Evaluation of a microcomputer program (OPT) for parameter optimisation in clinical pharmacokinetics: gentamicin and tobramycin

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1 Several nomograms and computer programs are available to aid in aminoglycoside dosing.

2 Due to the variability in the relationship between dosage and serum drug levels, monitoring through the acquisition of serum drug levels is mandatory.

3 All clinical data, including serum drug levels, are subject to errors.

4 The program we have evaluated, OPT, calculates the most likely set of pharmacokinetic parameter estimates for individual patients by applying Bayes' theorem and the principle of Maximum Likelihood Estimation. Through a feedback process all available data are used, taking possible errors into account.

5 Our study shows that OPT is able to predict serum aminoglycoside levels accurately in the routine clinical setting. It may thus contribute to the quality of aminoglycoside therapy.

Keywords aminoglycosides pharmacokinetics Bayes' theorem computer program therapeutic drug monitoring

Introduction

Adequate therapy with aminoglycosides can only be achieved if the serum concentrations of the drug are maintained within certain limits. Departure outside this narrow range may lead to either toxicity or lack of efficacy. The variability in the relationship between dosage of an aminoglycoside and serum drug concentrations has been well documented (Barza *et al.*, 1975; Kaye *et al.*, 1974). Therapeutic drug monitoring of aminoglycosides aims to improve drug therapy by ensuring that the serum drug concentrations lie within this narrow therapeutic range. However, dosage adjustment based only on serum levels can be hazardous due to variations in drug administration, specimen collection and drug analysis (Gorsky & Latts, 1983). A program that uses all available data and takes these possible

errors into account has therefore theoretical advantages.

Sheiner *et al.* (1977) originally proposed such an approach by applying Bayesian Statistical Theory and the principle of Maximum Likelihood to estimate the pharmacokinetic parameters for an individual patient. A program based on these principles (OPT) was developed by Kelman *et al.* (1982a,b). OPT consists of a package of computer programs that estimates the most likely set of pharmacokinetic parameters for an individual patient, using all available data. The optimal dosage schedule can then be determined. The program has been successfully applied to digoxin, theophylline and phenytoin therapy (Whiting *et al.*, 1984).

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We have evaluated OPT for the aminoglycosides, gentamicin and tobramycin.

Methods

Patients

During this study, 138 consecutive patients with a severe illness that was proven or suspected to be bacterial in origin were treated with gentamicin or tobramycin. Only patients with stable renal function (change in serum creatinine less than $50 \mu\text{mol l}^{-1}$ during study) were accepted. One hundred and twenty-nine patients (73 male) of which 57 had an impaired renal function, fulfilled this criterion (data in Table 1).

Data acquisition

Relevant data such as height, age, sex, body weight and serum creatinine were obtained at the first consultation of the microbiologist. Creatinine clearance was obtained from Jelliffe's nomogram (1973). Impaired renal function was defined as a creatinine clearance of 60 ml min^{-1} or less. Initial dosage was calculated using either the nomogram from Hull *et al.* (1976) or the program from Hallynck *et al.* (1981).

Gentamicin ($n = 64$) was given in combination with cephamandole, tobramycin ($n = 65$) in combination with ticarcillin (Young, 1983). Drug administration and blood sample collection was done by the ward nurses. They were not informed of the study.

The aminoglycoside was administered in a

20 min i.v. infusion. The first serum concentrations were taken after 24–36 h. A set of two serum drug levels was collected: a 'trough' immediately before the next dose and a 'peak' defined at 1 h after the start of the infusion. Drug analysis was performed within 2 h after blood sampling to make a dosage adjustment possible before the next dose.

Drug assay system

Analysis of the aminoglycosides was performed with the fluorescent polarised immunoassay (TDx, Abbott Laboratories, North Chicago, USA). The between assay coefficient of variation was below 5%.

Estimation of the pharmacokinetic parameters

Using the aforementioned patient data and the serum aminoglycoside levels, the most likely set of pharmacokinetic parameters, clearance and volume of distribution, for the individual patient and the predicted serum levels for a given dosage were calculated by OPT. Dosage was adjusted if necessary. In some of the patients ($n = 11$) dosage adjustment could not be performed with OPT because the program was not always available at weekends. Therefore 118 patients were eventually used to assess the number of patients within the therapeutic ranges before and after using OPT.

OPT runs on a Sirius (Victor 9000) micro-computer and is currently also available for the IBM-PC and compatible machines (Nodecrest Ltd, Byfleet, UK).

Table 1 Patient data

	Mean $\pm$ s.d.	Range
Age	56.2 ± 18.4	14–87 years
Body weight	68.7 ± 13.4	45–140 kg
Height	170.9 ± 9.0	150–191 cm
Serum creatinine	104 ± 55	45–320 $\mu\text{mol l}^{-1}$
Creatinine clearance	78 ± 42	12–201 ml min^{-1}
Initial dosage	332 ± 100	100–600 mg day^{-1}
Final dosage	352 ± 126	100–640 mg day^{-1}
	5.28 ± 2.15	1.38–13.9 $\text{mg kg}^{-1} \text{ day}^{-1}$
Volume of distribution*	17.5 ± 3.6	10.9–33.3 l
	0.26 ± 0.05	0.18–0.40 l kg^{-1}
Clearance*	3.9 ± 1.8	1.1–10.5 l h^{-1}
Elimination half-life*	3.9 ± 2.2	1.3–12.1 h

*Pharmacokinetic parameters of gentamicin and tobramycin as calculated by OPT.

The data of the patients treated with gentamicin and with tobramycin were combined, because the pharmacokinetic properties of the drugs are identical (Regamey *et al.*, 1973). Therapeutic goal was defined as peak levels between 6 and 10 mg l⁻¹ with trough levels below 2 mg l⁻¹ (Young, 1983). In severely ill patients with impaired renal function, trough levels below 4 mg l⁻¹ were accepted to avoid prolonged periods at subtherapeutic levels.

Statistical analysis

The statistical comparison of the predicted and actual trough and peak levels was made by calculating the prediction error (predicted - observed value) for each sample and then determining the mean and standard deviation of the prediction error. The unpaired *t*-test was used to show whether or not the mean prediction error differed significantly from zero.

Results

Seven out of the 129 patients died during or within 48 h after the aminoglycoside course. Five of these patients were treated with tobramycin. Another 15 patients died later during the hospital stay (range 3 days to 4 months). No significant differences could be detected with respect to age, sex, weight, creatinine and initial serum levels of the aminoglycoside between the groups of patients who died during the aminoglycoside course and the other patients (unpaired *t*-test or Chi-square test).

The nine patients not included in the study, because the serum creatinine rose more than 50 µmol l⁻¹, had a period of prolonged, severe circulatory failure documented before or at the initiation of aminoglycoside therapy.

Plots of predicted vs measured serum aminoglycoside levels are depicted in Figures 1 and 2. The correlation coefficients for the trough and peak concentrations were 0.88 and 0.82 respectively ($P < 0.0001$). A plot of the residuals against the fitted values (Y-fit) gave no indication for the existence of a systematic error.

The mean prediction errors were -0.06 ± 0.39 mg l⁻¹ for the trough levels and 0.05 ± 0.79 mg l⁻¹ for the peak levels respectively. They were not different from zero.

No significant difference could be detected when the prediction errors were compared for different groups of patients (Table 2). A frequency distribution of the prediction errors was plotted for the trough and peak levels (Figures 3

Figure 1 Correlation between predicted and measured trough serum drug concentrations.

Figure 2 Correlation between predicted and measured peak serum drug concentrations.

and 4). The distribution of the trough prediction errors appears symmetrical.

The frequency distributions of the actual aminoglycoside trough and peak concentrations, before and after optimisation with OPT for normal and impaired renal function respectively are shown in Figures 5 and 6. The number of patients with peak serum levels within the therapeutic range increased from 48 (51%) to 95 (89%). The number of patients with trough levels outside the therapeutic range before OPT was 7 (6%) and after OPT 6 (5%).

Table 2 Prediction errors for subgroups of patients

Subgroups	Prediction error	
	Peak concentrations (mg l ⁻¹)	Trough concentrations (mg l ⁻¹)
Type of drug		
Gentamicin (n = 64)	-0.06 ± 0.79	-0.07 ± 0.41
Tobramycin (n = 65)	0.15 ± 0.79	-0.06 ± 0.32
	NS	NS
Renal function		
Impaired (n = 57)	0.01 ± 0.90	0.08 ± 0.38
Normal (n = 72)	0.08 ± 0.72	-0.05 ± 0.35
	NS	NS
Sex		
Male (n = 73)	0.03 ± 0.80	-0.07 ± 0.36
Female (n = 56)	0.08 ± 0.81	-0.05 ± 0.38
	NS	NS
Body mass index		
< 27 kg m ⁻² (n = 107)	0.02 ± 0.80	-0.04 ± 0.37
> 27 kg m ⁻² (n = 22)	0.22 ± 0.75	-0.10 ± 0.32
	NS	NS

Data expressed as mean ± s.d.

NS is not significant, unpaired *t*-test. **Figure 3** Frequency distribution of the prediction errors (predicted concentration - actual concentration) for the trough serum drug concentrations.

Figure 4 Frequency distribution of the prediction errors (predicted concentration - actual concentration) for the peak serum drug concentrations.

Figure 5 Frequency distributions of measured serum drug concentrations before and after optimisation for patients with normal renal function.

Figure 6 Frequency distributions of measured serum drug concentrations before and after optimisation for patients with impaired renal function.

Discussion

Aminoglycosides are antimicrobial drugs used in the treatment of serious gram negative bacterial infections. Their great potency coincides firstly with a narrow therapeutic range and secondly with a variable relationship between dosage and serum concentrations (Barza *et al.*, 1975). This makes careful dosing mandatory and justifies the considerable attention given to this class of drugs in clinical pharmacokinetics consultative activities. Aminoglycoside pharmacokinetic counselling has been shown to be cost effective (Schloemer & Zagozen, 1984).

Tables, nomograms and computer programs based on patient factors, such as weight, height, sex and serum creatinine, are available to aid in aminoglycoside dosing (Chan *et al.*, 1972; Hull & Sarubbi, 1976; Schentag & Adelman, 1983). However, because of their severe illness, patients eligible for aminoglycoside therapy may have pharmacokinetic characteristics that deviate from the population parameters used in standard nomograms. Validation of the weight and height is often impossible in these patients because of their serious illness. The values obtained in our study were the best guess by the physician. The accuracy of these patient parameters is questionable. Furthermore, serum creatinine gives a poor estimate of aminoglycoside clearance

(Davey *et al.*, 1984). This may result in serum drug levels outside the therapeutic range (Ris-tuccia & Cunha, 1982).

Acquisition of serum drug levels is mandatory for optimisation of aminoglycoside therapy. Not only for patients with impaired renal function, but also for patients with normal renal function because they often receive an inadequate dosage of the antibiotic (Reymann *et al.*, 1979). However, serum drug levels are also subject to errors (Gorsky & Latts, 1983).

Because all data obtained in the often hectic daily routine of a hospital ward are prone to inaccuracy, results must be interpreted in the light of the reality that errors take place. A program such as OPT, that uses all available data and takes these errors into account has the advantage that an error in the available data cannot easily result in a deleterious change in therapy. OPT warns the user when data entered leads to unlikely parameter estimates (outwith two standard deviations of the initial population parameter estimates) and will only resume the calculations at the operator's discretion.

Our study shows that OPT is able to predict serum aminoglycoside levels accurately. This is based on the high correlation between predicted and actual serum drug peak and trough levels and the fact that the prediction errors were not significantly different from zero. The magnitude

of the errors taken into account by OPT is apparently sufficient to correct for these aforementioned errors. Thus the values of volume of distribution and clearance estimated by OPT using average population parameters and serum concentrations of gentamicin and tobramycin have lead to the 'most likely' set of pharmacokinetic parameters for the individual patient.

Errors are inevitable in the daily hospital routine, therefore all programs or nomograms should be tested under these circumstances before anything meaningful can be said about their applicability in the hospital setting.

The initial dosage in our study was taken from standard nomograms. A considerable number of patients had initial serum drug levels outside our desired therapeutic range. It seems safe to conclude from these data that the nomograms used are more concerned about preventing toxicity than about guaranteeing efficacy, since 50 patients (42%) had peak serum levels below 6 mg l^{-1} . It has been shown that adequate initial peak serum levels are mandatory for a favourable outcome (Noone *et al.*, 1974). As is shown in the present study, there was a significant improvement in the number of patients with serum levels inside the therapeutic range after optimisation.

Only patients with a stable renal function (serum creatinine fluctuations $< 50 \text{ } \mu\text{mol l}^{-1}$) were included in this study. Unstable situations

call for more frequent concentration measurements. In severely ill, haemodynamically unstable patients it may even be necessary to obtain trough levels before each dose to guarantee optimal treatment. OPT could be useful under these circumstances where the parameters are revised at more frequent intervals. The down weighting of the effect of previously entered data by OPT ensures that the latest measurement has the greatest influence on the calculations. However, it remains to be determined whether or not those corrections are sufficient to adjust for the rapid changes in pharmacokinetic characteristics that may occur in unstable patients.

Some computer programs available use two compartments for the pharmacokinetic model. Our study shows that with a one compartment model satisfactory results can be obtained. This is in agreement with Hatton *et al.* (1984), who stated that a two compartment model has no advantages over the one compartment model for clinical purposes.

In conclusion, OPT predicts serum levels reliably and contributes through its flexibility to the quality of routine aminoglycoside therapy.

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