

PHARMACOKINETIC ANALYSIS AND CALCULATIONS USING A PROGRAM FOR THE MINICALCULATOR TI-59

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(Received 19 August, 1980)

The described pharmacokinetic program for TI-59 is in clinical practice applicable in analyses of plasma concentration profiles established after single-dose, intravenous or oral administration of drugs showing one- or two-compartment first-order pharmacokinetics. Analysis of multiple dose, steady state plasma concentration data may also be carried out. Predictions of mean steady state plasma concentrations related to multiple dose drug administration are obtainable on the basis of a preceding single-dose pharmacokinetic analysis. The program contains routines for: exponential regression analysis, determination of and treatment of residuals, simulation of plasma concentration curves, corrections for time-defined intravenous infusion substituting for bolus injection, determination of and correction for lag-time and routines for calculation of fitted and derived pharmacokinetic parameters. Naproxen and theophylline plasma concentration data were used to demonstrate the practical applications of the program.

Introduction

Rational drug therapy is in general directly dependent upon attainment of a certain effective concentration of the drug in blood plasma. Also, too high plasma concentrations may produce possibly dangerous toxic effects. The plasma concentration of a drug is a function of a number of factors: the dose of the drug and its systemic availability, the dosing interval, the characteristics of distribution of the drug to the various tissues in the organism and the rate of its elimination from the body. The correct dose consequently depends in a complex way upon several pharmacokinetic parameters, which, if known, often only are available as average estimates obtained from experiments on normal individuals. Several disease states and interindividual variability may, however, influence pharmacokinetic parameters related to a particular drug. An individual assessment of each patient is thus the most rational approach in drug therapy, in particular when potentially toxic drugs are used.

The plasma concentration profile obtained after administration of a single dose of a drug may generally be described by a number of exponential terms reflecting first order kinetics, and, when analysed accordingly, the relevant pharmacokinetic parameters can be obtained. The following text contains a description of the most essential theoretical features and a practical instruction for using a program developed for pharmacokinetic analysis and parameter calculations by means of the minicalculator

TI-59. The pharmacokinetics of drugs with one- or two-compartment characteristics after intravenous or oral single-dose administration may be analysed by means of the program. Analysis of multiple-dose, steady state plasma concentration data is also possible. Mean steady state drug concentrations in plasma related to multiple-dose administration may be calculated by the program as a function of determined pharmacokinetic parameters, maintenance dose and dosing interval.

Methods

The mini-calculator TI-59 from Texas Instruments was used with the adaptable printer PC-100 A. It was equipped with the statistics library 'solid state software' module, but only the linear regression initialization routine of this module was used.

The pharmacokinetic program developed for the calculator incorporates a routine for exponential regression analysis of: (1) the time/concentration data related to the eliminatory β - or k_e -phase and (2) the time/residual data defining a distributory α -phase and/or a k_a -phase of absorption in the time course of plasma (or serum) concentration curves obtained after single dose administration of drugs with two- or one-compartment characteristics. The extension with time of the various phases is judged graphically from semilogarithmic plots and possibly from a test analysis of selected data among the very last, the intermediate, and the initial experimental time/concentration values.

The zero-time concentration constants (B^* and A^* and/or possibly C^*) and the corresponding rate constants (k_e or β , α and/or k_a) determined by exponential regression analysis are used in the program to simulate the relevant theoretical plasma concentration/time course in accordance with the following functions related to intravenous administration by a short-lasting infusion of one-compartment (eqn. 1) and two-compartment (eqn. 2) drugs or single-dose oral (or other paravascular) administration of drugs with one-compartment (eqn. 3) and two-compartment (eqn. 4) characteristics:

$$c = \frac{k^0}{-k_e V_d} (1 - e^{k_e T}) e^{-k_e t} \quad (1)$$

and

$$c_1 = \frac{k^0 (k_{21} - \alpha) (1 - e^{\alpha T})}{-\alpha (\beta - \alpha) V_c} e^{-\alpha t} + \frac{k^0 (k_{21} - \beta) (1 - e^{\beta T})}{-\beta (\alpha - \beta) V_c} e^{-\beta t} \quad (2)$$

and

$$c = \frac{a_0 k_a e^{k_e t L}}{V_d (k_a - k_e)} e^{-k_e t} - \frac{a_0 k_a e^{k_a t L}}{V_d (k_a - k_e)} e^{-k_a t} \quad (3)$$

and

$$c = \frac{a_0 k_a (k_{21} - \alpha) e^{\alpha t L}}{V_c (\beta - \alpha) (k_a - \alpha)} e^{-\alpha t} + \frac{a_0 k_a (k_{21} - \beta) e^{\beta t L}}{V_c (\alpha - \beta) (k_a - \beta)} e^{-\beta t} + \frac{a_0 k_a (k_{21} - k_a) e^{k_a t L}}{V_c (\alpha - k_a) (\beta - k_a)} e^{-k_a t} \quad (4)$$

In eqns. (1) and (2) T is equal to t during infusion of the drug and attains a constant value at time of its termination, which then is reckoned as zero time. The rate of infusion is k^0 ($= a_0/T$, where a_0 is the dose administered). V_d is the apparent one-compartment volume of distribution, whereas V_c is the apparent central volume of distribution of drugs with two-compartment characteristics. The complete coefficients to $e^{-k_e t}$ or $e^{-\beta t}$, $e^{-\alpha t}$ and $e^{-k_a t}$ equals the concentration constants B^* , A^* and C^* , respectively. A possible lag-time (t_L) related to oral (or paravascular) administration of drugs with one-compartment characteristics is in the program calculated as $t_L = (\ln C^* - \ln B^*)/(k_a - k_e)$. Lag-times related to two-compartment drugs are determined in the curve simulation procedure.

In order to calculate the remaining pharmacokinetic parameters relevant to intravenous time(T)-limited infusion of a one-compartment drug B^* is corrected to the value (B') corresponding to bolus injection: $B' = B^* k_e T / (1 - e^{-k_e T})$. In case of a two-compartment drug the corresponding corrections are used: $B' = B^* \beta T / (1 - e^{-\beta T})$ and $A' = A^* \alpha T / (1 - e^{-\alpha T})$. Zero-time concentration constants obtained in analysis of true bolus injection data are, of course, not corrected. If a positive lag-time for a one-compartment drug has been demonstrated, B^* and C^* are both corrected to B' in accordance with eqn. (3), from which it may be derived that $B' - C' = 0$ at $t = t_L$. In case of a calculated 'negative' lag-time, C^* is corrected to B^* . In relation to two-compartment drugs B^* , A^* and C^* are corrected for lag-time in accordance with the equation: $A' + B' + C' = 0$, which is derived from eqn. (4) at $t = t_L$.

In analyses of a multiple-dose steady state plasma concentration curve, the backward projection concentration constants corresponding to the time for the last dose (B'' , A'' , and C'' corrected for a possible lag-time) have to be transformed to the corresponding single-dose constants (B' , A' and C') before calculation of the remaining relevant pharmacokinetic parameters can take place. This is executed in the program by multiplication of the constants in question with the factor $(1 - e^{-k_i T})$, where k_i represents α , β and k_a , whereas T is the dosing interval.

The area under the function-fitted plasma concentration curve is in the program calculated as: $AUC = (B'/\beta) +$ possibly (A'/α) and/or (C'/k_a) . Plasma clearance is then calculated as: $Cl = a_0/AUC$. The apparent total volume of distribution during the β -phase is determined as: $V_{d\beta} (= V_{d\text{area}}) = Cl/\beta$. In case of intravenously administered drugs the apparent volume of distribution of the central compartment is found as

a_0/c_0 , where $c_0 = A' + B'$ in relation to drugs with two-compartment characteristics. For one-compartment drugs the apparent volume of distribution is calculated as $V_d = B'/k_e$.

If an absorption process is involved, c_0 is for two-compartment drugs calculated as: $c_0 = (\alpha A' + \beta B' + k_a C')/(-k_a)$. The uncomposite rate constants related to the open two-compartment pharmacokinetic model are in the program calculated according to the equations: $k_{10} = c_0/AUC$, $k_{21} = \alpha\beta/k_{10}$ and $k_{12} = \alpha + \beta - k_{10} - k_{21}$. The apparent volume of the peripheral compartment at steady state is derived as: $V_{pe} = V_c k_{12}/k_{21}$, whereas the total volume of distribution at that state is calculated as: $V_{de} (= V_{dss}) = V_c + V_{pe}$.

In the case of paravascular administration of drugs with one-compartment characteristics the program calculates the time (corrected for a possible lag-time) of occurrence of the maximum plasma concentration as: $t_{max} = \ln(k_a/k_e)/(k_a - k_e)$ and $c_{max} = (k_e/k_a)^{k_e/(k_a - k_e)} B' (k_a - k_e)/k_a$. For two-compartment drugs these parameters may be obtained in the simulation procedure.

The program also contains a routine for calculation of the mean steady state plasma

000	CMS	050	GTO	100	X:T	150	IXI	200	LNK	250	16	300	LBL	350	GE	400	17	450	RCL	500	x	550	13	600	INV
1	L/X	R/S	GTO																						
0	LBL	LBL	LNK																						
STO	B'	D	LBL																						
07	3	STFF	C'																						
LBL	INV	01	1	STO	E'																				
X ²	SUM	GTO	+/-	31	ADV																				
PGM	07	X ²	PRD	SUM	RCL																				
01	CLR	LBL	16	19	13	10	x	00	RCL	14	25	33													
SBR	ST*	INV	RCL	RCL	GE	:	+	=	20	=	STO	LBL													
010	CLR	060	07	110	STO	160	16	210	22	260	16	310	RCL	360	RCL	410	PRT	460	=	510	PRT	560	14	610	STO
LBL	GTO	08	INV	x	IXI	11	10	STO	PRT	LBL	LBL	4													
CLR	CLR	X:T	GE	RCL	LNK	+	=	20	GTO	x	CE	SUM													
R/S	LBL	STO	(17	=	RCL	PRT	LBL	x	ADV	3	33													
PRT	C	09	1	=	10	EQ	29	ADV	-	A	1	07													
X:T	OP	x	+/-	+/-	10	EQ	29	ADV	-	A	1	07													
CLR	12	RCL	PRD	INV	LNK	=	:	1/X	RCL	RCL	14	1	PRD												
R/S	INV	11	13	LNK	=	:	x	29	14	RCL	1	INV													
PRT	LNK	+/-	LBL	x	:	RCL	RCL	:	:	00	STO	STFF													
IFF	PRT	=	(RCL	(14	09	RCL	RCL	PRT	33	03													
020	01	070	ST*	120	INV	170	R/S	220	16	270	RCL	320	+	370	=	420	32	470	11	520	=	570	13	620	ADV
INV	07	LNK	LBL	=	14	RCL	PRT	=	16	STO	PRT	10													
LBL	1	x	E	SUM	-	16	STO	PRT	10	LNK	21	(
LNK	SUM	RCL	ADV	19	RCL	EQ	20	STO	:	:	(PRT													
LNK	07	10	RCL	RCL	11	=	ADV	27	(RCL	RC*	RCL													
IFF	X:T	=	22	19)	:	GTO	1/X	RCL	25	33	13													
02	PRT	+	PRT	PRT	=	RCL	:	x	14	PRT	x	PRT													
)	+/-	(x	RCL	PRT	=	17	LBL	RCL	-	RCL	RCL													
)+	ST*	RCL	RCL	23	INV	LBL	+/-	11	RCL	PRT	34	16													
LBL	07	09	=	11	SUM	GE	=	RCL	x	11	ADV	16													
030	1/X	080	1/X	130	x	180	=	230	22	280	?	330	=	380	10	430	RCL	480)	530	R/S	580	+/-	630	3
RCL	x	14	INV	GTO	x	+	-	PRT	x	14	STO	LNK	INV	STO											
03	2	14	INV	E	11	32	11	STO	RCL	=	26	D'	LNK	22											
PRT	LNK)	1	LNK	LBL	1	=	1/X	PRT	=	RCL	+/-	LBL												
ADV	=	+/-	x	A'	=	1/X	=	STO	PRT	24	+	LBL													
GTO	PRT	INV	RCL	ADV	+/-	x	RCL	28	(x	1	LBL													
CLR	1	LNK	10	RCL	INV	RCL	13	+/-	RCL	RCL)	STT													
LBL	SUM	x	=	30	LNK	00	x	-	11	11	x	03													
B	07	RCL	STO	STO	x	=	RCL	RCL	:	=	1	GTO													
STF	OP	13	30	10	LBL	STO	14	27	RCL	PRD	INV	SBR													
040	02	090	13	140	=	190	STO	240	PRT	290	:	340	21	390	+	440	+	490	14	540	10	590	SUM		
GTO	X ²	INV	19	+	RCL	PRT	10	:	16	11	x	24													
CLR	PRT	SUM	RCL	RCL	10	:	16	11	x	24															
LBL	ADV	08	22	31	=	RCL	x	+	(STO	EQ														
)	ST*	RCL	x	STO	STO	11	RCL	RCL	RCL	34	STO														
INV	07	09	RCL	13	10	=	17	14	11	x	IFF														
STF	1	X:T	14	PRT	PRT	=	17	14	11	x	IFF														
02	SUM	RCL	=	+/-	RCL	+	16	1	+	RCL	14	RCL													
INV	07	08	+/-	+/-	STO	16	1	+	ADV	26	=	PD*													
1+	CLR	PRT	INV	STO	13	INV	RCL	:)	PRD	33														

Fig. 1. Listing of the pharmacokinetic program for TI-59.

concentration (\bar{c}_∞) related to regular multiple administration (dosing interval T) of systemic available maintenance doses (a_0) of a drug for which the relevant pharmacokinetic parameters have been determined by means of the program: $\bar{c}_\infty = a_0/(Cl T)$.

A listing of the pharmacokinetic program for TI-59 is shown in Fig. 1. The program occupies three sides of two magnetic cards.

Instructions for using the program

The following is an outline of procedures for the practical use of the program with TI-59 and PC-100 A:

0. Partitioning of the calculator memory: Enter 4, press 2. OP 17.
1. Press CLR, enter side 1 of magnetic card No. 1, CLR enter side 2 and CLR enter side 1 of card No. 2.
2. Press 2. FIX 5 to obtain print out to 5 decimal places.
3. Initialization of the program: Press RST and then R/S.
4. Entering of data: Enter time value, press R/S, enter plasma concentration value (unit: mg l^{-1} or mmol l^{-1}) and press R/S. Repeat for all data judged as belonging to the terminal β - or k_e -phase of the plasma concentration time course. The entered data are printed out followed by a numerator.
5. Deleting of entered data: Press B and enter the unwanted data pair as above.
6. 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 $-\beta$ or $-k_e$, the biological half-life of the drug and the coefficient of determination r^2 .
- 6a. Entering of supplementary data after analysis: Press 2. B' and enter data as stated in 4.
7. Initialization for determination of and analysis of residuals of first order: Press D.
8. Entering of time/plasma concentration data corresponding to the α -phase of two-compartment drugs or the k_a -phase of drugs with one-compartment characteristics; procedure and comments as described in 4, except that the residual value is also printed out just before the numerator.
9. Exponential regression analysis of residuals of first order: Press C, which effectuates print out of A^* or C^* , $-\alpha$ or $-k_a$, the half-time of the phase of distribution or absorption and the relevant coefficient of determination r^2 .
- 9a. In analysis of two-compartment paravascular (oral) data with an absorption phase, initialisation for residuals of second order, entering of data and exponential regression analysis are carried out as described in 7, 8 and 9, by which C^* , k_a and r^2 are determined.
10. Simulation by tabulation of theoretical plasma concentration curves based upon data fitted mono-, bi- or triexponential functions is performed by entering an adequate time interval value (t' , e.g. stated in hours) in the program: t' STO 23, followed by pressing E, which effectuates printing out of the time/concentration course from zero

time and at consecutive t' -intervals. In case of one- or two-compartment pharmacokinetics with a first order absorption phase, the above procedure has to be preceded by: Press 2.C'. 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 carried out by entering the relevant starting time in register 22, followed by pressing E.

10a. A possible lag-time (t_L), 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 $A' + B' = -C'$. In most cases an accuracy corresponding to two decimal points is sufficient. This is obtained by using $t' = 0.01$ in the curve simulation around function zero, and then determine t_L corresponding to the lowest simulated positive concentration value. Correction of the concentration constants for lag-time is performed as follows: t_L is entered in register 22 (t_L STO 22), register 23 is zeroed (0 STO 23), press E and after print-out of t_L and the lowest positive C -value, press R/S and afterwards 2.A', which causes the program to store A' , B' and $-(A' + B' = C')$ in the registers 10, 13 and 16, respectively. The lag-time corrected constants are printed out. In cases, where a 'negative' lag-time is found ($A^* + B^* + C^* > 0$), the function is forced through zero by pressing 2.A' at $t = 0$. For drugs with one-compartment characteristics calculation of and correction for lag-time is performed automatically by the program.

11. Correction of B^* and/or A^* for time-defined intravenous infusion of a single dose is necessary before calculation of the relevant pharmacokinetic parameters can be performed. This is done by the program if the time of duration of the infusion (T_i , e.g. in hours) is stored in register 24 (enter T_i STO 24) before pressing 2.D'. The corrected constants (B' and/or A') are printed out.

12. The systemic available dose (a_0 , generally stated in mg or mmol/kg of body weight) is stored in register 00: Enter a_0 STO 00.

13. Calculation of pharmacokinetic parameters: Press 2.E'. The program will now execute the calculations in accordance with the previously stated equations. In case of two-compartment intravenous pharmacokinetics the resulting parameters are printed out as follows: (1) a_0 (unit: mg or mmol kg^{-1}); (2) AUC (mg or mmol $\text{l}^{-1} \text{t}$); (3) plasma clearance, $Cl = a_0/\text{AUC}$ ($1 \text{ kg}^{-1} \text{t}^{-1}$); (4) the apparent volume of distribution $V_{d\beta} = V_{d\text{area}}$ (1 kg^{-1}); (5) c_0 (mg or mmol l^{-1}); (6) V_c (1 kg^{-1}); (7) the uncomposite rate constants k_{10} , k_{21} and k_{12} (unit: t^{-1} , e.g. h^{-1}); and (8) V_{pe} and $V_{de} = V_{dss}$ (1 kg^{-1}).

In relation to one-compartment pharmacokinetics the following parameters are calculated and printed out: (1) A possible lag-time and the corresponding concentration constant C' ; (2) the systemic available dose, a_0 ; (3) AUC, (4) plasma clearance, Cl ; (5) the apparent volume of distribution, V_d ; and (6) in relation to first order absorption also the lag-time-corrected t_{max} -value and the corresponding maximum plasma concentration of the drug, c_{max} .

14. The concentration constants B^{**} , A^{**} and/or possibly C^{**} obtained in analyses of intravenous or paravascular (oral), multiple-dose steady state plasma concentration

curves may (after correction for a possible lag-time) be transformed to the corresponding single-dose constants B' , A' and/or C' prior to execution of 13. This is achieved by storing the dosing interval (T) in register 25 (T STO 25) followed by pressing SBR SBR. The transformed parameters are printed out. It is assumed that T is of longer duration than the α -phase. These transformations may be reverted by a program routine, which is executed by pressing SBR 2. LBL. This last routine is useful in predictions from single-dose pharmacokinetics, of the plasma concentration/time course at steady state during multiple dose administration. Function simulation may be executed by pressing E after print-out of the corrected parameters. Register 22 may have to be zeroed (0 STO 22) or readjusted to any wanted time.

15. In cases where intravenous, multiple-dose administrations are carried out as time-defined infusions, the procedures given in 11 and 14 may be used in succession.

16. Determination of the systemic available dose (a_0) in conjunction with oral (or paravascular) drug administration has to be carried out in advance of the program calculation of the apparent volumes of distribution and plasma clearance. The following equation is used $a_0 = \text{dose}_{i.v.} \times (\text{AUC}_{\text{oral}}/\text{AUC}_{i.v.})$. A further correction for an intrasubject (or possibly intersubject) variability in the experimentally determined biological half-life of the drug in relation to the intravenous and oral administration of the drug may be carried out by multiplication with the factor defined by the ratio: k_e or β (oral)/ k_e or β (i.v.). The areas may be determined by performing the program routine as described in 13, but without entering a_0 , or they may be measured by means of the trapezoidal method.

17. The mean steady state plasma concentration (\bar{c}_∞) to be expected in relation to multiple dose administration of a drug that has been pharmacokinetically analysed as stated above on basis of single dose administration may be calculated by the program after entering the systemic available dose of maintenance (a_0) and the dosing interval (T): a_0 STO 00 and T STO 25. After pressing key A the parameters are printed out in the following order: a_0 , T and \bar{c}_∞ .

Results

The procedure and the obtained results of a pharmacokinetic analysis of time/serum concentration data referring to a short-lasting intravenous infusion of a single dose of 250 mg (3.23 mg/kg body wt) of theophylline, administered as aminophylline to an adult, male person, are shown in Fig. 2. The analysed data, which are plotted semilogarithmically in Fig. 3, were: 0.17 h/7.15 $\mu\text{g ml}^{-1}$, 0.25/6.51, 0.33/6.26, 0.50/5.87, 0.67/5.53, 1/5.28, 2/4.27, 4/2.69, 6/1.81, 8/1.30, 12/0.54 and 16/0.22. The 8 last data pairs (cf. Fig. 2) constituting the β -phase of disposition of theophylline were in 1 entered, printed out and then subjected to exponential regression analysis resulting in print out of B^* ($\mu\text{g ml}^{-1}$), β (h^{-1}), $t_{1/2\beta}$ (h) and the determination coefficient r^2 . The remaining data pairs judged as belonging to the α -phase of distribution were in 2 entered and printed out together with the calculated residuals, which finally

<u>1</u>	0.67000	16.00000	3.33072	4.00000	<u>4</u>	6.50459
	5.53000	0.22000	-8.04330	2.79747		4.57075
	1.00000	8.00000	0.08618			0.00000
			0.99303	6.00000		
	1.00000	6.44834		1.84257		
	5.28000	-0.20878				3.23000
	2.00000	3.32004	<u>3</u>	0.00000	8.00000	
		0.99904		9.77906	1.21362	31.72403
	2.00000					0.10182
	4.27000		0.20000	12.00000		0.48768
	3.00000	<u>2</u>	6.85129	0.52650		11.07534
		0.17000				0.29164
		7.15000				
	4.00000	0.92651	0.40000	16.00000		
	2.69000	1.00000	6.06514	0.22841		
	4.00000					0.34912
		0.25000	0.60000	20.00000		4.81002
	6.00000	6.51000	5.71583	0.09909		3.09294
	1.81000	0.38960				
	5.00000	2.00000	0.80000	24.00000		0.18753
			5.46191	0.04299		0.47917
	8.00000	0.33000				
	1.30000	6.26000	1.00000			
	6.00000	0.24097	5.23439		<u>5</u>	3.23000
		3.00000				4.00000
	12.00000		2.00000			7.93089
	0.54000	0.50000	4.24724			
	7.00000	5.87000				
		0.06085				
		4.00000				

Fig. 2. A pharmacokinetic analysis of serum theophylline concentration data obtained after a single short-lasting intravenous infusion of the drug. A detailed information is given in the text.

were treated by exponential regression analysis ending up with printing out of A^* , α , $t_{1/2\alpha}$ and r^2 . The fitted biexponential function is simulated by tabulation in 3, which shows corresponding times (h) and serum concentrations ($\mu\text{g ml}^{-1}$) up to 24 h. In 4 are shown the infusion-corrected ($T_i = 5$ min) concentration constants B' and A' , which equals the corresponding bolus injection constants, then a_0 (total dose in mg kg^{-1}), and the final analytical results, which in succession are: AUC ($\mu\text{g ml}^{-1} \text{h}$), Cl ($1 \text{ kg}^{-1} \text{h}^{-1}$), $V_{d\beta}$ (1 kg^{-1}), c_0 ($\mu\text{g ml}^{-1}$), V_c (1 kg^{-1}), k_{10} , k_{21} , k_{12} (all in h^{-1}), V_{pe} and V_{de} (1 kg^{-1}). In 5 are stated as an example: a systemic available steady state maintenance dose (in mg kg^{-1}), the regular dosing interval (in hours) and the resulting steady state serum concentration of theophylline (in $\mu\text{g ml}^{-1}$), which was calculated by the program on basis of the preceding pharmacokinetic analysis.

The analysed intravenous data and the pharmacokinetically fitted theoretical serum concentration curve of theophylline are shown graphically in a semilogarithmic plot in Fig. 3. The curve is based on the function $c_1 = 3.33072 \exp(-8.04330t) + 6.44834 \exp(-0.20878t)$.

Figure 4 shows the analysis of time/serum theophylline concentration data referring to oral administration to the same person of a single dose of 3.23 mg kg^{-1} of a micro-

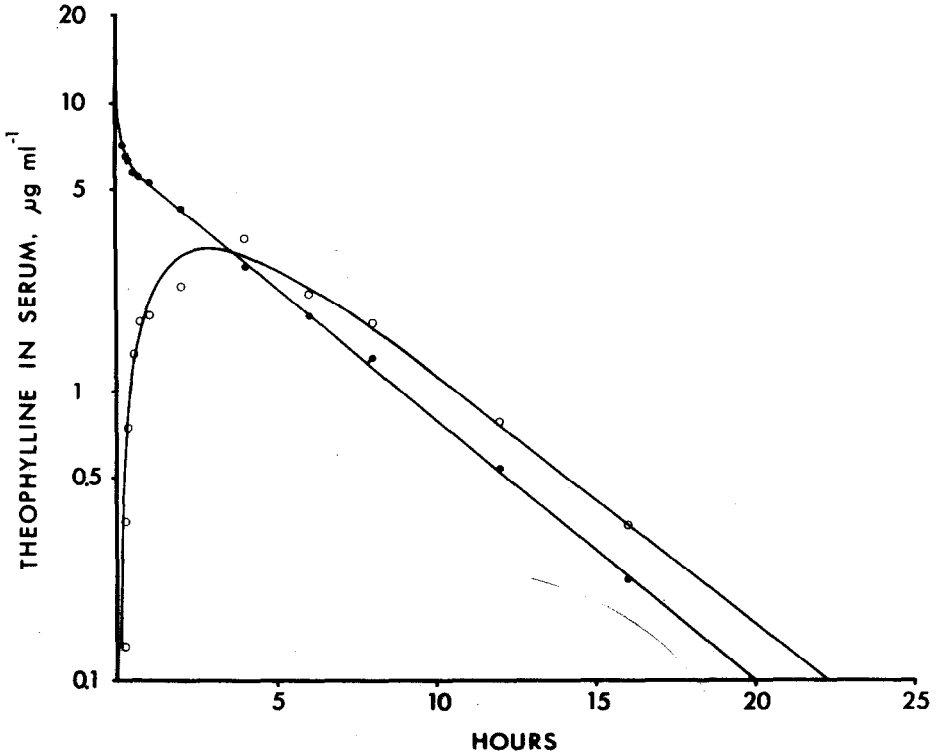


Fig. 3. Theoretical theophylline serum concentration curves based upon the analyses stated in Fig. 2 and Fig. 4, which were performed on data obtained after intravenous and oral administration of the drug, respectively.

particulate theophylline tablet preparation. The analysed data, which are stated in hours and $\mu\text{g ml}^{-1}$, may be read from the figure. They are plotted semilogarithmically in Fig. 3. The 4 last data pairs (1) were judged as belonging to the k_e -phase of elimination related to one-compartment pharmacokinetics. Exponential regression analysis of these data yielded B^* ($\mu\text{g ml}^{-1}$), k_e (h^{-1}), $t_{1/2}k_e$ (h) and r^2 . In 2 the remaining data pairs belonging to the absorption phase were entered, and the corresponding residuals were calculated, printed out and subjected to exponential regression analysis, which ends up with print-out of C^* , k_a , $t_{1/2}k_a$ and r^2 . Simulation by tabulation of the fitted biexponential function describing the time/serum concentration course of theophylline is executed in 3. Determination of lag-time (in hours) and the correspondingly corrected concentration constant C' ($= B'$) is performed in 4, which further incorporates the determinations of AUC ($\mu\text{g ml}^{-1} \text{h}$), t_{max} (h) and c_{max} ($\mu\text{g ml}^{-1}$). In 5 the calculated (cf. methods) systemic available dose, a_0 (mg kg^{-1}), has been entered and this allows further calculation and print-out of plasma clearance, Cl ($1 \text{ kg}^{-1} \text{ h}^{-1}$) and the apparent volume of distribution, V_d (1 kg^{-1}). In 6 is given an example of calculation of the

<u>1</u>	8.00000	0.25000	4.00000	1.00000	<u>4</u>	0.03746
	1.71000	0.35000	3.36000	2.07661		8.49640
	1.00000	-7.79206	-0.47981			
		2.00000	8.00000	2.00000		
	12.00000			2.93372		0.00000
	0.79000	0.33000	6.00000			
	2.00000	0.74000	2.16000	4.00000		27.37087
		-7.27254	-0.41168	2.93670		0.00000
	16.00000	3.00000	9.00000			0.00000
	0.34000			6.00000		2.84067
	3.00000	0.50000	8.67836	2.28035		3.10445
		1.34000	-0.56569			
	24.00000	-6.40413	1.22532	8.00000		
	0.07000	4.00000	0.94911	1.62838	<u>5</u>	0.00000
	4.00000					8.49640
		0.67000		12.00000		
	8.56043	1.72000	<u>3</u> 0.00000	0.76279		2.67533
	-0.20043	-5.76470	-0.11793			
	3.45827	5.00000		16.00000		27.37087
	0.99984		0.20000	0.34552		0.09774
		1.00000	0.47404			0.48767
		1.80000		20.00000		2.84067
<u>2</u>	0.17000	-5.20566	0.40000	0.15534		3.10445
	0.13000	6.00000	0.97993			
	-8.14366			24.00000		
	1.00000	2.00000	0.60000	0.06971	<u>6</u>	2.68000
		2.29000	1.40982			4.00000
		-3.44328				6.85467
		7.00000	0.80000			
			1.77272			

Fig. 4. A pharmacokinetic analysis of serum concentration data obtained after oral administration of a single dose of a tablet preparation of theophylline to an adult person. A detailed information is stated in the text.

mean serum steady-state concentration (\bar{c}_∞) of theophylline related to multiple, regular administration of the stated systemic available maintenance dose, a_0 (mg kg⁻¹), and the stated dosing interval, T_i (h). The parameters are printed out in the following succession: a_0 , T_i and \bar{c}_∞ .

The analysed serum theophylline data referring to oral administration of the drug and the pharmacokinetically fitted theoretical serum concentration curve are depicted in a semilogarithmic plot in Fig. 3. The curve represents the biexponential function: $c = 8.49640 \exp(-0.20043t^*) - 8.49640 \exp(-0.56569t^*)$, where t^* is the lag-time (0.0375 h)-corrected time.

Figure 5 shows the analysis of plasma naproxen concentration data (stated in hours and $\mu\text{g ml}^{-1}$), which were obtained in an adult male volunteer, who ingested a single oral dose of 2.5 mg/kg body wt. The data are plotted semilogarithmically in Fig. 6. The last 4 data pairs were in 1 entered and subjected to exponential regression analysis as representatives of the β -phase of disposition related to two-compartment pharmacokinetics. The results, B^* , β , $t_{1/2\beta}$ and r^2 , are printed out finally. In 2 are shown the entered data pairs, which were judged as belonging to the α -phase, and the calculated

<u>1</u>	11.00000	171.59158	0.50000	18.00000	<u>6</u>	2.50000	
	9.45000	-0.65793	-19.10644	7.58071			
	1.00000	1.05353				473.79592	
		0.99923	0.70000	22.00000		0.00528	
	21.50000		-0.05834	6.64551		0.16048	
	6.85000					63.97578	
	2.00000	<u>3</u>	1.00000	26.00000		0.03908	
		4.30000	18.31180	5.82647			
	27.50000	-132.66388				0.13503	
	5.61000	1.00000	1.50000	30.00000		0.16021	
	3.00000		31.98584	5.10844		0.39558	
		1.00000					
	32.25000	4.70000	2.00000	34.00000		0.09649	
	4.67000	-97.42626	34.68255	4.47890		0.13557	
	4.00000	2.00000					
			2.50000				
	13.69827	2.00000	32.76121	<u>5</u>	0.70100	<u>7</u>	42.01621
	-0.03288	32.00000			0.02125		171.65553
	21.08163	-26.85475	3.00000				-290.61758
	0.99757	3.00000	29.27937		13.38616		
					108.19203		
		3.00000	4.00000		-121.57819		
	4.00000	29.90000	22.34640				
<u>2</u>	24.10000	-6.35066					
	12.08984	4.00000	6.00000	0.00000			
	1.00000		14.39051				
		290.61748			473.79592		
	6.00000	-1.24340	8.00000		0.00000		
	14.70000	0.55746	11.40458		0.00000		
	3.45420	0.98807			63.97578		
	2.00000		10.00000		0.00000		
			10.09707				
	8.00000	<u>4</u>	0.00000		0.13503		
	11.40000	-105.32763	14.00000		0.16021		
	0.86992		8.66197		0.39558		
	3.00000						
					0.00000		
					0.00000		

Fig. 5. An analysis of the single-dose, oral pharmacokinetics of naproxen based upon plasma concentration data from an adult person, who ingested 2.5 mg/kg body wt. Confer with the text for a detailed description of the analytical procedures used.

residuals of first order are also printed out together with a numerator. Exponential regression analysis of the residuals yielded A^* , α , $t_{1/2}\alpha$ and r^2 , which are printed out at last in this program routine. The remaining data pairs belonging to the k_a -phase of absorption were in 3 entered and the corresponding residuals of second order were calculated, printed out and subjected to exponential regression analysis, which ends up with print-out of C^* , k_a , $t_{1/2}k_a$ and r^2 . Simulation by tabulation of the fitted triexponential function describing the time/plasma concentration course of naproxen is carried out in 4. Determination of the lag-time (in hours, accurate to the third digit, cf. methods) and the accordingly corrected concentration constants B' , A' and C' is executed in 5, which also incorporates the calculations of AUC ($\mu\text{g ml}^{-1} \text{h}$) and the

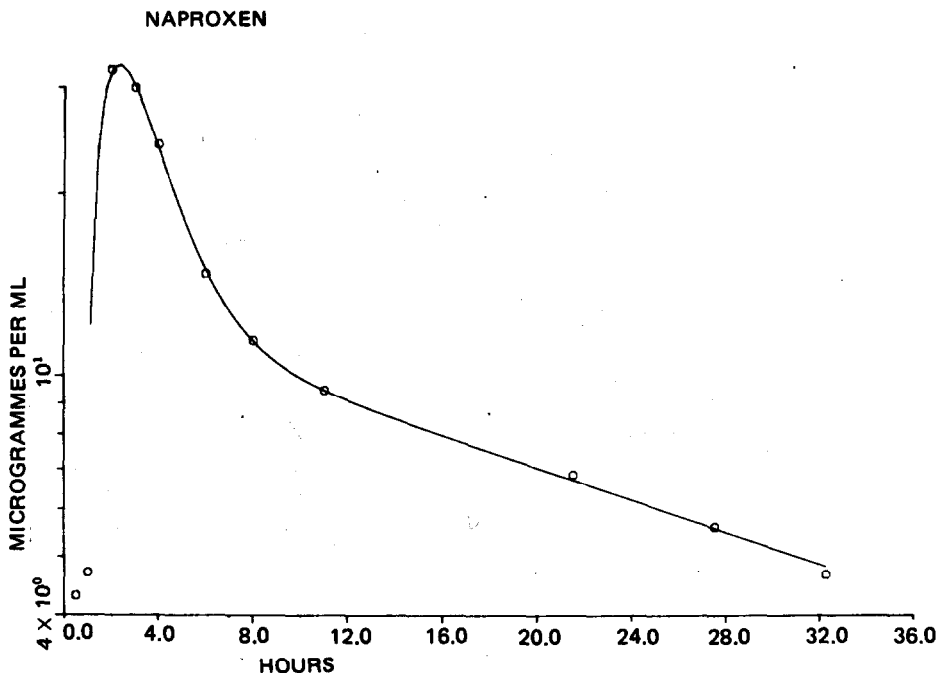


Fig. 6. The single-dose naproxen plasma concentration data stated in Fig. 5 are shown in a semi-logarithmic plotframe together with the NONLIN-derived and computer generated curve of best fit. Further information is given in the text.

uncomposite rate constants k_{10} , k_{21} and k_{12} (h^{-1}). In 6 the assumed systemic available dose, a_0 (2.5 mg kg^{-1}), has been entered and the calculation and print-out of plasma clearance, Cl ($1 \text{ kg}^{-1} \text{ h}^{-1}$), $V_{d\beta}$ ($= V_{d\text{area}}, 1 \text{ kg}^{-1}$), c_0 ($\mu\text{g ml}^{-1}$), V_c (1 kg^{-1}), k_{10} , k_{21} and k_{12} (h^{-1}), V_{pe} and V_{de} ($= V_{dss}, 1 \text{ kg}^{-1}$). In 7 is as an example stated the theoretical steady state concentration constants (B^{**} , A^{**} and C^{**}) which were calculated on basis of a maintenance dose of 2.5 mg kg^{-1} , a dosing interval of 12 h and the original single-dose concentration constants, using the program routine SBR 2. LBL (cf. methods). The theoretical steady state function, which could have been simulated by pressing E, is thus: $c_1 = 42.01621 \exp(-0.03288t) + 171.65553 \exp(-0.65793t) - 290.61758 \exp(-1.24340t)$, where t is in hours and c in $\mu\text{g ml}^{-1}$.

The naproxen plasma concentration data were for comparative reasons also analysed by means of a slightly modified version of Metzler's (1969) program NONLIN for iterative non-linear least squares regression analysis. The parameters determined in the above described analysis were used as starting input for NONLIN. The concentrations were treated unweighted. Figure 6 shows the naproxen data and the computer generated curve of best fit in a semilogarithmic plot-frame. The curve expresses the function: $c_1 = 12.633 \exp(-0.03078t^*) + 129.368 \exp(-0.6533t^*) - 142.001$

$\exp(-1.0818t^*)$, where t^* is the time corrected for a lag-time of 0.927 h. The pharmacokinetic parameters derived from this analysis were: AUC: 477.26 ($\mu\text{g ml}^{-1} \text{h}$), k_{10} : 0.1331, k_{21} : 0.1511, k_{12} : 0.3999, k_a : 1.0818 (h^{-1}), c_0 : 63.52 ($\mu\text{g ml}^{-1}$), Cl : 0.00524 ($1 \text{ kg}^{-1} \text{ h}^{-1}$), $V_{d\beta}$: 0.170, V_c : 0.039, V_{pe} : 0.104 and V_{de} : 0.143 (1 kg^{-1}).

Discussion

By comparing the above stated NONLIN-derived pharmacokinetic naproxen parameters with the in Fig. 5 stated parameters obtained by using the described program for TI-59 it becomes clear that only smaller and clinically unimportant differences exist. It should however, be acknowledged that greater differences may occur, if poorer data are analysed comparatively in this way. The actual data were obtained under experimental conditions, which have been described previously (Nielsen-Kudsk *et al.* 1980b; Nielsen-Kudsk, 1980a). HPLC-methods were used for the determinations of theophylline in serum (Nielsen-Kudsk and Pedersen, 1978) and naproxen in plasma (Nielsen-Kudsk, 1980a). It should be emphasized that the specificity and accuracy of the method of drug analysis used in a pharmacokinetic investigation are of major importance with regard to the validity of the derived pharmacokinetic parameters.

The decision that has to be taken about what number of data pairs belong to the β -phase, the α -phase and/or the k_a -phase related to drugs with two- or one-compartment characteristics, respectively, may in some cases be facilitated by a preliminary pharmacokinetic test analysis incorporating three of the initial, three of the possible intermediate and three of the terminal data pairs. The obtained preliminary half-times multiplied by six offers a rough initial estimate of the duration of either one of these phases in the plasma concentration/time course.

The described simple pharmacokinetic program for TI-59 cannot compete on equal terms with complex and advanced automatic computer programs, which incorporates iterative non-linear regression analysis of the data. But it is easy and fast to use and the obtained parameters are in general comparable to results based upon the use of such complex automatic programs, which, as commented upon (Pedersen, 1977), have often resulted in an authoritativeness going as far as using these programs as a substitute for rational thought. Even if the limitations of such programs are observed, it must be realized that they only produce analytical results 'usually comparable to or better than' manual graphical methods and poorer results may occasionally be experienced (Pedersen, 1977). It should also be emphasized that the used method of weighting has a very distinct influence upon the results obtained by iterative non-linear least squares regression analysis in pharmacokinetic curve fitting (Boxenbaum *et al.*, 1974; Wagner, 1975; Poland and Woloszczak, 1980).

The pharmacokinetic parameters obtained in analyses of serum or plasma concentration/time data by means of the described program are in general sufficiently valid for clinical use. They may also serve as excellent starting parameters for a further iterative non-linear regression analysis of the data, executed by a suitable digital com-

puter program like Metzler's (1969) NONLIN. The simulation routine for curve function tabulation contained in the program may be useful in the prediction of the time course of plasma concentrations of drugs in relation to single dose administration, and also, by using the relevant conversion routine in the program, in predictions of steady state concentration profiles.

References

- Boxenbaum, H.G., Riegelman, S. and Elashoff, R.M., Statistical estimations in pharmacokinetics, *J. Pharmacokin. Biopharm.*, 2 (1974) pp. 123-148.
- Metzler, C.M., NONLIN, Technical Report No. 7292/69/7293/005, The Upjohn Co., Kalamazoo, 1969.
- Nielsen-Kudsk, F., HPLC-determination of some antiinflammatory, weak analgesic and uricosuric drugs in human blood plasma and its application to pharmacokinetics, *Acta Pharmacol. Toxicol.*, (47) (1980a) pp. 267-273.
- Nielsen-Kudsk, F., Magnussen, I., Staehelin Jensen, T. and Naeser, K., Bioavailability and pharmacokinetics in man of orally administered theophylline, *Acta Pharmacol. Toxicol.*, 46 (1980b) pp. 205-212.
- Nielsen-Kudsk, F. and Kirstein Pedersen, A., Simultaneous and specific determination of proxiphylline, theophylline and other xanthine derivatives in serum by HPLC, *Acta Pharmacol. Toxicol.*, 42 (1978) pp. 298-302.
- Pedersen, P.V., Curve fitting and modeling in pharmacokinetics and some practical experiences with NONLIN and a new program FUNFIT, *J. Pharmacokin. Biopharm.*, 5 (1977) pp. 513-531.
- Poland, H. and Woloszczak, R., A program library for computing the parameters of linear compartment models in pharmacokinetics, *Int. J. Bio-Med. Comput.* 11 (1980) pp. 115-128.
- Wagner, J.G., *Fundamentals of Clinical Pharmacokinetics*. Drug Intelligence Publ., Inc., Hamilton, Illinois, 1975.