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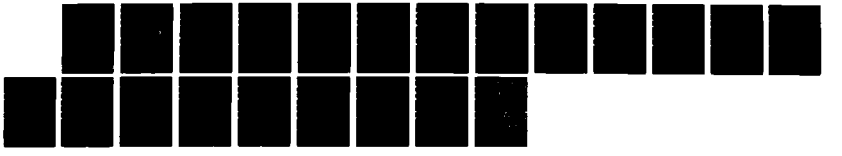

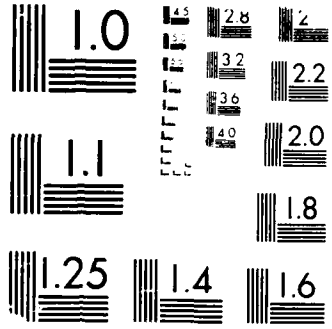

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DEVELOPMENT OF MICROCOMPUTER METHODS FOR ANALYSIS AND SIMULATION OF CLINICAL PHARMACOKINETIC DATA RELEVANT TO NEW DRUG DEVELOPMENT

ANNUAL/FINAL REPORT

THORIR D. BJORNSSON

ROBERT WAGONER

AUGUST 2, 1985

Supported by

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The research proposed under this contract is a feasibility study in the development of applications of new microcomputer graphics techonology to the analysis and interpretation of clinical pharmacological data. This involves continuing development of comprehensive programs for analysis, interpretation, and simulation of pharmacokinetic data, dose-response kinetic data, and other data relevant to new drug development, for use with the Tektronix 4052 Microcomputer Graphics System. The combination of such modern analytical and illustrative methods in clinical pharmacology, based on new high-speed

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microcomputers and associated graphics, are thought to greatly reduce both cost and time involved in the overall process of clinical evaluation of new drugs in the U.S. Army Drug Development Program.

The work performed during the past twelve months of the contract includes the following:

1. Program for Linear Pharmacokinetic Data Analysis by Non-Linear Curve Fitting Using Compulsory Graphics

2. Program for Analysis of Concentration-Response Kinetic Data

3. Program to Simulate Time Courses of Drug Concentrations After Drug Administration, for Any Number of Doses and Route of Administration

4. Program to Compute the Area under the Zero Moment (AUC) and the First Moment (AUMC) of the Plasma Concentration vs Time Curve

5. Program to Compute the Urinary Excretion Rate Constant of Drugs

6. Program for Pharmacokinetic Parameter Conversion

7. Programs for the Analysis and Simulation of Non-linear Pharmacokinetic Data

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9. Development of a Program Helpful in the Design of Drug Dosage Regimens

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11. Program for Quantal Dose-Response (Probits) Analysis

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SUMMARY

The research performed under this contract was a feasibility study in the development of applications of new microcomputer graphics technology to the analysis and interpretation of clinical pharmacological data. This involved continuing development of comprehensive programs for analysis, interpretation, and simulation of pharmacokinetic data, dose-response kinetic data, and other data relevant to new drug development, for use with the Tektronix 4052 Microcomputer Graphics System. The combination of such modern analytical and illustrative methods in clinical pharmacology, based on new high-speed microcomputers and associated graphics, are thought to greatly reduce both cost and time involved in the overall process of clinical evaluation of new drugs in the U.S. Army Drug Development Program.

The work performed under this contract includes the following:

1. Development of a program for the analysis of linear pharmacokinetic data based on the method of separate exponentials and using compulsory graphics.

2. Development of a program for the analysis of concentration vs response data based on a logarithmic-logistic function for both mono- and di-chotomous dose-response curves.

3. Development of a program to simulate time courses of drug concentrations for any number of doses and route of administration.

4. Development of a graphic program to compute area under the curve and area under the first moment of the curve for drug concentration vs time data.

5. Development of a graphic program to compute the urinary excretion rates of drugs.

6. Development of a program for the analysis of concentration vs effect data using probits.

7. Development of a program to convert pharmacokinetic parameters to their exponential forms.

8. Development of programs for the analysis and simulation of non-linear pharmacokinetic data.

9. Development of statistical programs useful for the analysis of clinical pharmacological data.

10. Work on a program to help design drug dosage regimens.

11. Analysis of data at special requests of COTR.

BACKGROUND

The process of drug development has been both complicated and facilitated by the trend toward early application of the methods of clinical pharmacokinetics. Current practice and existing and proposed new Food and Drug Administration Regulations demand sophisticated evaluation of drug bioavilability and descriptive pharmacokinetics in Phase I clinical studies. This requires development of assay methods for new drugs and their metabolites and methods for evaluation of concentration vs time data to obtain relevant parameters to characterize drug behavior. Of similar importance is knowledge of characteristics of relationships between dose or concentrations and pharmacologic response. The information thus obtained from pharamcokinetic and pharmacodynamic studies relates directly to the optimal design of dosing schedules of new drugs in man, including individualization of therapy due to disease processes or other factors which may affect drug behavior. In this regard the eventual course of development through Phase II and Phase III clinical studies is rendered less empirical and ultimately more efficient in both time and cost, by minimizing the use of scarce resources.

Modern computer technology has greatly enhanced the capability of these methods and made possible their applications to clinical pharmacokinetics. A number of available computer programs have been frequently employed for this purpose. Those which have been developed for use specifically in clinical pharmacokinetics are based on compartmental methods of analysis and yield estimates of parameters associated with preselected compartmental models. While useful and informative, they lack the ease of use and cognitive appeal of direct graphic simulations and graphics-assisted data analysis. It was in the interest of developing general purpose programs with the advantages of computer graphics that the present contract was initially pursued.

Previous experience with the Tektronix 4051 and 4052 Microcomputer Graphics System indicated that this was an especially suitable microcomputer system for our purpose. While similar systems are now available from a variety of sources, it is in the interest of conformity with existing systems in the U.S. Army Drug Development Program at the Walter Reed Army Institute of Research that the Tektronix System has been employed. The present Tektronix 4052 System in our laboratory and for which the programs to be described were developed is identical to that now in use at Walter Reed. A data communications interface has been installed to facilitate direct transmission of programs and data between these two facilities.

SUMMARY OF PROGRESS

A. Program for Linear Pharmacokinetic Data Analysis by Non-Linear Curve Fitting Using Compulsory Graphics.

The foundation upon which this assembly of integrated programs was built originated several years ago in a series of programs developed by one of the investigators (Dr. Desjardins) and the contract monitor, Dr. Charles Pamplin, in the Department of Pharmacology, Division of Experimental Therapeutics, Walter Reed Army Institute of Research. While a version of these programs had been used successfully in the analysis of data which have been previously published, they had not, in fact, been properly verified and documented. These programs have now been documented, and modified and expanded substantially to generalize their usefulness to the greatest extent possible.

In the course of this work a concept, not entirely original but new in the extent to which it has been applied, began to emerge and was incorporated in the program package. This is the principle of separate exponentials (Shand, Desjardins, Bjornsson, Hammill and Pritchett: The method of separate exponentials: A simple aid to devising intravenous drug-loading regimens. Clin. Pharmacol. Ther., 29:542-547, 1981). In conjunction with the unique compulsory graphics feature of the program, the application of this principle has resulted in the assembly of programs to which we have given the title, "Pharmacokinetic Data Analysis by the Method of Separate Exponentials with Compulsory Computer Graphics".

The method of separate exponentials relies on Dost's law of superimposition for resolving the exponents involved, which simply states that the concentration vs time curve of a drug is made up of the sum of the exponential terms involved. It represents a departure from classical pharmacokinetics as it has evolved over the past two decades in that it is not directly dependent upon compartmental models. It provides, instead, a descriptor model which is "statistically sufficient" to define the behavior of a drug with respect to the time course of blood (plasma) concentrations. The model involves a nonlinear regression function consisting of a sum of the exponential terms which describe the total time course of the drug concentrations in the body. The model provides predicions of drug behavior which are amenable to testing by suitable clinical pharmacokinetic studies and can be used in a simulation mode to optimize drug administration.

The equations employed for each route of administration are as follows:

1. Intravenous bolus or oral administration

$$C_t = \sum_{i=1}^{n} A_i e^{-E_i t} \qquad n = 1 \text{ to } 4$$

2. Continuous or finite infusion

$$C_t = \frac{R}{Cl} \sum_{i=1}^{n} f_i \left(1-e^{-E_i(t_{MIN})}\right) e^{-E_i(t-t_{MIN}-\tau)} \quad n = 1 \text{ to } 4$$

where

f_i = fractional area
τ = infusion time
R = infusion rate (constant)
Cl = clearance

3. Oral administration

$$C_t = \sum_{i=2}^{n} A_i \left(e^{-E_i t} - e^{-E_1 t}\right) \text{ force through 0, or}$$

$$C_t = \sum_{i=2}^{n} A_i \left(e^{-E_i(t-\tau)} - e^{-E_1(t-\tau)}\right) \text{ lag time } \tau$$

The simplicity of these equations when compared with compartment model dependent equations with individual intercompartmental rate constants is immediately apparent. They, nevertheless, when statistically valid, provide estimates of relevant parameters and serve as useful predictor models of drug behavior in a linear pharmacokinetic system. The unique feature of compulsory graphics for selecting optimal initial parameter estimates and for model selection was developed in the original programs on which the present package is based and adapted for use with these models. Likewise, a series of statistical evaluations for model selection similar to that originally used has been adapted. Modifications include the use of a combinatorial function rather than a table of numbers for the sign test (Bury KV: Stastical Models in Applied Science, John Wiley and Sons, New York 1975, pp. 224-228) and the use of Akaike's information criterion-AIC (Yamaoka K, Nakagavia T and Uno T: Application of Akaike's Information Criterion in the Evaluation of Linear Pharmacokinetic Equations. J. Pharmacokinet. Biopharm., 6:165-175, 1978). The latter (AIC) was derived from the maximum likelihood estimation which is equivalent to estimating the parameters so as to minimize "Kullback-Leibler's mean information". The equation with the minimum AIC is regarded as the best representation of the time course data. Therefore, this method is called "minimum AIC estimation" (MAICE). It provides a statistically valid method for estimation of the number of exponential terms in a series needed to sufficiently describe the fitted data.

The parameter estimation routine used in the present package was adapted from Bailey and Homer (Interactive Parameter Estimation, Work Unit No. M0098-PN.01.0037, Naval Medical Center, Bethesda, MD, September 1976). This program, based on the Marquardt algorithm for least-squares estimates of non-linear parameters, has been modified slightly to provide a more rapid convergence, especially with the optimal initial parameter estimates provided by "Compulsory Graphics". It has furthermore been verified by comparison with the BMDPAR (Ralston, 1979, UCLA) program for pharmacokinetic model fitting.

B. Program for Analysis of Concentration-Response Kinetic Data

A second major program, first developed by one of the investigators (Dr. Desjardins) and the COTR in the Department of Pharmacology, Division of Experimental Therapeutics, Walter Reed Army Institute of Research, involves describing concentration-response kinetics by nonlinear curve fitting. In this program a set of X, Y (concentration-response) data are fit to a logistic-logarithmic function which was parameterized to yield a direct estimate of the IC-50 (50% inhibitory concentration) with an associated variance estimate from which an approximate 95% confidence interval is calculated. This program, which had been used in the analysis of data which were subsequently published, had not been properly documented and verified.

The original program employed the graphics capabilities of the Tektronix 4051 to optimize initial parameter estimates associated with a hyperbolic tangent form of the logistic-logarithmic function as follows:

$$Y_i = \frac{U-L}{2}\left[1 + \tanh\left(\beta\log C - \beta\log X_i\right)\right] + L$$

where

Y_i, X_i = Response and concentration respectively of the i^{th} point or sample
U = Response at X = 0
L = Response at X = ∞
C = IC-50
β = A slope or "scaling" parameter

This is a modification of a similar function described by Emmons in 1942 and is only one of several algebraically equivalent forms of the logistic-logarithmic function, all of which describe a symmetrical sigmoid relation between a dependent variable Y and the logarithm of an independent variable X.

The hyperbolic tangent form of the equation was selected originally because it could be written to include the IC-50 as one of the parameters of the function. Several other alternate functions were subsequently sought which would require less execution time and would also be flexible with regard to its parameterization. Three general types of equations were considered, all of which provide a symmetrical sigmoid function for f(x,p), i.e., the cumulative normal or logistic function, the arc tangent function, and the modified logarithmic logistic function. The last one was selected, as follows:

$$Y_i = \frac{Y_0 - Y_\infty}{1 + \frac{f}{1-f}\left(\frac{X_i}{ED_f}\right)^S} + Y_\infty$$

where

Y_i, X_i = the response and concentration respectively of i^{th} sample.

Y_0 = the response at X = 0
Y_∞ = the response at X = ∞
f = (0 < f < 1)
ED_f = the concentration associated with f x 100% response
S = a scaling (slope) parameter

This form of the logarithmic logistic equation permits a direct estimation of any response point with its associated variance estimate from which a confidence interval can be calculated. It also offers a considerable degree of flexibility and ease of use presently not available in other programs for dose-response kinetic data analysis. The program in its present form, following input of X,Y data and graphics-assisted selection of initial parameter estimates for f = 0.5, will optimize these parameters by nonlinear least squares curve fitting. Following this, the data will automatically be fitted again for f = 0.1, f = 0.9 and f = 0.95, yielding estimates and variances for the ED-10, ED-50, ED-90 and ED-95. With minor modification of the program any value of f can be obtained to yield an estinate for ED-f. The run time for this program has also be shortened considerably by including exact calculations rather than numerical approximations of the partial derivatives.

In 1980, work at WRAIR on two sets of data pertaining to the <u>in vitro</u> concentration-response kinetics for the drug Pentostam^R against promastigotes of Leishmania donovani showed a consistent deviation from a simple sigmoid curve. Work on this phenomenon resulted in the development of the option in the program to fit the data to a "dichotomous dose-response" function. Conceptually, the model assumes that some proportion of the organisms (P) respond to the drug with an ID-50 = C_1, and the remaining organisms (1-P) respond with a higher ID-50 = C_2, i.e., a "dichotomous dose-response". Mathematically, the model thus involves two dose-response curves, each with its ID-50, slope characteristics, and the proportion of the total curve corresponding to that part. An alternative explanation for the dichotomous dose-response of Leishmania promastigotes to Pentostam can be suggested. Namely, it is possible that the drug has two separate mechanisms of antileishmanial activity mediated by two different receptors with differing sensitivity to the drug.

A new program was therefore developed, based on the existing dose-response program, which allows the analysis of data exhibiting a dichotomous, or two-step, concentration-effect relationship. This type of analysis allows estimates of parameters for each of the two sections of the dose-response curve, i.e., two ED-50's are estimated, as well as the relative fractions of the total response due to each portion of the curve. This program has proved valuable in analyzing data which could not be successfully fitted by the conventional dose-response program.

Plans had been made to convert the dose-response analysis program for use on a TRS-80 computer. This was not possible, however, since we were unable to get access to such a computer for the required amount of time to finish the conversion, and it was not felt to be justified to purchase such a computer solely for this project.

C. Program to Simulate Time Courses of Drug Concentrations after Drug Administration, for Any Number of Doses and Route of Administration

A comprehensive and versatile pharmacokinetic simulation program has been developed for the Tektronix 4052 Microcomputer Graphics System to enable simulation of concentration vs time curves for any number of doses, dosing intervals, and routes of administration, and any changes in these values. The Tektronix 4050 Series Microcomputer Graphics System is uniquely well suited for such a program because of its exceptional graphics features. The development of this pharmacokinetic simulation program was a logical extension of the graphically-oriented pharmacokinetic data fitting program previously developed. Thus, the pharmacokinetic simulation program can serve as a useful companion to the clinical pharmacokinetics program package developed under this contract and designed for use in the U.S. Army Drug Development Program.

While the data fitting program focuses on sophisticated statistical analysis of single or multiple dose pharmacokinetic data with compulsory graphics, including simulation of the best-fitted concentration vs time curve, it has been designed to perform pharmacokinetic simulations involving selected kinetic parameters. Thus, in terms of use, it can be said that the simulation program takes over where the fitting program ends. The program will simulate predicted drug concentrations for any given dosing regimen when pharmacokinetic data are available, e.g., using the best-fitted pharmacokinetic parameters form the fitting program, or pharmacokinetic parameters from the literature.

The potential uses of the simulation program are many and include:

1) Design of drug dosage regimens. This is particularly important when designing an appropriate chronic dosage regimen of drugs or drug antagonist when plasma concentrations have to be maintained in a certain concentration range or above some minimal effective concentration, either for prophylaxis or treatment.

2) Illustration of the effects of intersubject variability in drug disposition on drug concentration vs time curves when fixed dosage regimens are utilized. This can be important for drugs with a narrow therapeutic index, and when different disease states, particularly liver, kidney, and heart disease, may affect drug disposition. The simulation program can also be used to predict the time course of drug concentrations after an appropriate dosage adjustments has been made.

3) Optimization of blood sample collection times. This is useful for prospective pharmacokinetics studies when there is some information available on the pharmacokinetics of the drug. The planned sampling times can then be superimposed on the expected (based on best available information) concentration-time curve.

4) Educational uses. This includes the evaluation of the effects of changes or difference in individual pharmacokinetic parameters on the concentration vs time profiles for different dosing regimens.

The user of this program has several options available, based on the user defined keys. After entering the pharmacokinetic parameters for the drug of

interest, single or multiple doses may be entered, using any route, amount, and time of dosing. The graph may be displayed after any or all of the doses have been entered, using either automatically scaled axes, or with axis lengths and tic intervals set by the user. Logarithmic scaling of the Y-axis is also available. The graphs may be titled, and the axes may be labeled at the user's discretion. The graph may be drawn on the screen or the plotter, and if on the plotter, the program will pause between drawing the axes and the curve, allowing the user to change pen colors for multiple plots.

The output of this program consists of a graph of the predicted concentration vs time curve, and a printout listing the pharmacokinetic parameters used for the simulation and the doses given, including amount, time, and route of administration.

A separate simulation program has been written for the simultaneous simulation of time courses of drug concentration and pharmacologic effect. Conceptually, this program involves the incorporation of the log-logistic equation into the linear pharmacokinetics simulation program. If concentrations are to be graphed, they may be shown on linear or logarithmic scales, while the effect axis is always linear and will be automatically scaled by the program (from 1% to 100% effect), but the user may override the choice of endpoints and tic intervals if desired, another feature which has been retained from the original simulation program. Another useful feature of this modified program is the pause feature, which stops the pen after drawing the axes and labels, and again after drawing the concentration curve and before drawing the effect curve, allowing the changing of pen colors for different sections of the plot. This pharmacokinetic/pharmacodynamic simulation program should prove most useful in designing drug dosage regimens on the basis of some desired range in effectiveness.

D. Program to Compute the Area under the Zero Moment (AUC) and the First Moment (AUMC) of the Plasma Concenration vs Time Curve

A program has been developed for the Tektronix 4052 Microcomputer Graphics System to compute the area under the plasma concentration vs time curve (AUC), and also, the area under the first moment of the plasma concentration vs time curve (AUMC). These two parameters are of prime interest in pharmacokinetic analysis since both allow non-compartmental or model-independent analysis. The parameter, AUC, can be used to calculate total clearance (Cl), apparent volume of distribution by area (Vd_{area}), renal clearance (Cl_R), and bioavailability (F), using conventional expressions.

The area under the first moment of the concentration vs time curve (AUMC) enables the calculation of two other pharmacokinetic parameters, the mean residence time (MRT) and the apparent volume of distribution at steady state (Vd_{ss}). These parameters are calculated, based on AUC, AUMC, dose (D), and duration of zero-order drug input (T), e.g., by continuous i.v. infusion, as follows:

$$MRT = \frac{AUMC}{AUC} - \frac{T}{2}$$

and

$$Vd_{ss} = MRT \times Cl$$

which in the case of i.v. injection becomes:

$$Vd_{ss} = MRT \times Cl = \frac{D \times AUMC}{AUC^2}$$

while for oral administration, MRT has to be computed as:

$$MRT = \frac{AUMC}{AUC} - \frac{1}{K_a}$$

where K_a is the first-order absorption rate constant.

The MRT represents the average lifetime expectancy of an individual molecule within the body, and while it has the same time units as half-life, these two differ significantly. We feel that this parameter will be of great use in toxicology, as it is thought to express the exposure of the body or a given organ to a given compound. The other parameter derived from AUMC, Vd_{ss}, is a volume term which has previously only been calculated after compartmental analysis. This volume is usually somewhat smaller than Vd_{area}. Thus, the program developed to computer AUC and AUMC allows calcuations of Cl, Cl_R, Vd_{area}, MRT, and Vd_{ss}, in addition to $t_{1/2\,\beta}$.

The area under the zero moment of the concentration vs time curve is calculated using the trapezoidal rule over the range of observed data points, and by extrapolation to time infinity using the best-fitted concentration at the last time point and the terminal elimination rate constant. Values for both the total, trapezoidal and extrapolated areas are listed.

The area under the first moment of the concentration vs time curve, AUMC, is similiarly computed by summing up the areas under the first moments for each trapezoid from time 0 to time t, $AUMC]_0^t$, and by then adding the area under the moment curve from time t to infinity, $AUMC]_t^\infty$, which is calculated from the equation:

$$AUMC]_t^\infty = \frac{C_t}{\beta} \times \left(t + \frac{1}{\beta}\right)$$

where C_t is the best-fitted concentration at the last time point, t, and β is the terminal rate constant.

The printout generated in association with the analysis lists the data, parameters of the final phase calculation (intercept and exponent), final half-life, and values of the two components for each area, plus the total for both areas.

Through the user definable keys using an overlay, the user has the option of entering data directly or from tape, deleting, changing or adding data points at any time, giving each data set a title which will be printed both on top of the graph and on the printout (both X-axis and Y-axis can also be labeled), and deciding which data points to use for computing λ_z. Both a copy of the graph, with a solid line indicating which data points were used to compute λ_z, and a printout will be generated.

E. Program to Compute the Urinary Excretion Rate Constant of Drugs

A program has been developed for the Tektronix 4052 Microcomputer Graphics System to compute the urinary excretion rate of drugs. The analysis yields an estimate of the final elimination half-life of the drug based on the amount of drug recovered in timed urine collections. This estimate of rate of drug elimination should be parallel to that of the final decline in drug concentration in plasma. However, unless durations of urine collections are short with respect to the eliminaton half-life, and the different collection periods are of similar lengths, the estimate of drug elimination based on the urinary excretion rate method tends to be lower than that based on plasma data. The reason is that in most studies durations of urine collections increase with time, and since midpoint values for urinary excretion rate are calculated for each collection period, the elimination will be artifactually decreased, yielding a longer final half-life value. However, in several instances, urine data may be the only available data.

The urinary excretion rate is computed by estimating the rates of excretion during each collection period, and then plotting these points vs time on semi-log axes. The values on the Y-axis are therefore $\Delta X_u / \Delta t$ values for each of the midpoint time values. The elimination rate constant is then calculated using the number of final data points determined by the user, in a manner similar to that used in the area program.

The printout generated in association with the analysis lists the data, midpoints, and rate of excretion for each collection period, and the calculated elimination rate constant and final half-life.

Through the user definable keys, using an overlay, the user has essentially the same options as for the AUC/AUMC program; these include direct data entry or from tape, deleting, changing, or adding data, entering titles, and generating a copy of the graph and a printout.

F. Program for Quantal Dose-Response (Probits) Analysis

The probit method is applicable to dose-response analysis when only a small number of subjects are examined, due to reasons of expense or convenience or when the observed response cannot be precisely measured. This program uses a probit function to fit the observed response data to a

cumulative normal distribution function. As a complement to our other dose-response program, which is based on a logistic logarithmic function, this method allows the user to analyze data from experiments in which the frequency of an all-or-nothing response, such as death, is measured. Interestingly, when this same kind of frequency data is analyzed by the logistic dose-response program, the results obtained are quite comparable with those from the probit program. However, the logistic program is only designed to be used with continuously varying effect data, while the probit method is to be used for discrete responses. Thus, the present availability of programs for the analysis of both graded and quantal responses offers means of analysing all dose-response data.

The method used for analysing quantal dose-response data involves converting the percentage responding to each dose level into probability units, or probits, and then performing a linear regression of probit response vs log dose. This has the effect of fitting a cumulative normal probability curve to the dose-response data. Due to the nature of this curve, the initial fitting is usually not sufficiently accurate to fully describe the data. To correct this, weights are assigned to each data point based on its position on the initial regression line, and a new weighted regression is computed. This process is repeated until the values of two successive interations are judged sufficiently close. Convergence is typically reached after 4-8 interations. The resulting line corresponds to a normal probability curve, with the mean representing the ED-50 and the standard deviation giving a measure of the sensitivity of the effect to changes in the dose. When comparing this program to the logistic pharmacodynamic data analysis program, we obtain very consistently comparable estimates of the ED-50.

G. Program for Pharmacokinetic Parameter Conversion

This program is intended to supplement the pharmacokinetic simulation program. A difficulty with the use of all simulation programs is the widely varying sets of parameters which are available in the published literature. For example, it is not uncommon to find for a given drug that the pharmacokinetic parameters provided in one publication are co-efficients and exponents, in the second the model-dependent compartment parameters, and in the third a selected combination of both. Since our simulation program is designed to be used in conjunction with the sum-of-exponentials model used in the linear kinetics analysis program, other sets of parameters must be translated into this format in order to be useful with this program for pharmacokinetic data simulation.

A program has therefore been developed to automatically convert any sufficient set of pharmacokinetic parameters into the separate exponential format for use with the programs already developed in this project. The program first determines whether the set of parameters available provides a "complete set" and if so, it will translate them into the exponential form. The program is capable of converting data representing one- or two-compartment pharmacokinetic model with input through injection, infusion, or oral administration into a single standard format using the sum-of-exponential-terms representation. The input to the program may be expressed in terms of volumes of distribution, half-lives, time of peak concentration, total clearance, rate constants of absorption or elimination, or concentration at

time of injection or maximal absorption. If requested, the program can perform unit conversions of some of the input parameters to make them consistent. Not only will this translation program be of great value to our simulation program but also to all individuals interested in applied clinical pharmacokinetics.

H. Programs for the Analysis and Simulation of Non-linear Pharmacokinetic Data

The programs developed earlier for curve fitting and simulation of pharmacokinetic data are capable of fitting and simulating time-concentration data following single or multiple dose administration by any route or method of administration for drugs which behave according to linear-pharmacokinetic principles. The absorption, distribution, metabolism and elimination processes are all assumed to be first-order and their net effect can therefore be described by a sum of exponential terms. The area under the corresponding time vs concentration curve can be functionally separated according to the fractional contribution of each exponential terms. This, indeed, is the foundation of the concept of separate exponentials.

While the majority of drugs in current use and new developmental drugs fit the concept based on these assumptions, some do not. Among the more common examples of drugs with non-linear pharmacokinetics are phenytoin, salicylic acid, para-aminobenzoic acid, ethyl alcohol, diphenhydramine and sulfasalazine. Nonlinearities have been described in drug absorption, distribution, metabolism and elimination, but most commonly for drug metabolism. These nonlinearities imply processes which are not first-order, but rather show evidence of saturation. The net effect of these nonlinearities on the time vs concentration curves of the drugs are such that they cannot be accurately described by a simple sum of exponential terms. They require a more complex model, either compartmental or physiological, in which at least one of the functions is nonlinear. This function is, in turn, most commonly described by Michaelis-Menten kinetics, i.e.:

$$\frac{dC}{dt} = \sum_{i=1}^{n} \frac{V_i C}{K_i + C}$$

The program developed for the analysis of nonlinear pharmacokinetic data is a modification of the linear pharmacokinetics program to accommodate sets of differential equations, instead of the current sum of exponentials. A critical component of it has therefore to be a rapid and convenient method for solving the differential equations. A number of different techniques have been evaluated, including Runge-Kutta methods, Hamming's predictor-corrector system, and Bulirsch-Stoer rational extrapolation. None of these has proved to be ideal, in the sense of computing solutions rapidly, and being easy to use and compatible with the other graphical and statistical components of the program. The existing fully functional version of this program uses a fourth-order Runge-Kutta integration technique, along with a simple means of determining step-size.

A program has also been developed for simulating time courses of drugs behaving in a nonlinear pharmacokinetic fashion in the body. This program is a modification of the linear pharmacokinetics simulation program, but due to the numerous complexities of possible nonlinear steps and lack of available data, the present program has only been written for the one-compartment model, with Michaelis-Menten type elimination and first-order absorption when administered orally. Otherwise, this program combines the flexibility of the existing linear pharmacokinetics simulation program with the various options available in the linear simulation program, such as mixed modes of dosing and user-selected logarithmic or linear scaling.

In the present version of the programs, the user does not have to enter the differential equations describing the model, but can now choose the appropriate equation from a menu of choices. This feature takes advantage of the ability of the Tektronix Basic to load code from a file into an executing program, using the APPEND statement. The nature of this operation makes it very easy to add to the menu of models by adding further files containing the necessary differential equations, and then editing the menu to reflect the additional choices available. Presently, the options available in the standard menu of models include one-compartment model with Michaelis-Menten elimination, with input from IV bolus, IV infusion, or oral first-order absorption. These models are the most commonly used for nonlinear kinetics, but they can also serve as a template for the development of further, more complex systems of differential equations for these programs.

Together with the already completed linear pharmacokinetics programs, these programs will provide a comprehensive package of programs for the analysis and simmulation of pharmacokinetic data associated with virtually any drug of interest to the U.S. Army Drug Development Program. The use of compulsory graphics in the selection of model selection continue to remain the unique features of this package of programs.

I. Statistical Programs for Clinical Pharmacological Problems

Work on the statistical program package began with an emphasis on development of nonparametric or distribtution-free techniques for comparing observations made under two or more courses of treatment. These tests are applied when the measurement of interest does not follow a normal distribution or when the number of observations is so small that the nature of the statistical distribution cannot be determined.

The nonparametric equivalents of the two-sample t-test and the paired t-test are the Mann-Whitney U-test and the Wilcoxon signed-rank test, respectively. Programs for performing each of these tests have been prepared, with both being designed for ease of use with respect to entering, listing and correcting data. In each of these programs, the user is allowed to test either a one-tailed or a two-tailed hypothesis, for which the significance level is then calculated. An expression for the exact probabilities has been developed and is used, thus avoiding the need for tables of critical values.

The nonparametric methods corresponding to 1-way and 2-way analysis of variance are the Kruskal-Wallis 1-way ANOVA and Friedman's 2-way ANOVA. Programs for these tests have now been added to our nonparametric analysis of

variance programs. Additionally, a program has been written for the parametric analysis of variance with multiple comparisons both when all possible comparisons between groups are to be made and when specific combinations are to be used. The multiple comparison methods now involve the method developed by Scheffe and the Bonferroni method of adjusting significance levels. These procedures can be computed directly without requiring the use of tables of critical values. We have been unable to find similar direct methods to use with the methods of Duncan and Dunnett. Because of this lack, these procedures are still not available as an automatic component of the program, although the user can easily apply either of these methods using the program output together with a table from any of standard references.

J. Development of a Program Helpful in the Design of Drug Dosage Regimens

The programs developed under this contract for the analysis and simulation of pharmacokinetic and pharmacodynamic data, i.e., drug concentration vs time data and pharmacological effect vs drug concentration data, respectively, will constitute a powerful program package for presenting clinical and basic pharmacological data relevant to new drug development. These programs, however, have not been designed to address directly the important issue of optimal design of drug dosage regimens. We have been interested in developing a general algorithm for designing optimal dosage regimens for drugs for which both pharmacokinetic and pharmacodynamic data are available.

Classically, dosage regimens for drugs used chronically have been determined either empirically or on the basis of pharmacokinetic data only. A commonly used dogma has been to select a dosing interval, τ, close to the elimination half-life of the drug, $t_{1/2}$, i.e.,

$$\text{Method I: } \tau \cong t_{1/2}$$

This approach ensures that the fluctuations in drug concentrations between doses at steady-state will neither be much more nor much less than two-fold. A more rational method would be to select τ on the basis of the desired range between the maximum drug concentration, C_{max}, and the minimum drug concentration, C_{min}, over a dosing interval, τ_c (τ_c optimized with respect to concentrations), e.g., as follows:

$$\text{Method II: } \tau_c = \frac{\ln (C_{max}/C_{min})}{K}$$

where K is the first-order elimination rate constant. Maintenance doses, D_M, and loading doses, D_L, are then determined based on pharmacokinetic principles so that the desired drug concentrations are achieved. Note that drug dosage

so that the desired drug concentrations are achieved. Note that drug dosage regimens thus designed are at best only indirectly optimized for the desired range in pharmacological effect between doses.

A more idealized approach would be to base the selection of τ on the basis of the desired range in pharmacological effect over a dosing interval, τ_e (τ optimized with respect to pharmacologic effect). Such relationships have been derived by one of us (Dr. Bjornsson). In the simplest case, τ_e can be determined as follows:

$$\text{Method III: } \tau_e = \frac{(\Delta E/m)}{K} = 1.44\ (\Delta E/m)\ t_{1/2}$$

where ΔE is the desired range in the pharmacological effect between doses, e.g., between 60% and 20% effect, m is the slope of the effect vs ln drug concentration relationship, and K and $t_{1/2}$ are as defined above. Note that this approach combines information obtained from both pharmacokinetic and pharmacodynamic studies. D_M and D_L can subsequently be determined using pharmacokinetic principles.

Examination of Methods II and III reveals that for any given value of ΔE, τ_e is determined, in addition to K or $t_{1/2}$ by the slope of the drug concentration vs response curve. Thus, the optimal dosing interval can be considerably longer than the elimination half-life for a drug with a shallow dose-response curve, and vice versa, the optimal dosing interval can be considerably shorter than the elimination half-life for a drug with a shallow dose-response curve. In addition to these pharmacokinetic and pharmacodynamic factors, however, other factors have to be considered in the design of the optimal drug dosage regimen. These factors include interpatient pharmacokinetic and pharmacodynamic variabilities, therapeutic index, toxic concentrations, time-dependency of pharmacologic effect, and convenience or patient acceptance of the dosage regimen.

We had proposed to devise an algorithm for designing optimal drug dosage regimens, taking into account the various kinetic, dynamic, and patient factors. In principle such an algorithm can be relatively simple, as it involves simple optimization procedures based on Methods II/III. We had anticipated to identify published pharmacokinetic/pharmacodynamic data in the public domain which could be used to help design and illustrate the approach. However, we were unable to identify a useful data set, and this project was therefore not pursued at the present time. This is justified as more theoretical work will now need to be done on this approach in order to overcome the lack of useful data. We plan to continue our work on this exciting project in the near future.

K. Special Requests for Data Analysis

In addition to the work outlined above on both continuing improvements of existing programs and developments of new programs, several special requests for data analysis were made by the contracting Officer's Technical Representative. These have included the following Special Reports, which have been sent to the COTR:

1. Data Analysis and Report on a Mefloquine Bioavailability Study Comparing Formulations E443 and B514.

2. Data Analysis and Report on a Mefloquine Bioavailability Study Comparing Formulations from Lafayette Pharmacal and Hoffman-La Roche.

3. Data Analysis and Report on Blood Chemistry and Hematology Studies after Mefloquine.

4. Data Analysis and Report on a Study on Methemoglobinemia Caused by Primaquine and Four Other Pharmacological Agents.

5. Data Analysis of Ribavirin Concentrations in Red Blood Cells and Plasma.

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