

# A Pharmacokinetic Program for TI-59

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A program for pharmacokinetic analysis and calculations by means of the inexpensive and generally available mini-calculator TI-59 in conjunction with the adaptable printer PC-100 A is presented and demonstrated. The program may be used in the analysis of plasma concentration curves originating from intravenous or paravascular administration of drugs with one- or two-compartment characteristics obeying first-order pharmacokinetics. In relation to peroral administration, one or two consecutive first order input steps may be used. The program incorporates routines for exponential regression analysis, extrapolation and determination of residuals, calculation of composite rate-constants and the corresponding zero-time concentration constants. Curves may be simulated by function tabulation thus allowing manual curve-fitting procedures and determination of a possible lag-time. Time-defined intravenous infusion substituting for bolus injection as well as multiple dose, steady state pharmacokinetics may also be treated by the program, which ends up with a routine procedure for calculation of the microscopic rate-constants, the various volumes of distribution, the area under the plasma concentration curve and total drug clearance. Lithium and dipyridamole plasma concentration data are used to demonstrate the practical application of the program.

**Key Words:** Pharmacokinetics; Program, Methods, Dipyridamole, Lithium

## INTRODUCTION

As commented upon by Veng Pedersen (1977) in a report on his new pharmacokinetic nonlinear curve-fitting program *FUNFIT*, the high complexity of the considerable number (about 15) of programs for automatic, nonlinear, least-square parameter estimation, which are more or less easily available, have often resulted in an authoritativeness, which may go so far as using the programs as a substitute for rational thought. Such programs, of which Sedman and Wagner's *AUTOAN* (1974), later modified to *NAUTOAN* (1977), are probably the most often used, constitute nevertheless very valuable and powerful tools in pharmacokinetic analyses if their limitations are recognized. But even then it must be realized that these programs as well as the less advanced programs, which only carry out automatic, exponential curve stripping (*CSTRIP* by Sedman and Wagner, 1976 and *ESTRIP* by Brown and Manno, 1978), are only stated to produce analytical results "usually comparable to or better than" manual graphical methods. Thus poorer results may

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occasionally be experienced by the use of these automatic computer techniques (Veng Pedersen, 1977).

The original method of manual graphic pharmacokinetic analysis is time-consuming, but the principle may be used in a program for feeding a modern electronic calculator, whereby exponential stripping in conjunction with exponential regression analyses can be carried out in a few minutes and thus provide the investigator with initial polyexponential parameter estimates.

The following text contains a description of the most essential theoretical features and practical instructions for the use of a program developed for pharmacokinetic analysis and calculations by means of the inexpensive and universally available mini-calculator TI-59. The program may be used in treating the most commonly experienced pharmacokinetic analytical problems related to single and multiple dose administration of drugs with one or two compartment characteristics obeying first-order kinetics.

## METHODS

The mini-calculator Ti-59 from Texas Instruments, which is programmable both directly from the keyboard and from magnetic cards, was supplied with the statistics library "solid state software" module, but only the linear regression initialization routine of this module was used. An adjunct use of the adaptable printer PC-100 A is assumed in the program.

The pharmacokinetic program developed for Ti-59 incorporates a routine for exponential regression analysis of the time/concentration data corresponding to the eliminatory  $\beta$ -phase and of the time/residual values defining the distributory  $\alpha$ -phase and the possible  $k_a$  and  $k_b$  phases related to absorption, dissolution, and disintegration processes in the time course of plasma (or serum) concentration curves experimentally established after intravenous or paravasal administration of drugs with two-compartment characteristics. Demarcation of the various phases is judged graphically from semilogarithmic plots and under the possible guidance of correlation coefficients, stepwise estimated in the exponential regression analyses. By eliminating the  $\alpha$ -phase, plasma concentration curves established by drugs with one compartment characteristics may be similarly treated.

The backward projections determined concentration constants at zero time ( $A^*$ ,  $B^*$ , and possibly  $C^*$  and  $D^*$ ) and the corresponding rate constants ( $\alpha$ ,  $\beta$ , and possibly  $k_a$  and  $k_b$ ) are used in the program to simulate the relevant theoretical plasma concentration/time lapse in accordance with one of the following functions related to intravenous (eq. 1) or paravasular administration (eqs. 2 and 3):

$$c_1 = \frac{(k_{21} - \alpha)k^0(1 - e^{\alpha T})}{-\alpha(\beta - \alpha)V_c} e^{-\alpha t} + \frac{(k_{21} - \beta)k^0(1 - e^{\beta T})}{-\beta(\alpha - \beta)V_c} e^{-\beta t} \quad (1)$$

and

$$c_1 = \frac{k_a a_0 (k_{21} - \alpha)}{(\beta - \alpha)(k_a - \alpha)V_c} e^{-\alpha t} + \frac{k_a a_0 (k_{21} - \beta)}{(\alpha - \beta)(k_a - \beta)V_c} e^{-\beta t} + \frac{k_a a_0 (k_{21} - k_d)}{(\alpha - k_d)(\beta - k_d)V_c} e^{-k_d t} \quad (2)$$

and

$$c_1 = \frac{k_b k_a a_0 (k_{21} - \alpha)}{(\beta - \alpha)(k_b - \alpha)(k_a - \alpha)V_c} e^{-\alpha t} + \frac{k_b k_a a_0 (k_{21} - \beta)}{(\alpha - \beta)(k_b - \beta)(k_a - \beta)V_c} e^{-\beta t} \\ + \frac{k_b k_a a_0 (k_{21} - k_d)}{(\alpha - k_d)(\beta - k_d)(k_b - k_d)V_c} e^{-k_d t} + \frac{k_b k_a a_0 (k_{21} - k_b)}{(\alpha - k_b)(\beta - k_b)(k_a - k_b)V_c} e^{-k_b t}. \quad (3)$$

In eq. (1)  $T$  is equal to  $t$  during infusion of the drug and attains a constant value at the time of its termination, which then is reckoned as zero time. The rate of infusion is  $k^0$ , whereas  $V_c$  is the apparent volume of the central compartment. The complete coefficients to  $e^{-\alpha t}$  and  $e^{-\beta t}$  equals the concentration constants  $A^*$  and  $B^*$ , respectively. In order to calculate the remaining pharmacokinetic parameters relevant to intravenous time-limited infusion,  $A^*$  and  $B^*$  are corrected to the values ( $A'$  and  $B'$ ) corresponding to bolus injection:  $A' = A^* \alpha T / (1 - e^{-\alpha T})$ , (4) and  $B' = B^* \beta T / (1 - e^{-\beta T})$ , (5). After calculating the ratio  $F = -A'/B'$ , (6), the uncomposite rate constants  $k_{21}$ ,  $k_{10}$ , and  $k_{12}$  are calculated according to the equations:  $k_{21} = (\alpha - F\beta)/(1 - F)$ , (7),  $k_{10} = \alpha\beta/k_{21}$ , (8), and  $k_{12} = \alpha + \beta - k_{10} - k_{21}$ , (9).

The apparent volume of the central compartment is determined as:  $V_c = a_0(k_{21} - \beta)/(B'(\alpha - \beta))$ , (10), where the total dose  $a_0 = k^0 T$ . The apparent volume of distribution corresponding to the  $\beta$ -phase is then  $V_{d\beta} = V_c k_{10}/\beta$ , (11), whereas at equilibrium (or steady state)  $V_{de} = V_c(1 + (k_{12}/k_{21}))$ , (12). The apparent volume of the peripheral compartment is calculated in the program as:  $V_{pe} = V_{de} - V_c$ , (13). The area under the function-fitted plasma concentration curve is determined as:  $AUC_{iv} = (A'/\alpha) + (B'/\beta)$ , (14), and  $V_c$  is as a control measure, also calculated as  $V_c = a_0/(AUC k_{10})$ , (15). Body clearance of the drug in question is calculated as  $Cl = k_{10}V_c$ , (16).

In analyses of plasma concentration curves obtained after paravasal (eg, peroral) drug administration, it may be necessary to carry out minor curve-fitting procedures and determination of a possible lag-time before fixing the backward projections ( $A'$ ,  $B'$ ,  $C'$  and possibly  $D'$ ) at the end of that time that correspond to the function zero. The procedures are given in the instructions for using the program. An  $F$ -value is then calculated as:  $F_1 = -A'(k_a - \alpha)/(B'(k_a - \beta))$ , (17) or possibly  $F_2 = -A'(k_a - \alpha)(k_b - \alpha)/(B'(k_a - \beta)(k_b - \beta))$ , (18). Then  $k_{21}$ ,  $k_{10}$  and  $k_{12}$  are calculated according to the eqs. (7), (8), and (9), whereas the area under the curve is given as:  $AUC_{pv} = (A'/\alpha) + (B'/\beta) + (C'/k_a)$  and possibly  $+ (D'/k_b)$ , (19).

In these cases the systemic available dose of the drug ( $a_0$ ) in the preparation used has to be determined on the basis of the ratio ( $AUC_{pv}/AUC_{iv}$ ) of the areas under the plasma concentration curves corresponding to equal paravasal and intravenous doses. The procedure is given in the program instructions.  $V_c$  may then be determined as:  $V_c = k_a a_0 (k_{21} - \beta)/(B'(\alpha - \beta)(k_a - \beta))$ , (20) or possibly as:  $V_c = k_a k_b a_0 (k_{21} - \beta)/(B'(\alpha - \beta)(k_a - \beta)(k_b - \beta))$ , (21), in case of a disintegration/dissolution phase. The remaining parameters are calculated according to the eqs. (11), (12), (13), (15), and (16).

In analysis of a multiple dose, steady state plasma concentration curve, the backward projection concentration constants at the time for the last dose (corrected

for duration of infusion or a possible lag-time),  $A'$ ,  $B'$ , and possibly  $C'$  and  $D'$ , have to be transformed by the program to the corresponding single dose constants before the above stated pharmacokinetic parameters can be calculated. This is effected by multiplication of the constants in question with the factor  $(1 - e^{-k_i T})$ , where  $k_i$  represent  $\alpha$ ,  $\beta$ ,  $k_a$  and  $k_b$ , whereas  $T$  is the dosage interval.

The pharmacokinetic program for Ti-59 is shown in Figure 1. The program is contained on three sides of two magnetic cards.

## INSTRUCTIONS FOR USING THE PROGRAM

The following is an outline of procedures used with the program:

1. Partitioning of the calculator memory: Enter 4, press 2. OP 17.
2. Press CLR, enter side 1 of magnetic card no. 1, CLR, enter side 2, CLR, enter side 1 of card no. 2.
3. Press 2. FIX 5 to obtain print out to 5 decimal places.
4. Press RST R/S to initialize the program, in repetitive runs preceded by 2. CMs.
5. Entering of data: Enter time value, press R/S, enter plasma concentration value

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000 1 050 GTO 100 GTO 150 RCL 200 = 250 STO 300 STP 350 +/- 400 - 450 1 500 : 550 = 600 17
0 0 OP 3 21 STO 16 01 + RCL - ( PRT EQ
STO 12 SUM PRT 38 RCL GTO 1 14 RCL : (
07 INV 07 ADV RCL 39 E ) = 25 14 RCL 1/X
LBL LNX GTO R/S 20 STO LBL x : ) - x
D PRT D LBL x 19 1/X 1 ( = RCL = RCL
PGM ST* LBL +/- RCL 0 RCL INV STO 11 STO 16
01 07 E RCL 22 STO 36 SUM 17 26 ) 30 =
SBR 1 ADV 22 = 22 1/X 33 - PRT : PRT SUM
CLR CLR SUM ADV PRT = GTO PRD = RCL EQ RCL RCL 32
010 LBL 060 07 110 RCL 160 x 210 INV 260 E 310 10 360 EQ 410 11 460 + 510 10 560 14 610 RCL
A X:T 10 RCL LNX LBL RCL EE 1/X ) - EQ 20
R/S PRT PRT 11 x E' 37 IFF = x STO = EQ
PRT +/- RCL = RCL RCL 1/X 01 PRD RCL 29 RCL (
X:T ST* 11 +/- 19 24 PRD LNX 25 14 RCL 28 1/X
CLR 07 PRT INV = x 13 PD* RCL x 17 : x
R/S 1 RCL LNX STO = RCL RCL 33 20 LBL EQ RCL RCL
PRT SUM 12 x 39 11 24 INV EQ + ) 26 19
LNX 07 PRT RCL RCL = STO 34 01 - 11 ( + -
E+ OP ADV 10 36 STO 34 01 - 11 ( + - SUM
020 RCL 070 13 120 RCL 170 = 220 + 270 36 320 GTO 370 EE 420 RCL 470 = 520 CE 570 = 620 32
03 PRT 13 STO RCL PRD CE LBL 14 LBL - x LBL
PRT ADV PRT 36 37 10 LBL LNX = 27 RCL RCL (
ADV ST* RCL RCL + RCL 1/X INV : PRT 11 29 RCL
GTO 07 14 14 RCL 24 STP PD* ( +/- ) = STO 32
A 1 PRT x 38 STO 01 33 RCL + - STO ADV
LBL SUM RCL RCL + 34 GTO LBL 20 RCL PRD 31 PRT
B 07 15 22 = RCL x d' EE' - 11 29 PRT ADV
PRT CLR PRT = +/- 14 v* SUM 11 RCL 20 RCL 1/X
LNX X:T ADV +/- RCL 14 v* SUM 11 RCL 20 RCL 1/X
030 INV 080 130 RCL 180 INV 230 PRT 280 = 330 4 380 33 430 ) 480 26 530 EQ 580 29 630 RCL
E+ LBL 16 LNX ADV STO STO DSZ = + ) = PRT :
RCL x2 1x1 x RCL 37 00 CLR 25 14 ( RCL RCL
03 PRT +/- RCL 23 PRD 1 CLR 25 14 ( RCL RCL
PRT OP STO 13 SUM 13 1 RTN LBL = CE 13 27
ADV 14 16 = 22 STP STO LBL SUM STO - : =
GTO INV PRT STO GTO 01 33 A' RCL 28 RCL RCL PRT
A LNX RCL 37 +/- GTO LBL RCL 25 PRT 11 14 ADV
LBL PRT 17 RCL LBL CE CLR 13 PRT ADV ) + R/S
B' +/- PRT 17 C' LBL ( : ADV RCL - LBL 0
040 3 090 + 140 RCL 190 x 240 RCL 290 D' 340 ( 390 RCL 440 x 490 26 540 PRD 590 - = RCL
INV R/S 18 RCL 36 RCL RC* 10 RCL - 29 RCL
SUM SUM PRT 22 STO 35 33 = 11 RCL LBL 10
07 = ADV = 10 STO x +/- +/- 11 ) :
GTO PRT RCL +/- RCL 34 RCL STO + - RCL RCL
A ADV 19 INV 37 LBL 34 25 RCL x 29 11
LBL R/S PRT LNX STO CE ) RCL 14 RCL 29 =
0 GTO RCL x 13 SBR +/- 17 = 38 x 32
CLR x2 20 RCL RCL Y* INV EQ : PRT RCL 20
EQ LBL PRT 16 38 INV LNX SUM 1 ADV 27 RCL

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FIGURE 1. Listing of the pharmacokinetic program for Ti-59.

(unit:  $\text{mass l}^{-1}$  or  $\text{mmol l}^{-1}$ ), R/S. Repeat for all data judged as belonging to the terminal  $\beta$ -phase of the plasma concentration time lapse. Entered data are printed out followed by a numerator.

6. Deleting of entered data: Enter the unwanted data pair as above, but terminate with pressing B instead of R/S.

7. Exponential regression analysis of entered data: Press C, which is followed by print out of the zero time Y-axis intercept  $B^*$ , the regression line slope  $-\beta$  and the correlation coefficient  $r$ .

8. Entering of supplementary data after analysis: Press 2. B and enter data as stated in 5.

9. Deleting of data after analysis: Press 2. B, enter  $t$  value, press R/S, enter  $c$  value and press B. New analysis as described in 7.

10. Extrapolation of the  $\beta$ -phase and determination of residuals: Enter preceding  $t$  value, press R/S, which is followed by print out of this and the extrapolated concentration value. Then enter the corresponding actual plasma concentration value, press R/S and the residual value is printed out. This is repeated for all data pairs preceding the  $\beta$ -phase.

11. Initialization for analysis of residuals: Press D.

12. Entering of time/residual data of first order corresponding to the judged  $\alpha$ -phase of the plasma concentration curve as described under 5 and 6.

13. Exponential regression analysis of residuals: Press C, which is followed by printing of  $A^*$ ,  $-\alpha$  and  $r$ . Supplementing or deleting of data as in 8 and 9.

13A. In case of drugs with only one-compartment characteristics, 11, 12, and 13 are substituted by keying D followed by C, whereby the  $\alpha$ -phase calculations are eliminated. In case of analysis of intravenous data proceed according to 18, 19, 21, and 22.

14. In analysis of paravascular (eg, peroral) data with an absorption phase ( $k_a$ -phase) an extrapolation of the linear first order residuals of the  $\alpha$ -phase and a determination of residuals of second order corresponding to the  $k_a$ -phase is carried out similarly as stated in 10. In case of one-compartment drugs the residuals of first order determined in 10 are used for further treatment.

15. The corresponding times and negative residuals related to the  $k_a$ -phase are entered as positive and analysed according to 11, 12, and 13, ending up with a print out of  $C^*$ ,  $-k_a$  and  $r$ .

16. In some cases the plasma concentration/time data necessitates introduction of a disintegration/dissolution phase ( $k_b$ -phase) in the analysis. This may be accomplished by extrapolation of the linear part of the residuals of second order corresponding to a  $k_a$ -phase with simultaneous determination of positive residuals of third order, which represents an initial linear  $k_b$ -phase. Procedure as in 10.

17. Analysis of the residuals of third order, as in 11, 12, and 13, whereby  $D^*$ ,  $-k_b$ , and the relevant  $r$  are determined and printed out.

18. Tabulation of the initial polyexponential parameter estimates: Press E.

19. Simulation by tabulation of the corresponding polyexponential function is carried out by entering a suitable time interval value ( $t'$ , eg, given in minutes) in the program:  $t'$  STO 23, followed by pressing R/S, which initiates the printing out of the time/concentration course from zero time and at consecutive  $t'$ -intervals. The

simulation may be started at times deviating from zero by entering the appropriate time in register 22:  $t$  STO 22. Simulation is stopped by pressing R/S. Repetition of the simulation (or parts of it) is done by entering the adequate starting time in register 22 followed by the key sequence GTO +/- R/S.

20. A final curve (function) fitting is often required for the  $k_a$ -phase. This may be carried out manually by successive minor changes of  $C^*$  and possibly  $k_a$ , making use of repetitive curve simulations according to 19. A possible lag-time, which is discovered by a negative sum of  $A^*$ ,  $B^*$  and  $C^*$  may be determined in the same simulation procedure as the positive time of function zero, where  $A' + B' = -C'$ . If the sum of  $A^*$ ,  $B^*$  and  $C^*$  is positive, then the function may be forced through the origin by reducing  $C^*$  adequately.

In case of a further  $k_b$ -phase, curve fitting may often be executed by manual changes of  $D^*$  and  $k_b$  alone, and as the corresponding polyexponential function has an initial minimum, then an existing lag-time is defined by the time at which this minimum is forced to attain the value of zero ( $A' + B' + C' + D' = 0$ ).

It is not possible to fit the initial absorptive plasma concentrations after oral administration to a simple polyexponential function (Kübler, 1972), and such data points should in general be excluded.

A possible lag-time ( $t_l$ ) is entered and stored in register 22 ( $t_l$  STO 22) and register 23 is zeroed (0 STO 23). Press key R/S, and after print-out of  $t_l$  and zero, press R/S, then 2. C, which causes the program to store  $A'$ ,  $B'$ ,  $C'$ , and possibly  $D'$  in the registers 10, 13, 16, and 19, whereas register 22 is zeroed. A tabulation of the polyexponential parameter estimates ( $A'$ ,  $B'$ ,  $C'$ , and possibly  $D'$ ) corresponding to the time  $t^* = t - t_l = 0$ , which equals function zero, is executed by the program and printed out.

21. Subsequent to the preceding analysis and fitting of curves, the program may calculate the remaining relevant pharmacokinetic parameters. The systemic available dose,  $a_o$  (see further under 27), which is generally stated as mass or mmol per kg of body weight, is entered and stored in register 8 ( $a_o$  STO 8). Then press 2. A, and the program will execute the calculations according to the previously stated equations and the resulting parameters are printed out as follows: (1) the calculating constant  $F$ , (2) the uncomposite rate constants  $k_{21}$ ,  $k_{10}$ , and  $k_{12}$  (unit:  $t^{-1}$ ), (3)  $a_o$  (unit: mass or mmol  $kg^{-1}$ ), (4)  $V_c$  (unit: l  $kg^{-1}$ ), (5)  $Cl = V_c k_{10}$  (unit: l  $kg^{-1} t^{-1}$ ), (6)  $V_{db}$  (unit: l  $kg^{-1}$ ), (7)  $V_{de}$  (l  $kg^{-1}$ ), (8)  $V_{pe}$  (l  $kg^{-1}$ ),  $AUC$  (unit: mass or mmol  $l^{-1} t$ ), and (10)  $V_e$ , calculated from  $AUC$ .

In case of drugs with one-compartment characteristics the program prints out  $F$ ,  $k_{21}$ , and  $k_{12}$  as zero, whereas  $k_{10}$  is printed as the elimination rate constant corresponding to  $\beta$ .  $V_d$  is printed equal to  $V_c$  and  $V_{db}$ , whereas neither  $V_{de}$  nor  $V_{pe}$  are calculated or printed.

22. In case of the administration of a single intravenous dose as a time-defined infusion, it is necessary, prior to the execution of 21, to enter and store the time ( $T_i$ ) for the duration of the infusion in register 24 ( $T_i$  STO 24) and then to press 2. E. The program will now correct  $A^*$  and  $B^*$  to  $A'$  and  $B'$ , which equal the corresponding bolus injection constants. The corrected parameters and the relevant rate constants are printed out.

23. The concentration constants  $A^*$  and  $B^*$  obtained in analyses of intravenous, multiple dose, steady state plasma concentration curves are similarly corrected to the corresponding single dose constants  $A'$  and  $B'$  prior to execution of 21. This is achieved by storing the dose interval ( $T$ ) in register 35 ( $T$  STO 35) and keying 2.  $D$ . The corrected parameters are printed out. It is assumed that  $T$  is of longer duration than the  $\alpha$ -phase.

24. In cases where intravenous, multiple dose administrations are carried out as time-defined infusions, the procedures given in 22 and 23 may be used consecutively.

25. In conjunction with paravasal (eg, peroral) multiple dose administration in steady state, the procedure given in 23 is followed in order to correct the constants  $A^*$ ,  $B^*$ ,  $C^*$ , and possibly  $D^*$  to the corresponding single dose constants  $A'$ ,  $B'$ ,  $C'$ , and possibly  $D'$  before carrying out the parameter calculation according to 21. The corrected parameters are printed out.

26. The corrections effectuated by the procedures stated in 22–25 may be reverted by means of program routines: GTO 1/x R/S in case of time-defined infusion, and GTO  $\sqrt{x}$  R/S at multiple dose administration in steady state. The routines can be useful in curve fitting procedures in steady state. The procedures may be used in reverse order. The second routine is very useful in predictions from single dose pharmacokinetics, of the plasma concentration/time lapse in steady state during multiple dose administration. It should be recalled that function simulation may be executed by pressing R/S just after printing out of the corrected parameters. The register 22, which is used for summing up the elapsed time, may have to be zeroed (0 STO 22) or readjusted to any wanted time.

27. Determination of  $a_o$ , the systemic available dose, in conjunction with paravasal (eg, peroral) administration has to be carried out in advance of calculation of the apparent volumes of distribution in accordance with section 21. The following equation is used:  $a_o = \text{dose}_{iv} \times (AUC_{pv}/AUC_{iv})$ . The areas may be determined by carrying out the program routine in 21 without  $a_o$ , or they may be measured using the trapezoidal rule.

## RESULTS

In Figure 2 is shown the printed out results of an analysis of some selected time/serum concentration data obtained after termination of an intravenous administration of a single infusion of dipyridamole at a rate of  $5 \text{ mg min}^{-1}$  for nine minutes (Nielsen-Kudsk and Pedersen, 1979). The analysed data were: 20 min/1.20  $\mu\text{g ml}^{-1}$ , 60/0.57, 100/0.35, 140/0.23, 200/0.15, and 260/0.09. Referring to Figure 2, the three last data pairs from the  $\beta$ -phase were in 1 entered and subjected to exponential regression analysis, which as a result shows  $B^*$  ( $\mu\text{g ml}^{-1}$ ),  $\beta$  ( $\text{min}^{-1}$ ) and  $r$ . In 2 are shown the determination of residuals: the entered  $\alpha$ -phase time, the extrapolated concentration, the entered actual measured concentration and the calculated corresponding residual value. The exponential regression analysis of the three residuals are shown in 3, which ends up with the results  $A^*$ ,  $\alpha$  and  $r$ . In 4 are the results tabulated corresponding to the two phases. The fitted pharmacokinetic function is

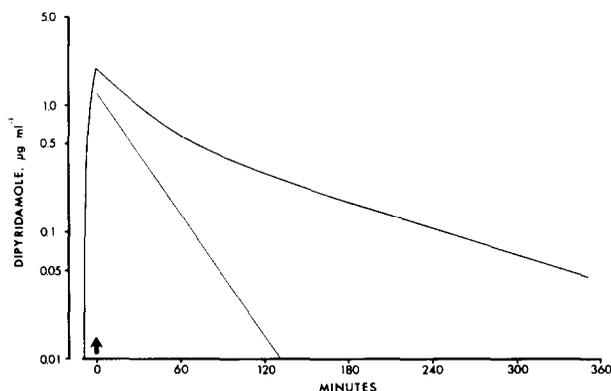
<u>1.</u> 140.00000	<u>2.</u> 20.00000	<u>3.</u> 20.00000	<u>4.</u> 0.69689	40.00000	<u>7.</u> -2.04969
0.23000	0.59600	0.60400	0.00782	0.79537	
1.00000	1.20000	1.00000	-0.99869		0.01741
	0.60400			60.00000	0.01665
200.00000		60.00000	1.25784	0.57206	0.01082
0.15000	60.00000	0.13407	0.03706		
2.00000	0.43593	2.00000	-0.99996	80.00000	0.56250
	0.57000			0.43770	
260.00000	0.13407	100.00000			0.25557
0.09000		0.03115	<u>5.</u> 0.00000		0.00425
3.00000	100.00000	3.00000	1.95473	<u>6.</u> 0.72170	0.54411
	0.31885			0.00782	0.41451
0.69689	0.35000	1.25784	20.00000	-0.99869	0.15893
-0.00782	0.03115	-0.03706	1.19542		
-0.99869		-0.99996		1.47925	132.21675
				0.03706	
				-0.99996	0.25557

**FIGURE 2.** A pharmacokinetic analysis of time/serum concentration data obtained after a single intravenous infusion of dipyridamole. A detailed explanation is given in the text.

simulated by tabulation in 5, which shows corresponding times (min) and concentrations ( $\mu\text{g ml}^{-1}$ ) up to 80 min. In 6 are shown the corrected concentration constants  $B'$  and  $A'$  corresponding to bolus injection. The final analytical results are given in 7, which in succession shows:  $F$  (calculation constant),  $k_{21}$ ,  $k_{10}$ ,  $k_{12}$  (all in  $\text{min}^{-1}$ ),  $a_0$  (total dose in  $\text{mg kg}^{-1}$ ),  $V_c$  ( $\text{l kg}^{-1}$ ),  $Cl$  ( $\text{l kg}^{-1} \text{min}^{-1}$ ),  $V_{d\beta}$ ,  $V_{d\epsilon}$ ,  $V_{pe}$  (all in  $\text{l kg}^{-1}$ ),  $AUC$  ( $\mu\text{g ml}^{-1} \text{min}$ ) and  $V_c$  (calculated from  $AUC$  as control).

A graphical presentation based upon the fitted function data (tabulated in part in 5) is shown in a semilogarithmic plot in Figure 3, which also shows the theoretical serum concentration/time lapse during the infusion. The linear curve fitted to the residuals is also depicted.

Figure 4 shows the analysis of selected time/serum lithium concentration data obtained after peroral administration of 24 mmol lithium chloride in a dilute solution (from Nielsen-Kudsk and Amdisen, 1979). The analysed single dose data were:



**FIGURE 3.** The theoretical serum concentration curve of dipyridamole based upon the postinfusional analysis given in Figure 2. The theoretical serum concentration/time lapse of dipyridamole during infusion as well as the linear curve fitted to the residuals are also shown.

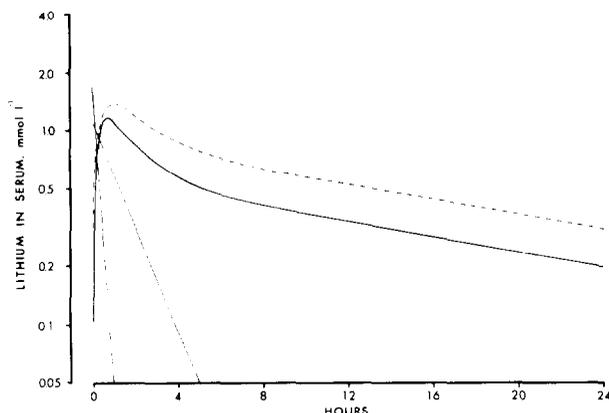
<u>1.</u>	16.00000 0.29000 1.00000	2.00000 0.52887 0.31113	<u>4.</u>	0.20000 0.98153 0.16697 -0.81456	<u>6.</u>	0.57816 0.04456 -0.99725	<u>8.</u>	-1.61574 0.26545 0.10447 0.29699	<u>10.</u>	-1.87329 0.23828 0.10972 0.29881	
	20.00000 0.23000 2.00000	4.00000 0.48378 0.57000 0.08622		0.40000 0.86666 0.47205 -0.39461		1.11163 0.62235 -0.99891		0.46154 0.46154		0.46154	
	32.00000 0.14000 3.00000	6.00000 0.44253 0.47000 0.02747		0.60000 0.76523 0.57709 -0.18814		-1.69941 3.66365 -0.99998		0.30894 0.03227 0.72432 0.65460 0.34565		0.28893 0.03170 0.73176 0.65125 0.36232	
	-0.57816 -0.04456 -0.99725	0.02747	-0.18814				14.30037 0.30894	14.55893 0.28893			
<u>2.</u>	0.20000 0.57303 0.74000 0.16697	<u>3.</u>	2.00000 0.33113 1.00000 0.16697	<u>5.</u>	0.20000 0.81456 1.00000 0.40000 0.08622 0.39461	<u>7.</u>	0.00000 0.00000 0.10000 0.44870	<u>9.</u>	0.88001 0.04332 -1.00000		
	0.40000 0.56795 1.04000 0.47205	4.00000 0.08622 2.00000	0.40000 0.60000 0.02747 3.00000	0.60000 0.18814 3.00000	0.60000 0.40000 1.04431	0.20000 0.74246 0.20000 0.40000 1.04431		1.52364 0.60348 -0.99897 -2.09252 1.90697 -0.99995			
	0.60000 0.56291 1.14000 0.57709	1.11163 -0.62235 -0.99891	1.69941 -3.66365 -0.99998			1.14056					

**FIGURE 4. Pharmacokinetic analysis of serum concentration/time lapses related to single and multiple dose peroral administration of lithium chloride. A detailed explanation is given in the text.**

0.2 h/0.74 mmol l<sup>-1</sup>, 0.4/1.04, 0.6/1.14, 2/0.86, 4/0.57, 6/0.47, 16/0.29, 20/0.23, and 32/0.14. The last three data pairs belonging to the  $\beta$ -phase are subjected to exponential regression analysis in 1 resulting in  $B^*$  (mmol l<sup>-1</sup>),  $\beta$  (hours<sup>-1</sup>) and  $r$ . Determination of first order residuals is carried out in 2, and exponential regression analysis of data from the hereby defined  $\alpha$ -phase is performed in 3, giving  $A^*$ ,  $\alpha$ , and  $r$ . Second order residuals are calculated in 4, and they are analysed in 5, which ends up with  $C^*$ ,  $k_a$  and  $r$ . The exponential parameters corresponding to the three phases are tabulated in 6. A correction of  $C^*$  to  $-1.68978$  equalling  $-(A^* + B^*)$  is carried out in order to force the fitted function through zero, as a possible lag-time may be considered insignificant. The fitted function is simulated by tabulation up to 0.6 hours in 7. In 8 are given the final analytical results in the same succession as stated above. Rate constants are given in h<sup>-1</sup>, volumes of distribution in l kg<sup>-1</sup>, and  $AUC$  in mmol l<sup>-1</sup> h.

In 9 are shown the exponential parameters resulting from a similar analysis of steady state serum lithium concentration data obtained after multiple administration of 24 mmol lithium chloride solution daily for eight days. The analysed selected data were: 0.2 h/0.79 mmol l<sup>-1</sup>, 0.4/1.09, 0.6/1.25, 3/1.03, 4/0.74, 6/0.72, 16/0.44, 20/0.37, and 32/0.22. After correction of the concentration constants ( $A^*$ ,  $B^*$ , and  $C^*$ ) to the corresponding single dose constants, the final pharmacokinetic parameters listed in 10 were obtained.

Figure 5 shows the theoretical serum lithium concentration curves based upon the data given in Figure 4.6 (fully drawn curve) and Figure 4.9 (dotted curve). The linear curves fitted to first and second order residuals belonging to the single dose serum concentration curve are also shown.



**FIGURE 5.** Theoretical serum lithium concentration curves after oral ingestion of a single dose of 24 mmol lithium chloride (—) and after multiple ingestion of the same dose daily for eight days (----). Linear curves fitted to first and second order residuals of the single dose curve are also depicted.

## DISCUSSION

The simple pharmacokinetic program for Ti-59 described and demonstrated above cannot compete on equal terms with complex and advanced automatic computer programs. But it is easy and fast to use as a replacement for graphical methods in analyses of plasma concentration data of drugs. Besides determination of initial polyexponential estimates, the program allows curve simulation and manual curve fitting procedures followed by calculation of the relevant pharmacokinetic parameters. The obtained estimates are in general comparable to results based upon automatic nonlinear curve fitting analyses. It may be considered an advantage that the described program is based upon the principles used in graphical methods and thus allows a direct interaction between the user and the program, with the user in the dominant role.

Besides the pharmacokinetic analytical capabilities, the curve simulation routines contained in the program may be very useful in predictions of the time course of plasma concentrations of drugs related to either single dose administration or multiple dose administration in steady state.

## REFERENCES

- Brown RD, Manno JE, (1978) ESTRIP, a BASIC computer program for obtaining initial polyexponential parameter estimates. *J Pharm Sci* 67:1687-1691.
- von Kübler W, (1977) Pharmakokinetik der enteralen resorption. In *Pharmakokinetik*, Second ed. Eds., Glatke E and von Hattingberg HM. Berlin, Heidelberg, New York: Springer-Verlag, pp. 77.

- Nielsen-Kudsk F, Amdisen A, (1979) An analysis of the pharmacokinetics of lithium in man. *Europ J Clin Pharmacol* 16:271-277.
- Nielsen-Kudsk F, Pedersen AK, (1979) Pharmacokinetics of dipyridamole. *Acta pharmacol et toxicol* 44:391-399.
- Pedersen PV, (1977) Curve fitting and modeling in pharmacokinetics and some practical experiences with NONLIN and a new program FUNFIT. *J Pharmacokin Biopharm* 5:513-531.
- Sedman AJ, Wagner JG, (1974) AUTOAN manual. Ann Arbor, Michigan: Publication Distribution Service University of Michigan.
- Sedman AJ, Wagner JG, (1976) CSTRIP, a FORTRAN iv computer program for obtaining initial polyexponential parameter estimates. *J Pharm Sci* 65:1006-1010.
- Sedman AJ, Wagner JG, (1977) NAUTOAN manual. Ann Arbor, Michigan: University of Michigan Medical Center.