b]	0.189
Sustained-release	0.955	0.0604[c]	0.271
(6)			
D	2.07	0.246	0.146
E	0.535	0.461	0.0826
L	0.635	0.400	0.0955
(7)	0.295	0.0723	0.906
(8)			
Fasting:			
penicillin acid	2.495	0.986	5.643[d]
cal. penicillin V	3.315	1.061	7.112[d]
pot. penicillin V	3.225	0.903	7.908[d]
sod. penicillin V	2.210	0.641	3.312[d]
Std. meal:			
penicillin acid	0.820	0.816	2.274[d]
cal. penicillin V	0.990	0.985	2.903[d]
pot. penicillin V	1.035	1.025	3.809[d]
sod. penicillin V	0.940	0.931	1.367[d]
(9)			
Buffered ASA	1.310	0.116	0.142
138	0.155	0.136	0.228
152	0.195	0.120	0.165
134 B	Poor fit		
134 C	0.435	0.154	0.129
(10)			
5 mg.	0.465	0.0860	0.000457
15 mg.	0.865	0.0800	0.000533
5 mg. t.i.d.	0.100	0.0835	0.000520
15-mg. sustained-release	0.0950	0.0931	0.000528

[a] 0.073 hr.$^{-1}$ reported. [b] 0.09 hr.$^{-1}$ reported for 1 patient. [c] 0.05 reported. [d] a_0/Vd values are not given because patient weights were not reported.

Later Swintosky *et al.* (4) reported blood concentrations from SETD given in 1.0, 2.0, 3.0, and 4.0-Gm. doses. These data could not be fitted by Eq. 1 using the previous program (2). There is an apparent "lag time" in the initial absorption of the drug before absorption becomes an exponential process, so that the concentration at 20 min. was omitted. This resulted in better fitting the observed data by the calculated data, and the variance was decreased by about one-half. The omission of the data at 20 min. resulted in only small increases in the values on the constants. The dose a_0 was calculated as indicated above. The present equation would require an additional term to fit the initial "lag time." This "lag time" is important in determining length of time for absorptive process to occur.

The constants calculated from these data differ considerably from those calculated from the first set of data described above. There is essentially no difference in the k_a for 1.0, 2.0, and 4.0-Gm. doses, and for k_d for 1.0 and 2.0-Gm. doses. The V_d for 1.0 and 2.0-Gm. doses are similar, as are those for 3.0 and 4.0-Gm. doses. The k_a and k_d for the 3.0-Gm. dose are smaller than those for the other doses. Some of the discrepancies are due to the fact that the calculated data cannot reproduce the high peaks in the 1.0 and 2.0-Gm. doses, so the computer-calculated k_a could be smaller than those reported by Swintosky *et al.* (3) in their earlier work. Also, if the data had been collected for longer than 4 hr., a different k_d might have been obtained. The k_d for the 3.0-Gm. dose may be only an estimate because of the lack of data to properly calculate the k_d. For the 4.0-Gm. dose, the calculated concentrations did not go so high as the observed concentrations. In the other three cases the calculated data appear to give a good approximation of the experimental data. Since the 3.0-Gm. dose gives different constants, the 4.0-Gm. dose a relatively small V_d, and the V_d for the 3.0 and 4.0-Gm. doses differ from the 1.0 and 2.0-Gm. doses, it is possible that different rate-limiting steps become important at the 3.0-Gm. dose and greater.

Nicholson *et al.* (5) compared blood levels due to SETD in plain tablets and as sustained-release tablets. The data were averaged and the computer calculated constants found in Table I verify the constants for rate of disappearance from the blood reported by Nicholson and co-workers. The k_a did not vary significantly between the plain tablets and the sustained-release tablets, although the rates of absorption vary. The decrease in k_d for the sustained-release tablets is accompanied by an increase in V_d indicating wider distribution or more SETD in the fluids which would be expected from Eq. 1. The smaller k_d indicates slower disappearance from the blood.

Liberman and Wood (6) compared three different aspirin formulations and reported serum salicylate levels up to 2.5 hr. The three formulations

were: *D*, aspirin, dihydroxyaluminum glycinate, and magnesium carbonate; *E*, commercial aspirin–starch granulation; and *L*, a commercial aspirin tablet. The constants for formula *E* could not be calculated by the previous program (2). The data showed higher and earlier peak of salicylate in serum with formula *D*. This can be seen from the k_a which is 3 to 4 times greater than the k_a for the other two preparations, a smaller k_d and a larger V_d, indicating a more rapid absorption and a slower loss from the blood.

The constants for the data of Walkerstein *et al.* (7) could not be calculated by the previous program but were satisfactorily calculated by the new program. Plasma levels of ^{14}C-oxazepam given orally to dogs were reported from 0.5–120 hr. The calculated constants are shown in Table I.

Juncher and Raaschou (8) gave 400,000 units of penicillin acid and various penicillin salts to 10 subjects, either fasting or after a standard meal. Blood levels were measured from 0.25 to 6 hr. The fasting subjects had higher blood levels and the calcium and potassium salts of penicillin V gave the highest blood levels. The authors' conclusions are verified by the calculated constants. The data from subjects which had fasted gave much higher k_a, indicating higher rates of absorption than the data from subjects who ate a standard meal. The rate of decline in the blood levels was about the same for all preparations.

Wood and Syarto (9) compared buffered aspirin to aspirin coated with different ratios of ethyl- and methylcellulose; for formula 138 the ratio was 100:1; for 152, 82.5:17.5; for 134B, 75:25; and for 134C, 25:75. The workers did not calculate any rate constants, but stated plots of cumulative *in vivo* release fit apparent first-order better than zero-order kinetics. The same amount of aspirin was used in all the formulas. Blood levels were obtained from 0.5 to 24 hr. The constants shown in Table I indicate that the absorption rate for buffered aspirin is much greater than for the other preparations. The rate of decrease in blood for all the preparations is similar; also V_d does not change very much with formulation changes. As the ethylcellulose content of the coatings decreases, the rate of aspirin absorption increases and the apparent specific body volume decreases. Therefore, the amount of ethylcellulose in the coating affects the rate of aspirin absorption.

Johnson and Masters (10) gave ^{35}S-labeled trimeprazine tartrate orally to patients. Serum levels up to 48 hr. were used to compare a 5-mg. dose, a 15-mg. dose, a 5-mg. dose given 3 times a day, and a 15-mg. dose sustained-release preparation. These workers reported the characteristic differences expected between a 5-mg. dose and a 15-mg. dose, and that 5 mg. given 3 times a day and the 15-mg. sustained-release product gave similar blood levels. The constants shown in Table I indicate that the rate of disappearance of the drug from the blood given by the various dosage regimens and the V_d closely agree. The V_d for the 5-mg. dose is smaller because there is only one-third the amount to be distributed in the body compared to the other 15-mg. doses. The V_d for the other three preparations are similar. The k_a for the 15-mg. dose is about 1.86 times greater than the k_a for the 5-mg. dose; assuming instantaneous availability for both dosages, this could indicate k_a is dose dependent. The more drug exposed to absorbing surfaces, the more rapid the absorption. The k_a for the 5-mg. dose given 3 times a day and the 15-mg. sustained-release preparation appear the same, the k_d are similar, and the V_d appear the same, indicating the divided dose therapy and the sustained-release preparation are similar.

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