MicroPharm-K, a Microcomputer Interactive Program for the Analysis and Simulation of Pharmacokinetic Processes

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Purpose. The microcomputer program, MicroPharm-K (MP-K) was developed for pharmacokinetic modeling, including analysis of experimental data and estimation of relevant parameters, and simulation. The intention was to provide a user-friendly, interactive, event-driven program for PC computers. ***Methods.*** The data are ascribed to a predefined model from a library including various routes of administration, oral or intra-venous, bolus or infusion, and various compartmental interpretations, 1 to 3. Single and multiple administrations are supported. The program provides initial estimates of the parameters in most cases, and the parameters are then fitted to the model by non linear model fitting using either the Simplex, Evol, Gauss-Newton, Levenberg-Marquardt or Fletcher-Powell algorithms. The non linear model fitting is based on the maximum likelihood method, and the criterion to minimize is either the weighted least squares (Chi^2 criterion) or the extended least squares. Graphical representations of non-fitted or curve-fitted data are immediately available (including log-scale representation), as well as pharmacokinetic typical parameters such as area under the curve, clearance, volumes, time-rate constants, transfer rate constants, etc. ***Results.*** Simulated and experimental data were analysed and the results were similar to those obtained by other programs. ***Conclusions.*** This non linear fitting program has been proved in our laboratory to be a very effective package for pharmacokinetic studies, including estimation and simulation. Because it is easy-to-use and runs on basic computers, the program could also be used for educational purposes.

KEY WORDS: pharmacokinetics; nonlinear minimisation; computer program; software; estimation; simulation.

INTRODUCTION

The main purpose of pharmacokinetic studies is to determine the distribution and elimination of drugs in the body. Mathematical models of various complexities have been developed to describe the time-concentration relationship that predicts the drug concentration in plasma at a given time after its administration. The analysis of the time-concentration data and estimation of the relevant pharmacokinetic parameters is best performed *via* a non linear fitting technique with the use of a computer program. Many computer programs have been developed (1) and are used in many laboratories.

The MicroPharm-K (MP-K) program has been recently developed for PC computers and runs under the MS-DOS® environment. The program is easy to use with the possibility of editing and saving the data. It occupies a small disk space (340 kbytes) and a small memory area, so that it can be run on most PC computers with basic equipment. In this paper, the MP-K program main features are presented, and several data sets are analysed and compared to those obtained with some other programs.

THEORETICAL SECTION

Non Linear Model Fitting. Fitting a function to a set of data is achieved by searching the minimum of a criterion. In the MP-K program, the user may choose either the weighted least squares (quadratic criterion) or the extended least squares criterion (non quadratic criterion).

The most commonly used criterion is "least squares", i.e., the least squares estimates are the values of model parameters that minimize the sum of weighted or unweighted squares between observed and model-predicted values of the dependent variable (the drug concentration). The objective least squares function is

$$OLS = \Sigma[C_i - C(t_i)]^2 \quad (1)$$

and the objective weighted least squares function is

$$WLS = \Sigma W_i[C_i - C(t_i)]^2 \quad (2)$$

where $C(t_i)$ is the calculated concentration at time t_i, C_i is the corresponding observed concentration, and W_i is the weighting coefficient of the observation. The minimization of eq. (2) is also called chi-square (χ^2) fitting when W_i equals the inverse of the variance ($W_i = 1/\sigma_i^2$). In MP-K, the W_i values can simply be related to $1/C_i$ or $1/C_i^2$ for example; these schemes are appropriate in most cases in pharmacokinetics (2).

The extended least squares criterion can be used when the question of proper weights arises in the modeling process (2). The objective function is

$$ELS = \Sigma \left(\frac{[C_i - C(t_i)]^2}{\sigma_i^2} + \ln(\sigma_i^2) \right) \quad (3)$$

In the MP-K program the variance values of the ith dependent variable, σ_i^2, are modeled as

$$\sigma_i^2 = a.C(t_i)^b \quad (4)$$

where $C(t_i)$ are the predicted concentrations, a (weighting factor) and b (weighting power) are the error parameters that are estimated by the non linear fitting procedure.

Provided the criterion has been chosen, the initial parameters are employed to generate better estimates that minimize this criterion. The following algorithms can be applied to the iterative process in MP-K, Simplex (3), Evol (4), Gauss-Newton (5), Levenberg-Marquardt (3) and Fletcher-Powell (6). The Simplex and Evol methods are heuristic methods, useful if the initial parameter guess is expected to be very far from the true values. They can minimize either a quadratic or a non-quadratic criterion. Parameters constraining is generally not advised when using the Evol method. The Gauss-Newton, Levenberg-Marquardt and Fletcher-

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Powell methods are analytic methods that only minimize a quadratic criterion and give the standard deviations of the estimates. The Gauss-Newton method requires that the initial parameter estimates are relatively close to their final values; typically this method is used after a previous Simplex run. By contrast, the Levenberg-Marquardt method may fail if the initial parameter estimates are too close to their final values. Detailed explanations of these iterative methods can be found in the book of Press et al (3).

Evaluation of the Goodness of Fit. After each estimation process, the visual examination of the drug concentration-time curve with the experimental data strongly suggests whether the fitting must be rejected or accepted. The Log(C) versus time representation is particularly useful in pharmacokinetic analysis. Note that if it is not correct to accept a fit because it looks good, the fitting will be rejected if it looks bad.

The value of the criterion and the coefficient of correlation are given. In the case of particularly delicate curve fitting, for example a three-compartment model with six parameters plus variance parameters (ELS fitting), it is possible that the best curve fitting is not obtained with one iterative process, and that a second one again lowers the criterion value and improves the correlation. Therefore, the best fit is thought to be obtained when successive attempts do not improve anymore the criterion.

The examination of the observed and calculated concentrations, along with the relative deviations from the observations is also a good measure of the adjustment of the data to the model by the fitting procedure. An appropriate method to evaluate this is to plot the residuals of each dependent variable (the concentration). MP-K provides the five following plots: predicted versus observed values, absolute deviations (observed minus calculated) versus predicted values, relative deviations (deviation divided by predicted value) versus predicted values, and absolute or relative deviations versus independent variable (the time).

When the curve fitting is finally achieved with an analytical algorithm, the standard deviations or coefficient of variations for the parameters are computed. Very large uncertainties of the parameters reasonably call for further examination. Additionally, the 95% confidence interval of the parameters are given (these are calculated according to the Students' t statistics criterion).

Model Comparison. In some cases, it may be difficult to decide whether the pharmacokinetic data are best explained by a one- or a two-compartment open model. Of course, the more complex model generally produces a best curve fitting of the data, but it is simply because the increase in the number of parameters of the model increases the flexibility of the predicted curve. The improvement of the curve fitting is then obtained by a supplementary cost in parameter estimation. Then some statistical tests must be performed to appreciate if this cost (a greater number of parameters) results in a significant reduction of the criterion. The Akaike information criterion (AIC) is automatically calculated (7). The lower the AIC value, the more appropriate the model parameterisation. The other facility provided in the program is an analysis of variance, the number of experimental points, and the function value (criterion) and corresponding number of parameters for each model serve to calculate the F(dnp,df) statistics, in which dnp (dnp = npl − np2) is the difference between the number of parameters of each model (npl, np2) and df (df = ndata − npl) is the number of experimental points (ndata) minus the number of parameters (npl) of the more complex model (8).

DESCRIPTION OF THE PROGRAM

A flow chart of the MP-k program is depicted in Fig. 1. Based on a user-friendly interface, with pull-down menu bars and standardised dialog boxes, the MP-K program was developed to perform pharmacokinetic modeling, estimation or simulation, in a convenient and interactive way. At each step, it is always possible to change the modelisation, the estimation options, to plot or to modify the data for example. An interesting feature of the MP-K program is that the user may choose among several options to perform the non linear curve fitting: different goodness of fit criterions and different algorithms are available, and parameters can be constrained. Printouts of complete results, including parameter estimates with their confidence limits, estimation options, and time, observed and predicted concentrations with their relative deviations are provided. Also, a complete printout of the derived pharmacokinetic parameters, model-independent and model-dependent (AUC, clearance, transfer rate microconstants etc . . .) is available. Data editing facilities are provided (spreadsheet-like interface) and data and curve-fitting results can be saved on disk files. There is virtually no limitation to the numerical data that can be entered, time-concentration pairs or number of administrations.

The data are ascribed to a pharmacokinetic model via a library of predefined models, according to the administration route and compartmental design. The MP-K program in-

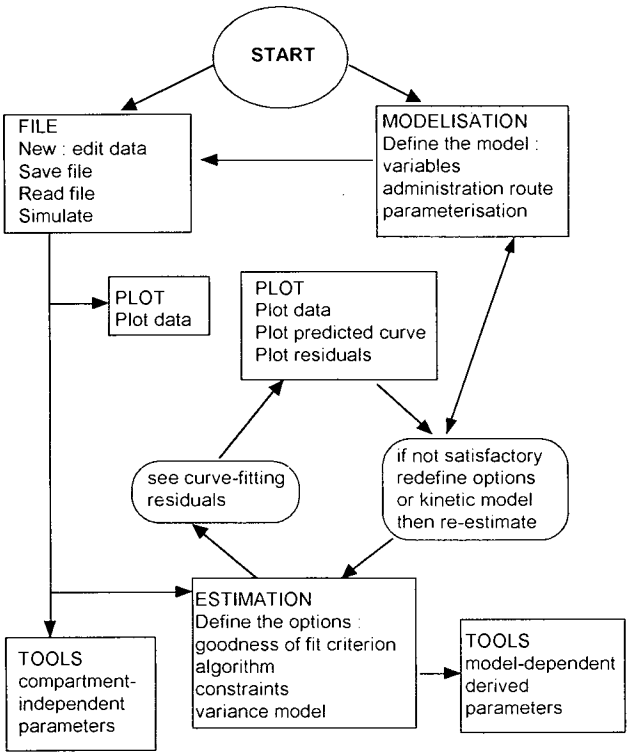
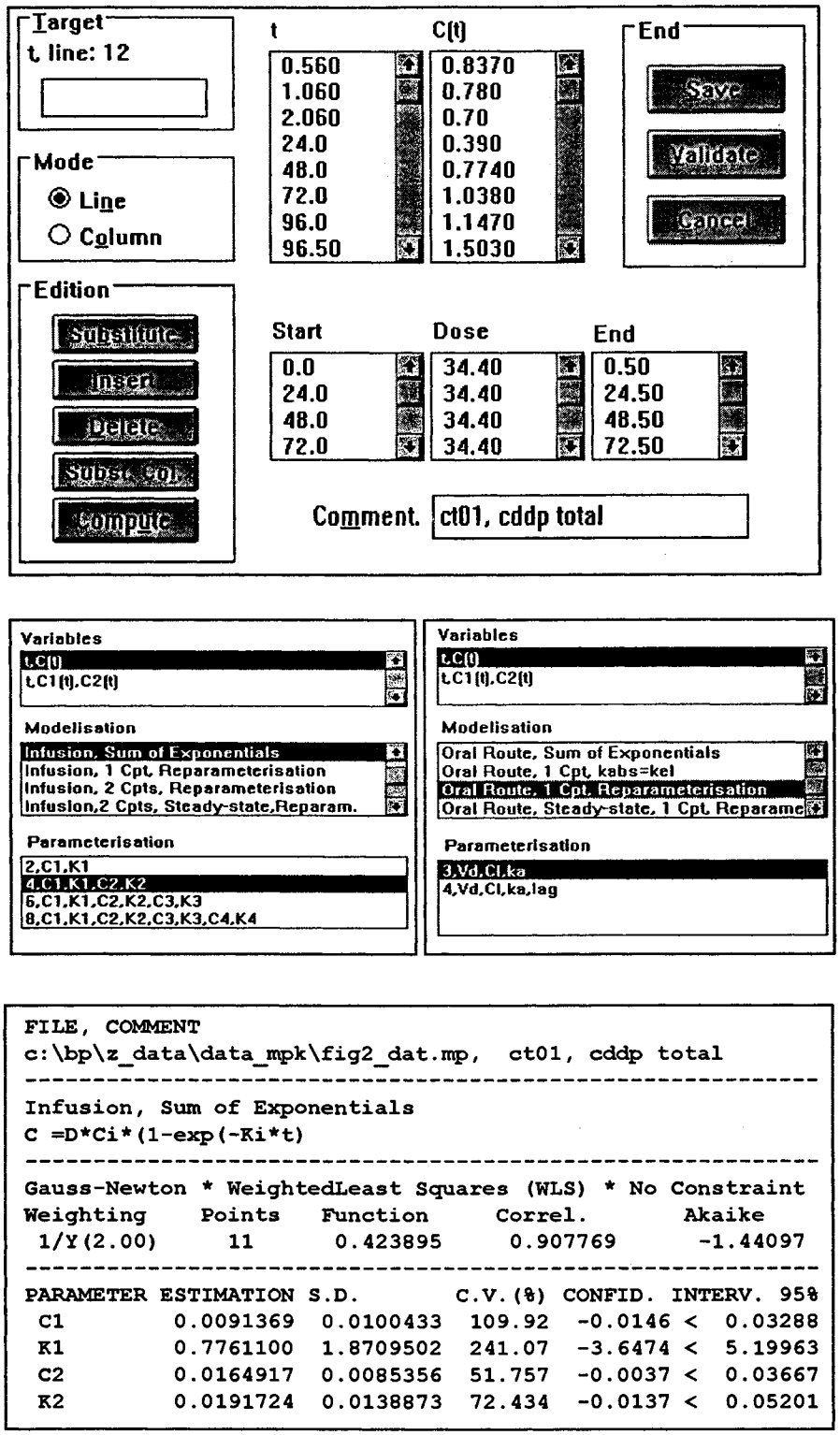


Fig. 1. Flowchart of MP-K, MicroPharm-Kinetics.

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FILE, COMMENT
c:\bp\z_data\data_mpk\fig2_dat.mp,  ct01, cddp total
-------------------------------------------------------------
Infusion, Sum of Exponentials
C =D*Ci*(1-exp(-Ki*t)
-------------------------------------------------------------
Gauss-Newton * WeightedLeast Squares (WLS) * No Constraint
Weighting     Points    Function      Correl.        Akaike
 1/Y(2.00)      11       0.423895      0.907769       -1.44097
-------------------------------------------------------------
PARAMETER ESTIMATION S.D.        C.V.(%) CONFID. INTERV. 95%
 C1         0.0091369  0.0100433  109.92  -0.0146 <  0.03288
 K1         0.7761100  1.8709502  241.07  -3.6474 <  5.19963
 C2         0.0164917  0.0085356  51.757  -0.0037 <  0.03667
 K2         0.0191724  0.0138873  72.434  -0.0137 <  0.05201
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Fig. 2. A brief view of MP-K screens for processing of data and non linear model fitting, the data entering box, the model choice box, a result window.

cludes 23 models that cover most of the possible pharmacokinetic interpretations. These are intravenous administration with (a) bolus input or (b) constant infusion input, conferring the characteristics of a one-, two-, three-, four-compartment open models, (c) oral administration with or without a lag-time, conferring the characteristics of a one- or two-compartment open model, including the special case where the absorption rate constant is equal to the elimination rate constant for the one-compartment model. The models are all parameterised as the sum of $C_i e^{-K_i t}$ terms. The one- and

Table 1. The Data Set for the One-Compartment Oral Input

Time (h)	Cnctr. (μg/ml)	Parameters	True values	Estimate ± SD
0.0	0.0	C (ml^{-1})	0.1428	0.14289 ± 0.00006
0.5	5.36	Ke (h^{-1})	0.0693	0.06930 ± 0.00002
1.0	9.95	ka (h^{-1})	0.231	0.2309 ± 0.0001
2.0	17.18			
4.0	25.78			
8.0	29.78			
12.0	26.63			
18.0	19.40			
24.0	13.26			
36.0	5.88			
48.0	2.56			
72.0	0.49			

The data were ascribed to the equation $C(t) = D\,C\,(e^{-K_e t} - e^{-k_a t})$., where C is the concentration factor, D the amount administered, and K_e and k_a are the elimination and adsorption rate constants respectively.

two-open compartment open models are also parameterised with physiologic and compartmental parameters (volume, clearance, rate transfer microconstants), as the three-compartment open model for the IV infusion. The reparameterised models are particularly useful for simulating the effect of modifying the value of some parameters (volume, clearance. . .) in relation with physiopathological considerations. In addition, it is also possible to simulate the drug concentration in the first and second compartment for the IV modes of administration. All these models and the corresponding equations are detailed in the book of Gibaldi and Perrier (9). Single or multiple administrations are indicated by entering one or several lines of time-dose data when entering the data.

The program was written in Pascal and uses the object-oriented programming techniques (Turbo Pascal® 7.0, Borland International). The main menu allows the user to choose the following commands, "File", "Model", "Estimation", "Plot", "Tools" and "Info". Figure 2 shows some representative screens of the application.

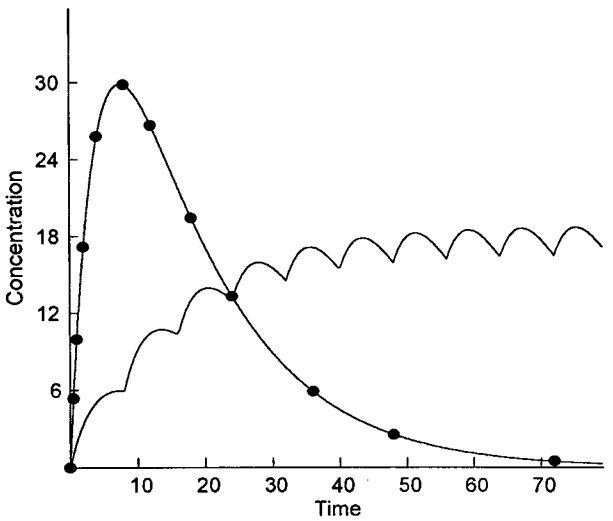

Fig. 3. Graphical plot of the non linear fit of the data set for a one compartment model with oral input (500 mg). The dashed line represents a multiple dosing simulation for 100 mg oral input every 8 h.

Table 2. Extended Least Squares Fitting of a Three-Open Compartment Model with IV Bolus Input, Comparison of MP-K, MKMODEL and SIPHAR

Time (min)	Observed cnctr. (μg/ml)	Predicted concentration (μg/ml) by MP-K	MKMODEL	SIPHAR
2	3.5777	3.0000	3.0063	2.1082
4	1.8332	1.9129	1.9136	1.5690
6	0.7659	1.2731	1.2720	1.1903
8	1.0945	0.8942	0.8929	0.9235
10	0.6339	0.6678	0.6668	0.7348
15	0.4723	0.4150	0.4151	0.4669
30	0.2607	0.2592	0.2597	0.2509
45	0.1858	0.1999	0.20001	0.1939
60	0.1472	0.1578	0.1578	0.1573
90	0.1192	0.1049	0.1048	0.1086
120	0.0916	0.0764	0.0763	0.0796
150	0.0533	0.0605	0.0604	0.0621
180	0.0470	0.0512	0.0512	0.0512
240	0.0301	0.0414	0.0414	0.0395
360	0.0419	0.0321	0.0321	0.0299
480	0.0267	0.0258	0.0258	0.0246
600	0.0192	0.0209	0.0209	0.0205
720	0.0140	0.0169	0.0169	0.0171
840	0.0139	0.0137	0.0137	0.0142
960	0.0121	0.0110	0.0111	0.0119
1440	0.0048	0.0047	0.0047	0.0057

The data from subject 9, ref. were fitted to the model equation $C(t) = C_1 e^{-K_1 t} + C_2\, e^{-K_2 t} + C_3\, e^{-K_3 t}$, where C_i and K_i are the concentration factors and time rate constants respectively.

GENERAL FEATURES

Hardware Requirements. The program can be run on IBM-PC or true compatible microcomputers operating under

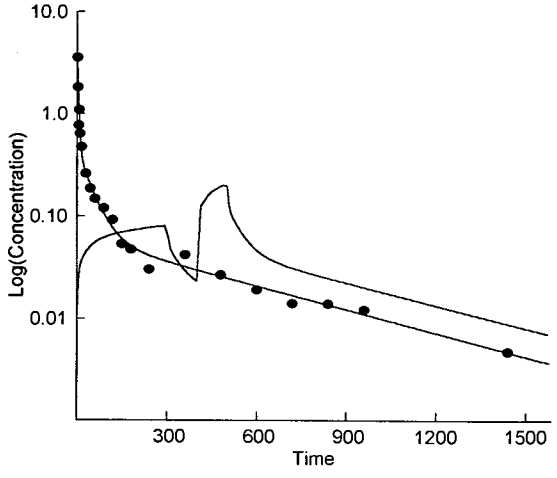

Fig. 4. Graphical plot of the non linear fit of the data set for a three compartment model with IV bolus input (1 mg). The dashed line represents a simulation with the same pharmacokinetic parameters for two successive constant IV infusions, first 0.5 mg is infused during the 300 first minutes, then the remaining 0.5 mg is infused between times 400 and 500.

Table 3. Comparison of MP-K Estimates with Those of PharmK, NONLIN and INTRAV

Program	C1 (μg/ml)	C2 (μg/ml)	K1 (h^{-1})	K2 (h^{-1})
MP-K	0.211 ± 0.051	0.564 ± 0.027	4.49 ± 2.64	0.028 ± 0.007
PharmK	0.211	0.565	4.50	0.028
NONLIN	0.213	0.563	4.52	0.028
INTRAV	0.211	0.569	5.12	0.029

The data from subject 1, ref. were fitted to the model equation $C = (C_1 e^{-K_1 t} + C_2 e^{-K_2 t})$. The residual sum of squares (function value) was 0.030 for all programs.

MS-DOS® or systems that emulate MS-DOS. The minimum configuration is basic equipment, a 80286 microprocessor, a floppy disk drive and 640 kbytes of random access memory. The recommended options are a mathematical coprocessor, a mouse, a color monitor with a high resolution graphics board (VGA) and a compatible printer (Epson for example) or a Hewlett-Packard printer. Once the program has been installed, the user has to type "MPK" on the keyboard and press the "Enter" key.

Software Features. The program is completely interactive, menu-driven and responds to mouse actions or to combination of keys (Alt key + highlighted letter or Fxx system keys). No programming is necessary. For data entering, corrections are possible. For non linear model fitting, modifications of the modelisation or of the estimation options are always possible.

Availability. The program is available at no charge in the year of publication. Those interested will have to send 3 high density 3½ diskettes to the author.

RESULTS AND DISCUSSION

Three data sets were used to evaluate the MP-K program. These are two simulated data sets for a one-compartment oral input model and a three-compartment open model, and experimental data for a two-compartment IV input model. The fitting results were compared to the results obtained with other programs, SIPHAR (10), MKMODEL (11), INTRAV (12), NONLIN (13) and PharmK (14).

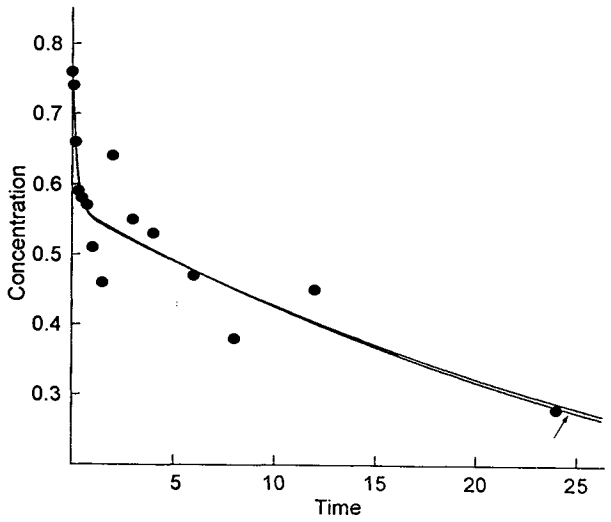

Fig. 5. Graphical plot of the MP-K non linear fit (solid line) of the data set for a two compartment model with IV bolus input. The dashed line represents a simulation with the parameters estimated by INTRAV, the arrow shows the (small) deviations between the two programs curve-fittings.

One-compartment Oral Input Model. These simulated data were obtained from ref. 9, appendix 3 (Table 1). The estimation used a simple least squares criterion (constant error model) and the result was the same irrespective of the algorithm chosen (Simplex, Gauss-Newton, Marquardt) for this simple model. Figure 3 depicts the curve-fitted data and a multiple dosing simulation. As shown in Table 1, the parameter estimates were identical to the true parameter values. The AUC value calculated by the trapezoidal rule was 723.782 μg.h/ml, equal to the value of 723.79 μg.h/ml given in appendix 4 of the same reference.

Three-compartment IV Bolus Model. The data were obtained from appendix 1 of a paper that compared the SIPHAR (version 3.39) and MKMODEL programs for extended least squares curve fitting (15). The simplest variance model was chosen, $\sigma i^2 = a.C(t_i)^b$. Four runs were necessary to find a stable minimum with the Simplex algorithm and the final ELS function was −150.394. The parameters had to be constrained to positive values ($P > 0$) for the Simplex curve fitting. When the Evol algorithm was used (without constraint on parameters), the minimum was attained with only one run, ELS = −150.41. The variance power parameter, b, was 2.2204, similar to the value obtained with MKMODEL, 2.2128, in agreement with the true error model, proportional to the square of concentration (variance power = 2). The true values of parameters for the data set of subject 9 were not given in the reference. However, the time-concentration data, simulated and calculated by MKMODEL and SIPHAR were given. On this basis, the MP-K predicted concentrations were similar to those of MKMODEL as shown in Table 2 that compares the "observed" and calculated concentrations for the three programs. The discrepancy between the results from MKMODEL and MP-K on the one hand and SIPHAR on the other were explained by a difference in the variance model. In this version of SIPHAR, a constant term was added to the variance model, resulting in distortions for the small concentration values and misestimation of the weighting power of the variance model (value of 5). Figure 4 depicts the corresponding curve fitting.

Two Compartment IV Input Model, Experimental Data. These secobarbital data were previously evaluated with three other programs, NONLIN, INTRAV (12) and PharmK (14). The simple least squares criterion was minimised (it is assumed that all data point have the same absolute error), since there was no information about the model error of the observations in the reference. Table 3 summarizes the results

Table 4. Comparison of MP-K and PharmK Pharmacokinetic Parameters

Parameter	MP-K	PharmK
AUC (mg · h/l)	20.283	20.278
Clearance (l/h)	0.986	0.986
Volume (l)	25.768	25.766
k10 (h^{-1})	0.038	0.038
k21 (h^{-1})	1.204	1.207
k12 (h^{-1})	3.278	3.285

The data from subject 1, ref. 15, were fitted to a two-compartment open model, the dose is 20 mg, for clearance and volume calculations (see also table 3).

obtained by MP-K (a Simplex run followed by a Gauss-Newton run) and the three other programs. The fit is depicted in Fig. 5. As shown, the estimates are nearly identical. The other relevant pharmacokinetic parameters can be calculated as above, they are similar to those calculated with PharmK (Table 4).

CONCLUSION

MP-K offers the capability of non linear fitting of numerous predefined pharmacokinetic models. Both weighted least squares and extended least squares criterions can be minimized, and the iterative process can be achieved with the Simplex, Gauss-Newton, Evol, Marquardt and Fletcher-Powell algorithms. Simulations, graphic displays and complete data and parameters printouts are easily available. Besides its interest for pharmacokinetic analysis, the program could also be used for educational purposes, demonstrating the various ways to perform a non linear model fitting or displaying simulated time-concentration curves from various models and routes of administration.

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REFERENCES

1. M. Gex-Fabry, L. P. Balant. Considerations on data analysis using computer methods and currently available software for personal computers. In P. G. Welling and L. P. Balant (eds.), Handbook of Experimental Pharmacology, Vol. 110, Pharmacokinetics of Drugs, Springer-Verlag, Berlin Heidelberg, 1994.
2. C. M. Metzler. Extended least squares (ELS) for pharmacokinetic models. J. Pharm. Sci. 76:565–571 1987.
3. W. H. Press, B. P. Flannery, S. A. Teukolsky, W. T. Vetterling. Numerical recipes in Pascal, The art of scientific computing, Cambridge University Press, New York, 1992.
4. P. Koeppe, C. Hamann. A program for non-linear regression analysis to be used on desk-top computers. Comput. Progr. Biomed. 12:121–128 (1980).
5. K. Yamaoka, Y. Tanigawara, T. Nakagawa, T. Uno. A pharmacokinetic analysis program (Multi) for microcomputer. J. Pharmaco-Biodyn. 4:879–885 1981.
6. G. Thomas, J. C. Thalabard, C. Girre. A program for the integrated Michaelis-Menten equation. Trends Pharm. Sci. 8:292–294.
7. H. Akaike. A new look at the statistical model identification. IEEE Trans. Autom. Control. 19:716–723 1974.
8. E. M. Landaw, J. J. Di Stefano. Multiexponential, multicompartmental, and non-compartmental modeling: II. Data analysis and statistical considerations. Am. J. Physiol. 246:R665–R667 1984.
9. M. Gibaldi, D. Perrier. Pharmacokinetics, Marcel Dekker, Inc., New York, 1975.
10. R. Gomeni. SIPHAR users manual, SIMED SA, Paris 1987.
11. N. Holford. MKMODEL: An extended least squares modelling program—Users Manual, Biosoft, Cambridge, England, 1986.
12. J. L. Valentine, S. Hunter. INTRAV and ORAL: basic interactive computer programs for estimating pharmacokinetic parameters. J. Pharm. Sci. 74:113–119 1985.
13. C. M. Metzler, G. L. Elfring, A. J. McEwen. A package of computer programs to pharmacokinetic modeling. Biometrics 30:562 (1974).
14. D. R. Lu, F. Mao. An interactive program for pharmacokinetic modeling. J. Pharm. Sci. 82:537–542 1993.
15. I. D. Cockshott, J. Haywood. Extended least squares curve fitting: a comparison of SIPHAR and MKMODEL. Biopharm. Drug Dispos. 13:461–480 1992.