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FLEX-FIT: A Flexible Bayesian Forecasting Program for Dosage Optimization in Clinical Pharmacokinetics

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= Abstract =A microcomputer program for prediction of individualized optimal drug dosage based on Bayesian Statistical Theory and Maximum Likelihood Estimation is presented. Model (one or two compartmental model) and parameter distribution (normal or log normal) can be selected to describe the plasma drug concentrations-time course. Simplex method is adapted for contraction of objective function in non-linear least square fitting to the final minimum. It is designed so that user can integrate universal dosing regimens with different doses, routes, and regular or irregular intervals. Complex dosage regimens and non steady-state conditions can be handled. This program can also generate graphic simulations of plasma and peripheral compartment drug levels of one or two compartmental model. It has been designed to run interactively to assist learning the pharmacokinetic concept and to be handled by user with little knowledge on mathematics or computer.

Kew words: ***Computer program, Bayesian theorem, Simplex method, Non-linear least square, Pharmacokinetics, One- or two-compartmental model, Dosage optimization***

INTRODUCTION

Recent advances in analytical technologies allow rapid determination of drug concentration in biological fluids with high precision (Jolley 1981; Oellerich 1980). As a result, clinicians have become increasingly interested in estimation of individual pharmacokinetic parameters for future precise dosage regimens. Although some durgs could be safely used by patients' characteristics alone (e.g. age, body weight or creatinine clearance), standard dosage regimens according to physical characteristics alone may produce significant variations in plasma drug concentrations achieved, that aspect which may be of particular importance in the management of drugs with narrow therapeutic windows (Benowitz and Meister 1978; Jusko *et al.* 1979; Smith *et al.* 1969).

For the rapid estimation of individual pharmacokinetic parameters, several methods based on simplified pharmacokinetic concepts have been proposed. However, frequently, these methods have several shortcomings such as fixed dose, fixed schedule for drug administrations and blood samplings and are aimed toward particular drug therapy. Recently, Sheiner *et al.* (1979) proposed a general method adapting Bayes approach, which has been shown to provide more accurate prediction of optimal dose (Sheiner and Beal 1982; Yuen *et al.* 1982). Thereafter, several programs based on Bayesian algorithm have been developed for this purpose. However, most of them were developed for particular drug therapy with fixed model and administration routes (Burton *et al.* 1985; Lenert *et al.* 1982; Vozeh *et al.* 1985). Although those restricted approaches remain indispensable in teaching of pharmacokinetics and analyzing pharmacokinetic data in specific condition, the dosage regimens are occasionally far more complicated in clinical practice.

The computer program described herein is developed in order to adapt Bayesian algorithm easily in any clinical situation and to assist medical students and physicians learning clinical pharmacokinetic concepts.

METHOD

Model

One and two compartmental pharmacokinetic models are used with an input function appropriate to the different modes of drug administation. Fig. 1

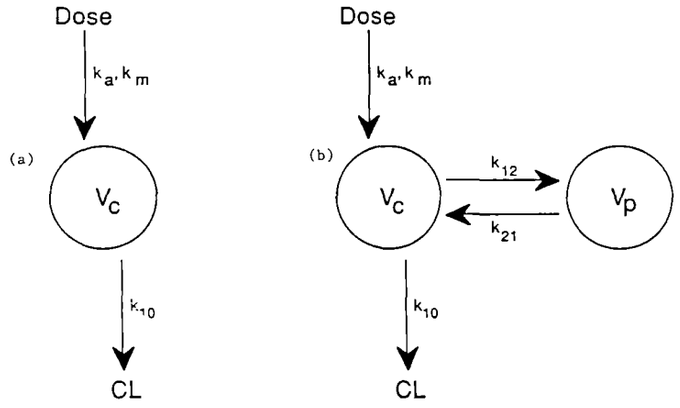

Fig. 1. One(a) and two(b) compartmental systems used for the distribution and elimination kinetics of drugs. In two compartmental model, drugs distribute instantaneously in cental compartment(V_c) after administration of dose and equilibrate with peripheral compartment(V_p) at rates determined by the intercompartmental rate constants (k_{12}, k_{21}). Clearance can be expressed as $V_c \cdot k_{10}$. Symbols of ka and km represent first order drug absorption rate constants of oral, and other parenteral routes, respectively.

shows two basic compartment systems used in this program. Herein, details of two compartmental model will be described.

Each dosage regimens can be defined as follows;

1) The time of administration of each dose, t(i), that is specified along a patient's "time-line" of dosing history.

2) The amount of each dose, D(i), that is administered through each route; D(i) for oral or intramuscular route includes bioavailability term(F) in itself.

3) Route of drug administration with each dosage regimen is verified as intravenous bolus, intravenous infusion, oral or other parenteral route; oral (including administration of different absorption rate formulations, e.g. regular and slow releasing formulations) and other parenteral routes are verified as same type routes as oral route to be used interchangeably.

4) The duration over which each dose is administered at uniform rate can be defined with $t(i_2)$-t(i), where $t(i_2)$ is the time of termination of infusion as expressed along a patient's "time-line".

5) Kinetic model parameters are CL, Vc and ka or km for Bayesian method and k_{12}, k_{21} can be included as variables for simple non-linear fitting, where appropriate.

6) Initial plasma level with uncertain dose history is presumed to be declined by single exponential function assuming complete distribution of the drug at the time of initial sampling.

Throughout the time courses of each dosage regimen, plasma concentrations, (C(i,t)), can be described by an equation of the following;

$$C(i,t) = Co(t) + Cp(D(i), F, CL, Vc, ka, km, k_{12}, k_{21}) \quad (1)$$

where Co represents initial plasma drug concentration, occasionally it shows uncertain dose history. Cp is the superimposed plasma drug concentration-time profile from initial dose to ith dose, and is the function of each dose, clearance, volume of distribution and the relevant rate constants. Depending on the mode of each dose, Cp can be given with superposition of the following functions (Gibaldi and Perrier 1982);

$$Civ = \frac{D(i)}{V_c}\left\{\frac{(k_{21}-\alpha)}{(\beta-\alpha)}e^{-\alpha t} + \frac{(k_{21}-\beta)}{(\alpha-\beta)}e^{-\beta t}\right\} \quad (2)$$

$$Cinf = \frac{D(i)}{(t(i_2) - t(i))Vc}\left\{\frac{(k_{21}-\alpha)}{\alpha(\beta-\alpha)}(1 - e^{-\alpha T})\right.$$
$$\left. e^{-\alpha t'} + \frac{(k_{21}-\beta)}{\beta(\alpha-\beta)}(1 - e^{-\beta T})e^{-\beta t'}\right\} \quad (3)$$

$$Cor,\ Cim = \frac{D(i)\cdot k_i}{V_c}\left\{\frac{(k_{21}-k_i)}{(\alpha-k_i)(\beta-k_i)}e^{-kit}\right.$$
$$+ \frac{(k_{21}-\alpha)}{(k_i-\alpha)(\beta-\alpha)}e^{-\alpha t}$$
$$\left. + \frac{(k_{2i}-\beta)}{(k_i-\beta)(\alpha-\beta)}e^{-\beta t}\right\} \quad (4)$$

$$\alpha = \frac{(k_{10}+k_{12}+k_{21}) + \sqrt{(k_{10}+k_{12}+k_{21})^2 - 4k_{21}\cdot k_{10}}}{2}$$

$$\beta = \frac{(k_{10}+k_{12}+k_{21}) - \sqrt{(k_{10}+k_{12}+k_{21})^2 - 4k_{21}\cdot k_{10}}}{2}$$

where Civ, Cinf, Cor and Cim are the plasma concenteration- time function of intravenous volus, intravenous infusion, oral and other parenteral administration, respectively,and ki acts as ka or km, depend on the route of administrataion. T and t′ are time variables during infusion. After stopping the infusion, T and t′ are duration of infusion and (t-T), respectively.

If we assume partition coefficient between plasma and peripheral compartment to be 1, drug levels in the peripheral compartment after the dos-

ing can be expressed as the following equations, which used in simulation, according to the defined two compartmental model.

$$Ct,\ iv = \frac{D(i)}{V_c} \left\{ \frac{k_{21}}{(\beta - \alpha)} e^{-\alpha t} + \frac{k_{21}}{(\alpha - \beta)} e^{-\beta t} \right\} \quad (5)$$

$$Ct,\ inf = \frac{D(i)}{(t(i_2) - t(i))\ V_c} \left\{ \frac{k_{21}}{\alpha(\beta - \alpha)} (1 - e^{-\alpha T}) e^{-\alpha t'} + \frac{k_{21}}{\beta(\alpha - \beta)} (1 - e^{-\beta T}) e^{-\beta t} \right\} \quad (6)$$

$$Ct,\ or,\ Ct,\ im = \frac{(D_i)k_i}{V_c} \left\{ \frac{k_{21}}{(\alpha - k_i)(\beta - k_i)} e^{-kit} + \frac{k_{21}}{(k_i - \alpha)(\beta - \alpha)} e^{-\alpha t} + \frac{k_{21}}{(k_i - \beta)(\alpha - \beta)} e^{-\beta t} \right\} \quad (7)$$

where Cts represent drug concentration changes in the peripheral compartment.

Parameter optimization

Calculation of the most likely set of parameters CL, Vc and ka or km for each individual patient is carried out by a procedure based on Bayes' Theorem and the application of the Maximum Likelihood Principle (Edwards 1976). If one can define the statistical distribution of a set of parameters of a given drug in the general population (the prior distribution), one or more measurements of plasma drug level after dosing can be used to obtain the posterior distribution of the set of parameters of that patient. With Bayes' Theorem, the posterior probability distribution of the patient can be given as follows;

$$p(\theta \mid C) = \frac{p(\theta) \cdot p(C \mid \theta)}{p(C)} \quad (8)$$

where $p(\theta)$ is the probablity density function for the set of parameters. p(C) is the probablity density function for the observation of plasma levels after dosing. $p(C \mid \theta)$ is conditional probability density function for the plasma level observation under a given set of parameters. $p(\theta \mid C)$ is the conditional probability density function for the parameters under given observation of plasma levels.

If each pharmacokinetic parameter (θ_i) is normally distributed in the population with mean $\bar{\theta}_i$ and variance σ_i^2, and each parameter is independent, $p(\theta)$ can be given by;

$$p(\theta) = \prod_{i=1}^{k} \frac{1}{\sqrt{2\pi\sigma_i^2}} e^{-\frac{(\theta_i - \bar{\theta}_i)^2}{2\sigma_i^2}} \quad (9)$$

Since each plasma level measurement (Ci) becomes a normal distribution under random error with variance σ_c^2, this conditional probability ($p(C \mid \theta)$) can be expressed as follow;

$$p(C \mid \theta) = \prod_{j=1}^{n} \frac{1}{\sqrt{2\pi\sigma_c^2}} e^{-\frac{(C_j - \hat{C}_j)^2}{2\sigma_c^2}} \quad (10)$$

Then, omitting constants values of the above equations and parameter independent p(C), a maximum likelihood estimator of the parameters of the patient can be obtained by minimizing the negative log likelihood function (Owls).

$$\frac{\partial}{\partial\theta} [\log p(\theta)m + \log p(C \mid \theta)] = 0$$

$$\text{at } \theta = \text{Owls}$$

Therefore

$$\text{Owls} = \sum_{i=1}^{k} \frac{(\theta_i - \bar{\theta}_i)^2}{\sigma_i^2} + \sum_{j=1}^{n} \frac{(C_j - \bar{C}_j)^2}{\sigma_c^2} \quad (11)$$

where C_j and σ_c^2 are model and parameter related expected plasma level and the variance of plasma level due to all forms of measurement error including model misspecification.

Minimization of objective function is carried out using Simplex method (Nelder and Mead 1965; Nicol *et al.* 1986). Although Simplex method can not give standard error of optimized parameter without Monte Carlo simulation, we chose this algorithm because it never diverge despite poor initial estimate. Weighing on measured plasma level is allowed with power function ($1/C^{wt}$).

For the optimal use of Bayesian algorithm on dosage optimization, precise population parameter is essential. Mean and the variance of population parameter, and experimental error can be calculated by mixed effects modeling (Sheiner *et al.* 1977) from fragmentary data of a large number of subjects or by the traditional two stage method or other new approach (Steimer *et al.* 1984).

Program description

This package is written in Microsoft BASIC to be used on many IBM PC XT/AT compatible microcomputers, and compiled by Turbo BASIC compiler (Borland Inc 1987) with numeric coprocessor option for maximum speed, precision and prevention

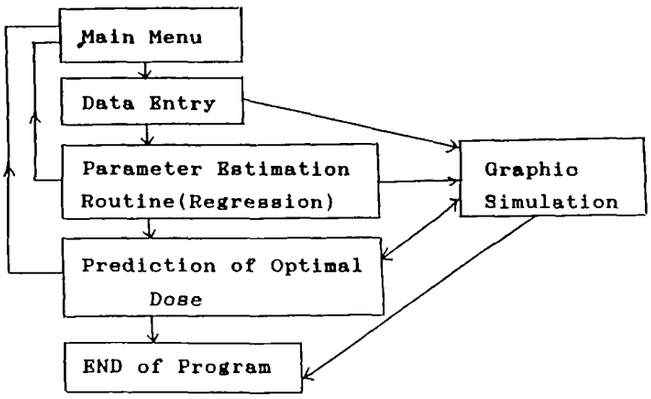

Fig. 2. Flow-chart showing organization of the program.

of overflow error during iterations. Compiled program occupies about 75 Kbytes. Graphic simulation runs on the screen of high resolution mode. Program is designed completely interactive and menu-driven for user with little knowledge on mathematics and computer. The general layout of the program is shown in Fig. 2. and consists of five main section.

As a primary option, Bayesian estimation, non-Bayesian non-linear least square fitting of parameters, and simulation for hypothetical case are provided. For Bayesian optimization, two distinct parameter distributions assumed (normal and log normal distribution) are provided, because distributions of kinetic parameters of some drugs are better explained by log normal distribution. Data entry allows input of patient's dose history, measured plasma drug level, and population parameter values with a mean and coefficient of variation according to defined distribution. Numbers of dose history and drug level can be accomodated without limit.

The non-linear regression section is automatically called on completion of data entry. Then, the program iterates until the objective function is minimized. The two microconstants, k_{12} and k_{21}, are assumed constant for only Bayesian two compartmental model over the entire population (Vozeh *et al.* 1985), therefore, individual estimates need to be obtained only for CL, Vc and ki. Drug levels of peripheral compartment can be predicted and graphically simulated by choosing the option. The predictive routine can be used after optimization of parameters or simply with population value. The predictive section for optimal dosage is designed to choose loading dose and/or maintenance dose for specific therapeutic goal with flexible route of administration. An experienced user can enter a realistic case and obtain individual parameters and forecast optimum dose within five minutes.

RESULTS AND DISCUSSION

The purpose of the results section is to illustrate the versatility of the FLEX-FIT program. Simulation, individual parameter estimation and future optimal dosing selection examples are presented and compared with other programs for specific use.

Simulation: Example 1. Simulation of a complex dosage regimen protocol.

Plasma and peripheral compartment drug level of a complex theophylline treatment protocol from Sebaldt and Kreeft (1987) is simulated assuming the appropriateness of two compartmental model with population average value for Vc = 9.9 L, CL = 4.574 L/hr, F = 0.8, k_{12} = 3.90/hr, k_{21} = 2.16/hr and ka = 0.5/hr (Powell *et al.* 1978). Dosage regimens assumed such as; initiation with 375 mg of theophylline orally 4 times daily (irregulary at 8, 12, 18, 22 h each day) for 2 days, 2 doses missed due to vomiting, admitted to hospital, and a rapid intravenous infusion of 180 mg over a period of 1 hr at 17 h of 3rd day and maintenance infusion starting at 18 h of 3rd day at a rate of 30 mg/hr for 30 hr and restarted same oral dosage regimens with 250 mg at 8 h of 5th day. The simulation is shown in Fig. 3a. The simulation above situation shows that serum concentrations-time course could well have been in non-toxic range (Fig. 3a). However, if we assume that the patient has pneumonia and abstinence of smoking, patient's parameter estimation will be Vc = 6 L and CL = 2.1 L/hr. The modified simulation shows toxic levels during initial two days of theophylline therapy (Fig. 3b).

Estimation of individual parameters: Example 2. Two compartmental model — Lidocaine

As a second example, the case treated with lidocaine from Vozeh *et al.* (1985) is analyzed with population mean and coefficient variation values of log normal distribution (Vc = 0.64 L/kg, 37% CV; CL = 0.58 L/hr/kg, 60% CV; intraindividual residual error = 21%; k_{12} = 1.35/hr, k_{21} = 0.53/hr). This male patient, weighed 60 kg, has a moderate heart failure. Fractional decrease of CL and Vc in moderate heart failure patient is predicted 45% and 24%, respectively.

Patient was treated with 100 mg intravenous bolus injection at 20 h of lst day and 120 mg/hr constant infusion for 4 hr simultaneously. At 23 h of that day, a 50 mg intravenous bolus dose was introduced. Plasma drug levels at 22 h and 24 h

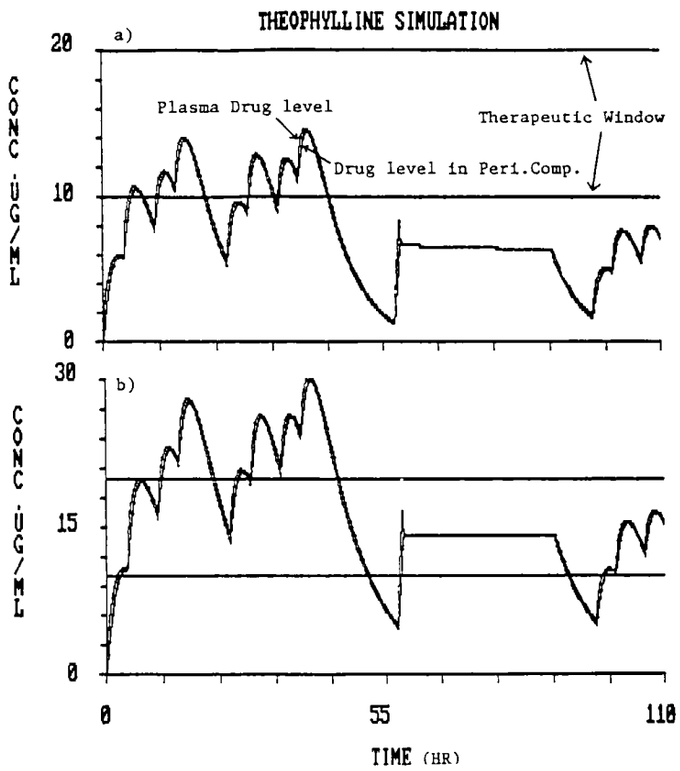

Fig. 3. Example 1. Time course of theophylline concentrations in plasma and peripheral compartment, after the complex regimen of theophylline.

were 1.5 and 1.9 μg/ml, respectively. Estimated parameters and predicted plasma levels were presented and typical future dosage regimen for 3.5 μg/ml of objective goal at 24 hr was simulated in Fig. 4. Difference between measured and predicted plasma level during parameter estimation was smaller than those of Vozeh *et al.* (1985) (predicted plasma levels, 1.7 and 2.1 μg/ml; estimated CL = 50.4 L/hr, Vc = 36.2 L).

Example 3. One compartment model — Theophylline.

Application of FLEX-FIT on theophylline therapy is tested with one compartmental model. The results are compared with those from OPT package of University of Glasgow (Kelman *et al.* 1982). Dose Regimens are slightly modified to more realistic situation, especially duration of intravenous drug administration. The results are almost same with assuming rapid intravenous bolus injection as Kelman *et al.* did. The 35 yr old patient (72 kg), who was a heavy smoker, with an episode of bronchospasm was given 500 mg aminophylline intravenously over 20 minutes, followed by 250 mg 6 hr later with same infusion period. Oral theophylline was started (Fig. 5). Blood samples were drawn at 6 hr after 2 nd oral dose. Plasma theophylline level was 9.0 μg/ml. At this point, the expected values for kinetic parameters were driven. Bayesian estimates based on population parameters from Jusko *et al.* (1979) and Peck *et al.* (1980) (ka = 0.35/hr, F = 0.79, CL = 4.71 L/hr, Vc = 36.01 L, σ_{CL} = 0.5 (CL), σ_{Vc} = 0.2 (Vc), σ_{ka} = 0.5 (ka), coefficient of variation of model and measurement error = 15%). On the following day, theophylline level was 14.5 μg/ml 2 hr after 8th dose. Anticipated theophylline concentration predicted with one plasma level were 8.87 and 13.37 μg/ml at both sampled times. The anticipated steady-state peak and trough level predicted with two plasma levels, assuming continuous oral dosing of 450 mg 6 hourly were 16.78 μg/ml and 14.24 μg/ml, respectively. The results were very similar to those of OPT package (predicted value with single plasma level: Ist plasma level = 8.84 μg/ml, estimated CL = 3.83 L/hr, Vc = 35.96 L, ka = 0.36/hr; predicted value with two plasma levels: estimated CL = 3.64 L/hr, Vc = 35.53 L, ka = 0.42/hr, steady-state peak = 17.3 μg/ml, trough = 14.4 μg/ml). The different estimation between this program and OPT package is due to the difference of weighing factor.

In this paper, the overall features of FLEX-FIT are described. Universal dosing approach with Bayesian forecasting algorithm can successfully applied in FLEX-FIT program. This program can be also used as non-linear fitting program without modification for pharmacokinetic research of single or multiple dose of regular or irregular interval. The most important feature of this program is an ability to utilize non steady-state data and the ease which complex dosage regimens can be handled. These features have particular advantages for analysis of data from different drug and different situations. Although Bayesian forecasting is known to be superior to alternative non stochastic methods (Sheiner and Beal 1982; Yuen *et al.* 1982), there are some points on most Bayesian forecasting program, which affect effectiveness of that system. For example, parameter distribution, weighing factor for serum level, etc. However, for the maximum effectiveness of Bayesian forecasting algorithm, slight modification of those factors according to individual drug characteristics can improve over all effectiveness of its use: these will be a subject of future communication.

This program would be useful in the general area of clinical pharmacology, especially applied pharmacokinetic area for dosage individualization; by simulation of time-course of compartmental drug

*** Plasma Concentration ***

NO.	Time(hr)	Measured C (ug/ml)	Predicted C (ug/ml)	Predicted Ct (ug/ml)
1	2.0	1.5	1.507	0.984
2	4.0	1.9	1.897	1.592

*** Estimated Patient's Parameter ***

	Est.from Popul.	Bayesian Est.
Vc (L)	29.184	41.516
CL (L/hr)	19.14	56.267
k_{12} (1/hr)	1.35(constant)	----
k_{21} (1/hr)	0.53(constant)	----

*** Predicted Dose ***

Therapeutic Goal(C ss)	Infusion Rate(mg/hr)
2.5 ug/ml	140.7
3.0 ug/ml	168.8
3.5 ug/ml	196.9
4.0 ug/ml	225.1

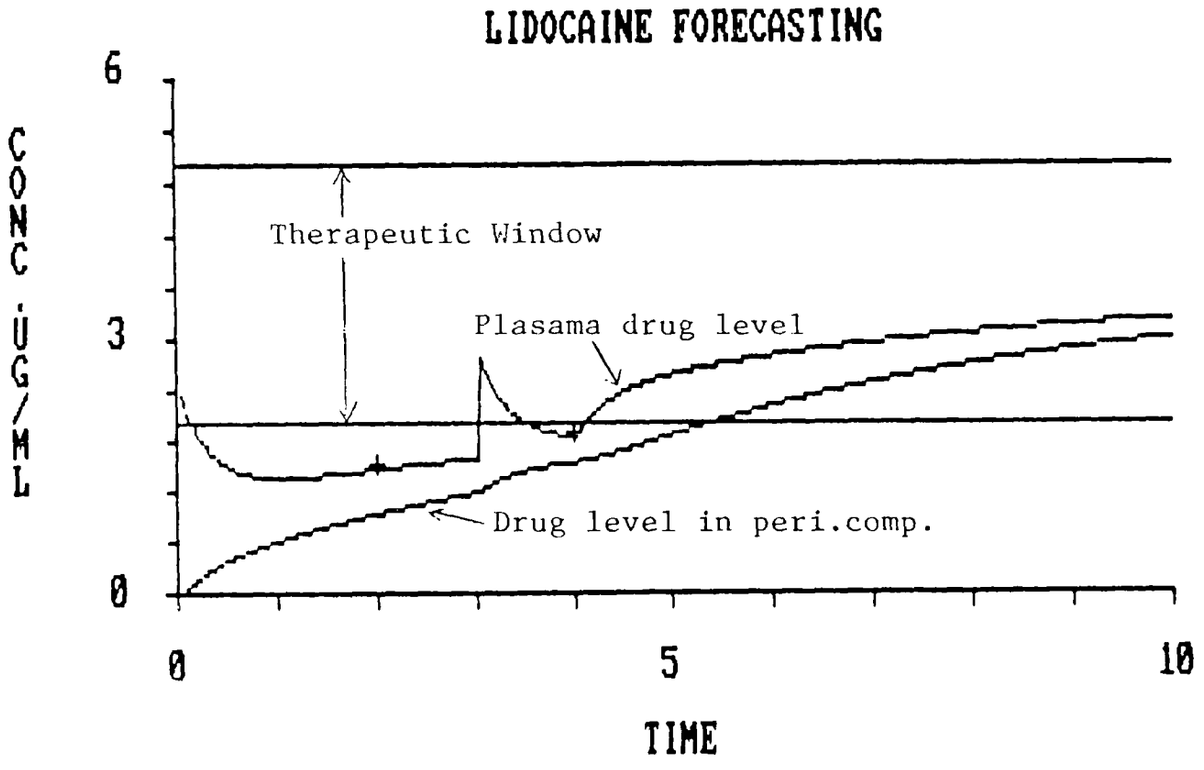

Fig. 4. Example 2.: Lidocaine, Bayesian parameter estimation and graphic simulation of drug concentrations in both of central and peripheral compartment. "+"; measured plasma levels.

*** Dosing Protocol ***

No.of Dose	Type	Time-interval (hr)	Inf.Time (hr)	Dose (mg)
1	IV Inf	0	0.33	500(amino.)
2	IV Inf	6	0.33	250(amino.)
3	Or	4		450
4	Or	12		450
5	Or	8		450
6	Or	6		450
7	Or	10		450
8	Or	6		450

*** Plasma Level ***

No.	Time(Dose)	C (ug/ml)	Est. C (ug/ml)
1	6(4)	9.0	9.19
2	2(8)	14.5	13.86

*** Estimated Pateint's Parameter ***

Parameter	Est.from Popul.	Bayesian Est.
Vc (L)	36.01	35.63
CL (L/hr)	4.71	3.73
ka (1/hr)	0.35	0.37

* Bayesian estimation was performed with two plasma level.

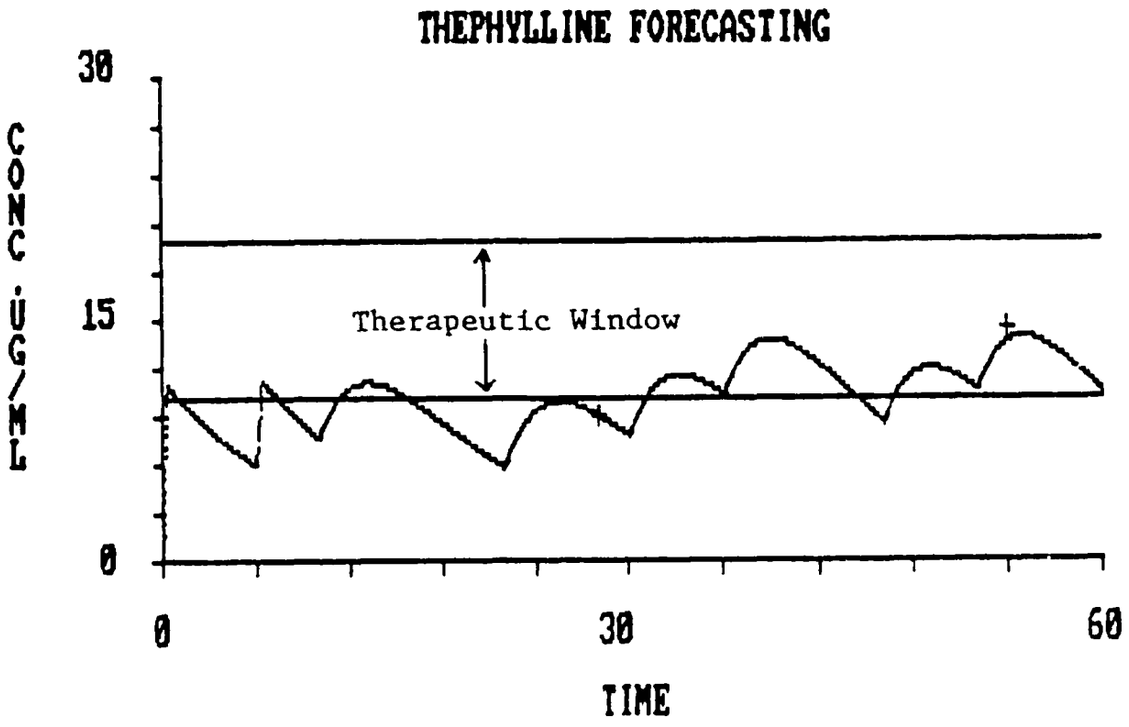

Fig. 5. Example 3.: Theophylline, Bayesian parameter estimation and graphic simulation of plasma concentrations "+"; measured plasma levels.

level with different dosing protocol; by parameter estimation from measured plasma concentration, even from single plasma level, and forecasting optimal future dose.

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= 국문초록 =

Flex-Fit: Bayesian 원리에 기초한 적정용량 결정을 위한 컴퓨터 프로그램

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신상구 · 박찬웅

실제 임상적으로 흔히 경험하는 다양한 투여 경로 및 부정간격의 약물 투여에도 Bayesian 원리 및 Maximum Likehood Estimation법을 이용한 적정용량 개별화를 위한 컴퓨터 프로그램을 제시하였다.

약력학적 성상이 상이한 여러 약물에 적용할 수 있도록 약력학적 모델은 1 및 2 compartment 모델을 다룰 수 있도록 하였다. Population pharmacokinetic parameter의 분포는 정규분포 및 로그정규분포 가정하에서 개개 환자의 약력학적 parameter를 Simplex법에 의해 약물 투여후 1회 혈장농도 측정 후부터 결정하여 이후의 적정투여 용량결정이 가능토록 하였다. 2 compartment 모델에 따른 약력학적 분석시 약물투여후 peripheral compartment 약물 농도 변화를 simulation 할수 있도록 하고, 개별환자의 약력학적 parameter 결정후 혈장 및 peripheral compartment 농도 변화의 도식이 가능케하였다. 환자 개인별 약력학적 parameter 결정후 약물 투여는 프로그램 사용자의 결정에 따라 부하용량 또는 유지용량을 선택할 수 있도록 하였다.

본 프로그램은 적정용량 결정을 위한 임상응용에 뿐 아니라 약력학적 연구 목적을 위한 non-linear curve fitting이 가능토록 디자인하였고, 다양한 투약법에 따른 혈장농도 및 peripheral compartment 농도 simulation으로 임상약력학 교육에 이용될 수 있도록 하였다.