PEDA: A MICROCOMPUTER PROGRAM FOR PARAMETER ESTIMATION AND DOSAGE ADJUSTMENT IN CLINICAL PRACTICE

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(Received May 22, 1987)

PEDA, an integrated program in BASIC for implementation on microcomputers, has been developed for use in clinical practice to assist dosage adjustment for individual patients. A parameter optimization for individual patients is based on the principle of Bayes' theory and Maximum Likelihood Estimation, and utilizes a prior information on the distribution of population pharmacokinetic parameters, means and variances, as well as serum drug concentrations. The program can accommodate a one-compartment open linear model and a non-linear model at steady state (Michaelis-Menten model) and handle both uniform and non-uniform multiple dosage regimens mostly arising from clinical settings. Clinical examples which demonstrate the ability and the flexibility of the program are provided. The program may also be used as an aid for instruction in clinical pharmacokinetics.

Keywords — Bayesian method; Maximum Likelihood Estimation; microcomputer; PEDA; blood levels; computer simulation; dosage regimen; gentamicin; phenytoin; lithium

INTRODUCTION

Serum drug concentration is a useful indicator of clinical efficacy for many drugs with narrow therapeutic indices in clinical practice. Unlike many other laboratory results, drug concentrations vary with time, depending on the mode of drug administration and pharmacokinetic parameters. Thus, in clinical practice, the wide use of pharmacokinetic calculation is necessary for reasonable interpretation of drug concentration data for each individual patient.

At present, a number of equations that describe pharmacokinetic behavior of drugs are available and are useful in predicting serum drug concentrations. Interindividual variability in pharmacokinetic parameters often makes it necessary to estimate pharmacokinetic parameters for each individual patient before predicting drug concentrations or making recommendations. Given sufficient drug concentration measurements, pharmacokinetic equations can be employed to estimate pharmacokinetic parameters using an appropriate method such as a linear or a non-linear least squares fitting method. At least four or five concentrations are necessary for accuracy and precision of prediction. In a routine clinical setting, unfortunately, very few serum drug concentration measurements, one or two

points, can be obtained because of assay costs or patient injuries. Moreover, in the real situation of patient care, doses may be missed or doubled, a dosage regimen may be changed frequently or more than one dosage regimen may be administered until a steady state is achieved. Thus, a complex dosing schedule may be formed. In addition, the clinical status of the patient may make it undesirable to wait for determination of drug concentrations until a steady state is achieved; *i.e.*, during the four to five half-lives as indicated in a standard sampling protocol. That is, a real case in a clinical setting rarely follows an ideal situation where pharmacokinetic interpretation, parameter estimation or dosage calculation can be done easily.

Several methods (deterministic type) have been proposed to estimate pharmacokinetic parameters using a few measurements to calculate dosage requirements, but most deal with steady state or restricted dosing schedules.¹⁾ Sheiner *et al.* have presented an implementation of the Bayesian algorithm for parameter estimation procedure on a stochastic basis.^{2,3)} This technique can work with as few as one drug concentration measurement.

We have previously presented microcomputer programs for simulation of concentration-

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time curves for various clinical conditions as mentioned above and also a preliminary microcomputer program for the Bayesian regression method.⁴⁾ In our experience, however, these programs did not provide adequate practicality in clinical use because they were separate modules which failed to work interactively (several microcomputer programs also have this problem) and, thus were time consuming. Yamaoka *et al.* also have presented a modified version of MULTI for Bayesian regression analysis.⁵⁾ However, this program is not easy to use in clinical settings because of the need to define pharmacokinetic equations in the program prior to analysis. Therefore, we developed a program on a microcomputer which integrated these modules to work interactively and provided support for the Therapeutic Drug Monitoring Service with ease in the process of pharmacokinetic calculations. The desired features of the program were as follows:

1. ability to describe and simulate any dosing schedule in clinical settings,
2. ability to estimate patient specific parameters from at least one observation by using the Bayesian algorithm,
3. ability to calculate dosage requirements based on desired concentration and population mean and/or patient specific pharmacokinetic parameters,
4. practicality of routine use by individuals without programming background.

The program was given the name PEDAs (Parameter Estimation and Dosage Adjustment).

THEORETICAL

Pharmacokinetic Models and Equations

The program includes four subroutines (FUNCS) for pharmacokinetic calculations requiring simulated drug concentrations. The first three of them are for multiple dosage regimens, in which the pharmacokinetic model employed is a one-compartment open linear model with an input function appropriate to the mode of drug administration, and the last is for a drug which obeys non-linear kinetics such as phenytoin.

FUNC I—This subroutine is used for uniform multiple dosage regimens. Throughout each dosing interval, the dose, the bioavailability and the route of administration are unchanged. The serum drug concentration after *I*th dosage

during multiple dosing, at a uniform dosing interval, is described by one of the following equations depending on the mode of administration.⁶⁾

For intravenous bolus;

$$C_p(I, t) = \frac{D}{V_d} \left(\frac{1 - e^{-I \cdot K_e \cdot \tau}}{1 - e^{-K_e \cdot \tau}} \right) e^{-K_e \cdot t} \quad (1)$$

For oral (or intramuscular) administration;

$$C_p(I, t) = \frac{F \cdot D \cdot K_a}{V_d (K_a - K_e)} \left\{ \left(\frac{1 - e^{-I \cdot K_e \cdot \tau}}{1 - e^{-K_e \cdot \tau}} \right) e^{-K_e \cdot t} - \left(\frac{1 - e^{-I \cdot K_a \cdot \tau}}{1 - e^{-K_a \cdot \tau}} \right) e^{-K_a \cdot t} \right\} \quad (2)$$

During the upswing after the start of the *I*th infusion ($t \leq T$);

$$C_p(I, t) = \frac{D}{T \cdot V_d \cdot K_e} \left[1 - e^{-K_e \cdot t} - \left(\frac{1 - e^{-(I-1)K_e \cdot \tau}}{1 - e^{-K_e \cdot \tau}} \right) \{ e^{-K_e(t+\tau)} - e^{-K_e(t+\tau-T)} \} \right] \quad (3)$$

During the downswing after the start of the *I*th infusion ($t \geq T$);

$$C_p(I, t) = \frac{D}{T \cdot V_d \cdot K_e} \left(\frac{1 - e^{-K_e \cdot \tau}}{1 - e^{-K_e \cdot \tau}} \right) [e^{-K_e(t-T)} - e^{-K_e \cdot t}] \quad (4)$$

where *I* is number of dosing and $C_p(I, t)$ is the drug concentration at time *t* in the *I*th dosing interval. *F* is the bioavailability, *D* is the maintenance dose, τ is the dosing interval, *T* is the infusion time, K_e is the elimination rate constant, V_d is the volume of distribution, and K_a is the absorption rate constant. The program needs the entry of *CL* (total body clearance) but K_e , prior to calculation, is introduced to the above equations by the formula: $K_e = CL/V_d$. This subroutine is operated by a flag for routes of administration and with at most three model parameters.

FUNC II—This subroutine can deal with non-uniform multiple dosage regimens. Throughout each dosage interval unequally spaced, a dose or a route of administration may

be changed. In such cases, depending on the mode of administration for I th dose, the serum drug concentration after I th dose can be described by one of the following equations:⁷⁾

For intravenous bolus;

$$C_p(I, t) = C_o(I)e^{-K_e t} + \frac{D(I)}{V_d} e^{-K_e t} \quad (5)$$

For oral (or intramuscular) administration;

$$C_p(I, t) = C_o(I)e^{-K_e t} + \frac{F \cdot D(I) \cdot K_a}{V_d (K_a - K_e)} (e^{-K_e t} - e^{-K_a t}) \quad (6)$$

During the upswing after the start of the I th infusion ($t \leq T$);

$$C_p(I, t) = C_o(I)e^{-K_e t} + \frac{D(I)}{T \cdot V_d \cdot K_e} (1 - e^{-K_e t}) \quad (7)$$

During the downswing after the start of the I th infusion ($t \geq T$);

$$C_p(I, t) = C_o(I)e^{-K_e t} + \frac{D(I)}{T \cdot V_d \cdot K_e} (1 - e^{-K_e T}) e^{-K_e (t-T)} \quad (8)$$

where $C_p(I, t)$ is the drug concentration at time t in the I th dosing interval. $C_o(I)$ represents the expected serum drug concentration at the start of the I th dosing interval. $C_o(I)$ is the function of the past dosing schedule and is calculated subsequently from the initial level (C_o). To obtain C_o , either the measured or the estimated concentration can be utilized. For the latter case, the estimation of C_o is carried out by using FUNC I or FUNC III. The ability of the combined use of these FUNCs provides the facility to handle the patient's data especially in the case where no details of a prior dosing schedule were given. Usually, C_o is handled as one of the model parameters. Therefore, FUNC II is operated with four parameters in addition to the three parameters as described for FUNC I.

For sustained-release preparations, the equations for intravenous infusion, Eq.(3), (4), (7) and (8), can also be used by substituting the infu-

sion time T with the time of peak concentration observed in oral administration.

FUNC III — The last subroutine for multiple dosage regimens is for a non-uniform but periodic dosage regimen. In a clinical setting, mostly for outpatients, the dosage regimens in a non-uniform manner are repeated for a period of 24 h. FUNC III is for such cases. Under this condition, the serum drug concentration in any period can be described by Eq.(9-1), (9-2), and (9-3):⁴⁾

$$C_p(I, t) = \sum_{i=1}^n f(I, D_i, t_i, R_I \sim R_m, P_I \sim P_m) \quad (9-1)$$

$$R_m = \frac{1 - e^{-P_m \cdot 24}}{1 - e^{-P_m \cdot 24}} \quad (9-2)$$

$$t_i = t - \sum_{j=0}^{i-1} \tau_j; \quad \sum_{i=1}^n \tau_i = 24; \quad (9-3)$$

if $t_i < 0$, $t_i = t_i + 24$

where I is the number of periods, n is the number of dosing intervals in the period of 24 h and the sum of each dosing interval equals the length of the period. $C_p(I, t)$ is the serum drug concentration at time t , time from the start of 1st dosage in the I th period. In the construction of the model for this case, the doses administered at the same time of each period during multiple dosing can be considered as doses given every 24 h period. Since there are n doses every period and each is administered at specific time of each period, n independent dosage regimens with a uniform dosing interval of 24 h are formed. The number of model parameters and the abbreviations are the same as those described in FUNC I. The function is given by one of the equations included in FUNC I by substituting τ with the period.

A function like FUNC III can not be found in any program previously reported.^{5,7,8)} This subroutine provides more practicality in the management of outpatients because they are often treated on a non-uniform but periodic multiple dosage regimen.

FUNC IV — A drug such as phenytoin can not be described by the equations described above. The serum concentration of phenytoin at steady state is given by the following:

$$C_{ss} = \frac{K_m D}{V_{max} - D} \quad (10)$$

where C_{ss} is serum concentration at steady state in $\mu\text{g/ml}$, D is the maintenance dose in mg/d . K_m is the Michaelis constant in $\mu\text{g/ml}$ and $V_{\max}$ is the maximum velocity of metabolic clearance in mg/d . This subroutine operates this case.

These four functions are defined from line 10000 in PEDDA and are listed in Appendix A.

Parameter Optimization

The main task of PEDDA is to calculate the most likely set of parameters for an individual. This is carried out by a procedure based on the principle of Bayes' Theory and the application of Maximum Likelihood Estimation technique. If we can define the prior distribution of a set of parameters in the general population, then one or more measurements from an individual can be used to obtain the posterior distribution of the set of parameters. The theoretical basis for the objective function used in Bayesian forecasting has been described in detail elsewhere.^{2,3)}

Bayesian Objective Functions

The method proposed by Sheiner *et al.* for obtaining pharmacokinetic parameter estimates that are revised from initial population- or subpopulation-based estimates requires minimization of the following objective function:^{8,9)}

$$O_{bj} = \sum_{j=1}^m \frac{(P_j - \hat{P}_j)^2}{\sigma_{pj}^2} + \sum_{i=1}^n \frac{(C_i - \hat{C}_i)^2}{\sigma_{ci}^2} \quad (11)$$

where P_j is the estimate of parameter, $\hat{P}_j$ is the population mean of the parameter, m is the total number of parameters to be revised, C_i is drug concentration measurement, $\hat{C}_i$ is the expected drug concentration at time t , given the parameter values $P_1 - P_j$ and the dosing history, and n is the number of measurements. σ_{pj}^2 is the prior, interindividual variance of the P_j and σ_{ci}^2 is referred to as the conditional, residual error variance of the C_i attributable to both assay error and intraindividual variability.

Equation (11) assumes that: (1) each parameter P_j is normally distributed with the mean $\hat{P}_j$ and variance σ_{pj}^2 in the population, (2) the parameters are independent, although this restriction may be relaxed, (3) each measurement C_i is normally distributed with the mean $\hat{C}_i$ and variance σ_{ci}^2 , and (4) the measurements are independent. Equation (12) assumes a log-normal distribution for parameter values:

$$O_{bj} = \sum_{j=1}^m \frac{\{\ln(P_j) - \ln(\hat{P}_j)\}^2}{\sigma_{\ln(pj)}^2} + \sum_{i=1}^n \frac{(C_i - \hat{C}_i)^2}{\sigma_{ci}^2} \quad (12)$$

The user can select the objective function in the program. The standard deviation (SD) of $\ln(P_j)$ in Eq.(12) is approximately equal to the value of the coefficient of variation (CV) itself (*i.e.*, $\sigma_{\ln(pj)} = \text{CV}$). In our experience, there is no difference between the above two objective functions with respect to the resulting predictive performance.²⁸⁾

The objective functions are minimized with a Gauss-Newton method with a damping factor.¹⁰⁾

In PEDDA, the partial derivative required in this method is calculated numerically by the following (see lines from 4370 in Appendix B):

$$Pd_i = \frac{fc_i(1.01 P_j) - fc_i(P_j)}{0.01 P_j} \quad (13)$$

where Pd_i is the partial derivative with respect to P_j and fc_i is the expected value for each data point C_i as a function of each parameter. Equation (13) requires only one calculation to obtain the partial derivative for each data point for each parameter, while other programs such as MULTI¹⁵⁾ require two calculations to do so. This advantage provides a shortening of the time required for each iteration and, therefore, the shortening of over-all execution time (the time required from data input to results output is reduced by approximately 25% by using Eq.(13)).

In the fitting process, the user can also select the parameter to revise in this program. In other words, the user can select a parameter to be fixed at an initial population estimate. This option has an advantage, especially in using FUNC II. If no details about dosing history is available, often due to variable noncompliance by outpatients, the initial estimate of C_0 should be revised as a patient-specific parameter with an appropriate weighting (this is described later). In the case where great certainty about the dosing schedule of a hospitalized patients exists, C_0 may be fixed at starting measured concentration.

Initial Parameter Estimates Based on Population

The expected values of the population mean pharmacokinetic parameters are available from

various sources. In the Bayesian procedure, the better the initial parameter estimates, the more sensible will be the parameter optimization. Therefore, this leads us not merely to define population values but also, if possible, to define subpopulation values based on demographic variables such as age, sex, weight, cardiac status and renal function. This can be achieved by a process of linear modeling such as has been exemplified by Jusko *et al.*¹¹⁾ or multiplying an average value (*e.g.*, clearance) by an appropriate "condition correcting factor".¹²⁾ Another achievement will be the use of population values obtained by the technique of population pharmacokinetics.¹³⁾ NONMEM which was recently developed will provide useful informations in the future.

Like mean values, estimates of variance for each parameter must be obtained. Peck *et al.* have set the population standard deviation of clearance at 50% as CV%, and that of volume of distribution at 20%, for theophylline.¹⁴⁾ As previously discussed for many pharmacokinetic parameters, the coefficient of variation of inter-individual variability is on the order of 20–50%, with volume of distribution often at the lower value and clearance at the upper value.⁹⁾ These variances have also been applied to the other drugs but their values will be altered as more data become available. When predicted concentration is used as the parameter, C_0 in FUNC II, the standard deviation of C_0 is usually set at 70% of the predicted value in order to reflect the uncertainties introduced by using population parameter values and possible non-compliance by outpatients. The selection of value of CV for C_0 is somewhat arbitrary and requires some experimentation.

Weighting of Measured Concentrations

The CV of the measured drug concentration is usually set at 10–15% of the measured value in order to account for analytical errors in the range of concentrations encountered clinically, any model misspecification or sampling time error. It is assumed that each parameter remains constant throughout the period of monitoring. However, in the case where more than two drug concentrations over several periods are available, the assumption as mentioned above may be unreasonable considering the temporal change of patient's disease or pharmacokinetic condition. Because the most recent observation must be the

most relevant to the current state of the patient, it is not appropriate to set the CV of each observation at the same magnitude in proportion to the observed value only, *i.e.*, further apart from the most recent observation, a greater reduction must be made in the weighting. Decreasing the weight for old data in the adaptive control systems was first proposed by Kalman (through the reference 15). Peck *et al.* have introduced a time dependent weighting factor for theophylline¹⁴⁾ and Vozeh *et al.* for lidocaine.¹⁵⁾

The effect of time is added to the CV of concentration by the following equation:

$$\sigma_{c_j} = Q^T CV C_j \quad (14)$$

where σ_{c_j} is the final SD of C_j , Q is the variable component with the drug of concern: *e.g.*, 1.01 for theophylline¹⁴⁾ and 1.005 for lidocaine,¹⁵⁾ C_j is the observed value, CV is the coefficient of variation of the most recent observation, and T is time in hours before the most recent observation. The upper limit on Eq.(14) was arbitrarily set at 0.5, corresponding approximately to the inter-individual variability in total body clearance for many drugs.

When drug concentration measurement is used as C_0 in FUNC II, the CV of C_0 is set in the same manner described here. PEDA provides five variations for the weighting function of measured concentrations (with unity, reciprocal of C_j , reciprocal of C_j^2 , incorporating of time dependent factor, or CV itself as a percent value). The weighting function can be selected from those by the user's option in the fitting process.

User's options described in this section were provided to assist in the understanding of the Bayesian procedure.

PROGRAM DESCRIPTION

The program has been implemented on both CASIO FP-6000 and NEC PC-9801 microcomputers. The program consists of interactive eight subprograms written in BASIC programming language and occupies 38K byte of random access memory as text area (version 1.32). The program can be executed on other microcomputers with slight modifications with respect to the commands for display work.

Figure 1 and 2 show the flowchart of PEDA and the menu of the main facilities of this pack-

FIG. 1. *Flowchart of PEDA's Major Functions*

[MODE=job menu PARAMETER=revised SCHEDULE=current FUNCTION=func2]

select the job with <function> key

» instruction for function keys—job menu «

- F1 — <INPUT> : data entry and initialize
- F2 — <DISPL> : display of data entered and calculated on CRT
- F3 — <CORRE> : correct and edit of data entered
- F4 — <PRINT> : print out of data entered and calculated on Printer
- F5 — <HELP> : instruction for function keys
- F6 — <CURVE> : generation of simulated curves
- F7 — <BAYES> : parameter estimation by Bayesian method
- F8 — <RECOM> : generation of recommended schedules
- F9 — <PREDI> : prediction of serum concentrations
- F10 — < > : undefined

INPUT DISPL CORRE PRINT HELP CURVE BAYES RECOM PREDI

FIG. 2. *Display of the 9 Options Available in the PEDA*

The upper part of the CRT display shows the current status of the program run and the lower part shows FUNCTION keys defined.

age flashed on the CRT display with HELP mode. The HELP mode gives the user the function definitions on the FUNCTION keys. The program is operated by selecting the routine required from those using FUNCTION keys. The

user is prompted to enter data by the questions asked on the CRT display.

Data entry (INPUT mode) requires the selection of pharmacokinetic model pre-programmed (see Pharmacokinetic Models and Equations section), patient demographic variables (age, weight and height *etc.*), details of current dosing history (dose, route, bioavailability and dosing interval), number of measurements, measured drug concentrations, their corresponding sampling times and population (or subpopulation) based parameter estimates.

Using CORRE mode, the user can correct or edit the data easily as necessary: *e.g.*, modification of either current or recommended dosage regimen. The entered or resulting data can be printed out on a serial-printer (PRINT mode) or displayed on the CRT (DISPL mode) in a similar format.

Figure 3 shows the flow diagram of subroutine BAYES. In the execution of the Bayesian

FIG. 3. Flow Diagram of Subroutine BAYES

The diagram outlines the various decisions (6 sided boxes) and operation (rectangle) steps involved in the subroutine BAYES described in the text. Arrows indicate the flow of program operation at steps of decision. Otherwise, flow is from the top to the bottom of the diagram. N_p refers to the number of model parameters.

profile of pharmacokinetic parameter (gentamicin)

valueM : population mean parameter
valueR : revised parameter by Bayesian
diff : % of (valueR-valueM)/valueM
SD : from inverse matrix
wgt : CV% in weighting

	valueM	valueR	diff	SD%	wgt
initial level	0.050	0.050	0.0	0%	0%
clearance (l/h)	0.638	0.512	-19.7	6%	50%
dist. vol (l)	12.240	10.842	-11.4	13%	20%
k_a (1/h)	1.790	1.790	0.0	0%	0%
$T_{1/2}$ (h)	13.300	14.673			

profile of serum levels

levelO : observed serum levels
levelM : predicted serum level by population means
levelR : predicted serum level by revised parameters
valueM : % of (levelM-levelO)/levelO
valueR : % of (levelR-levelO)/levelO

No	dose#	time	levelO	levelM	levelR	valueM	valueR	wgt
1	3	18.8	2.500	1.996	2.638	-20.2%	5.5%	15%
2	4	1.5	6.000	4.151	5.073	-30.8%	-15.4%	15%

FIG. 4. Example of Computer Output on Printer

Population mean values and the Bayesian estimates derived from two concentration measurements in Case I. Details are described in the section of Applications for patient S. S.

FIG. 5. Flow Diagram of Subroutine RECOM
The representation is the same as the one described in Fig. 3.

method (BAYES mode), prior to the fitting process, definition of type of error distribution, selection of parameters to revise and weighting of both parameters and measured concentrations are required as described in the section of Parameter Optimization. Thereafter, PEDA iterates until the Bayesian objective function is minimized. The program of subroutine BAYES are listed in Appendix B. Figure 4 shows an example of computer output after BAYES mode.

For recommendations (RECOM mode, see Fig. 5), the user can select the desired peak and trough concentrations (for FUNC III, the desired average concentration in the period

must be entered), and the program will provide a dosage regimen based on either population mean pharmacokinetic parameters or revised pharmacokinetic parameters by BAYES mode.

Prediction of serum concentrations (PREDI mode) or generation of simulated curves (CURVE mode) are obtainable with either population mean pharmacokinetic parameters or the Bayesian estimates, and for either current dosing schedule or recommended dosing schedule. Figure 6 shows the flow diagram of subroutine CURVE.

In INPUT, CORRE, PREDI, DISPL and PRINT modes, according to the subroutine FUNC selected, the questions on the CRT display slightly differ with each other. The program's full listings and the diskette are available from the first author upon request.

APPLICATIONS

The following cases were selected to demonstrate the utility of the PEDA program in clinical practice.

Case I — S.S. was a 57-year-old male with suspected sepsis. His serum creatinine was 3.8 mg/dl, and his weight was 51 kg. The patient was given an initial dose of 80 mg gentamicin as an 1 h infusion in the Coronary Care Unit. Fourteen hours later, an additional three doses of 30 mg were given subsequently as 1 h infusions in unequally spaced intervals: 13 h between the 1st and 2nd doses, 19 h between the 2nd and 3rd doses, and 16 h between the 3rd and 4th doses. Two blood samples were obtained just before and 1.5 h after the 4th dose. The gentamicin concentrations were 2.5 $\mu\text{g/ml}$ and 6.0 $\mu\text{g/ml}$, respectively. These events and the FUNC II were used to estimate his gentamicin parameters.

Gentamicin pharmacokinetics has been described by one- and multi-compartment models.¹⁶⁾ While the multi-compartment models are more accurate in describing gentamicin pharmacokinetics, the one-compartment model has been shown to be useful in accurately predicting serum gentamicin concentrations in clinical settings.¹⁷⁾ The Sawchuk and Zaske method,¹⁸⁾ based on the one-compartment model, is one of the most widely used dosing methods for gentamicin. However, this method requires at least 3 concentration measurements to adjust the dosage of gentamicin. Hence, this is a case where the Bayesian method was applica-

FIG. 6. Flow Diagram of Subroutine CURVE
The representation is the same as the one described in Fig. 3.

ble. Initial population-based parameter estimates were selected on the basis of the one-compartment model: $CL = 0.638$ l/h; $V_d = 12.24$ l. CL was obtained as the product of K_e and V_d . Based on creatinine clearance (CL_{cr} derived from Cockcroft's equation¹⁹); his CL_{cr} was 15.5 ml/min), K_e was estimated from the following equation:²⁰

$$K_e = 0.015 + 0.00238 CL_{cr}$$

V_d was obtained by using the following equation on the basis of actual body weight (ABW in kilogram):

$$V_d = 0.24 ABW$$

C_0 was set at zero because there was no previous dosing of gentamicin. However, C_0 was actually converted to 0.05 to avoid the division by zero in the fitting process. Final Bayesian parameter estimates were: $CL = 0.512$ l/h; $V_d = 10.84$ l; $C_0 = 0.05$ μ g/ml, and estimated half life was 14.7 h (see Fig. 4). According to these revised parameters, it was recommended that a 80 mg gentamicin as an 1 h infusion every 48 h would produce a peak concentration of 8.05 μ g/ml and a trough of 0.88 μ g/ml. Following this recommendation, the dosing schedule was changed and two blood samples were taken at 6 h and 18 h. The observed concentrations were 5.9 and 3.3 μ g/ml, respectively, which were nearly identical to those predicted (6.2 and 3.5

FIG. 7. *Simulated Serum Gentamicin Concentrations Resulting from the Dosage History Described in the Text for Patient S. S.*

Open circles are observed concentrations used in the PEDA (FUNC II) to estimate patient specific parameters. Closed circles are subsequent observed concentrations. Closed square is the initial concentration.

FIG. 8. *Simulated Serum Lithium Concentrations Resulting from the Dosage History Described in the Text for Patient M. H.*

Open circle is the observed concentration used in the PEDA (FUNC III) to estimate patient specific parameters. Closed circle is the subsequent observed concentration.

µg/ml, respectively). The simulated concentration vs. time curve is shown in Fig. 7.

Case II — This is a case where FUNC III was used. M.H. was a 25-year-old female with a typical psychosis, and her weight was 65 kg. She was taking an oral dose of 200 mg of lithium carbonate three times daily at 8 a.m., 12 noon and 6 p.m. She was admitted to the Department of Psychiatry in poor control. Noncompliance was suspected from the observed lithium concentration which was nearly zero at admission. The patient was then hospitalized with the same dosing schedule as above. Two days later, a blood sample was taken 15 h after the third dose in the day (just before the first dose in the next day; one day refers to one period in this case). The lithium concentration was 0.29 mEq/l. The current dosing schedule and the observed concentration were used to obtain the patient's specific parameters.

Initial population-based parameter estimates were: $CL = 1.405$ l/h; $V_d = 51.35$ l. CL and V_d were calculated by the following equations, respectively:²¹⁾

$$CL = 0.021 \text{ ABW}$$

$$V_d = 0.79 \text{ ABW}$$

K_a was set at 1.5 h^{-1} arbitrarily. Final parameter estimates by the Bayesian procedure were:

$CL = 1.565$ l/h; $V_d = 51.4$ l; $K_a = 1.51 \text{ h}^{-1}$. Once the revised parameters were obtained, the program can calculate the daily dosage requirement following the desired average concentration in a day. It was recommended that four divided doses of 1000 mg Li_2CO_3 daily, 200 mg at morning, 200 mg at noon, 200 mg at evening and 400 mg at bed time, would produce 0.69 mEq/l as an average concentration in a day. The serum lithium concentration was determined at 48 h after the change in the dosing schedule. The measured concentration showed 0.54 mEq/l nearly identical to the predicted value (0.59 mEq/l). Figure 8 shows the simulated concentration vs. time curve.

Case III — K.K. was a 34-year-old male with epilepsy and his weight was 53 kg. He had been started with 50 mg phenytoin *p.o.* twice daily for control of seizure. Two weeks after the initiation of therapy, the plasma phenytoin concentration was 2.4 µg/ml and he was not well controlled. Then, the phenytoin dose was increased to 150 mg by physician's opinion. Approximately one month later, the patient's serum phenytoin concentration was 4.3 µg/ml showing no improvement in occurrence of seizures. At this time, the patient's parameters for phenytoin were estimated by the Bayesian procedure using two observed points upon the physician's request. Initial population-based

FIG. 9. Dose-Serum Concentration Curve of Phenytoin for Patient K.K.

Open circles are observed concentrations used in the PEDa (FUNC IV) to estimate patient specific parameters. Closed circle is the subsequent concentration. Broken line shows the dose-serum concentration curve obtained from the population mean values.

parameter estimates were: $K_m = 3.8 \mu\text{g/ml}$; $V_{\max} = 351 \text{ mg/d}$. The CV of 15% and 50% were used in weighting of the recent and previous observations, respectively (see Weighting of Measured Concentrations). The K_m obtained was based on his age and $V_{\max}$ was estimated from the following equation:²²⁾

$$V_{\max} = 415 (\text{ABW}/70)^{0.6}$$

Final Bayesian parameter estimates were: $K_m = 4.7 \mu\text{g/ml}$; $V_{\max} = 318 \text{ mg/d}$. On the basis of the revised parameters, it was predicted that 200 mg phenytoin daily would produce $8.0 \mu\text{g/ml}$ of plasma concentration at steady state. One and half months after the readjustment of the dosage, the patient showed improvement with $7.3 \mu\text{g/ml}$ of serum phenytoin concentration. Figure 9 shows the dose vs. concentration curve.

DISCUSSIONS

The examples presented in this article demonstrate the ability of the PEDa program to deal with several different cases, where dosing schedules were complex with regard to route, size and frequency of administration or where steady state was not achieved. Three subroutines included for the multiple dosing regimen provided us the facility to handle various dosing schedules. The flexibility of the program will be valuable in real clinical settings, since dose ad-

ministration and sample collection rarely follow ideal schedules.

The pharmacokinetic models used at present are one-compartment open linear models, but other pharmacokinetic models, such as two-compartment open linear models, non-linear models with certain numerical integration methods, or pharmacokinetic-dynamic models may also be used with appropriate program modifications.

The selection of CV of observations as well as those of parameters are very important in the Bayesian method. For instance, given the reduction of CV for observation by 50% in Case I (from 15% to 5%), the estimated CL and V_d were lower than those obtained with 15% of CV concentration measurements by 10–20%: CL was lowered from 0.512 to 0.471 l/h and V_d from 10.84 to 7.97 l. As less CV was given (i.e., carrying more weight to concentration measurements), the estimates of the parameters achieved were similar to those obtained by ordinary weighted non-linear least squares fitting methods.

Regarding the uncertainties due mostly to unreliable dosing history in outpatients (e.g., non-compliance), the interpretation of initial concentration, C_0 , in FUNC II is more difficult to define. Such uncertainties are more reflected to the estimate of C_0 with increasing of the standard deviation of C_0 . A reasonable background for the selection of the standard deviation of C_0 must be clarified. On the other hand, the equations in both FUNC I and FUNC III do not contain the term C_0 . Thus, those uncertainties may be reflected to mainly the estimate of clearance in the case of using FUNC I and FUNC III. We are now investigating the possibility of incorporating a function accounting for the uncertainties.

In recent years, programs for microcomputers in which the Bayesian procedure is involved have been presented: ADVISE by Sheiner,⁸⁾ Peck *et al.*¹⁴⁾; OPT by Kelman *et al.*⁷⁾ The superiority of the Bayesian procedure for the accuracy and precision of predictions has been demonstrated by both retrospective and prospective analyses with various drugs such as digoxin,²³⁾ theophylline,²⁴⁾ aminoglycoside²⁵⁾ and lidocaine,²⁶⁾ using these programs or slightly modified versions or other programs. By using the linearized Bayesian procedure in which the

algorithm differed slightly from that described above, Vozeh *et al.* have also reported good predictive performance for phenytoin dosage adjustments.²⁷⁾ However, as discussed in their report, there are several problems still remaining to improve the predictive performance of the Bayesian procedure. Additional investigations are needed to evaluate the predictive performance regarding the minimum number of sam-

ples required and the selection of best sampling schedules to give clinically useful estimates. In addition, the assessment of the effect of the selection of population pharmacokinetic parameters (*i.e.*, means and their variances) on predictive performance of the Bayesian procedure is also required. An evaluation study²⁸⁾ of the predictive ability of the Bayesian method in our institution will be published subsequently.

APPENDIX A. Program List of Subroutine FUNCs

```

10000 ' **** DEFINED FUNCTIONS FOR MULTIPLE DOSING ****
10010 ' DO(,):dose, F(,):availability, FS(,):conversion factor
10020 ' R%(,):flag for route of administration
10020 '
10025 ' FUNC1 ---- Cp=f(CL,Vd,Ka...) ----
10025 ' N0=dosing number, T=time from last dose
10030 ' P(RV,1)=CL, P(RV,2)=Vd, P(RV,3)=Ka, K0=Ke
10030 N0=DD%(J2):T=TX(B%+J2)
10040 K0=P(RV,1)/P(RV,2):I%=1:GOSUB 10110
10050 DB=DO(RS,I%)*F(RS,I%)*FS(RS,I%)
10060 ON R%(RS,I%) GOSUB 10630,10640,10650,10650:CP=CZ:RETURN
10105 ' calculation of cumulation factor for FUNC1
10110 K1=(1-EXP(-N0*K0*TR(RS)))/(1-EXP(-K0*TR(RS)))
10120 K2=(1-EXP(-N0*P(RV,3)*TR(RS)))/(1-EXP(-P(RV,3)*TR(RS)))
10130 IF R%(RS,I%)=3 THEN K3=(1-EXP(-(N0-1)*K0*TR(RS)))/(1-EXP(-K0*TR(RS)))
10140 RETURN
10150 '
10155 ' FUNC2 ---- Cp=f(Co,CL,Vd,Ka...) ----
10155 ' D2=dosing number, LT=time from last dose, C0=initial level
10160 ' P(RV,0)=C0, P(RV,1)=CL, P(RV,2)=Vd, P(RV,3)=Ka, K0=Ke
10160 D1=1:D2=D1%(B%+J2):LT=TX(B%+J2):C0=P(RV,0)
10170 K0=P(RV,1)/P(RV,2)
10180 FOR I%=D1 TO D2:DB=DO(RS,I%)*F(RS,I%)*FS(RS,I%)
10190 IF I%=D2 THEN T=LT ELSE T=LT(RS,I%+1)
10200 CP=C0*EXP(-T*K0):ON R%(RS,I%) GOSUB 10590,10600,10610,10610
10210 C0=CP:NEXT I%:RETURN
10270 '
10275 ' FUNC3 ---- Cp=f(CL,Vd,Ka...) ----
10275 ' DD%=dosing period, LT=time from 1st dose in period
10280 ' P(RV,1)=CL, P(RV,2)=Vd, P(RV,3)=Ka, K0=Ke
10280 DD%=DD%(J2):LT=TX(B%+J2)
10290 K0=P(RV,1)/P(RV,2):GOSUB 10540:T0=0:CP=0
10300 FOR I%=1 TO DP%(RS):IJ%=1:DB=DO(RS,I%)*F(RS,I%)*FS(RS,I%):
10310 T0=T0+LT(RS,I%)
10310 IF LT<T0 THEN T=TR(RS)-T0+LT:IJ%=IJ%-1 ELSE T=LT-T0
10320 K1=K1(IJ%):K2=K2(IJ%):K3=K3(IJ%)
10330 ON R%(RS,I%) GOSUB 10630,10640,10650,10650
10340 CP=CP+CZ:NEXT:RETURN
10470 '
10470 ' FUNC4 ---- Cp=f(Km,Vmax...) ----

```

```

10475 '   LT=daily dose
      '   P(RV,1)=Km, P(RV,2)=Vmax
10480 LT=TX(B%+J2)
10490 CP=LT*P(RV,1)/(P(RV,2)-LT):RETURN
10535 ' calculation of cumulation factor for FUNC3
10540 IJ%=1:FOR N0=DD% TO DD%-1 STEP -1
10550 K1(IJ%)=(1-EXP(-N0*K0*TR(RS)))/(1-EXP(-K0*TR(RS)))
10560 K2(IJ%)=(1-EXP(-N0*P(RV,3)*TR(RS)))/(1-EXP(-P(RV,3)*TR(RS)))
10570 K3(IJ%)=(1-EXP(-(N0-1)*K0*TR(RS)))/(1-EXP(-K0*TR(RS)))
10580 IJ%=IJ%-1:NEXT:RETURN
10582 '
10585 ' ** PHARMACOKINETIC EQUATIONS FOR FUNC2 **
      '   for intravenous bolus
10590 CP=CP+DB/P(RV,2)*EXP(-K0*T):RETURN
10595 '   for oral/intramuscular administration
10600 CP=CP+DB*P(RV,3)/P(RV,2)/(P(RV,3)-K0)*(EXP(-K0*T)-EXP(-P(RV,3)*T)):
      RETURN
10605 '   for intravenous infusion
      '   TI(:):infusion time
10610 IF T<TI(RS,I%) THEN CP=CP+DB/TI(RS,I%)/P(RV,2)/K0*(1-EXP(-K0*T)):
      RETURN
10620 CP=CP+DB/TI(RS,I%)/P(RV,2)/K0*(1-EXP(-K0*TI(RS,I%)))*EXP(-K0*(T-TI(RS,I%))):
      RETURN
10625 ' ** PHARMACOKINETIC EQUATIONS FOR FUNC1 AND FUNC3
      '   for intravenous bolus
10630 CZ=K1*DB/P(RV,2)*EXP(-K0*T):RETURN
10635 '   for oral/intramuscular administration
10640 CZ=DB*P(RV,3)/P(RV,2)/(P(RV,3)-K0)*(K1*EXP(-K0*T)-K2*EXP(-P(RV,3)*T)):
      RETURN
10645 '   for intravenous infusion
10650 X=DB/TI(RS,I%)/P(RV,2)/K0:IF T<=TI(RS,I%) THEN 10660 ELSE 10670
10660 Y=T+TR(RS):Z=Y-TI(RS,I%):CZ=X*(1-EXP(-K0*T)-K3*(EXP(-K0*Y)-EXP(-K0*Z))):
      RETURN
10670 CZ=X*K1*(EXP(-K0*(T-TI(RS,I%)))-EXP(-K0*T)):RETURN

```

APPENDIX B. Program List of Subroutine BAYES

```

4000 '**** EXECUTION OF BAYESIAN ALGORITHM ****
4010 IF L0=0 THEN RETURN ' if no observation
4015 ' LINE 700 display of current status on CRT
      ' LINE 3260 definition of error distribution of parameters.
      ' DT%(flag for distribution: DT%=0;normal, DT%=1;log-normal)
4016 ' RS (flag for schedule: RS=0;current, RS=1;recommended)
      ' RV (flag for parameter: RV=0;mean, RV=1;revised)
4020 CLS:RS=0:RV=1:BA%=1:TI%=7:GOSUB 700:GOSUB 3260
4030 FOR I=0 TO P0:P(1,I)=P(0,I):NEXT:IF DT%=0 THEN 4060
4040 FOR I=0 TO P0:IF P(RV,I)<>0 THEN P(RV,I)=LOG(P(RV,I))
4050 NEXT
4055 ' LINE 1880 selection of parameter to revise and weighting.
      ' LINE 2000 selection of weighting function for Serum Levels.
      ' LINE 1500 calculation of weight for parameters and serum levels.
4060 GOSUB 1880:GOSUB 2000:GOSUB 1500
4070 COLOR 2,,0:PRINT"start !! wait a minute ";:COLOR 0,0,0,7:

```

```

PRINT:PRINT
4075 ' P(,) dimension of parameters
      ' P0   number of model parameters.
      ' PN   number of parameters to revise.
4080 FOR I=1 TO PN:A(I,0)=P(1,PX(I)):NEXT:GOSUB 4500:S1=SS:K%=1
4085 ' LINE 4500 calculation of sum of residuals.
      ' LINE 4340 creation of normal equation.
      ' LINE 4210 elimination with Pivot.
4090 GOSUB 4340:GOSUB 4210:DA%=0
4100 DA%=DA%+1:IF DA%>25 THEN 4170
4110 FOR I=1 TO PN:P(1,PX(I))=A(I,0)+A(I,PN+1):NEXT I:GOSUB 4500
4120 IF ABS(S1-SS)<=.001*S1 THEN 4170
4130 IF SS>S1 THEN FOR I=1 TO PN:A(I,PN+1)=.5*A(I,PN+1):NEXT I:GOTO 4100
4140 FOR I=1 TO PN:A(I,0)=P(1,PX(I)):NEXT I
4150 PRINT USING"iteration #  ##.##decrease of SS ";K%:(S1-SS)/S1*100:S1=SS
4160 K%=K%+1:IF K%<>100 THEN 4090
4170 GOSUB 4540:IF DT%=0 THEN 4200
4175 ' LINE 4540 calculation of inverse matrix.
4180 FOR I=0 TO P0:IF P(RV,I)<>0 THEN P(RV,I)=EXP(P(RV,I))
4190 NEXT
4195 ' LINE 4710 prediction of serum levels for observations.
      ' LINE 7620 prediction of serum levels at steady state.
4200 RV=1:GOSUB 4710:GOSUB 7620:CI(1,0)=P(1,0):PRINT:PRINT"executed.":
      GOTO 310 ' return to main menu
4205 '
4210 ' ** ELIMINATION WITH PIVOT **
4220 FOR KS=1 TO NP-1:WQ=0:FOR IS=KS TO NP
4230 IF ABS(A(IS,KS))>=WQ THEN JS=IS
4240 NEXT IS:IF JS=KS THEN 4260
4250 FOR IS=KS TO NP+1:SWAP A(KS,IS),A(JS,IS):NEXT IS
4260 FOR JS=KS+1 TO NP+1
4270 A(KS,JS)=A(KS,JS)/A(KS,KS):WQ=-A(KS,JS):IF WQ=0 THEN 4290
4280 FOR IS=KS+1 TO NP:A(IS,JS)=A(IS,JS)+A(IS,KS)*WQ:NEXT IS
4290 NEXT JS,KS
4300 A(NP,NP+1)=A(NP,NP+1)/A(NP,NP)
4310 FOR IS=2 TO NP:LS=NP-IS+1:WQ=-A(LS,NP+1)
4320 FOR JS=LS+1 TO NP:WQ=WQ+A(LS,JS)*A(JS,NP+1):NEXT JS
4330 A(LS,NP+1)=-WQ:NEXT IS:RETURN
4335 '
4340 ' ** CREATION OF NORMAL EQUATION **
4350 N%(0)=0:B%=0:FOR J1=1 TO 2:B%=B%+N%(J1-1)
4355 ' LINE 4650 calculation of serum levels.
      ' LINE 4640 return of parameter values.
4360 FOR J2=1 TO N%(J1):ON J1 GOSUB 4650,4640
4365 ' calculation of partial derivatives.
4370 ES(B%+J2,0)=CY(B%+J2)-CP:DD=CP
4380 FOR J3=1 TO PN:PT=P(1,PX(J3))
4390 P(1,PX(J3))=PT*1.01:ON J1 GOSUB 4650,4640
4400 ES(B%+J2,J3)=(CP-DD)/(PT*.01):P(1,PX(J3))=PT
4410 NEXT J3,J2,J1
4420 FOR J1=1 TO PN:FOR J2=1 TO PN:A(J1,J2)=0
4430 FOR J3=1 TO DN:A(J1,J2)=A(J1,J2)+ES(J3,J1)*ES(J3,J2)*WT(J3):NEXT J3
4440 A(J2,J1)=A(J1,J2):X(J1,J2)=A(J1,J2):X(J2,J1)=A(J1,J2):NEXT J2,J1
4450 '
4460 FOR J1=1 TO PN:A(J1,PN+1)=0:FOR J2=1 TO DN
4470 A(J1,PN+1)=A(J1,PN+1)+ES(J2,J1)*ES(J2,0)*WT(J2):NEXT J2,J1

```

```

4480 AZ%=0:FOR J1=1 TO PN:IF A(1,J1)=0 THEN AZ%=AZ%+1
4490 NEXT J1:NP=PN:RETURN
4495 '
4500 ' ** CALCULATION OF SUM OF RESIDUALS **
4510 SS=0:B%=0:N%(0)=0:FOR J1=1 TO 2:B%=B%+N%(J1-1)
4520 FOR J2=1 TO N%(J1):ON J1 GOSUB 4650,4640
4530 SS=SS+(CY(B%+J2)-CP)^2*WT(B%+J2):NEXT J2,J1:RETURN
4535 '
4540 ' ** CALCULATION OF INVERSE MATRIX **
4550 FOR J1=1 TO PN:X=1/X(J1,1):FOR J2=2 TO PN
4560 X(J1,J2-1)=X(J1,J2)*X:NEXT X(J1,PN)=X
4570 FOR J3=1 TO PN:IF J3-J1=0 THEN 4610
4580 WQ=X(J3,1):FOR J2=2 TO PN
4590 X(J3,J2-1)=X(J3,J2)-X(J1,J2-1)*WQ:NEXT
4600 X(J3,PN)=-X(J1,PN)*WQ
4610 NEXT J3:NEXT J1
4620 FOR J1=1 TO PN:VE(J1)=SQR(X(J1,J1)*SS/(DN-PN))/P(1,PX(J1))*100:
NEXT:RETURN
4625 '
4630 ' ** CALCULATION OF SERUM LEVELS **
4640 CP=P(1,PX(J2)):RETURN
4650 IF DT%=0 OR RV=0 THEN 4680
4660 FOR I=0 TO P0:IF P(RV,I)>>0 THEN P(RV,I)=EXP(P(RV,I))
4670 NEXT
4680 ON EQ%(0) GOSUB 10030,10160,10280,10480:
IF DT%=0 OR RV=0 THEN RETURN
4685 ' LINE 10030(FUNC1) uniform multiple dosing.
' LINE 10160(FUNC2) non-uniform multiple dosing.
' LINE 10280(FUNC3) non-uniform but periodic dosing.
4685 ' LINE 10480(FUNC4) non-linear type.
4690 FOR I=0 TO P0:IF P(RV,I)>>0 THEN P(RV,I)=LOG(P(RV,I))
4700 NEXT:RETURN

```

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