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# PEELFIT: AN INTEGRATED COMPUTER PROGRAM FOR PHARMACOKINETIC ANALYSIS

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## ABSTRACT

An integrated program PEELFIT is reported for the Apple IIe microcomputer, which performs pharmacokinetic analysis for intravenous and first order absorption (oral or intramuscular) data. PEELFIT, written in basic language, uses plasma concentration and time for input. Upon the user's choice, it carries out non-linear regression on the data for curve fitting, according to a one or two compartment model. The curve fitting can be done with three weighting schemes. Parameters of the plasma

concentration equations are obtained from the regression analysis and further, these are employed to calculate the relevant pharmacokinetic parameters. Finally, the percentage of dose absorbed (absorbable fraction) is calculated as a function of time. Various known data were analysed with PEELFIT and the results obtained confirmed its accuracy.



## INTRODUCTION

Most of the existing programs which perform similar estimations of pharmacokinetic parameters, need relatively powerful and expensive computers. PEELFIT was developed to be used on the Apple IIe computer, which is financially affordable by most laboratories and educational institutes. PEELFIT requires an Apple IIe (64K) with two disc drives. It is integrated to run 12 programs which are needed to perform various tasks and calculations, necessary for the pharmacokinetic analysis. All the programs are on a single disc and once PEELFIT is started, they run automatically as and when needed during the analysis. Pharmacokinetic analysis of data obtained by intravenous injection has been previously reported with the Apple III (2) but it employs log-linear regression for curve fitting.

## THEORETICAL SECTION

The program PEELFIT (Fig.1) starts with a data input routine. An initialised disc, called DATA DISC, is required to be inserted in second drive on which all entered data are saved. Upto 10 sets of data can be entered at a time. The data entered are saved on the data disc under specific file names, given by the user and may be used at any time by telling PEELFIT to analyse the specific name file. To enter more than 10 sets of data, the program may be run again. PEELFIT accepts '-' for missing or undetected values. Once all the data are entered, the values are displayed on the screen and the user is asked for corrections,if any. Corrected values are again displayed, continuing till the user's satisfaction before saving the data.

**INITIAL ESTIMATIONS** : After saving the data, the next program to estimate initial starting values of polyexponential equation parameters (Fig.2) is run. All the subsequent programs are designed to run automatically. The data can be analysed for one compartment or two compartment IV or first order absorption models, as chosen by the user. The initial estimation of parameters is done by the 'peeling' technique. For one compartment models, the initial estimates of equation parameters are made without

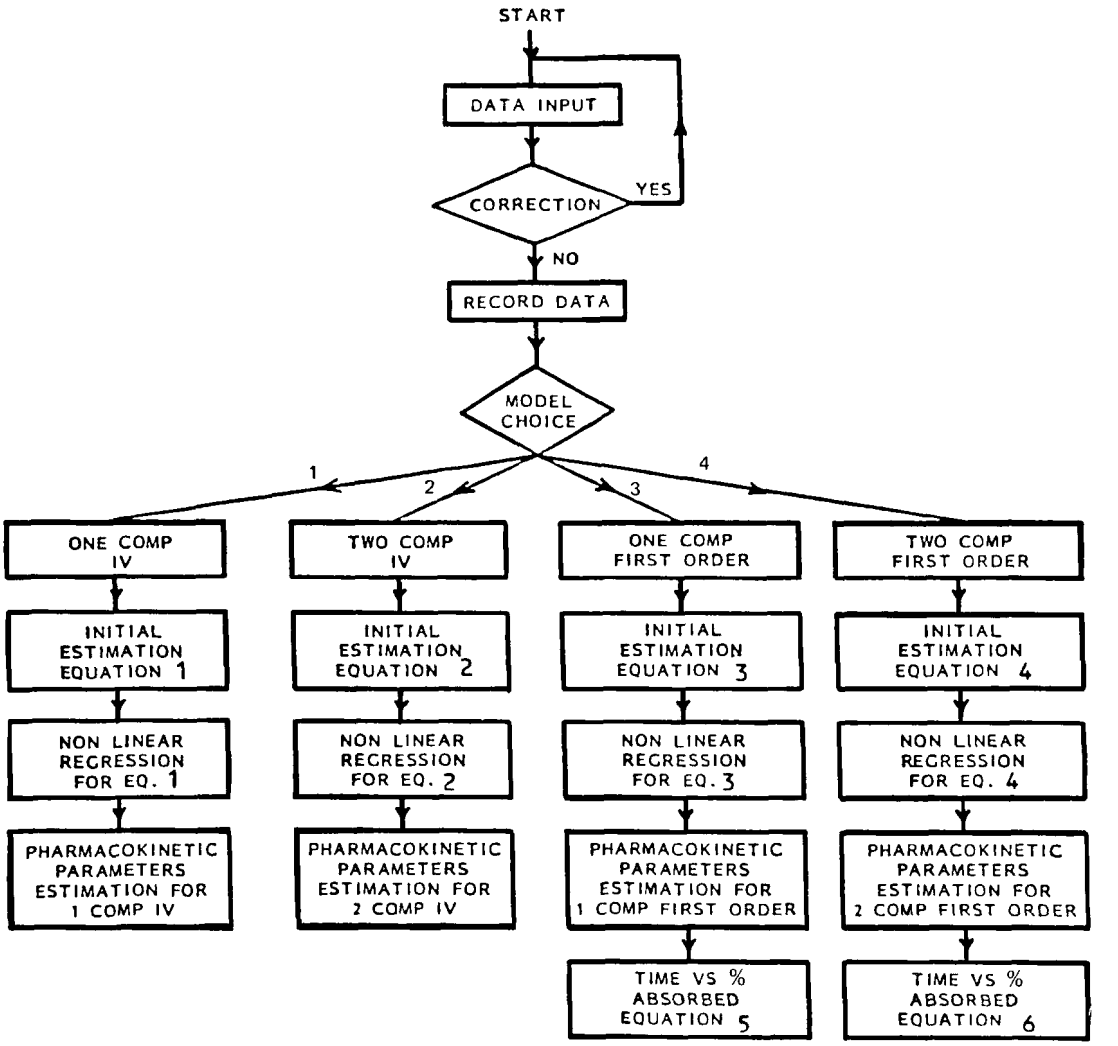


**Fig. 1** : SCHEMETIC PRESENTATION OF VARIOUS PROGRAMS AND ROUTINES INTEGRATED IN PEELFIT.

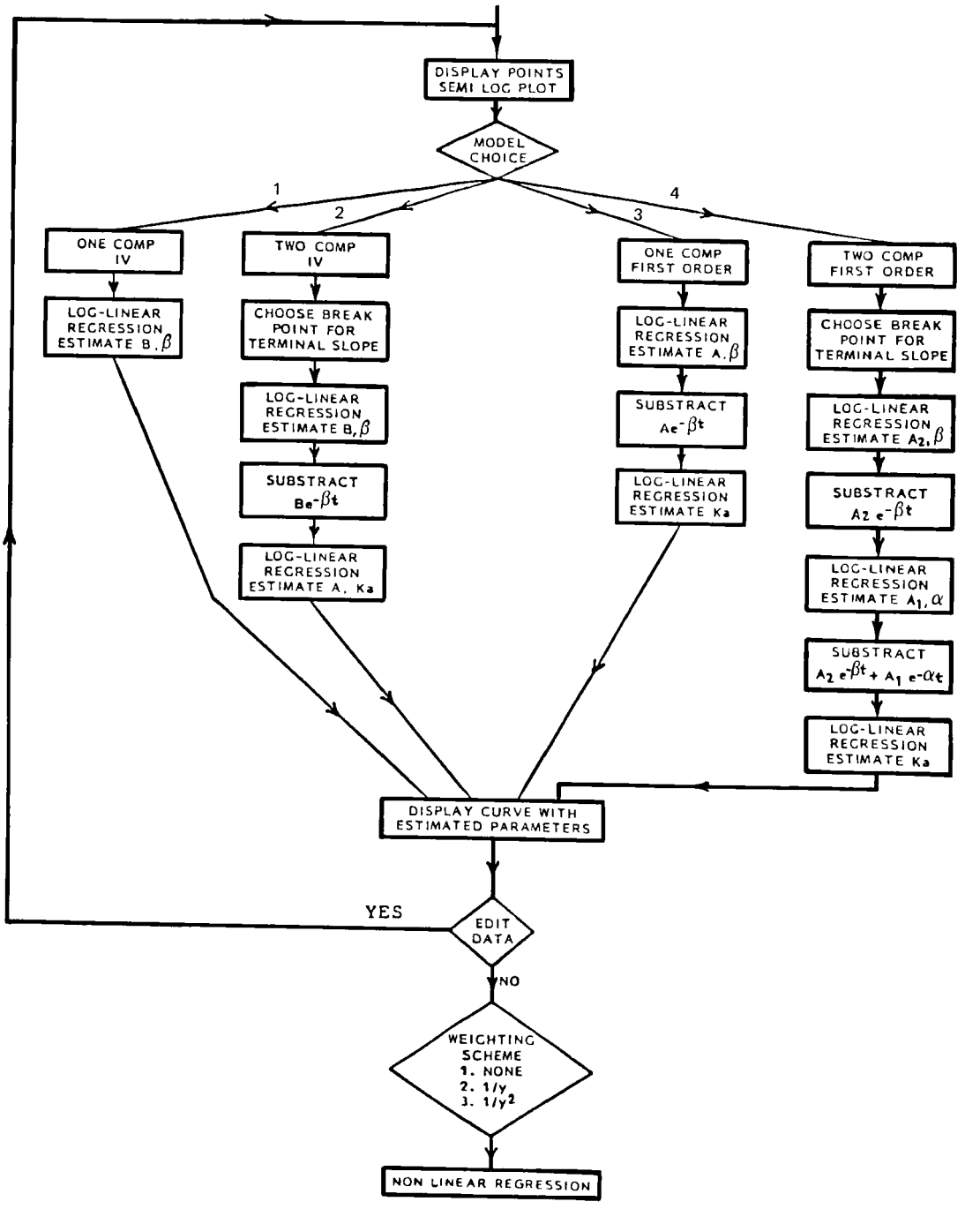


**Fig. 2** : ROUTINE FOR INITIAL ESTIMATION OF POLYEXPONENTIAL EQUATION PARAMETERS.

further information, but for two compartment models, the operator is required to choose the break point where the terminal phase of the curve begins. The points are displayed on a semi-log plot and the break point is selected by moving the cursor. An approximate value for the lag time, if any, is required to be entered. The curve corresponding to the appropriate equation and estimated parameters appears on the screen. At this stage the operator can choose another model or edit the data by adding, deleting or changing a point. On continuation the 'weighting scheme' is selected from three choices: none, $1/Y$ and $1/Y^2$ .All further processing is done on the edited data.

**CURVE FITTING** : The initial estimates are taken as the starting values by the non-linear regression program (Fig.3). Curve fitting is done by a 'weighted least square fit' method. The procedure adopted was described by Bevington (9). During the curve fitting, the user has 6 options to monitor the operation: priority results, priority plot, alternate results and plot (default), plot and continue, results and continue, and proceed with pharmacokinetic parameter calculations with present values. Any of the above monitoring modes can be choosen between each iteration. The curve fitting continues till the %

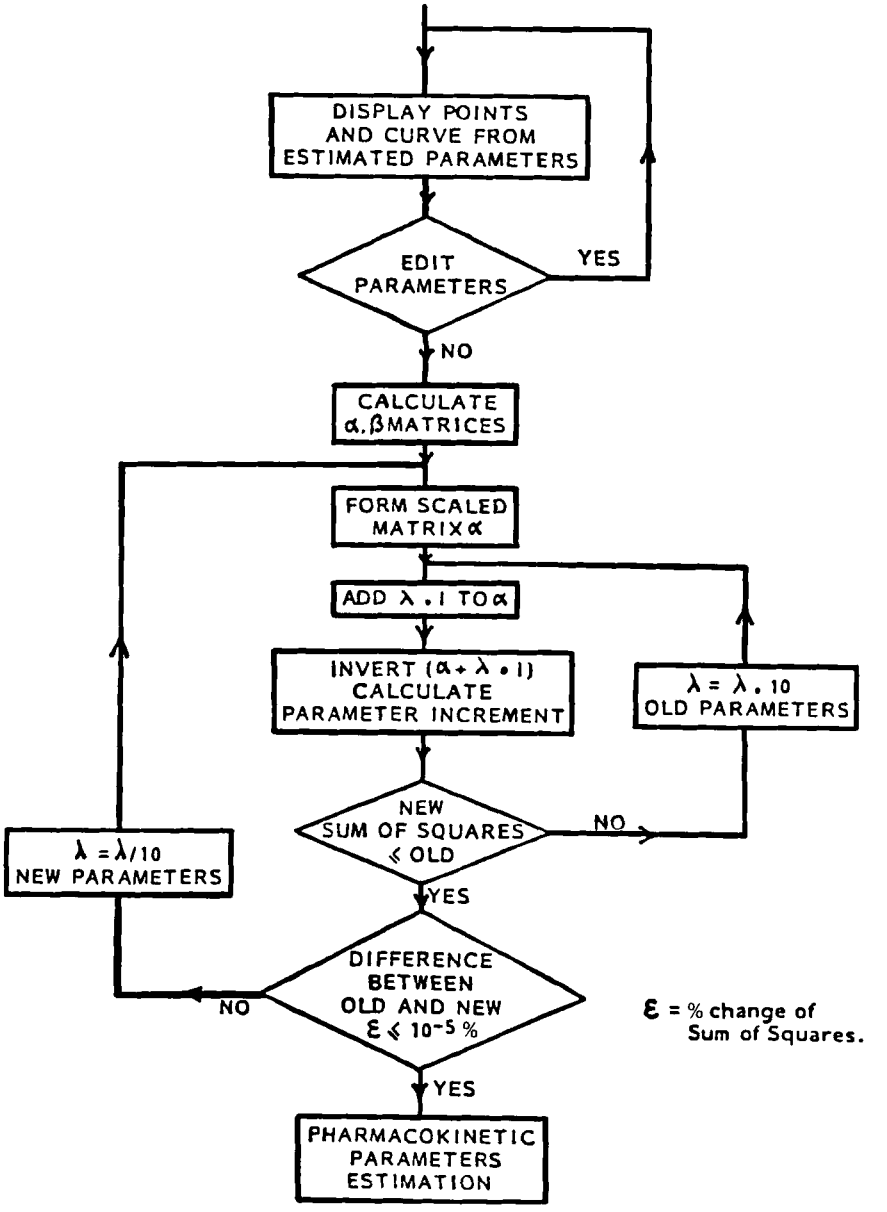


**Fig. 3** : ROUTINE FOR NON-LINEAR REGRESSION.

change between last and present sum of squares is less than or equal to 0.00001 %.

**ESTIMATION OF PHARMACOKINETIC PARAMETERS** : The final polyexponential parameters obtained after non-linear regression are used for estimating the pharmacokinetic parameters, illustrated in table 1.

The inputs required for the IV models are dose in mg, units of time and plasma concentration. For the first order absorption models, the fraction of dose absorbed is also required for calculations. If the fraction of dose absorbed is not known, the default value is 1.

The equations representing plasma concentration are :

One compartment IV model

$$C = Be^{-\beta \cdot t} \qquad ..(1)$$

Two compartment IV model

$$C = Ae^{-\alpha \cdot t} + Be^{-\beta \cdot t} \qquad ..(2)$$

One compartment first order absorption model

tl = lag time

$$C = -Ae^{-Ka.(t-tl)} \; Ae^{-\beta.(t-tl)} \qquad ..(3)$$

Two compartment first order absorption model

$$C = Ale^{-\alpha.(t-tl)} + A2e^{-\beta.(t-tl)} + A3e^{-Ka.(t-tl)} \qquad ..(4)$$

**TABLE 1 : PHARMACOKINETIC PARAMETERS ESTIMATED BY PEELFIT.**

| PHARMACOKINETIC PARAMETERS | ONE COMP IV | TWO COMP IV | ONE COMP.1st ORDER ABS. | TWO COMP.1st ORDER ABS. |
|---|---|---|---|---|
| INITIAL PLASMA CONCENTRATION | + | + | | |
| AUC (TRAP) | + | + | + | + |
| AUC (PARA) | + | + | + | + |
| APP. VOLUME OF DISTRIBUTION (TRAP) | + | + | + | + |
| APP. VOLUME OF DISTRIBUTION (PARA) | + | + | + | + |
| Ka | | + | + | + |
| Ke | + | + | + | + |
| K12 | | + | | + |
| K21 | | + | | + |
| HALF LIFE (ELI) | + | + | + | + |
| HALF LIFE (ABS) | | + | + | + |
| VOL.CENTRAL COMP. | | + | | + |
| VOL.SECOND COMP. | | + | | + |
| PLASMA CLEARANCE (TRAP) | + | + | + | + |
| PLASMA CLEARANCE (PARA) | + | + | + | + |
| CONC. IN 2nd COMPARTMENT | | + | | + |
| C max | | | + | |
| T max | | | + | |
| MRT | | | + | + |
| VRT | | | + | + |

In one compartment first order absorption model, the time vs % absorbed is calculated using WAGNER-NELSON equation (1,11). While plotting the curve of time vs % absorbed, the first point (0,0) is added to the data.

$$(A/Vd)tn = Ctn + \beta . \int_{t_o}^{tn} C \, dt \qquad ..(5)$$

For two compartment first order absorption model, the time vs % absorbed is calculated using LOO-RIEGELMAN equation (1,10).

$$(A/Vl)tn = Ctn + Ke . \int_{t_o}^{tn} C \, dt + Ttn \qquad ..(6)$$

Ttn being the tissue concentration at time tn and is given by the equation:

$$Ttn = Ttn-1.e^{-K21.\Delta t} + [(Kl2/K21). Ctn-1 .(1-e^{-K21.\Delta t})] + (Kl2.\Delta C.\Delta t/2) \qquad ..(7)$$

The statistical moments are calculated, as described by Kiyoshi Yamaoka et al (14).

## RESULTS AND DISCUSSIONS

To evaluate the accuracy of curve fitting, the following procedure was adopted. With an HP41C (Hewlett Packard) computer, four short programs were made. Each program calculated C values according to one of equations 1,2,3 and 4. Arbitrary values for t and equation parameters were input and C values were obtained as output from the HP41C. This was repeated,

**TABLE 2 : Equation $C = Be^{-\beta \cdot t}$ .Fitted to One Compartment IV Model. S=Sum of squares.**

| PARAMETERS INPUT HP41C | t INPUT HP41C | C OUTPUT HP41C | PARAMETERS OUTPUT PEELFIT WHEN INPUT C AND t | | |
|---|---|---|---|---|---|
| | | | WEIGHTING SCHEME | | |
| | | | 1 | 1/Y | $1/Y^2$ |
| | 0.0 | 10.00 | | | |
| | 1.0 | 8.19 | | | |
| B=10.0 | 2.0 | 6.70 | B=9.997098 | B=10.002365 | B=10.004597 |
| $\beta$= 0.2 | 3.0 | 5.49 | $\beta$ =0.199836 | $\beta$ =0.1999923 | $\beta$ =0.2000631 |
| | 5.0 | 3.69 | | | |
| | 10.0 | 1.35 | S=.0001312 | S=.00014842 | S=.000175 |
| | 15.0 | 0.498 | | | |
| | 20.0 | 0.183 | | | |

selecting each of the above equations. Four sets of data were thus collected for C, t and the equation parameters, each satisfying one of the above mentioned equations. These values of C and t were input in PEELFIT and equation parameters were calculated by it, carrying out nonlinear regression on the data. The results obtained are summarized in tables 2-5.

The equation parameters estimated by PEELFIT were highly accurate. Further evaluation was done by utilizing known data and recalculating them with PEELFIT.

DATA Ref.1.Page 30 - These data were analysed by NOTARI for a one compartment IV model. The data were slightly modified by us, as the original data for

**TABLE 3 : Equation $C = Ae^{-\alpha \cdot t} + Be^{-\beta \cdot t}$ .Fitted to Two Compartment IV Model. S=Sum of squares**

| PARAMETERS INPUT HP41C | t INPUT HP41C | C OUTPUT HP41C | PARAMETERS OUTPUT PEELFIT WHEN INPUT C AND t | | |
|---|---|---|---|---|---|
| | | | WEIGHTING SCHEME | | |
| | | | 1 | 1/Y | $1/Y^2$ |
| | 0.0 | 30.00 | | | |
| | 0.5 | 25.18 | | | |
| A=20.0 | 1.0 | 21.18 | A=19.989165 | A=20.002508 | A=19.995589 |
| $\alpha$= 0.5 | 2.0 | 15.55 | $\alpha$=0.4999507 | $\alpha$=0.4995265 | $\alpha$=0.4998401 |
| B=10.0 | 3.0 | 11.87 | B=10.01077 | B=9.9960737 | B=10.004412 |
| $\beta$= 0.1 | 5.0 | 7.71 | $\beta$=0.1001757 | $\beta$=0.1000675 | $\beta$=0.1001015 |
| | 10.0 | 3.81 | | | |
| | 20.0 | 1.35 | S=.00002906 | S=.00003605 | S=.00003149 |
| | 30.0 | 0.498 | | | |
| | 50.0 | 0.067 | | | |

**TABLE 4 : Equation $C = -Ae^{-Ka(t-tl)} + Ae^{-\beta \cdot (t-tl)}$ .Fitted to One Comp.First Order Absorption Model. S=Sum of squares.**

| PARAMETERS INPUT HP41C | t INPUT HP41C | C OUTPUT HP41C | PARAMETERS OUTPUT PEELFIT WHEN INPUT C AND t | | |
|---|---|---|---|---|---|
| | | | WEIGHTING SCHEME | | |
| | | | 1 | 1/Y | $1/Y^2$ |
| | 1.0 | 2.98 | | | |
| | 2.0 | 4.51 | | | |
| A=10.0 | 3.0 | 5.18 | A=9.987498 | A=9.991473 | A=9.993804 |
| Ka=0.5 | 5.0 | 5.24 | Ka=0.50067 | Ka=0.50038 | Ka=0.50016 |
| $\beta$= 0.1 | 7.0 | 4.66 | $\beta$=0.099946 | $\beta$=0.099970 | $\beta$=0.099980 |
| | 10.0 | 3.61 | | | |
| | 15.0 | 2.226 | | | |
| | 20.0 | 1.352 | S=.0000413 | S=.0000431 | S=.0000477 |
| | 30.0 | 0.498 | | | |
| | 50.0 | 0.067 | | | |

**TABLE 5 : Equation $C = A1e^{-\alpha(t-tl)} + A2e^{-\beta(t-tl)} + A3e^{-Ka(t-tl)}$ ;A3= -(A1+A2). Fitted to Two Comp.First Order Absorption Model. S=Sum of squares.**

| PARAMETERS INPUT HP41C | t INPUT HP41C | C OUTPUT HP41C | PARAMETERS OUTPUT PEELFIT WHEN INPUT C AND t | | |
|---|---|---|---|---|---|
| | | | WEIGHTING SCHEME | | |
| | | | 1 | 1/Y | $1/Y^2$ |
| | 0.1 | 0.89 | | | |
| | 0.3 | 2.35 | | | |
| | 0.6 | 3.88 | | | |
| A1=10.0 | 1.0 | 5.07 | A1=10.060042 | A1=10.117808 | A1=10.318445 |
| α = 0.5 | 2.0 | 5.74 | α =0.5001883 | α =0.5023754 | α =0.5073754 |
| A2= 5.0 | 3.0 | 5.19 | A2=4.9873478 | A2=4.9978771 | A2=5.0104096 |
| β = 0.1 | 5.0 | 3.75 | β =0.0998044 | β =0.0999254 | β =0.1000273 |
| Ka= 1.0 | 8.0 | 2.42 | Ka=0.9984017 | Ka=0.9975773 | Ka=0.9938583 |
| | 10.0 | 1.91 | | | |
| | 14.0 | 1.24 | S=.00003032 | S=.00003176 | S=.00004458 |
| | 20.0 | 0.68 | | | |
| | 25.0 | 0.41 | | | |
| | 30.0 | 0.25 | | | |
| | 40.0 | 0.091 | | | |
| | 50.0 | 0.033 | | | |

**TABLE 6 : Comparison of results found by NOTARI Ref.1.Page 30 and calculated by PEELFIT for one compartment IV model.**

| PARAMETER | B | β | Ke | Po |
|---|---|---|---|---|
| NOTARI | 45.710 | 0.141 | 0.441 | 142.86 |
| PEELFIT | 45.78365 | 0.14123 | 0.44069 | 142.857 |

plasma levels was in terms of fraction of dose. A dose of 500 mg was assumed and values for plasma concentration were converted from fraction to mg/ml. Values obtained are compared in table 6.

**TABLE 7 : Comparison of parameters found by NOTARI and PEELFIT for data in Ref.1.Page 24. fitted to Two Compartment IV Model.**

| PARAMETERS | A | α | B | β | Po | K2 | K21 | K12 |
|---|---|---|---|---|---|---|---|---|
| NOTARI | 5.25 | 1.34 | 1.75 | 0.13 | 7.0 | 0.40 | 0.43 | 0.64 |
| PEELFIT | 5.252 | 1.337 | 1.727 | 0.129 | 6.979 | 0.405 | 0.429 | 0.633 |

DATA Ref.1.Page 24 - The refered data were fitted to a two compartment IV model by NOTARI. As the data are arbitrary, a dose of 25 mg and units of plasma concentration. as ug/ml were assumed. This did not affect the parameters calculated (table 7, Fig.4).

TETRACYCLINE HCl - These data were originally reported by Wagner (5) and then subsequently fitted with a computer program CSTRIP (4). Wagner has reported CSTRIP as a program for obtaining 'Initial Polyexponential Parameter Estimates'. These data were also analysed by Valentine and Hunter (3) with the ORAL program.

The values obtained for the parameters by NON LINEAR LEAST SQUARES after using CSTRIP and GRAPHICAL values as initial starting estimates, are practically the same as those found by PEELFIT (table 8). The sum of squared residuals is also exactly the same and is less than those obtained by ORAL, CSTRIP and GRAPHIC, which confirms an appropriate fit of the curve to the data (Fig 5,6).

PHARMACOKINETIC PARAMETERS OF:

NOTARI IV 2 COMP P(24)

ANALYSED FOR TWO COMPARTMENT IV

| TIME HRS | C.OBS UG/ML | C.CALC UG/ML | C.TISSUE UG/ML | RESIDUE |
|---|---|---|---|---|
| 0 | 7 | 6.97868534 | 0 | .0213146564 |
| .25 | 5.38 | 5.43144513 | .62486124 | -.0514451265 |
| .5 | 4.33 | 4.30986165 | 1.0522255 | .0201383475 |
| .75 | 3.5 | 3.4933498 | 1.33884048 | 6.55019656E-03 |
| 1 | 2.91 | 2.89594032 | 1.52531131 | .0140596805 |
| 1.5 | 2.12 | 2.12807016 | 1.70574601 | -8.07016063E-03 |
| 2 | 1.7 | 1.69402644 | 1.7400959 | 5.973564E-03 |
| 2.5 | 1.43 | 1.43361987 | 1.70323221 | -3.61986505E-03 |
| 3 | 1.26 | 1.26459159 | 1.63329718 | -4.59159305E-03 |
| 4 | 1.05 | 1.05191961 | 1.46191759 | -1.91961462E-03 |
| 5 | .9 | .908353852 | 1.29103959 | -8.35385197E-03 |
| 6 | .8 | .793626938 | 1.13563002 | 6.37306157E-03 |
| 7 | .7 | .695859755 | .997751329 | 4.14024526E-03 |

| PARAMETER | VALUE | S.ERROR |
|---|---|---|
| A: | 5.25178444 | .0537109713 |
| ALPHA: | 1.33687071 | .0213937816 |
| B: | 1.72690091 | .0553148536 |
| BETA: | .129940975 | 6.95523065E-03 |

VARIANCE : 4.45919419E-04

R.M.S : .0211168042

SUM OF SQUARES : 4.01327476E-03

DEGREE OF FREEDOM : 9

WEIGHTING SCHEME : NONE

| | |
|---|---|
| DOSE | : 25 MG |
| INITIAL PLASMA CONC | : 6.97668535 UG/ML |
| AREA UNDER CURVE (TRAP) | : 13.48625 |
| AREA UNDER CURVE (PARA) | : 17.2183034 |
| APPARENT VOLUME OF DISTRIBUTION (TRAP) | : 14.2660152 LT |
| APPARENT VOLUME OF DISTRIBUTION (PARA) | : 11.1738679 LT |
| ELIMINATION RATE CONSTANT | : .405306214 |
| RATE CONSTANT FROM 1 -> 2 COMP (K12) | : .632905372 |
| RATE CONSTANT FROM 2 -> 1 COMP (K21) | : .4286001 |
| HALF LIFE (ELI) | : 5.3331907 HRS |
| HALF LIFE (ABS) | : .518374735 HRS |
| VOLUME OF CENTRAL COMP | : 3.58233661 LT |
| VOLUME OF SECOND COMP | : 5.2899663 LT |
| PLASMA CLEARANCE (TRAP) | : 1.85373992 L/HRS |
| PLASMA CLEARANCE (PARA) | : 1.45194329 L/HRS |

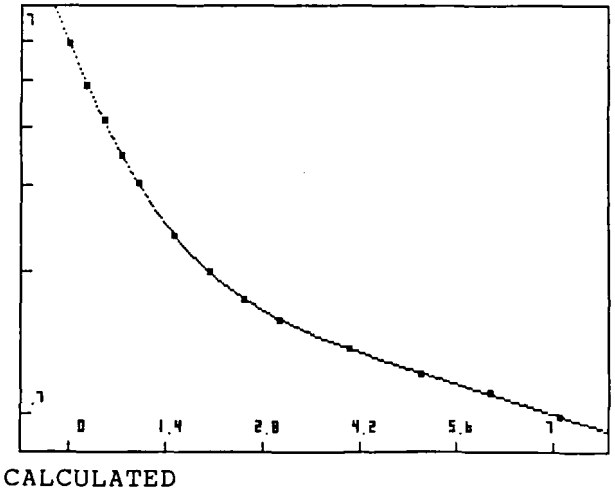


**Fig. 4** : PRINTOUT OF CALCULATED PHARMACOKINETIC PARAMETERS OF NOTARI DATA (REFERENCE 1, PAGE 24) FITTED TO TWO COMPARTMENT IV MODEL.

**TABLE 8 : Comparison of Equation Parameters and Curve-Fitting results for Tetracycline Oral data.**

(a)Data from Ref.3. (b)Graphical values used as initial least square estimates. (e)CSTRIP values used as initial least square estimates. Data fitted to equation ( 3 ). S=Sum of squares. Va=Variance

| PARAMETERS | ORAL | CSTRIP | GRAPHIC | NONLINEAR LEAST SQ | | PEELFIT | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | WEIGHTING SCHEME | | |
| | a | b | c | d | e | 1 | 1/Y | $1/Y^2$ |
| A | 2.133 | 2.130 | 2.30 | 2.650 | 2.420 | 2.650 | 2.420 | 2.256 |
| Ka | 1.034 | 1.030 | 0.81 | 0.716 | 0.794 | 0.716 | 0.794 | 0.873 |
| β | 0.128 | 0.129 | 0.13 | 0.149 | 0.139 | 0.149 | 0.139 | 0.132 |
| Tlag(hr) | 0.610 | 0.610 | 0.33 | 0.421 | 0.436 | 0.412 | 0.435 | 0.458 |
| S | 0.026 | 0.026 | 0.024 | 0.010 | 0.011 | 0.010 | 0.011 | 0.015 |
| Va | 0.003 | - | - | - | - | 0.002 | 0.002 | 0.003 |

SPECTINOMYCIN INTRAMUSCULAR - These data were originally reported by Wagner et al (6) , then evaluated by CSTRIP (4) and also used in ORAL (3). In CSTRIP the absorption phase was forced through 0,0. In ORAL the point 0,0 was not added, but the point at 4h was included in both absorption and elimination phases. We processed the data without any modification at all. The sum of squared residuals obtained by PEELFIT are less than those found by either CSTRIP or ORAL (table 9), conforming a better curve fit to the data (Fig 7,8).

## CONCLUSIONS

Most of the present curve fitting and pharmacokinetic analysis programs can be broadly classified in two

PHARMACOKINETIC PARAMETERS OF:

WAGNER TETRACYCLINE

ANALYSED FOR ONE COMPARTMENT FIRST ORDER ABSORPTION

| TIME HRS | C.OBS UG/ML | C.CALC UG/ML | RESIDUE |
|---|---|---|---|
| 1 | .7 | .692210491 | 7.7895089E-03 |
| 2 | 1.2 | 1.2491494 | -.0491493968 |
| 3 | 1.4 | 1.37946612 | .0205338849 |
| 4 | 1.4 | 1.33272147 | .0672785291 |
| 6 | 1.1 | 1.08853302 | .0114669823 |
| 8 | .8 | .840747796 | -.040747796 |
| 10 | .6 | .640210545 | -.0402105453 |
| 12 | .5 | .485671967 | .0143280332 |
| 16 | .3 | .278860034 | .0211399656 |

| PARAMETER | VALUE | S.ERROR |
|---|---|---|
| A: | 2.41996232 | .262899631 |
| Ke: | .138824235 | .0104625011 |
| Ka: | .794282676 | .142747104 |
| LAG TIME: | .435281338 | .0960718371 |

VARIANCE : 2.48482471E-03

R.M.S : .0498480161

SUM OF SQUARES : .0114853338

DEGREE OF FREEDOM : 5

WEIGHTING SCHEME : 1/Y

| | |
|---|---|
| AREA UNDER CURVE (TRAP) | : 13.1 |
| AREA UNDER CURVE (PARA) | : 14.3851166 |
| APPARENT VOLUME OF DISTRIBUTION (TRAP) | : 137.468573 LT |
| APPARENT VOLUME OF DISTRIBUTION (PARA) | : 125.187606 LT |
| C MAX | : 1.4 UG/ML |
| T MAX | : 2.66108523 HRS |
| ELIMINATION RATE CONSTANT | : .138824235 |
| ABSORPTION RATE CNSTANT | : .794282676 |
| HALF LIFE (ELI) | : 4.99192378 HRS |
| HALF LIFE (ABS) | : .872485352 HRS |
| PLASMA CLEARANCE (TRAP) | : 19.0839695 L/HRS |
| PLASMA CLEARANCE (PARA) | : 17.3790736 L/HRS |
| MRT | : 8.46235084 HRS |
| VRT | : 53.4733725 HRS |

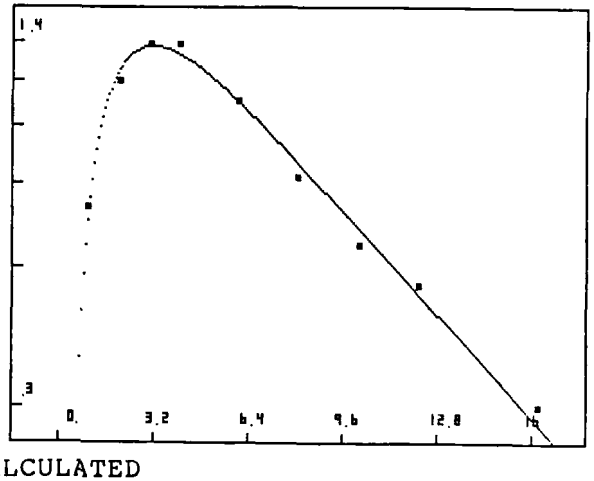


**Fig. 5** : PRINTOUT OF CALCULATED PHARMACOKINETIC PARAMETERS OF WAGNER TETRACYCLIN DATA (REFERENCE 5) FITTED TO ONE COMPARTMENT FIRST ORDER ABSORPTION MODEL.

TIME VS % ABSORBED PLOT OF:

WAGNER TETRACYCLINE

| TIME(HRS) | % ABSORBED |
|---|---|
| 1 | 36.8195794 |
| 2 | 71.2235688 |
| 3 | 86.7806053 |
| 4 | 93.8193474 |
| 6 | 98.3923528 |
| 8 | 99.3894028 |
| 10 | 99.6408653 |
| 12 | 99.7284654 |
| 16 | 100 |

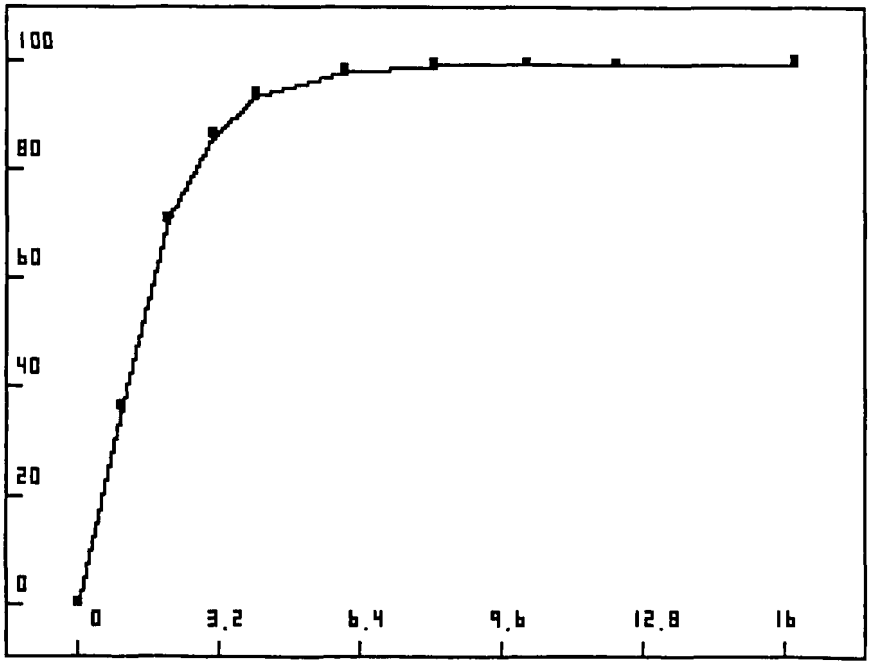


**Fig. 6** : PLOT OF TIME VS % ABSORBED, WAGNER TETRACYCLIN DATA. CALCULATED BY USING PARAMETERS OBTAINED FROM NON-LINEAR REGRESSION ROUTINE OF PEELFIT.

**TABLE 9 : Comparison of Equation Parameters and Curve-Fitting results for Spectinomycin intramuscular data.**

Data fitted to equation ( 4 ). S=Sum of squares. Va=Variance. (a,b) Data from Ref.3.

| PARAMETERS | ORAL | CSTRIP | PEELFIT | | |
|---|---|---|---|---|---|
| | | | WEIGHTING SCHEME | | |
| | a | b | 1 | 1/Y | $1/Y^2$ |
| A | 68.3710 | 68.5020 | 56.9691 | 60.0205 | 62.5374 |
| Ka | 1.8803 | 1.8752 | 2.3367 | 2.2357 | 2.1644 |
| β | 0.4185 | 0.4185 | 0.3721 | 0.3930 | 0.4045 |
| Tlag(hr) | 0.0 | 0.0 | 0.0 | 0.0 | 0.0 |
| S | 17.7153 | 18.6380 | 12.3350 | 12.9349 | 14.0549 |
| Va | 2.8903 | - | 2.4670 | 0.0938 | 0.0039 |

categories; programs like CSTRIP, ESTRIP, INTRAV, ORAL etc. are for estimating 'initial equation parameters' which may be further refined by using them as starting values in second category of programs like NONLIN, ELSFIT etc.

PEELFIT is designed to do the work of both types of programs. The initial estimates of equation parameters are made first, and are then refined to give the final best estimates, comparable to the second category of programs. The iterative technique used for minimising the sum of squares is in principle similar to that of NONLIN, which Valentine and Hunter (3) have considered to be impractical for most of the microcomputers. PEELFIT overcomes another apparent disadvantage,

PHARMACOKINETIC PARAMETERS OF:

WAGNER SPECTINOMYCIN

ANALYSED FOR ONE COMPARTMENT FIRST ORDER ABSORPTION

| TIME HRS | C.OBS UG/ML | C.CALC UG/ML | RESIDUE |
|---|---|---|---|
| .166 | 15.7 | 14.8140262 | .885973811 |
| .333 | 23.1 | 24.2383351 | -1.13833513 |
| .5 | 31.2 | 29.8946292 | 1.30537079 |
| 1 | 31.6 | 34.5496971 | -2.94969704 |
| 2 | 28.2 | 27.0211396 | 1.17886039 |
| 4 | 12.8 | 12.3876939 | .412306122 |
| 6 | 5.6 | 5.52046491 | .0795350876 |
| 8 | 2.4 | 2.45811508 | -.0581150753 |

| PARAMETER | VALUE | S.ERROR |
|---|---|---|
| A: | 62.5374351 | 4.8979127 |
| Ke: | .404546218 | .0140786592 |
| Ka: | 2.16443058 | .196780992 |

VARIANCE : 3.92996193E-03

R.M.S : .0626894084

SUM OF SQUARES : 14.0548733

DEGREE OF FREEDOM : 5

WEIGHTING SCHEME : 1/Y^2

| | |
|---|---|
| DOSE | : 1000 MG |
| AREA UNDER CURVE (TRAP) | : 124.01365 |
| AREA UNDER CURVE (PARA) | : 125.693376 |
| APPARENT VOLUME OF DISTRIBUTION (TRAP) | : 19.9325272 LT |
| APPARENT VOLUME OF DISTRIBUTION (PARA) | : 19.6661553 LT |
| C MAX | : 34.119707 UG/ML |
| T MAX | : .952986822 HRS |
| ELIMINATION RATE CONSTANT | : .404546218 |
| ABSORPTION RATE CONSTANT | : 2.16443058 |
| HALF LIFE (ELI) | : 1.71303048 HRS |
| HALF LIFE (ABS) | : .320176589 HRS |
| PLASMA CLEARANCE (TRAP) | : 8.06362848 L/HRS |
| PLASMA CLEARANCE (PARA) | : 7.95586874 L/HRS |
| MRT | : 2.93392073 HRS |
| VRT | : 6.32377466 HRS |

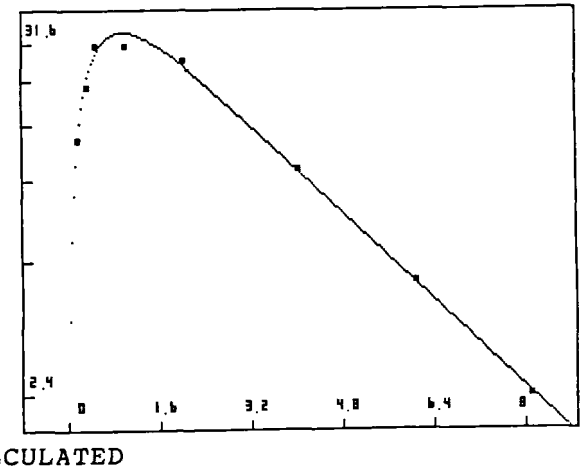


**Fig. 7 :** PRINTOUT OF CALCULATED PHARMACOKINETIC PARAMETERS OF WAGNER SPECTINOMYCIN DATA (REFERENCE 6) FITTED TO ONE COMPARTMENT FIRST ORDER ABSORPTION MODEL.

TIME VS % ABSORBED PLOT OF:

WAGNER SPECTINOMYCIN

| TIME(HRS) | % ABSORBED |
|---|---|
| .166 | 29.736629 |
| .333 | 50.6017413 |
| .5 | 65.1382713 |
| 1 | 86.8370623 |
| 2 | 96.4030956 |
| 4 | 98.9458115 |
| 6 | 99.678862 |
| 8 | 100 |

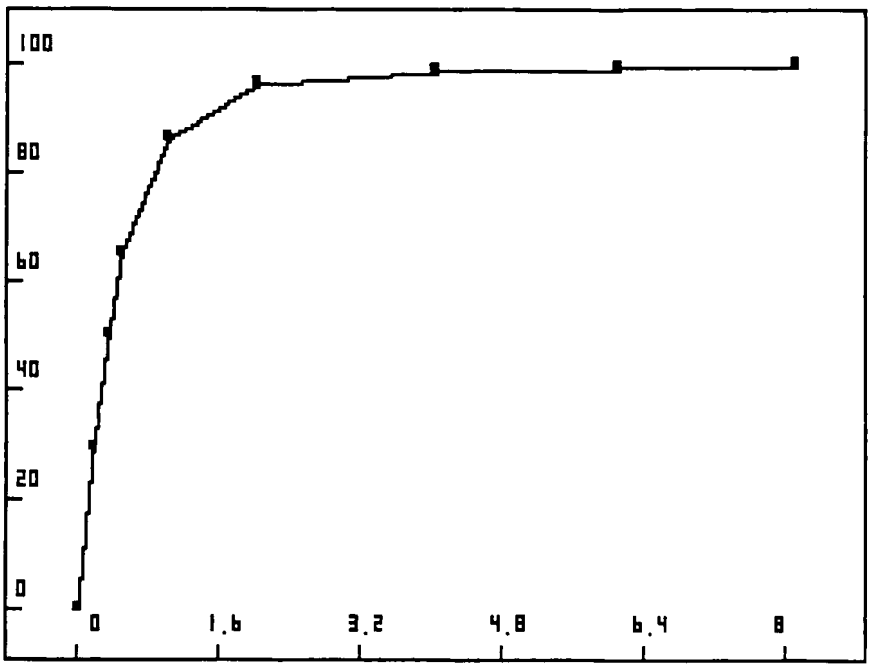


**Fig. 8** : PLOT OF TIME VS % ABSORBED, WAGNER SPECTINOMYCIN DATA. CALCULATED BY USING PARAMETERS OBTAINED FROM NON-LINEAR REGRESSION ROUTINE OF PEELFIT.

unlike NONLIN where the resultant estimates are greatly affected, depending upon the initial starting values chosen (7,8), the final results obtained are always practically the same by PEELFIT even if the initial estimates used differ to some extent. Calculation and plot of the '% absorbed' is another additional feature, not found in most of the programs. PEELFIT on the whole is easy and convenient to use, various editing features need confirmation for most of the operations. Monitoring choice during curve fitting is extremly helpful in deciding the options that may be chosen in the subsequent run.



## FOOT NOTES

(1) A copy of the program can be obtained from the authors.

(2) The program is designed to print the graphics with IMAGEWRITER printer.

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