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RESEARCH ARTICLES

INTRAV and ORAL: BASIC Interactive Computer Programs for Estimating Pharmacokinetic Parameters

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Abstract □ Two interactive computer programs, INTRAV and ORAL, were written to permit pharmacokinetic modeling of experimental data and to obtain pertinent values based on derived estimates. Both programs utilize BASIC language and were developed on a microcomputer with graphics capability. Drug concentration in blood, plasma, or serum with time following either nonabsorptive (intravenous) or absorptive (oral or intramuscular) administration is input, and a semilogarithmic display of data appears on a cathode-ray tube (CRT). The user selects limits for various linear segments using a movable cursor. On command, coefficients and exponents for the differential equation which describes those limits is computed and a nonlinear curve is fitted through the data set. Results from statistical tests are available in output formats permitting the user to determine the goodness of the selected limits. Commonly used pharmacokinetic parameters are also computed and appear on the output. Numerous graphic output options are also available to permit comparisons between data sets and/or estimates derived from other computer programs. INTRAV and ORAL were compared with the widely used programs CSTRIP, ESTRIP, and NONLIN. Both INTRAV and ORAL gave estimates which were almost identical with CSTRIP and ESTRIP, whereas those obtained with NONLIN were very similar, although not identical.

Recent innovations and cost reductions in personal digital computer hardware have made this type of equipment available to most laboratories and for student instruction. Microcomputers have not been widely used for estimating various pharmacokinetic parameters due to the lack of appropriate BASIC language programs, although a BASIC program was previously described to obtain initial polyexponential parameter estimates.¹ Therefore, most laboratories engaged in performing pharmacokinetic studies commonly use either graphic techniques^{2,3} or CSTRIP, a FORTRAN IV program,⁴ to obtain initial polyexponential parameter estimates. Further refinement of such nonlinear estimations can be made with a program such as NONLIN,⁵ also a FORTRAN IV program. The availability of a microcomputer (Hewlett-Packard 9845B with graphics raster) prompted us to investigate the feasibility of developing an interactive program that would permit the operator to model blood concentration versus time data, determine the goodness of a nonlinear estimation, and obtain esti-

mates of the more commonly used pharmacokinetic parameters.

The purpose of this paper is to describe two BASIC programs:⁶ INTRAV, used to model intravenous blood concentration versus time data, and ORAL, used to model enteral or absorptive parenteral administration blood concentrations versus time data. With either program the operator is cued to enter blood concentration and time postdose data which is then semilogarithmically plotted on a cathode-ray tube (CRT) screen. The operator then decides where various linear segments of the data occur and marks those limits using a movable cursor, whereupon a nonlinear fit of the data is executed by the computer. Once an appropriate nonlinear fit has been obtained, a variety of output graphics can be generated to display the fit of data.

Theoretical Section

The computer programs INTRAV and ORAL are stored on magnetic cassette tapes which are loaded into the microcomputer prior to use. Interactive questions which require operator responses appear on the CRT screen. As an initial response, the operator has to select either INTRAV or ORAL. INTRAV is used for acute intravenous bolus dosing data derived by determining blood, serum, or plasma concentrations at various times postdose. ORAL is used for all acute enteral or parenteral dosing in which an absorptive phase is apparent. After selecting either the INTRAV or ORAL program, the operator will be queried as to units of concentration and time, units of initial dosing (i.e., mg or mg/kg) and its value, a two-line title of up to 60 characters per line, and then an input of observed blood, serum, or plasma concentration at their respective times. Individual concentrations at their respective times do not have to be entered in a specific order since the program is designed to sort the values according to ascending time. At this point, a verification of the input data will be asked for and any corrections necessary can be made. If the ORAL program was chosen, an additional query will be made for calculation of a bioavailability constant. Choosing this option will require an input of

both dose and area under the curve (AUC) from an intravenous administration of the drug. All these entry choices constitute the initial data entry as shown in Fig. 1. Following initial data entry the program proceeds to the main menu.

Main Menu—Both INTRAV and ORAL have identical menu selections and, although the option selected may produce slightly different actions, the options parallel each other in function. After program start-up and interrogation for required information is complete, the operator has to choose one of the following options: construct a model and perform a curve fit (fitting models); print the results of a curve fit (output results and statistics); plot data and results of a curve fit (plot options); edit data (edit options); enter curve model parameters and check against data (entering parameters); or restart program. Entrance into each of these program options is illustrated in Fig. 1 and each, with the exception of the restart program option, is briefly discussed below. The restart program option erases all parameters and simply starts the program over at its beginning.

Constructing a Model and Fitting the Data—This option is the heart of both INTRAV and ORAL since it permits the user to specify which data points on a semilogarithmic plot of concentration versus time data are to be considered in a given order. (Order is used here to refer to that set of data which most closely approximates a linear segment within the display of data.) Thus, a given display of data may have more than one order. Once this option is selected, a display of the data input appears, and it is plotted semilogarithmically on the CRT with concentration on the ordinate and time on the abscissa. The user selects various orders within the data by moving a cursor to either side of the order and marking the limits of that order. Each order is entered as specified in the program and proceeds from the order corresponding to highest concentration and lowest time to that for lowest concentration and highest time. If ORAL is selected, the first order to be entered is the absorption phase, which corresponds to first-order absorption. This option can be used to determine up to five postabsorptive orders and one absorptive order. User spec-

ification of the order is analogous to graphic techniques, and subsequent computation of the microscopic rate constants and differential equation to obtain a nonlinear fit of data are performed by the "feathering" technique.^{2,3}

After all orders have been specified, no errors detected, and the user is satisfied with the specified order, a nonlinear curve computed using one of the equations⁷ given in Table I will be drawn through the data displayed on the CRT along with a display of select pharmacokinetic parameters. In addition, the orders specified will be marked, and fitted linear lines obtained by the feathering technique will be displayed for each order. At this point, the user may observe if the nonlinear curve fit conforms to the displayed data and proceed to another option or choose to perform another curve fit using this option.

Print the Results of a Curve Fit—Once a curve fit has been obtained, the user can evaluate mathematical exactness of the fit and derived pharmacokinetic parameters using this option. Five criteria are delineated by this option for determining the exactness of the curve fit. These five criteria are: (a) correlation coefficient of each linear order specified by the user for purposes of performing a curve fit; (b) a table of actual values, fitted values, and relative errors; (c) the variance, standard deviation, sum of squares, and mean of error between actual and fitted points with respect to time; (d) correlation coefficient of the fitted curve; (e) a plot of the standardized residuals.

Plot Data and Results of a Curve Fit—This option allows the user to create various plots of the fitted data either on the CRT or an x-y plotter.

Edit Data—This option allows the user to delete a datum point from the set of input data, correct an input value, add a new point either on the graphics display or directly, and/or weight data according to several schemes.

Enter Curve Model Parameters and Check Against Data—This option allows a user to enter parameters for a curve model directly and have these plotted as a nonlinear estimation for data just as in the "Construct Model" option. For example, a user could enter estimated microscopic rate

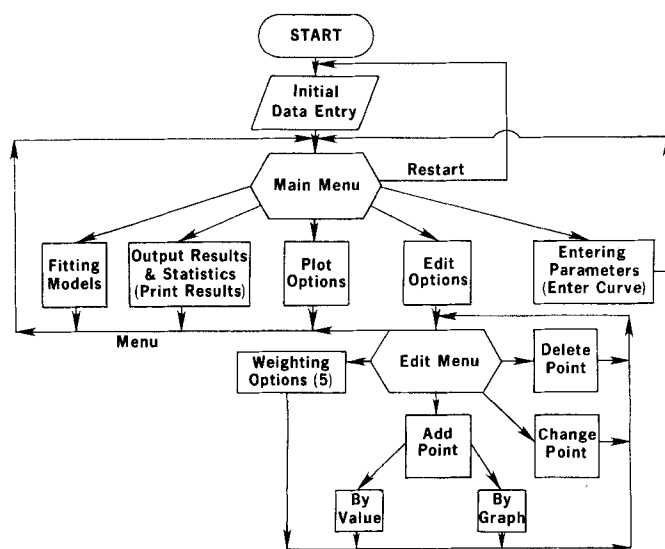


Figure 1—Flowchart of options available in both INTRAV and ORAL within the main menu for modeling, outputting parameters, plotting, and editing data input as well as entering other available curve parameters.

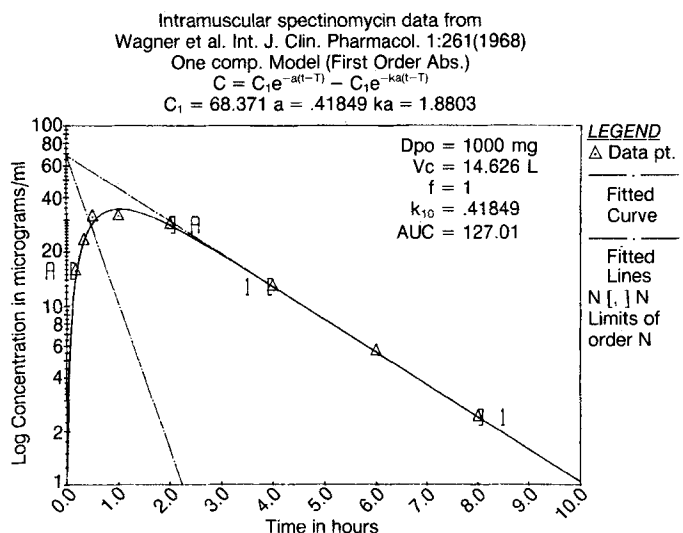


Figure 2—Semilogarithmic plot of spectinomycin data illustrating one type of graphic output. Broken lines are those generated by feathering, whereas limits used for each regression line are depicted by open and closed brackets.

Table I—Equations Used to Compute Nonlinear Curves in INTRAV and ORAL

Route of Administration	Generalized Equation ^a
Intravenous bolus	$C = C_1e^{-\lambda_1 t} + \dots + C_2e^{-\lambda_2 t}$
Extravascular ^b	$C = C_1e^{-\lambda_1(t-t_{lag})} + \dots + C_2e^{-\lambda_2(t-t_{lag})} - (C_1 + C_2)e^{-k_d(t-t_{lag})}$

^a C = coefficient and λ = corresponding exponent. ^b Oral, intramuscular, etc.

RESULTS OF CURVE FIT

Intramuscular spectinomycin data from
Wagner et al. Int. J. Clin. Pharmacol. 1:261(1968)

Time (hours)	Concentration (micrograms/ml)	Fitted Value	Weight	Relative Error
0.17	15.700	14.010806	1.000	+0.1076
0.33	23.100	22.790115	1.000	+0.0134
0.50	31.200	28.758406	1.000	+0.0783
1.00	31.600	34.560763	1.000	-0.0937
2.00	28.200	28.014608	1.000	+0.0066
4.00	12.800	12.782608	1.000	+0.0014
6.00	5.600	5.550203	1.000	+0.0089
8.00	2.400	2.403661	1.000	-0.0015

* = Point not used in fit
c = Value of observed concentration altered by operator
a = This point added by operator

Fitted Values are for the One compartment model with First Order Absorption:

$$C = C_1 e^{-a(t-T)} - C_2 e^{-ka(t-T)}$$

$C_1 = 68.371$ $a = .41849$ $ka = 1.8803$
T (lag time) = 0 hours

Model Independent Parameters

Initial dose of drug (Dpo): 1000.000 mg
Plasma clearance by trap. rule (CLtrap): 0.343 L/hours
Area under curve by trap. rule (AUCtrap): 2918.627 hours-ug/ml

Model Dependent Parameters

Area under fitted curve (AUCpo): 127.012 hours-ug/ml
Fraction of dose absorbed (f): 1.00000
Plasma clearance (CL): 7.873 L/hours
Rate constant of absorption (ka): 1.88027 1/hours
Pharmacokinetic vol. of central comp. (Vc): 14.626 L
Pharm. vol. of dist. in terminal phase (Vz): 18.813 L
Volume of distribution, steady state (Vdss): 24.199 L
Half-life of absorption (t1/2ka): 0.369 hours
Half-life of central compartment (t1/2a): 1.656 hours

Statistics:

Degrees of Freedom (df): 6
Correlation coeff. for fitted curve (r^2): 0.98060
Mean error of data on curve (rbar): 0.216
Variance of error w.r.t. time (s^2): 2.89029
Sum of Squares (SS): 17.71525
Error Standard Deviation w.r.t. time (SD): 1.70009

LINEAR CORRELATION

Order	Correlation coefficient
Absorption	0.9947
1	1.0000

RESULTS OF CURVE FIT (contd.)

PLOT OF STANDARDIZED RESIDUALS

TIME	ACTUAL	FITTED	-4	-3	-2	-1	0	1	2	3	4	RESIDUAL
.17	15.700	14.0108					!	*				+0.86650
.33	23.100	22.7901					*					+0.05518
.50	31.200	28.7584					!	*				+1.30906
1.00	31.600	34.5610			*		!					-1.86875
2.00	28.200	28.0146					*					-0.01805
4.00	12.800	12.7826					*					-0.11687
6.00	5.600	5.5502					*					-0.09781
8.00	2.400	2.4037					*					-0.12925

* = Standard deviations from mean error

X = Off of scale

Figure 3—Printed output from ORAL for the spectinomycin data as shown in Fig. 2.

constants derived from NONLIN or a literature source and compare the generated curve to experimentally derived data or graphic solution such as derived by the present programs. After this option has been executed, the "Print Results" option will function normally, except that it will not display any brackets (which mark limits) since no orders were specified.

Results

To evaluate the programs described herein, both previously published data and some unpublished experimental data from our laboratory were utilized. Each set of data so studied with INTRAV or ORAL is presented and discussed in the following sections.

Spectinomycin—Data originally published by Wagner et al.⁸ for intramuscular administration of spectinomycin and later evaluated by CSTRIP⁴ were examined with ORAL. These data were evaluated by CSTRIP using both two and three exponentials. For two exponentials, three data points were used to define the terminal phases and six points (including a 0,0

Oral tetracycline data from
Wagner et al. Clin. Pharmacol. Ther. 8;210(1967)

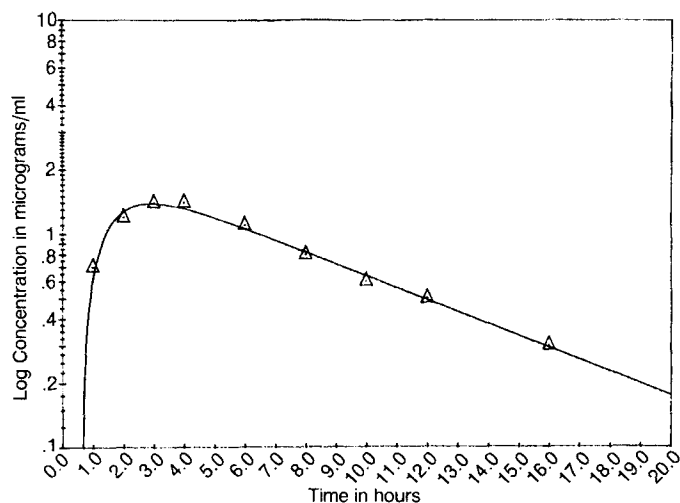


Figure 4—Semilogarithmic plot of tetracycline data using graphic output without legends, feathered lines, or marking of orders used in obtaining the estimated curve. Note that the title is always printed when legends are omitted.

Table II—Comparison of Coefficients, Exponents, Lag Time, and Curve-Fitting Results from Intramuscular Spectinomycin Data Evaluated by CSTRIP and ORAL^a

Computer Method	C ₁	λ ₁	k _a	t _{lag} , h	r̄	s ²	SD	r ²	Sum of Squares
CSTRIP ^b	68.502	0.4185	1.8752	0.0 ^g	—	—	—	0.9848	18.6380
ORAL ^c	68.371	0.4185	1.8803	0.0	0.216	2.8903	1.7001	0.9806	17.7153
ORAL ^d	68.414	0.4185	1.8786	0.0	0.190	2.4929	1.5789	0.9855	17.7765
ORAL ^e	68.920	0.4185	1.8391	0.0	0.317	3.1378	1.7714	0.9785	19.6329
ORAL-CSTRIP ^f	68.502	0.4185	1.8752	0.0 ^g	0.211	2.9253	1.7103	0.9804	17.9080

^a Fitted to $C = C_1 e^{-\lambda_1(t-t_{lag})} - C_2 e^{-k_a(t-t_{lag})}$ using data in ref. 8. ^b Values from ref. 4. ^c Limits from 0.17 to 2.0 h and from 4.0 to 8.0 h, as in ref. 4. ^d Using a 0,0 data point and limits of 0.0–2.0 h and 4.0–8.0 h. ^e Limits from 0.17 to 4.0 h and from 4.0 to 8.0 h. ^f Values from ref. 4 input into ORAL. ^g No lag time was needed to describe the data (see ref. 4).

Table III—Comparison of Coefficients, Exponents, Lag Time, and Curve Fitting Results from Oral Tetracycline Data Evaluated by CSTRIP and ORAL^a

Computer Method	C ₁	λ ₁	k _a	t _{lag} , h	r̄	s ²	SD	r ²	Sum of Squares
CSTRIP ^b	2.1337	0.1289	1.0342	0.6100	—	—	—	0.9794	0.0265
ORAL ^c	2.1335	0.1290	1.0342	0.6105	0.013	0.0036	0.0597	0.9794	0.0265
ORAL ^d	1.9999	0.1241	1.2386	0.6979	0.022	0.0065	0.0804	0.9614	0.0498
ORAL-CSTRIP ^e	2.1337	0.1289	1.0342	0.610	0.013	0.0036	0.0597	0.9795	0.0264

^a Fitted to $C = C_1 e^{-\lambda_1(t-t_{lag})} - C_2 e^{-k_a(t-t_{lag})}$ using data in ref. 9. ^b Values from ref. 4. ^c Limits from 1 to 3 h and from 4 to 16 h as in ref. 4. ^d Limits from 1 to 3 h and from 3 to 16 h. ^e Values from ref. 9, input into ORAL.

point) were used for the absorption phase. Using the same limits in ORAL, with the exception that a 0,0 data point was not used, a nonlinear fit of data was obtained (Fig. 2) with pharmacokinetic and statistical output (Fig. 3). Alternately, ORAL had different limits marked to include the data point at 4 h in both the absorption–distribution and elimination phases. Several other evaluations were made in which the coefficients and exponents estimated by CSTRIP were input into ORAL and a 0,0 data point was added as in the previous work.⁴ A comparison of coefficients, exponents, and curve-fitting evaluations from the various estimations of spectinomycin data is given in Table II. The coefficients and exponents estimated by either CSTRIP or ORAL are comparable. Using sum of squares (SS) as one statistical parameter to judge appropriateness of the nonlinear curve estimation, it is seen that ORAL gave slightly better estimates than CSTRIP when a 0,0 data point was included or not included for limits (Table II). Similarly, the other statistical parameters tend to confirm the comparability between ORAL and CSTRIP. Using a 0,0 data point in ORAL gave the best estimate, as judged by all statistical parameters except correlation coefficient for the fitted curve (r²).

Tetracycline—This data was originally reported by Wagner⁹ and subsequently fitted with CSTRIP⁴ using six data points to describe the terminal phase and three data points for the absorptive phase following oral administration. Using these same limits in ORAL, the determined lag time of 0.6105 h was virtually identical with that of 0.61 h obtained by CSTRIP, as were the coefficient and exponent values (Table III). The estimates given by ORAL were not improved when a common datum point was used in each specified limit. Figure 4 gives a graphic output for these data in a different format than that used in Fig. 2, whereas Fig. 5 gives the output of pharmacokinetic parameters and statistics. Other fits of these data with ORAL were tried, but none were found which gave better nonlinear-curve statistics. This included a triexponential fit as reported⁴ with CSTRIP using limits of 3, 3, 3.

Secobarbital—Previously unreported data obtained in our laboratory following intravenous infusion of 0.63 and 0.65 mg/kg of secobarbital to two different subjects, respectively, are given in Table IV. The infusion was accomplished over a 15-min period; postinfusion blood specimens taken at various times were then analyzed by a GC method.¹⁰ These data was analyzed by both INTRAV and NONLIN.⁵ Initial estimates for NONLIN were obtained graphically by the feathering technique. Estimates obtained by all three methods are given in

RESULTS OF CURVE FIT

Oral tetracycline data from
Wagner et al. Clin. Pharmacol. Ther. 8:210(1967)

Time (hours)	Concentration (micrograms/ml)	Fitted Value	Weight	Relative Error
1.00	0.700	0.602993	1.000	+0.1386
2.00	1.200	1.276707	1.000	-0.0639
3.00	1.400	1.387740	1.000	+0.0088
4.00	1.400	1.314276	1.000	+0.0612
6.00	1.100	1.057032	1.000	+0.0391
8.00	0.800	0.822065	1.000	-0.0276
10.00	0.600	0.635919	1.000	-0.0599
12.00	0.500	0.491496	1.000	+0.0170
16.00	0.300	0.293509	1.000	+0.0216

* = Point not used in fit
c = Value of observed concentration altered by operator
a = This point added by operator

Fitted Values are for the One compartment model with First Order Absorption:

$$C = C_1 e^{-a(t-T)} - C_2 e^{-ka(t-T)}$$

$C_1 = 2.1335$ $a = .12889$
 T (lag time) = .61047 hours $ka = 1.0342$

Model Independent Parameters

Initial dose of drug (Dpo): 250.000 mg
 Plasma clearance by trap. rule (CLtrap): 20.515 L/hours
 Area under curve by trap. rule (AUCtrap): 12.186 hours-ug/ml

Model Dependent Parameters

Area under fitted curve (AUCpo): 14.490 hours-ug/ml
 Fraction of dose absorbed (f): 1.00000
 Plasma clearance (CL): 17.254 L/hours
 Rate constant of absorption (ka): 1.03423 1/hours
 Pharmacokinetic vol. of central comp (Vc): 117.177 L
 Pharm. vol. of dist. in terminal phase (Vz): 133.860 L
 Volume of distribution, steady state (Vdss): 152.918 L
 Half-life of absorption (t1/2ka): 0.670 hours
 Half-life of central compartment (t1/2a): 5.377 hours

Statistics:

Degrees of Freedom (df): 7
 Correlation coeff. for fitted curve (r^2): 0.97942
 Mean error of data on curve (rbar): 0.013
 Variance of error w.r.t. time (s^2): 0.00357
 Sum of Squares (SS): 0.02653
 Error Standard Deviation w.r.t. time (SD): 0.05973

LINEAR CORRELATION

Order	Correlation coefficient
Absorption	0.9931
1	0.9980

RESULTS OF CURVE FIT (contd.)

PLOT OF STANDARDIZED RESIDUALS

TIME	ACTUAL	FITTED	-4	-3	-2	-1	0	1	2	3	4	RESIDUAL
1.00	0.700	0.6030										+1.40401
2.00	1.200	1.2767			*							-1.50413
3.00	1.400	1.3877										-0.01474
4.00	1.400	1.3143										+1.21511
6.00	1.100	1.0570						*				+0.49934
8.00	0.800	0.8221				*						-0.58936
10.00	0.600	0.6359				*						-0.82130
12.00	0.500	0.4915										-0.07761
16.00	0.300	0.2935						*				-0.11132

* = Standard deviations from mean error

X = Off of scale

Figure 5—Printed output from ORAL for the tetracycline data as shown in Fig. 4.

Table V. In general, the estimates obtained with INTRAV compared favorably with NONLIN. The secobarbital data presented here were difficult to model due to the presence of a secondary absorption phase, perhaps due to enterohepatic circulation. For purposes of graphic modeling using either the feathering technique or INTRAV, 10 or 9 data points for subjects 1 and 2, respectively, were used to constitute the terminal limits. Statistical evaluations given in Table V demonstrate that NONLIN gives a slightly better fit for each subject, but INTRAV is comparable. The coefficient values given in Table V would have to be adjusted according to the method of Loo and Riegelman¹¹ since the fitted data was from a postinfusion study.

Sodium Hippurate—In a recent publication,¹² a comparison has been made between five different computer methods for estimating a three-compartment open model fit of data following a bolus administration of 250 mg of sodium hippurate. Using limits consisting of 6, 4, and 10 data points, respectively, INTRAV gave absolutely identical values to ESTRIP: $C = 27.41e^{-0.221} + 11.64e^{-0.0467} + 3.63e^{-0.0086}$.

Flunitrazepam—Data from subject 14 in a publication by Boxenbaum et al¹³ were evaluated by ORAL, CSTRIP, and NONLIN as shown in Table VI. Using limits consisting of 3,

3, 6, ORAL gave microscopic constants and statistical values which were essentially identical to those derived by CSTRIP. Using these estimates in NONLIN produced additional refinement of the values, as judged by the better statistical values generated by entering the NONLIN estimates into ORAL.

Discussion

Two interactive computer programs, INTRAV and ORAL, both written in BASIC, were developed to estimate coefficients and exponents of linear differential equations used to describe the absorption, distribution, and excretion of a drug. These estimates are then used to compute the most widely used pharmacokinetic parameters, perform a nonlinear curve estimation, and compute various statistical values to judge the appropriateness of the curve estimation. In addition, the programs have numerous output options which permit the user to display the data in varied formats for other comparisons or reproductions. An additional input option permits the user to compare experimental data with coefficients and exponents estimated from other programs such as NONLIN, CSTRIP, ESTRIP, etc., or literature citations.

Results presented compared INTRAV and ORAL with CSTRIP-, NONLIN-, and ESTRIP-generated values. In most instances, these new programs gave essentially identical values to CSTRIP and ESTRIP. Some minor variations in statistical parameters (Table V) were noted between INTRAV and NONLIN on one set of data from the intravenous infusion of secobarbital (subject 2). Similar variations were observed between ORAL and CSTRIP when compared with NONLIN (Table VI). Such results are not entirely surprising since NONLIN uses an iterative method to minimize the sums of squares, which is not practical with most microcomputer hardware. However, as several groups have shown,^{12,14} choosing the proper initial estimates for NONLIN can greatly affect the resultant estimates. Thus, either INTRAV or ORAL should aid a user in developing initial estimates similar to CSTRIP and ESTRIP; in some cases these estimates may be similar to those developed following input into other programs like NONLIN.

The major advantage that these newer programs offer is being more "user friendly." That is, the input data are displayed in a graphic form on a CRT, and the user can model this data to obtain various estimates in a manner similar to that used with analog computers. However, the user must be willing to perform many fits using different limits to obtain the best estimates. After some initial experience with the programs, a

Table IV—Concentration versus Time Data Following a 15-min Infusion of Secobarbital in Two Subjects*

Time, h	Secobarbital Found, $\mu\text{g/mL}$	
	Subject 1 (0.63 mg/kg)	Subject 2 (0.65 mg/kg)
0	0.76	1.08
0.083	0.74	1.06
0.166	0.66	0.94
0.333	0.59	0.82
0.50	0.58	0.66
0.75	0.57	0.54
1.0	0.51	0.48
1.5	0.46	0.55
2.0	0.64	0.52
3.0	0.55	0.47
4.0	0.53	0.57
6.0	0.47	0.44
8.0	0.38	—
12.0	0.45	0.29
24.0	0.28	0.21

* Studies performed at Southern California Research Institute, Los Angeles, and approved by Human Use Committees at that institution as well as the University of Missouri-Kansas City.

Table V—Comparison of Parameter Estimates Obtained by Graphics, INTRAV, and NONLIN for Secobarbital Data and Resultant Statistical Evaluations by INTRAV

Method	Subject	C_1	λ_1	C_2	λ_2	\bar{r}	s^2	SD	r^2	Sum of Squares
Graphic	1	0.213	4.56	0.562	0.028	—	—	—	—	—
	2	1.10	6.88	0.560	0.043	—	—	—	—	—
NONLIN	1	0.213	4.52	0.563	0.028	0.0017	0.0028	0.0524	0.8918	0.0303
	2	0.589	2.82	0.548	0.041	0.0003	0.0034	0.0582	0.9962	0.0338
INTRAV	1	0.211	5.12	0.569	0.029	0.009	0.0028	0.0526	0.9390	0.0304
	2	0.607	3.06	0.600	0.043	-0.0062	0.0035	0.0592	1.0932	0.0355

Table VI—Comparison of Parameter Estimates Obtained by ORAL, CSTRIP, and NONLIN for Flunitrazepam Data* and Resultant Statistical Evaluations by ORAL

Method	C_1	λ_1	C_2	λ_2	k_a	t_{lag}, h	\bar{r}	s^2	SD	r^2	Sum of Squares
ORAL	15.549	0.364	5.130	0.043	0.875	0.414	0.092	0.1991	0.4462	0.9814	1.6950
CSTRIP	15.562	0.364	5.130	0.043	0.875	0.411	0.077	0.2014	0.4488	0.9815	1.6815
NONLIN	19.215	0.342	4.780	0.042	0.791	0.434	0.019	0.0991	0.3147	0.9912	0.7969

* Data from subject number 14 in ref. 13.

user can often get the best estimates within a few minutes.

Judging the appropriateness of the model is aided by a nonlinear curve through the data and some statistical parameters outputted by the programs. A visual inspection of the nonlinear curve is often invaluable for a preliminary evaluation of fit exactness. Next, the user can evaluate linear correlation coefficients for values which approach unity as an indicator that proper limits have been chosen. This is particularly true for the terminal limits. Often one can choose the proper terminal order using INTRAV by setting limits about various combinations of data points which are possibly part of the terminal order and having the program execute as if only one order was present. The set of data which gives a linear correlation coefficient value nearest to unity will often constitute the terminal order. This principle is similar to that required to obtain best estimates with either CSTRIP or ESTRIP. However, an apparent advantage of INTRAV and ORAL is that overlapping points within orders or data points which extend beyond the limit of the previous order may produce better estimates for the resulting nonlinear curve.

Boxenbaum et al.¹⁴ have discussed various statistical parameters which can be used to judge the exactness of a curve fit. In INTRAV and ORAL, different statistical parameters than those previously suggested¹⁴ have been utilized, but it should not be construed by potential users that these offer more advantages or are better choices. Rather, the chosen statistical parameters were selected as alternatives and have proven to be useful. For example, as summarized in Tables II, III, V, and VI, values for r^2 , \bar{r} , s^2 , sum of squares (SS), and SD are predictive as to which estimates give the best nonlinear fit. Further verification can be obtained by visual inspection of the plot of standardized residuals versus time. A completely random distribution, such as shown in Fig. 5, rather than systematic deviations additionally suggest that the proper model has been chosen. Further refinement of the model parameters may then be possible by using the various weighting techniques available in the "Edit" option.

Plotting options available in both INTRAV and ORAL permit the operator to display fitted data in a variety of formats, such as illustrated in Figs. 2 or 4. If the user wishes to see the feathered lines used to generate the curve, then a format such as in Fig. 2 is chosen. Legends, feathered lines, and marking of orders can be omitted as shown in Fig. 4.

Conclusions

The developed programs are comparable with the widely used programs CSTRIP, ESTRIP, and NONLIN for obtaining coefficient and exponent estimates used to determine pharmacokinetic parameters and, like ESTRIP, they can be executed on many microcomputers since BASIC language is utilized. Both INTRAV and ORAL have extensive graphic capabilities not found in the other programs, which permit the user to compare experimental data and/or previously reported data. In addition, many of the commonly used pharmacokinetic parameters are also computed.

References and Notes

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7. Symbols and equations for pharmacokinetic parameter determination throughout the text conform to those recommended by the American College of Clinical Pharmacology, May 1982, in *J. Clin. Pharmacol.* **1982**, *22*, 15. However, on the computer printout a, b, . . . , z is used instead of λ .
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