Development of a microcomputer program for statistical evaluation of potential pharmacokinetic drug interactions*

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Abstract: A simple and self-explanatory program in BASIC for the statistical evaluation of potential pharmacokinetic drug interactions is described. This program, using the data (times and drug concentrations) obtained from two different populations, and with the help of graphic computing techniques, allows the determination and statistical comparison of pharmacokinetic parameters (disposition constants, transfer rate constants, area under the concentration–time curves, etc.) for one- and two-compartment open models after intravenous or extravasal administration. The program is organized in subroutines so that it can be easily modified or extended to other pharmacokinetic models by the user.

Keywords: *Microcomputer program; drug interactions; statistical analysis; pharmacokinetics.*

Introduction

Drug interaction is the phenomenon which results when the pharmacokinetics and/or pharmacodynamics of one drug is modified by the prior or concurrent administration of another. A pharmacokinetic interaction occurs when one drug interferes with the absorption, transport, distribution, or elimination of the other, and a pharmacodynamic interaction arises when both drugs act on the same receptors, sites of action, or physiological systems.

Within the last two decades an increasing number of epidemiological studies have clearly demonstrated that many undesirable reactions to drugs, such as unexpected toxicity, heightened pharmacological response, or therapeutic failure, can be ascribed to pharmacokinetic drug interactions [1]. However, this interaction is sometimes beneficial, and the efficacy of penicillin, for example, is often intentionally enhanced by concurrent administration of probenecid [2]. The investigation of potential pharmacokinetic drug interactions is a necessary measure in some pharmacodynamic studies. For example, when the antiepileptic activity of a drug is tested using an experimental model of epilepsy induced by systemic administration of a chemoconvulsant, it is essential to exclude the potentially confounding influence of changes in pharmacokinetics [3]. For all these reasons, the evaluation of potential pharmacokinetic drug interactions is a desirable objective in basic biomedical research.

The aim of this study was to develop a simple microcomputer program to analyse experimental data for time and drug concentration and thus provide an easy estimation of the main pharmacokinetic parameters of the drug. Further analysis detects potential pharmacokinetic drug interaction and also enables one to estimate the nature of the interaction.

Computational Methods

The pharmacokinetic parameters are evaluated by the residual method, also called feathering method [4]. This method . was chosen because it is direct, noniterative, and gives meaningful results on the models described for the sum of up to three exponentials.

The program has been developed for the pharmacokinetic models most commonly used. These are: (1) one-compartment open model for intravenous administration; (2) one-com-

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partment open model with first-order absorption; (3) two-compartment open model for intravenous administration; and (4) two-compartment open model with a rapid first-order absorption. In all cases, the regression lines, and also the appropriate residual regression lines are calculated using standared least-squares linear regression techniques. The corresponding disposition constants are calculated from these data, and the subsequent statistical analysis of the results is made by testing the slopes of the regression lines for parallelism using the analysis of covariance (ANCOVA) [5].

The areas under the curves are calculated by adding the term (last drug concentration/elimination rate constant) to the linear trapezoidal areas.

In the case of a two-compartment open model for intravenous administration, the equation used was

$$C(t) = Ae^{-\alpha t} + Be^{-\beta t},$$

and the distribution and elimination microconstants are calculated according to

$$K_{21} = \frac{A\beta + B\alpha}{A + B} \quad K_{10} = \frac{A + B}{\dfrac{A}{\alpha} + \dfrac{B}{\beta}}$$

$$K_{12} = \frac{AB(\beta - \alpha)^2}{(A + B)(A\beta + B\alpha)}.$$

For a two-compartment open model with a first-order absorption, the equation used was

$$C(t) = Le^{-\alpha t} + Me^{-\beta t} - Ne^{-K_a t},$$

and the corresponding microconstants are calculated according to

$$K_{21} = \frac{M\alpha(K_a - \beta) + L\beta(K_a - \alpha)}{M(K_a - \beta) + L(K_a - \alpha)},$$

$$K_{10} = \frac{M(K_a - \beta) + L(K_a - \alpha)}{\dfrac{M}{\beta}(K_a - \beta) + \dfrac{L}{\alpha}(K_a - \alpha)},$$

$$K_{12} = \frac{(\alpha - \beta)^2}{\alpha + \beta + \dfrac{M\alpha(K_a - \beta)}{L(K_a - \alpha)} + \dfrac{L\beta(K_a - \alpha)}{M(K_a - \beta)}}.$$

For the statistical analysis of these parameters, a two-tailed Student's *t*-test is used. However, when the program encounters an inequality in variances, the statistical comparison is made with Satterthwaite's approximation method [6].

Program Description

This program, written in BASIC (Microsoft GW-BASIC, version 3.2) for microcomputers (IBM-PC and compatibles), has been designed to be self-explanatory. The flow diagram of the program is shown in Fig. 1 and operates in the following way. It admits up to 20 different time values for each set of data, and a further maximum of 20 different drug concentrations per time value. Obviously, this range of values may be modified by the user. After the experimental data from the two groups to be compared have been introduced, the screen displays a corresponding semilogarithmic graph (Fig. 2). This allows a visual evaluation of the curves so that the user can decide which is the most appropriate pharmacokinetic model. If the curves displayed have a single phase (one-compartment open model without absorption phase) no further information is needed so that the program can give both regression and pharmacokinetic parameters, as well as the results of the corresponding statistical comparisons. When the curves have two phases (one-compartment open model with absorption phase or two-compartment open model without absorption phase), the graphs on the screen will help the user to decide on the number of time points in the elimination phases so that the corresponding results can be given. If there are three phases (two-compartment open model with absorption phase), then the semi-logarithmic graphs of the first residuals are displayed after entering the number of time points in the elimination phases. In this way the user can also enter the number of time points in the linear terminal phase of these graphs, and then all the corresponding results will be given (Fig. 3). In all cases, the user will be also asked to enter one or two *F*-distribution values (5% two-tailed) so that the program can make the test of the equality of two variances.

Finally, as can be seen in Fig. 1, the program is composed of four subroutines, which enable easy user modification or extension to other pharmacokinetic models.

start

input data

gosub A

semilog plot

A: Subroutine for graphic screen display

B: Subroutine for linear regression analysis and contrast of slopes

C: Subroutine for counter reset

D: Subroutine for Student's t-test and Sutterthwaite's approximation

input pharmacokinet. model 1

input no. time-points elimin. phase

gosub B

regression and pharmacokinet. parameters

calculation residuals

gosub C

gosub B

regression and pharmacokinet. parameters

2

1

area under the curve 3,4

other pharmacokinet. parameters

gosub D

printout results

end

calculation 1st-residuals 3

gosub A

semilog plot

input no. time-points terminal phase

gosub C

gosub B

3 regression and pharmacokinet. parameters

calculation 2nd-residuals

gosub C

gosub B

regression and pharmacokinet. parameters

Figure 1
Flow diagram of the computer program. Pathways: 1, one-compartment open model for intravenous administration; 2, one-compartment open model with first-order absorption; 3, two-compartment open model for intravenous administration; 4, two-compartment open model with first-order absorption.
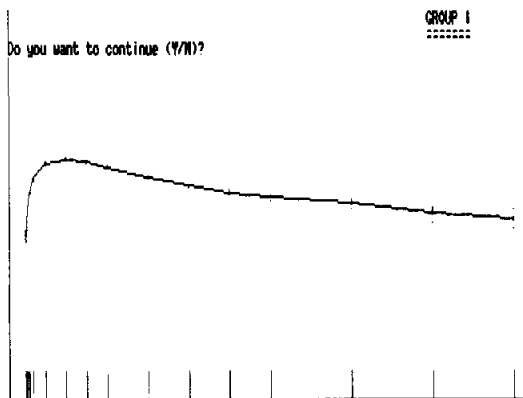
GROUP I

Do you want to continue (Y/N)?

Figure 2
Typical graph display after data input, representing a semilogarithmic plot of drug concentration versus time. The horizontal line is drawn through the mean drug concentrations.
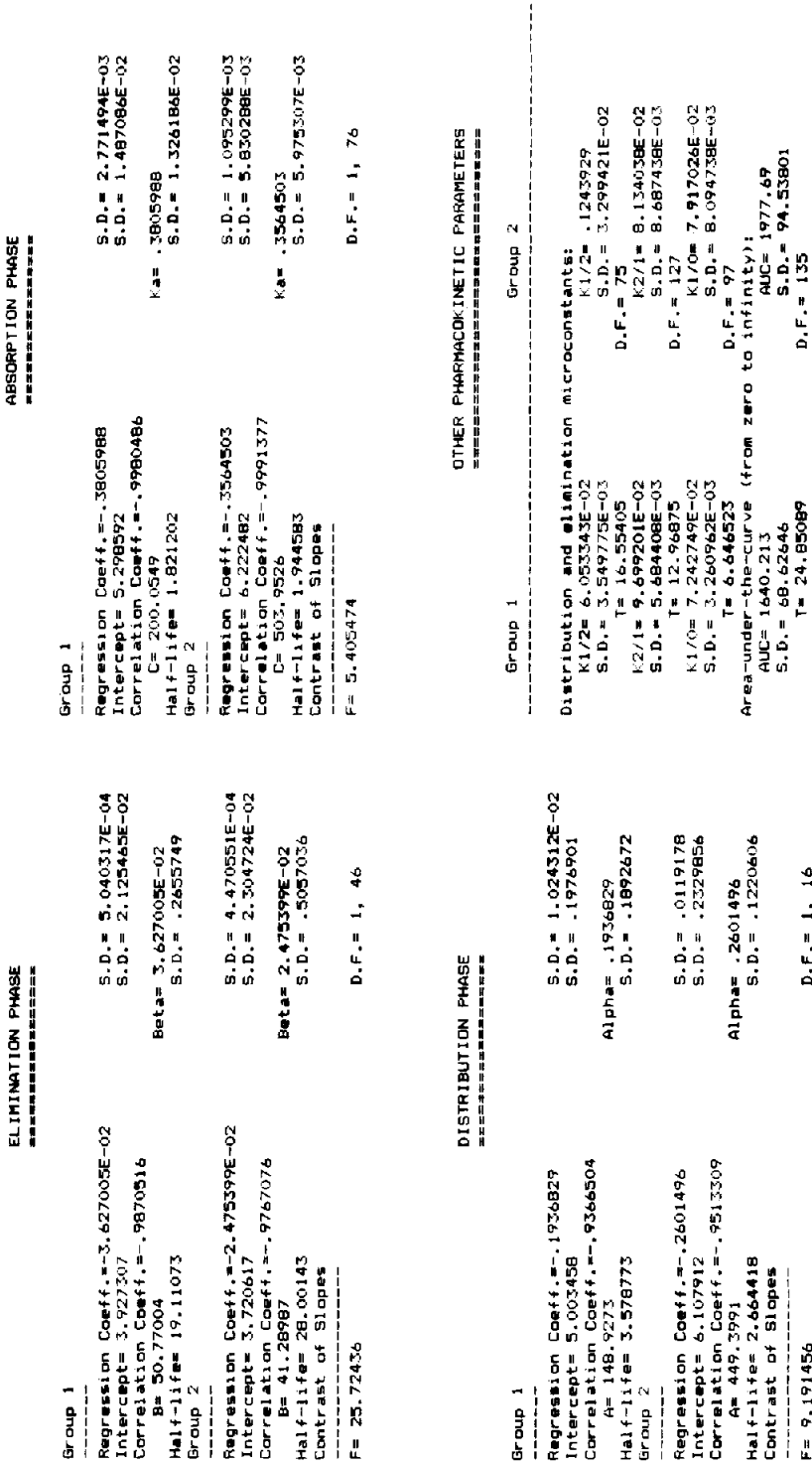
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ELIMINATION PHASE                            ABSORPTION PHASE
=================                            ================

Group 1                                     Group 1
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Regression Coeff.=-3.627005E-02  S.D.= 5.040317E-04    Regression Coeff.=-.3805988   S.D.= 2.771494E-03
Intercept= 3.927307              S.D.= 2.125465E-02    Intercept= 5.298592           S.D.= 1.487086E-02
Correlation Coeff.=-.9870516                           Correlation Coeff.=-.9980486
B= 50.77004              Beta= 3.627005E-02            C= 200.0549           Ka= .3805988
Half-life= 19.11073      S.D.= .2655749                Half-life= 1.821202   S.D.= 1.326186E-02
Group 2                                                Group 2
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Regression Coeff.=-2.475399E-02  S.D.= 4.470551E-04    Regression Coeff.=-.3564503   S.D.= 1.095299E-03
Intercept= 3.720617              S.D.= 2.304724E-02    Intercept= 6.222482           S.D.= 5.830288E-03
Correlation Coeff.=-.9767076                           Correlation Coeff.=-.9991377
B= 41.28987              Beta= 2.475399E-02            D= 503.9526           Ka= .3564503
Half-life= 28.00143      S.D.= .5057036                Half-life= 1.944583   S.D.= 5.975307E-03
Contrast of Slopes                                     Contrast of Slopes

F= 25.72436              D.F.= 1, 46                    F= 5.405474           D.F.= 1, 76


DISTRIBUTION PHASE                           OTHER PHARMACOKINETIC PARAMETERS
==================                           ================================

Group 1                                     Group 1                      Group 2
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Regression Coeff.=-.1936829  S.D.= 1.024312E-02    Distribution and elimination microconstants:
Intercept= 5.003458          S.D.= .1978901          K1/2= 6.053343E-02           K1/2= .1243929
Correlation Coeff.=-.9366504                          S.D.= 3.549775E-03           S.D.= 3.299421E-02
A= 148.9273          Alpha= .1936829                  T= 16.55405                  D.F.= 75
Half-life= 3.578773  S.D.= .1892672                   K2/1= 9.699201E-02           K2/1= 8.134038E-02
Group 2                                               S.D.= 5.684408E-03           S.D.= 8.687438E-03
-------                                               T= 12.96875                  D.F.= 127
Regression Coeff.=-.2601496  S.D.= .0119178           K1/0= 7.242749E-02           K1/0= 7.917026E-02
Intercept= 6.107912          S.D.= .2329856           S.D.= 3.260762E-03           S.D.= 8.094738E-03
Correlation Coeff.=-.9513309                          T= 6.646523                  D.F.= 97
A= 449.3991          Alpha= .2601496           Area-under-the-curve (from zero to infinity):
Half-life= 2.664418  S.D.= .1220606                   AUC= 1640.213                AUC= 1977.69
Contrast of Slopes                                    S.D.= 68.62646               S.D.= 94.53801
                                                      T= 24.85089                  D.F.= 135
F= 9.191456          D.F.= 1, 16
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Figure 3
Typical printout of the results obtained from two sets of data, using a two-compartment open model with a first-order absorption.

Program Availability

A listing can be supplied on request or a copy of the program can be obtained by sending a 5.25" or 3.5" disk to the authors.

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