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OPT: A PACKAGE OF COMPUTER PROGRAMS FOR PARAMETER OPTIMISATION IN CLINICAL PHARMACOKINETICS

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1 OPT is a series of computer programs designed to assist dose optimisation for individual patients. It is based on Bayesian Statistical Theory and Maximum Likelihood Estimation.

2 OPT uses prior information on the distribution of population pharmacokinetic parameters and plasma drug concentration measurements to obtain the 'most likely' set of parameters for the individual.

3 Complex dosage regimes and non-steady state conditions can be handled.

4 OPT is designed for use in a Clinical Pharmacokinetics Laboratory where informed interpretation of results is essential.

5 The drugs for which the system is currently available include theophylline, digoxin, lignocaine, disopyramide, gentamicin and phenytoin (steady state data only).

Introduction

Optimum treatment with many drugs depends on the achievement of drug concentrations which lie between specific limits set by a minimum effective concentration and a maximum safe concentration. While there may be some dispute about the most appropriate values for these limits, concentrations outwith these ranges are considered to be subtherapic or toxic respectively. Such a strategy highlights the difficulties caused by intersubject variability in drug disposition because standard dose regimes will produce significant variations in the drug concentrations achieved. Moreover, within individuals, there may be considerable changes in plasma concentration throughout one dosage interval, an aspect which may assume particular importance when drugs with narrow therapeutic ranges are given. With these basic considerations in mind, a Clinical Pharmacokinetics Laboratory (CPL) has two essential tasks (a) to measure the plasma concentration of a selected number of drugs whose activity and safety depend on the strategy outlined above and (b) to interpret these concentrations in a way that will assist in the optimisation of treatment in individual patients. This latter task has encouraged us to develop a package of computer programs, OPT (Whiting *et al.*, 1981, 1982) which estimates the most likely set of pharmacokinetic parameters for an individual patient using a relatively simple pharmacokinetic model and patient specific data such as age, weight, sex etc. This approach was originally proposed by Sheiner *et al.*, (1979) and by Peck *et al.* (1980). Its success in practice when applied to digoxin and phenytoin has been demonstrated by Sheiner *et al.* (1975, 1979) and by Vozeh *et al.* (1981).

Theory

(A) *The model*

The pharmacokinetic model used is the one compartment open model, with an input function appropriate to the mode of drug administration. Throughout each dosage interval, plasma concentration can be described by an equation of the form:

$$\overline{Cp(I,t)} = CO(I).e^{-k_e t} + Q\ (\text{Dose(I)},F,R,k_a,\ k_m,\ \text{clearance},\ V_d) \quad (1)$$

where $Cp(I,t)$ describes the concentration profile during the i^{th} dosage interval. CO(I) represents the drug concentration at the start of the i^{th} interval (Figure 1) and is a function of past dosage history. Q is that part of the concentration time profile due to the i^{th} dose, DOSE(I), and is a function of clearance (Cl), volume of distribution (V_d) and the relevant rate constants. Depending on the mode of administration, Q is given by one of the following expressions:

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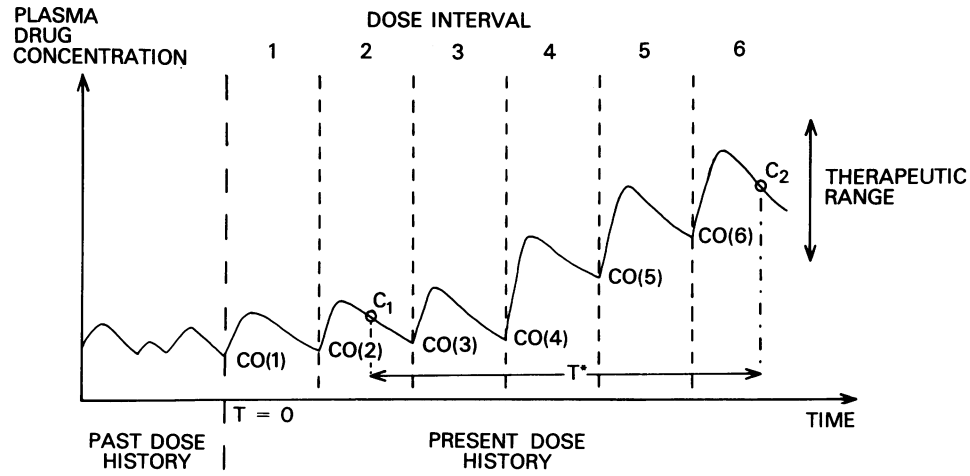

Figure 1 Diagrammatic representation of the kind of data analysed by OPT. Past dose history is relatively uncertain: present dose history is well defined, starting at T = 0. C_1 and C_2 are two measured plasma concentrations and T* (see text) is the time interval between these measurements. There are six dosage intervals, and an increment in dosage (based on information from C_1) has achieved a concentration profile within the therapeutic range by interval 6 (confirmed by C_2).

$$Q = \frac{\text{DOSE(I)}}{V_d}.e^{-k_e t} \quad \text{Intravenous bolus} \qquad (2)$$

$$Q = \frac{F.\,\text{DOSE(I)}\,.k_a}{V_d\,(k_a - k_e)}\left[e^{-k_e t} - e^{-k_a t}\right] \quad \text{Oral} \qquad (3)$$

$$Q = \frac{R}{V_d\,.k_e}\left[1 - e^{-k_e t}\right] \quad \text{Intravenous infusion} \qquad (4)$$

or

$$Q = \frac{k_m\,.\,\text{DOSE(I)}}{V_d\,(k_m - k_e)}\left[e^{-k_e t} - e^{-k_m t}\right] \quad \text{Intramuscular} \qquad (5)$$

where k_a = first order oral absorption rate constant

k_m = first order intramuscular absorption rate constant

k_e = elimination rate constant $= \frac{CL}{V_d}$

F = oral bioavailability (assumed constant)

and R = zero order infusion rate.

Note that intramuscular administration is modelled as a first order process. Using this type of formulation, the kinetic model parameters are CL, V_d and k_a or k_m, where appropriate, and any combination of dose, dosage interval or mode of administration can be accommodated.

As indicated in Figure 1, the dosage history is divided into two portions, 'past' and 'present'. The 'past' refers to the period in which, although the *recommended* dose regime is known, there may be considerable doubt about the *actual* regime followed. In other words compliance may be suspect. The 'present' refers to a period (e.g. during hospitalisation) when the dose history is known with much greater certainty. As far as the kinetic model is concerned, zero time is defined as the start of the 'present' dosage history, and the plasma drug concentration at that time now becomes a further model parameter, CO. The 'past' dosage history may not be relevant in every case when, for example, treatment is initiated in an in-patient situation.

Thus in its final form, the model has four parameters, CO, CL, V_d and where appropriate, k_a or k_m. It is important to note, however, that although the one compartment model represents a useful approximation, the errors implicit in this approximation must be seen in the light of the performance of the system as a whole.

(B) *Parameter optimisation*

The main task of OPT is to calculate the most likely set of parameters CO, CL, V_d and k_a or k_m for each individual patient. This is carried out by a procedure based on Bayes' Theorem and the application of the principle of Maximum Likelihood (Wonnacott & Wonnacott, 1970; Edwards, 1976) and is illustrated in Figure 2. If we can define the statistical distribution of a set of parameters, θ, in the general population (the prior distribution) then one or more measurement, Y, from an individual can be used to obtain the

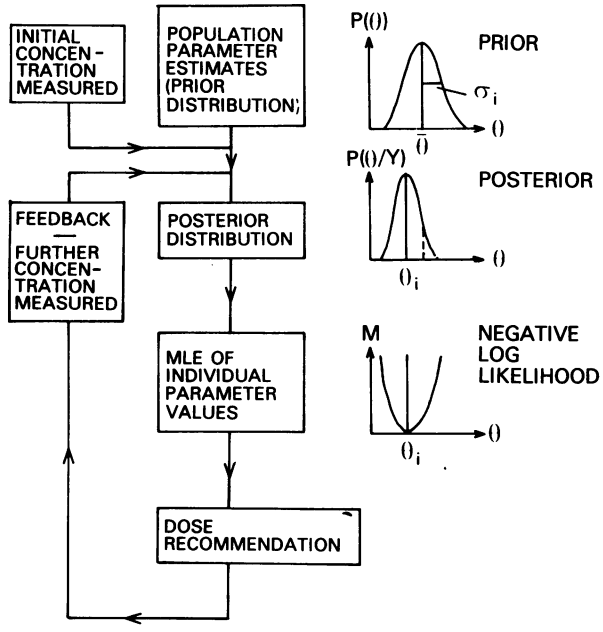

Figure 2 Diagrammatic representation of parameter optimisation. Information from the prior distribution (θ, σ_i) and the initial concentration measurement is used to obtain the revised posterior distribution which yields maximum likelihood estimates (MLE) of the parameters (θ_i). These are then used to make a dose recommendation and further concentration measurements can be used to refine the posterior distribution through feedback of this additional information.

posterior distribution of the set of parameters, i.e. the conditional probability distribution for the set of parameters and the set of observations.

Explicitly, if $p(\theta)$ = the joint probability density function for the set of parameters θ_i (i = 1,k)
i.e. the prior distribution

$p(Y)$ = the joint probability density function for the observations Y_j (j = 1,n)

$p(Y|\theta)$ = the conditional probability density function for the observations Y_j (j = 1,n), given the set of parameters θ_i

and $p(\theta|Y)$ = the conditional probability density function for the parameters θ_i given the observations Y_j
i.e. the posterior distribution

$$\text{then } p(\theta|Y) = \frac{p(\theta) \cdot p(Y|\theta)}{p(Y)} \quad (6)$$

Since $p(Y)$ is independent of the θ_i, $p(Y)$ is merely a constant multiplying factor and can be neglected.

If the expected values of the observations, Y_E are related to the parameters through a model equation:

$$Y_E = g(\theta_1, \ldots, \theta_k, t, \ldots) \quad (7)$$

then it has been shown that a Maximum Likelihood Estimators (MLE) of the parameters, θ, are the set which minimises the negative Log Likelihood function, M, (Kelman *et al.*, 1981)

$$\text{where } M = \sum_{i=1}^{k} \left\{\frac{\theta_i - \bar{\theta}_i}{\sigma_i}\right\}^2 + \sum_{j=1}^{n} \left\{\frac{Y_j - Y_{Ej}}{\sigma_{Yj}}\right\}^2 \quad (8)$$

This assumes that

(a) each parameter, θ_i, is normally distributed in the population, with mean $\bar{\theta}_i$ and standard deviation, σ_i.

(b) the θ_i are independent, although this restriction may be relaxed.

and (c) each measurement, Y_j, is subject to a normally distributed random error.

In the current application, the parameter set, θ, is CO, CL, V_d and k_a or k_m, and the observations Y_j are the plasma drug concentration measurements, c_j. The model equation is given by equation (1) combined with equations (2), (3), (4), or (5) as relevant, and equation (8) becomes:

$$M = \sum_{i=1}^{4} \left\{\frac{\theta_i - \bar{\theta}_i}{\sigma_i}\right\}^2 + \sum_{j=1}^{NCONC} \left\{\frac{c_j - c_{Ej}}{\sigma_{cj}}\right\}^2 \quad (9)$$

It can be seen that if there are no concentration measurements available, i.e. NCONC = O, then the MLE of the θ_i are the population mean values θ_i. If, however, there are many observations available, the second term in equation (9) dominates, and the problem reduces to one of standard weighted nonlinear least squares.

(C) *Population estimates*

The technique presented above produces intuitively sensible results in the extreme cases where there are either no observations or plentiful observations. However, in practical application, both terms in the function M of equation (9) will be important and good estimates of the population parameter values $\overline{\theta}_i$, and σ_i and also σ_{cj} will be essential.

The expected values of CL and V_d are available from various sources. If sufficient data are available the population can be divided into subpopulations on the basis of variables such as age, sex, smoking habits, alcohol consumption, cardiac status etc. by a process of linear modelling. This has been achieved, for example, for theophylline by Jusko *et al.* (1979) and an abbreviated version of that nomogram is shown in Figure 3. At present, data of similar complexity are not available for the other drugs, and a summary of the mean population or subpopulation values used in OPT is shown in Table 1. Where appropriate, drug clearances are related to renal function via creatinine clearance and body weight. The V_d values are also related to body weight and/or creatinine clearance, an are used for all patients. The values of k_a and k_m are obtained from the literature and also from manufacturer's data. Programs such as NONMEM (Beal & Sheiner, 1979) can be used to simultaneously fit fragmentary data from a large number of subjects to obtain estimates of mean population parameter values (Sheiner *et al.*, 1977). The bioavailability factor, F, only enters equations (1) and (3) in combination with V_d, and if F is considered to be a constant, any resulting variation is modelled as increased variation in V_d.

As proposed by Peck *et al.* (1980) the following values for the population standard deviations for theophylline were used:

$$\sigma_{Cl} = 0.5\,(\overline{CL})$$

$$\sigma_{V_d} = 0.2\,(\overline{V}_d)$$

and also

$$\sigma_{k_a} = 0.5\,(k_a)$$

and $\sigma_{k_m} = 0.5\,(k_m)$.

The standard deviation for the distribution of CO was set at:

$$\sigma_{CO} = 0.7\,(\overline{CO})$$

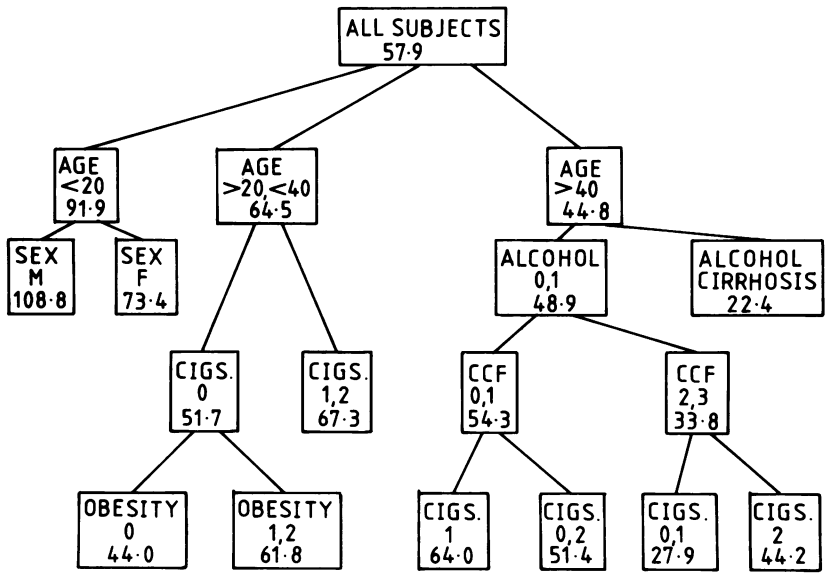

Figure 3 Abbreviated version of the theophylline clearance nomogram published by Jusko *et al.* (1979). All clearance values are in units of ml h^{-1} kg^{-1} ideal body weight. The figures 0, 1, 2, 3 refer to different degrees of the relevant factors.

Table 1 Pharmacokinetic data. Derivation of initial parameter estimates: mean values.

Drug	*Clearance* *CL (l/h)*	*Volume of distribution* V_d *(l)*	*Absorption rate constant* k_a *(h^{-1})*	*Bioavailability* F
Digoxin	$CL = (0.06\ CL_{cr} + 0.02\ wt)$ (a)	$V_d = 3.12\ CL_{cr} + 3.84\ (wt)$ (a)	1.5	0.8 (a),(b)
Theophylline	Reduced nomogram (Figure 3) (c)	$V_d = 0.5\ (wt)$	0.35	0.79
Disopyramide	$CL = (0.000392\ CL_{cr} + 0.0236)\ (wt)$ (d)	$V_d = 0.6\ (wt)$ (e)	1.5	0.75 (e),(f)
Gentamicin	$CL = 0.0438\ CL_{cr} + 0.0036\ (wt)$ (a)	$V_d = 0.25\ (wt)$ (a)	($k_m = 1.39$)	—
Lignocaine	$CL = 0.6\ (wt)$ Cirrhosis, C.C.F. : $CL = 0.36\ (wt)$ (g)	$V_d = 1.3\ (wt)$ Cirrhosis : $V_d = 0.9\ (wt)$ (g)	—	—

where CL_{cr} = creatinine clearance (ml/min), wt = body weight (kg)

Population parameter estimates:

References
(a) Benet & Sheiner (1980).
(b) Iisalo *et al.* (1973).
(c) Jusko *et al.* (1979)
(d) Shen *et al.* (1980).
(e) Bryson *et al.* (1982).
(f) Bryson *et al.* (1978).
(g) Winter (1980).

to account for (a) uncertainty in the actual dose regime followed by the patient during the 'past' dosage history and (b) deviation from the actual CO produced by using the mean population parameter estimates instead of individual values. In the absence of adequate data for the other drugs the same values have been utilised. The value of σ_{cj} accounts for both measurement error and a degree of model misspecification. It is set to 15% of the measured concentration. Considering that each concentration measured for any patient is equally important, but that the latest concentration must be the most relevant to the patient's current condition, a time weighting factor has also been introduced into σ_{cj} (Peck *et al.*, 1980). Thus the final value of σ_{cj} is given by

$$\sigma_{cj} = (1.01)^{T^*}\, 0.15\, c_j$$

where T^* = time from previous measurement to the latest measurement. Thus, progressively less weight is attributed to past measurements as more become available.

The foregoing analysis applies to the drugs whose pharmacokinetics follow linear first order processes. This does not apply, however, to phenytoin, and this drug is dealt with exactly as described by Vozeh *et al.* (1981). Only data obtained during steady state on an oral dosage regime can be utilised for phenytoin.

Details of OPT

OPT is a series of programs CHAINED together. The programs are written in FORTRAN and are implemented on a NODECREST V70 Series digital computer, with multi-terminal access, and 32K words of memory assigned to each terminal. The general flow of OPT is shown schematically in Figure 4. All data are entered interactively in response to simple prompts. In the case of a new patient, details such as age, weight, creatinine clearance, smoking habits etc. are entered as necessary in order to calculate the expected values of CL and V_d as outlined in Table 1. Details of past dosage history are then entered to allow the estimated value of CO to be calculated using the expected values of CL and V_d. The mean population values of k_a and k_m and also the values of F are all pre-programmed. The values of σ_{CO}, σ_{CL}, σ_{V_d}, and σ_{k_a} or σ_{k_m} are calculated. Details of the present dosage history (dose, dose interval, and mode of administration), and concentration measurements and the date and time the samples were taken are now entered.

These data are all stored in a WORKFILE. All data are checked to allow correction of errors if necessary before passing on to the next stage. The data in the WORKFILE can be transferred to another file for permanent storage, for example on

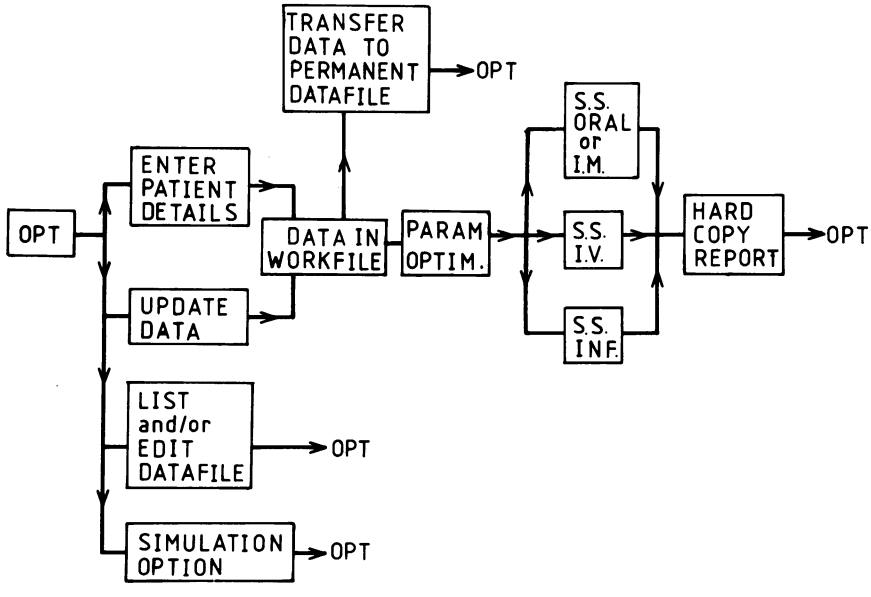

Figure 4 Schematic representation of the OPT system. SS = steady state dose recommendation.

magnetic tape. The data file can also be updated by adding details of subsequent doses and concentration measurements.

The next step is to obtain the MLE of the set of parameters CO, CL, V_d and k_a or k_m by minimising the function M of equation (9). This is carried out using a SIMPLEX routine (Nelder & Mead, 1965) and the estimated errors in the parameter values are obtained. In practice, the distributions are considered to be log normal and this transformation is carried out in the program: the analysis is not influenced by this transformation. The package then chains to one of a series of programs, depending on the drug under test to allow the optimal dose regime to be calculated. This is achieved interactively by entering a series of doses and dosage intervals until the required steady state concentration profile is obtained, characterised by peak, trough or mean steady state concentrations or a combination of these. Comments can be added at this point, including dosage recommendations or cautions, and a detailed report form is then produced for the CPL records. A simplified version is also produced for the patient's case record. These include a graphical display of the concentration profile relevant to the present dosage history and any concentrations available.

The main features of OPT are illustrated in the examples presented in Figures 5, 6, 7 and 8.

Example 1. *THEOPHYLLINE* (Figures 5 and 6)

The patient was admitted as an emergency during an acute episode of bronchospasm. 500 mg aminophylline were given intravenously on admission, followed by 250 mg 6 h later. Oral theophylline (Phyllocontin) was then started and a blood sample was taken the following day at 14.00 h, 6 h after the previous oral dose. The measured theophylline concentration was 9.0 μg/ml.

The *expected* values for the four parameters were derived as follows:

Clearance (4.71 l/h), on the basis of ideal body weight (70 kg), age (35) and the fact that he was a heavy smoker.

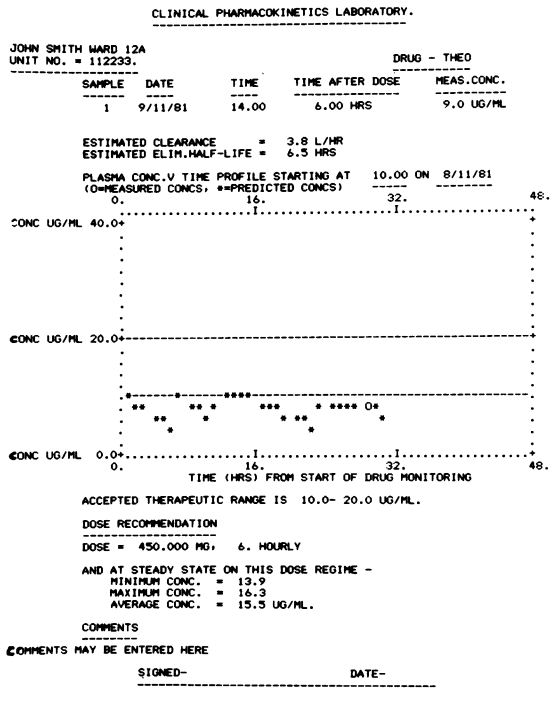

Figure 5 Example 1: THEOPHYLLINE. Clinical Pharmacokinetcs Laboratory report for permanent record in case sheet. Parameter optimisation is based on subpopulation parameter estimates and one concentration measurement.

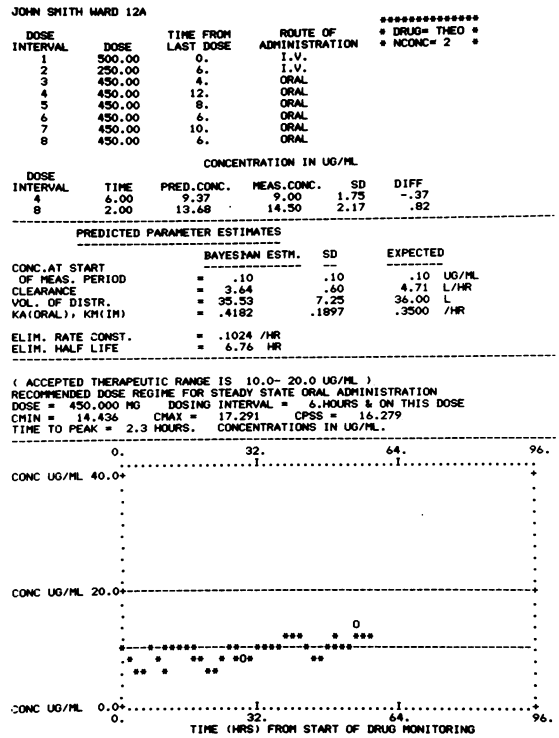

Figure 6 Example 1: THEOPHYLLINE. Full computer output: parameter optimisation is based on subpopulation parameter estimates and two concentration measurements.

Volume of distribution (36.0 l) on the basis of actual body weight (72 kg).

k_a, arbitrarily set to 0.35 h^{-1}

CO (effectively zero) on the basis that no previous theophylline had been given.

Corresponding Bayesian estimates were

CL. 3.83 (±0.74) l/h; V_d, 35.96 (±7.34) l; k_a, 0.36 (±0.21) h^{-1} and CO, effectively zero.

The predicted concentration (8.84 μg/ml) was very close to that actually measured. On the basis of the revised parameter estimates (notably clearance) it was predicted that a dose of 450 mg 6 hourly would produce more acceptable levels (Figure 5; abbreviated output for case sheet). The following day, a second blood sample was taken 2 h after a dose. The theophylline concentration was 14.5 μg/ml. Using both concentration measurements then, the Bayesian estimates were

CL, 3.64 (±0.6) l/h; V_d, 35.53 (±7.25) l; k_a, 0.42 (±0.19) h^{-1} and CO, effectively zero.

This confirms that clearance was less than that expected originally and that satisfactory steady state levels with a trough (CMIN) of 14.4 μg/ml, a peak (CMAX) of 17.3 μg/ml and an average steady state concentration of 16.3 μg/ml could be anticipated from a dose of 450 mg 6 hourly (Figure 6; full computer output).

Example 2. *DISOPYRAMIDE* (Figure 7)

A lady with paroxysmal supraventricular tachycardia was given a series of intravenous doses of disopyramide. She was then started on oral therapy and two blood samples were taken after the first and second oral doses. The measured disopyramide concentrations were high at 7.6 and 5.6 μg/ml respectively. The expected values for the four parameters were derived as follows:

Clearance (2.09 l/h) on the basis of creatine clearance and body weight

Volume of distribution (33.6 l) on the basis of body weight

k_a, arbitrarily set at 1.5 h^{-1}

CO, (effectively zero) on the basis that no previous disopyramide had been given.

Corresponding Bayesian estimates (using both concentrations) were

CL, 1.3 (±0.22) l/h; V_d, 34.11 (±5.91) l/h; k_a, 1.48 (±0.9) h^{-1} and CO, effectively zero.

Predicted concentrations were 7.89 and 5.29 μg/ml. On the basis of the revised parameter estimates (again, notably clearance) it was predicted that a dose of 150 mg daily would achieve levels within the therapeutic range. This advice was followed and a sample taken three days later confirmed that satisfactory therapeutic levels had been achieved. This concentration measured 4.0 μg/ml, 6 h after a dose, and the Bayesian estimates, now using all three concentrations, were very similar to those estimated previously (Figure 7; full computer output).

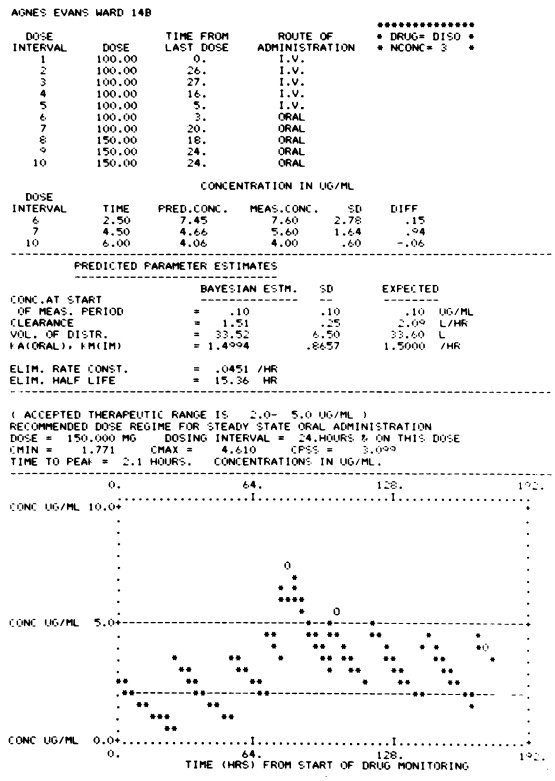

Figure 7 Example 2: DISOPYRAMIDE. Full computer output: Bayesian estimates derived from three concentration measurements.

Example 3. *GENTAMICIN* (Figure 8)

The patient was given an intitial dose of 120 mg gentamicin intravenously followed by two further 80 mg doses. A blood sample was taken 7.5 h after the third dose. The measured gentamicin concentration was 1.5 μg/ml. The *expected* values for the three parameters were derived as follows:

Clearance (3.5 l/h), on the basis of creatinine clearance and body weight.

Volume of distribution (15.0 l), on the basis of body weight

CO (effectively zero) on the basis that no previous gentamicin had been given.

Corresponding Bayesian estimates were

CL, 3.03 (±0.33) l/h; V_d, 15.14 (±2.0) l and CO, effectively zero.

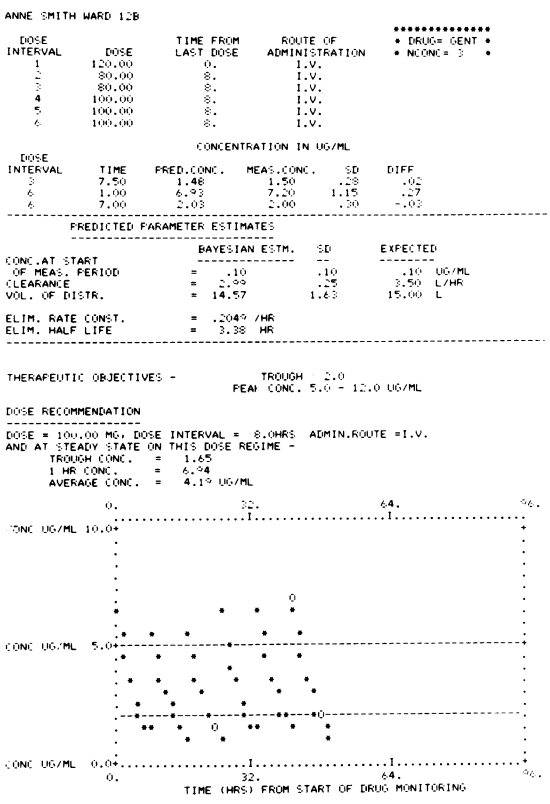

Figure 8 Example 3: GENTAMICIN. Full computer output: Bayesian estimates derived from three concentration measurements.

The predicted concentration was practically identical to that measured. On the basis of the revised parameter estimates, a slight increase in dose to 100 mg 8 hourly was recommended.

The following day, two blood samples were taken, 1 h and 7 h after a dose, representative of high and low levels on this dose. Corresponding concentrations were 7.2 and 2.0 μg/ml respectively. Using all three measurements, Bayesian parameter estimates were then

CL, 2.99 ($\pm$0.25) l/h; V_d, 14.57 ($\pm$1.63) l and CO, essentially zero.

This confirmed that therapeutic objectives, in terms of peak and trough levels, would be achieved on this regime (Figure 8; full computer output).

Discussion

OPT is a package of programs which uses Bayes' Theorem and the principle of Maximum Likelihood to estimate the most likely set of pharmacokinetic parameters for an individual patient. This process is based on prior knowledge of population parameter distributions and any plasma concentration measurements available. Once the optimal parameter values have been calculated, recommendations for future dose adjustments can be made to achieve the relevant therapeutic concentrations. The usefulness of a package such as OPT can be maximised by combining it with rapid and accurate drug concentration measurements, most effectively in the setting of a Clinical Pharmacokinetics Laboratory, using techniques such as EMIT or h.p.l.c. We acknowledge that the sophistication of such a system may not always be necessary, where, for example, a patient is in steady state on a drug which exhibits linear pharmacokinetics but this may be the exception rather than the rule particularly in hospital practice. The most important features of OPT, however, are the ability to utilise non-steady state data and the facility with which drug regimes of great complexity are handled. These features represent particular advantages for the analysis of data collected in relatively acute clinical situations, for example, the treatment of arrhythmias with lignocaine in a Coronary Care Unit, the administration of intravenous and intramuscular gentamicin in a Surgical or Intensive Care Unit and the treatment of severe bronchospasm with theophylline by rapid and slow intravenous infusions. The use of individual patient parameter values should prove more appropriate than those derived from nomograms. The latter may be of value for patients who conform to the population mean, but may give misleading results for those who do not.

There are many assumptions implicit in OPT about parameter distributions, weighting schemes etc; these must be judged by the effectiveness of the system as a whole. For example, the same variances have been assigned to the population parameters for each drug. While these terms represent satisfactory approximations at present, prospective studies will allow their more accurate determination. All assumptions are now being scrutinised and we will make recommendations in the future about certain operational details such as optimal sampling times. At present the package is used routinely in the Clinical Pharamacokinetics Laboratory and printouts are incorporated into the case sheets as permanent documents. Rigorous validation of the whole procedure is being performed continuously: this will be the subject of future communications.

Further details of OPT can be obtained from AWK.

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