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## PHARMACOKINETIC ANALYSIS AND CALCULATIONS USING A PROGRAM FOR THE MINICOMPUTER SHARP-PC 1500

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This paper describes a biomedical computer program for computing blood level data after intravenous administration of the drug. This program may be utilized to determine pharmacokinetic parameters like $C_1$ , $\lambda_1$ , $C_z$ , $\lambda_z$ , $K_{12}$ , $K_{21}$ , $K_{10}$ , $V_c$ and CL. The program is written in BASIC language for minicomputer Sharp-PC 1500. However, it can be utilized with minor adjustment to a variety of computers working with this language.

### INTRODUCTION

Pharmacokinetics seeks to provide a mathematical basis for the description and prediction of the time-course of drugs in the body. A compartmental representation of the body is often used to explain the principles of pharmacokinetics, where the compartments are purely hypothetical and bear no relationship to real tissues or organs. In pharmacokinetics relatively simple compartmental models are mostly used, namely single-and two compartment open systems. The first conceives the drug as reaching instantaneous distribution equilibrium throughout the body following administration, and is synonymous with having a single exponential disposition function; the second conceives the body as being divided into a central compartment containing blood and well-perfused tissues and a peripheral compartment containing less-perfused tissues. Elimination is usually assumed to occur from the central compartment. These models assume that drug transfer between compartments and elimination from compartments are first-order kinetic processes.

The single compartment model has found great utility in conceptualizing and describing in quantitative terms the in vivo dynamics of many drugs. But, with most drugs, the levels in serum after intraveous administration do not decline in a monoexponential fashoin. Very often the decline is biexponential, that is semilogarithmic profile exhibit a curved segment ($\lambda_1$ phase) followed by a straight line segment ($\lambda_z$ phase). This behaviour suggests that the body consists of at least two kinetically distinct compartments, and a kinetic model which includes an extravascular tissue compartment should be of great value in describing in *vivo* dynamics of these drugs.

Pharmacokinetic analysis are complex and time consuming thus usually performed with the help of computers. However, fullscale computers are expensive and every research worker does not have access to them. Recently there appeared papers describing such computations on programmable calculators. Niazi (1979), described a program of multicompartment analysis for programmable calculators HP-97. Poland & Woloszczak (1980), Nielsoen-Kuask (1981), and Nawaz & Nawaz (1982), reported different programs of compartmental analysis and simulations for programmable calculator TI-59 Ahmed (1982-83), published two programs for Casio Fx-501/502P and Fx-602P to perform kinetic analysis of blood levels after oral administration of the drug.

The present paper describes the theoretical feature of two compartment open model fitting to the data obtained after intravenous administration of the drug, and a program developed for pharmacokinetic analysis and parameter calculations by means of the minicomputer Sharp-PC 1500.

### METHODS

A semilogarithmic plot of plasma concentration versus time after intravenous administration of a drug frequently yields a biexponential curve (Table 1, Figure 1). The terminal portion of the curve is linear and can be described by its slope ($\lambda_z$) and an extrapolated zero-time intercept

Table 1. Plasma concentration of warfarin following administration of 200 mg intravenous dose* (Div).

| Time (hr) | Concentration (mcg/ml) |
|---|---|
| 0.25 | 41.3 |
| 0.50 | 33.8 |
| 0.75 | 30.2 |
| 1.00 | 28.4 |
| 3.00 | 26.2 |
| 6.00 | 24.0 |
| 8.50 | 25.0 |
| 12.50 | 23.0 |
| 24.00 | 19.0 |
| 37.00 | 15.6 |
| 48.00 | 13.0 |
| 72.00 | 9.0 |
| 90.00 | 7.0 |
| 117.00 | 4.5 |
| 145.00 | 2.9 |
| 168.00 | 2.0 |
| 192.00 | 1.4 |

* Data from Wagner (1975).

($C_z$). The initial portion of the biexponential curve represents the combined effects of distribution and elimination processes on plasma levels of the drug. Resolving the curve into its two components by the method of residuals (Reigelman, 1968) yields a second linear segment characterised by a slope ($\lambda_1$) and a zero-time intercept ($C_1$). Accordingly, the concentration of drug in the plasma (C) as a function of time is given by the following equation:

$$C = C_1 e^{-\lambda 1 t} + C_z e^{-\lambda_z t}$$

The terms $C_1$ , $C_z$ , $\lambda_1$ , and $\lambda_z$ are actually hybrid constants which may be defined in terms of the pharmacokinetic parameters of the two compartment open model.

To perform pharmacokinetic analysis of blood level data obtained after intravenous injection of the drug. A straight line is fitted to the last few points by standard exponential regression. The regression constants b and a represent $\lambda_z$ and $C_z$ whereas $r^2$ , the decision coefficient is a measure of goodness of fit. The exponential regression constants b, a, and $r^2$ are obtained by the following formulae:

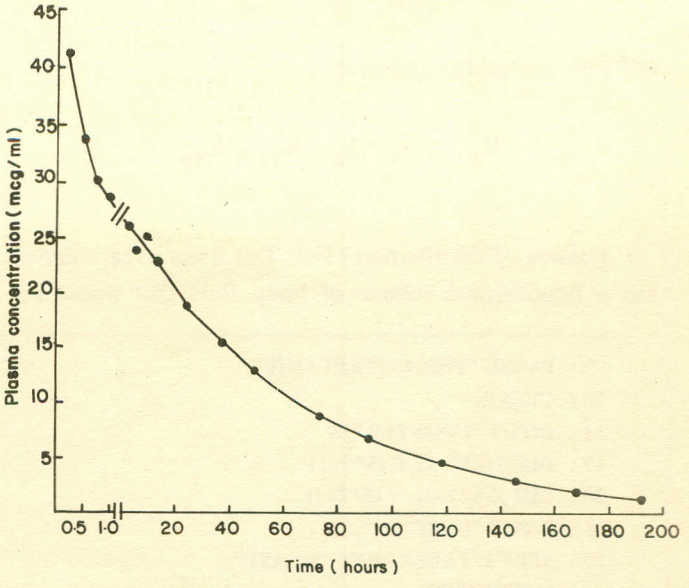


Fig.1. Plasma concentration vs time profile of warfarin following administration of 200 mg intravenous dose.

$$r^2 = \frac{a \Sigma \ln y + b \Sigma x \ln y - 1/n (\Sigma \ln y)^2}{\Sigma \ln y^2 - 1/n (\Sigma \ln y)^2}$$

$$b = \frac{\Sigma x \ln y - 1/n \Sigma x \Sigma \ln y}{\Sigma x^2 - 1/n (\Sigma x)^2}$$

$$a = 1/n (\Sigma \ln y - b \Sigma x)$$

The fitted line is extrapolated to estimate the contribution of the elimination exponent ($C_z e^{-\lambda} z^t$) to the first few experimental blood levels. Substracting these estimates from experimental levels gives values representing the contribution of the distribution exponent ($C_1 e^{-\lambda} 1^t$). A straight line fitted to these residual points in the same way is used to estimate the exponential constants of the distribution phase ($C_1$ and $\lambda_1$). From these basic kinetic estimates, $C_1$ $\lambda_1$ , $C_z$ and $\lambda_z$ , other useful kinetic parameters are derived as under:

*Transfer Rate Constants ($K_{21}$ , $K_{12}$ , $K_{10}$):* The rate constants for transfer from peripheral to central compartment:

$$K_{21} = C_1 \lambda_z + C_z \lambda_1 / C_1 + C_z$$

and from central to out side:

$$K_{10} = \lambda_1 \lambda_z / K_{21}$$

and from central to peripheral:

$$K_{12} = \lambda_1 + \lambda_z - K_{21} - K_{10}$$

*Volume of Distribution (Vc):* This is not a real volume but a hypothetical volume of body fluid that would be required to dissolve the total amount of drug at the same concentration as that found in the blood or plasma. It is a proportionately constant relating the amount of drug in the body to the measured concentration in biological fluids, blood, plasma, or serum (Allen *et al*, 1982). For its estimate the following equation (Gibaldi and Perrier, 1975) is utilized.

$$Vc = D_{iv}/C_1 + C_z$$

```
 1 : PAUSE "THIS IS FIRST LINE"
10 : CLEAR
11 : INPUT "COUNTER"; S
19 : DIM T(S*2+1), C (S*2+1)
20 : DIM X(S*2+1), Y (S*2+1)
21 : INPUT "DOSE = X"; X
22 : BEEP 2: PAUSE "ENTER LAST";
     S; "POINTS"
23 : BEEP 3
30 : FOR I=1TO S
31 : BEEP 1
40 : INPUT "T"; T(I), "C"; C(I)
41 : X(I) = T(I) : Y(I) = C(I)
50 : GOSUB "A"
55 : NEXT I
60 : GOSUB "B"
139 : B0=B : B1=EXP A: R1=R
140 : C=0 : T1=0 : T2=0 T3=0 : C1=0 :
      C2=0 : C3=0 : TC=0 : R=0
145 : BEEP 2 : PAUSE "ENTER FIRST";
      S; "POINTS"
147 : BEEP 2
150 : FOR 1=S+1TO S*2
151 : BEEP 1, 88, 188
155 : INPUT "T"; T(I)
156 : X(I)=T(I)
160 : C0=A+B*T(I) : C0=EXP C0
165 : INPUT "C"; C(I)
166 : Y(I)=C(I)
167 : C(I)=C(I)-C0
170 : GOSUB "A"
175 : NEXT I
180 : GOSUB "B"
190 : GOSUB "C"
220 : "=", PRINT "B"; B0
222 : PRINT "R"; RI

224 : PRINT "EXP A"; BI
226 : PRINT "BI"; B
228 : PRINT "r"; R
230 : PRINT "exp a"; A
232 : PRINT "k21"; K1
234 : PRINT "k10"; K0
236 : PRINT "k12"; K2
238 : PRINT "V01 "; V0
240 : PRINT "TBC"; TB : END
280 : "B": B=(TC-TI/S*C1)/(T2-T1/
      S*T1)
285 : A=(C1-B*T1)/S
290 : R=(A*C1+B*TC-C3/S)/(C2-
      C3/S)
291 : RETURN
300 : "A": C=LN C(I)
305 : T1=T1+T(I)
310 : C1=C1+C
315 : T2=T2+T(I) ^ 2
320 : C2=C2+C ^ 2
330 : TC=TC+T(I)*C
335 : T3=T1 ^ 2
340 : C3=C1 ^ 2
341 : RETURN
350 : "C": A=EXP A
355 : K1=(A*B0+B1*B)/(A+B1)
360 : K0=(B*B0)/K1
362 : K2=B+B0-K1-K0
370 : V0=X/(A+B1)
375 : TB=K0*V0
380 : RETURN

B - 1. 548985204E - 02
R  9. 994199346E - 01
EXP A     27.26403619
B1 - 2.940360572
r  9.999844716E - 01
exp a     29.44488215
k21 - 1.421684565
k10 - 3.203646669E - 02
k12 - 1.502129392
V01  3.526782133
TBC - 1.129856383E - 01
```

Fig. 2. Reprint of program list and results of two compartment pharmacokinetic analysis by the minicomputer SHARP PC 1500.

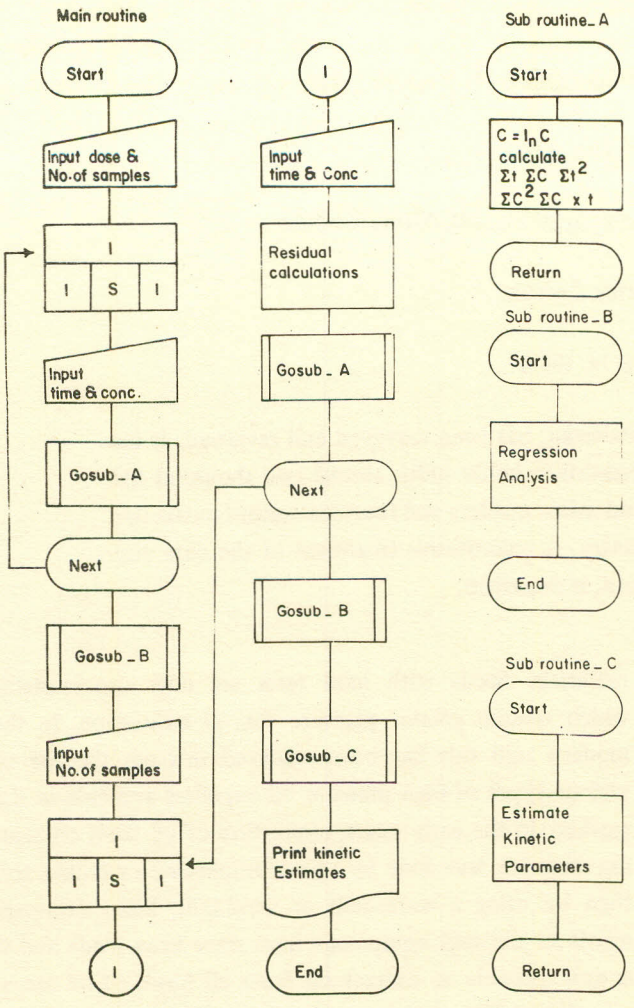


Fig. 3. Follow chart for two compartments pharmacokinetics analysis.

*Total Body Clearance (CL):* It is the sum of individual clearances of eliminating organs, where clearance is the ratio of the overall elimination rate of a drug to its concentration in the reference fluid (i.e., plasma). Following formula is employed in the program for its claculation:

$$CL = K_{10}Vc$$

## RESULTS AND DISCUSSIONS

The original print out of program developed for the above mentioned kinetic analysis is reproduced in Figure 2. In Figure 3, flow chart illustrates diagramatically the sequence of input, different operations and output during computer job.

Table 2. Pharmacokinetic estimates by Sharp-PC 1500 alongwith the values computed for the same data by HP-97.

| Pharmacokinetic parameters | Sharp-PC 1500 | HP-97 |
|---|---|---|
| $*r^2$ | 0.9994 | 0.9994 |
| $C_z$ , mcg/ml | 27.2640 | 27.2640 |
| $C_1$ , mcg/ml | 29.4448 | 29.4448 |
| $_z$ , $hour^{-1}$ | 0.01549 | 0.01549 |
| $_1$ , $hour^{-1}$ | 2.9403 | 2.9403 |
| $K_{21}$ , $hour^{-1}$ | 1.42168 | 1.42166 |
| $K_{10}$ , $hour^{-1}$ | 0.03204 | 0.03204 |
| $K_{12}$ , $hour^{-1}$ | 1.50213 | 1.50213 |
| Vc, litre | 3.52678 | 3.52678 |
| CL, $hour^{-1}$ | 0.11298 | 0.11299 |

$*r^2$ = Decision coefficient.

The estimates of pharmacokinetic analysis are reported in Table 2. For the comparison purpose the results of kinetic analysis of the data obtained by another minicomputer HP-97 (Niazi, 1979) are also given in this Table.

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