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Intra-ocular concentration-time relationships of subconjunctivally administered gentamicin

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Summary

Eighty-nine patients scheduled for cataract removal or lens implantation were divided randomly into three groups. Each received 5, 10 or 20 mg gentamicin subconjunctivally at times varying between 0,2 and 19 hours pre-operatively. At surgery a sample of aqueous humour was obtained and analysed for gentamicin concentration. The data for each group were subjected to non-linear regression analysis to fit an open one-compartment pharmacokinetic model with first-order kinetics. A statistically acceptable fit was obtained.

The average values of the pharmacokinetic parameters obtained from the single doses were used to simulate multiple-dose kinetics. The average target intra-ocular gentamicin concentrations and dosage interval were specified in the computer program, which subsequently allowed calculation of the dose required. This allowed the construction of a simple linear nomogram that can be used to read off the dose needed for handling specific clinical situations.

The aminoglycoside antibiotic, gentamicin, is a valuable agent for treatment of severe bacterial eye infections as well as for pre-operative prophylaxis. Its hydrophilic nature excludes topical application in eye drops as an effective method to achieve bactericidal concentrations in the aqueous humour. Soft contact lenses soaked with the drug can, however, be used successfully because the time allowed for diffusion is lengthened considerably.[1] Intravenous and intramuscular injections are ineffective routes of administration because of the resulting low concentration-gradient required across the blood-eye barrier. It is reasonable to assume that the required increased gradient for significant diffusion across the barrier would give rise to the well-known oto- and nephrotoxic side-effects of the aminoglycosides.[2] Subconjunctival or retrobulbar injections are therefore the preferred methods of administration in order to assure adequate concentrations in different tissues of the eye.

Several reports[3-10] have dealt with gentamicin concentration-time relationships in the eye after subconjunctival or retrobulbar injections. Apart from those in experimental animals,[6,9,10] the concentrations of gentamicin in humans were measured in the aqueous humour, the vitreous humour and cornea.[3-5] A high degree of interpatient variation was evident in all these studies. Furthermore, diffusion into different tissues of the eye is apparently governed by different rate constants and consequently no efforts have been made to establish on a pharmacokinetic basis a dosing strategy that would ensure adequate concentrations in the eye over a specific period.

We have studied the aqueous humour concentrations of subconjunctivally injected gentamicin as a function of time after single fixed doses in patients elected for eye surgery. The data were analysed as a single-dose one-compartment pharmacokinetic model. Simulated concentration-time relationships of multidose regimens were constructed using the average pharmacokinetic parameters. This enabled us to calculate the doses needed at specific intervals in order to achieve an average specified target concentration in the aqueous humour. We believe that these guidelines can assist the clinician in treating different bacterial infections with adequate doses and dosage intervals.

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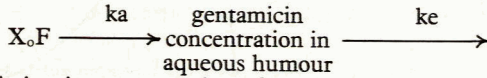D. F. DU TOIT, M.B. CH.B., F.C.S. (S.A.), PH.D. (MED.), F.R.C.S.
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Patients and methods

Patients scheduled for cataract extraction and/or lens implantation were divided randomly into three groups who received 5, 10 or 20 mg gentamicin subconjunctivally at times varying from 0,2 hours to 19 hours pre-operatively. Each dose was administered in 0,5 ml saline by a team of surgeons who followed a similar technique of subconjunctival injection, i.e. the conjunctiva was penetrated between the limbus and 10 mm from the limbus with the needle parallel between the

conjunctiva or Tenon's fascia and sclera. The injection was given 10 mm from the puncture and allowed to spread without much pressure build-up. The area and position of spread was noted.

The age of the 89 patients used in this study varied from 54 years to 88 years (mean 70 years).

At surgery a sample of 50 μl aqueous humour was obtained and analysed within 3 hours for gentamicin concentration by enzyme-mediated immunotechnology (EMIT, Syva, Palo Alto, California, USA). Appropriate controls and standards were run with each patient sample in order to ensure maximum accuracy and minimum day-to-day and batch variation.

The data from each group was treated as a one-compartment open pharmacokinetic model with first-order absorption and elimination:

$$X_oF \xrightarrow{k_a} \begin{array}{c} \text{gentamicin} \\ \text{concentration in} \\ \text{aqueous humour} \end{array} \xrightarrow{k_e}$$

Variation in concentration of gentamicin in intra-ocular fluid (C) with time (t) is described by the expression:

$$C = \frac{k_a \, F \, X_o}{V_d \, (k_a - k_e)} \; (e^{-k_e t} - e^{-k_a t})$$

where X_o = dose
  F = fraction of drug absorbed
  k_a = absorption rate constant
  k_e = elimination rate constant
  V_d = volume of distribution.

Non-linear regression analysis for each data set at a fixed dose was performed using the program STATIS 2 (Clydesoft Statistical and Scientific Software, Larkhall, UK). The Akaike information criterion and Schwarz value were used as measures of good fit while P-values and correlation coefficients (r) were calculated according to standard statistical methods.[11,12]

Standard equations derived from pharmacokinetic theory[13,14] were used to calculate elimination half-life (t½) in hours, clearance (Cl) in ml/h, volume of distribution (Vd) in ml and area under the concentration time curve (AUC) in μg/ml/h.

A computer simulation program based on the average values of the parameters of the pharmacokinetic model obtained for the three single doses (5, 10 and 20 mg) was written in TURBO BASIC in order to estimate various dosing strategies according to standard theory of multiple-dose pharmacokinetics.[13,14] The program enabled us to specify an average target intra-ocular gentamicin concentration and the dosage interval in hours with subsequent calculation of the required dose and maximum and minimum and time-to-peak gentamicin concentrations.

Results

Fig. 1 depicts the variation in intra-ocular gentamicin concentration with time for the 5, 10 and 20 mg doses respectively. Each point represents an individual patient (23 each for the 5 and 10 mg doses and 43 for the 20 mg doses). The wide scatter is obviously related to interpatient variation. Nevertheless a statistically acceptable fit for each dose was obtained, as shown by the Alkaike, Schwarz, r- and P-values summarised in Table I.
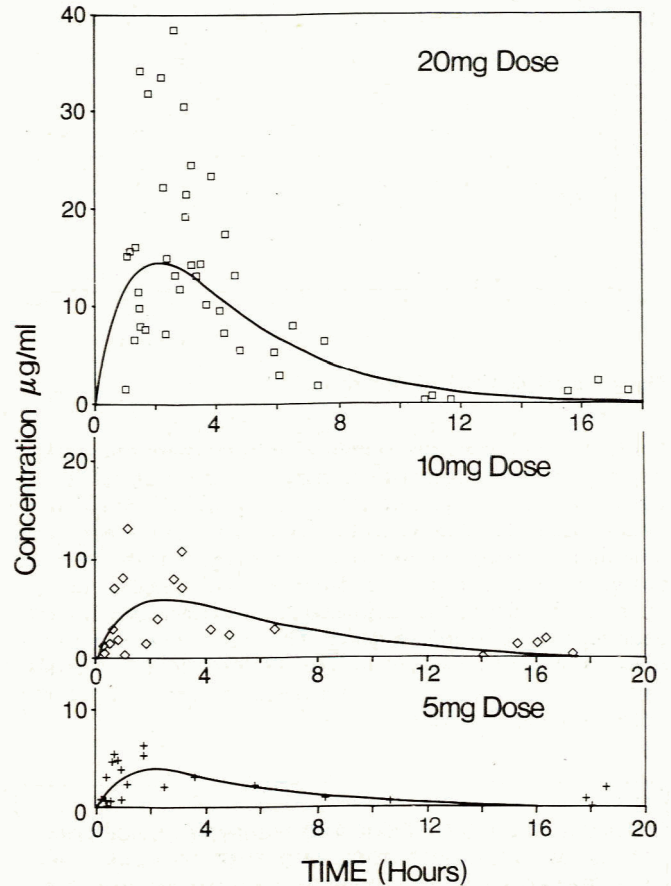

Fig. 1. Variation of intra-ocular gentamicin concentration with time after single subconjunctival doses of 5, 10 and 20 mg. Each point represents the value found in a patient's aqueous humour. The curves represent the best fit of an open single-compartment pharmacokinetic model.

	Dose (mg)			
	5	10	20	Mean $\pm$ SD
Ke (/h)	0,239	0,216	0,393	0,283 $\pm$ 0,079
Ka (/h)	0,847	0,657	0,433	0,646 $\pm$ 0,169
t½ (h)	2,9	3,2	1,77	2,623 $\pm$ 0,616
Cl/F (ml/h)	183,0	209,0	172,0	188,00 $\pm$ 15,513
Vd/F (ml)	770,0	965,0	437,0	724,000 $\pm$ 217,995
AUC (0 $\rightarrow \infty$)	27,4	47,8	116,6	
Akaike value	97,7	135,0	342,0	191,567 $\pm$ 107,457
Schwarz value	101,0	138,0	347,0	195,333 $\pm$ 108,303
r-value	0,603	0,563	0,646	0,604 $\pm$ 0,034
P-value	< 0,01	< 0,01	< 0,001	

TABLE I. RESULTS OF PHARMACOKINETIC MODELLING OF THE DATA SHOWN IN FIG. 1

Fig. 2 shows a linear relationship between the AUC and the three doses employed ($r = 0,994$). It is clear that first-order elimination kinetics was followed for the three doses used and that the pharmacokinetic model employed is a reasonable assumption.
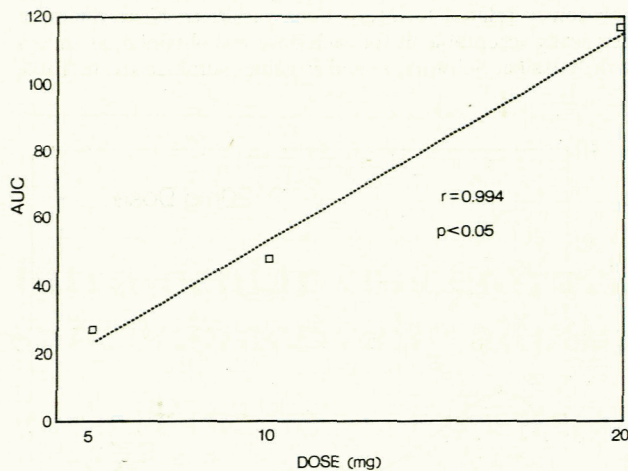

Fig. 2. Correlation of AUC with dose.

Fig. 3 shows computer simulated curves where the average target intra-ocular gentamicin concentration was set at 10 μg/ml and the dosage intervals at 8, 12 and 24 hours. It is evident that the difference between maximum (peak) and minimum (trough) concentrations is the largest at the 24-hour dosage interval and that it decreases with smaller dosage intervals. Similarly, the maintenance dose decreases linearly because of the first-order kinetics. The time to peak concentrations also remains constant for the different dosage intervals. The calculated values are summarised in Table II for the different dosage intervals.
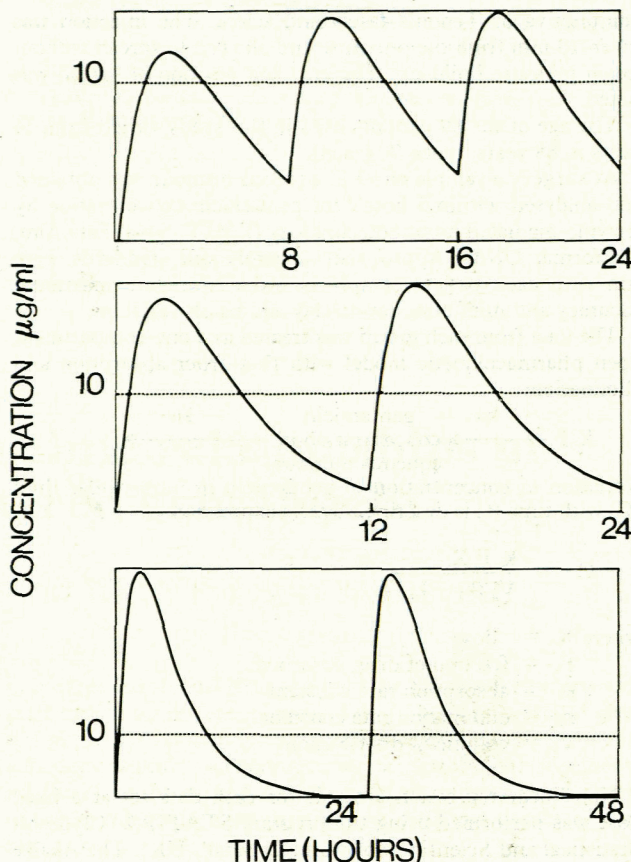

Fig. 3. Computer-simulated concentration-time relationships for 8, 12 and 24-hourly dosage schedule calculated from standard multidose pharmacokinetic equations in which the average values of the parameters of the pharmacokinetic model summarised in Table I were used.

TABLE II. VALUES OF PEAK AND MINIMUM CONCENTRATIONS, MAINTENANCE DOSE AND TIME TO PEAK CONCENTRATION CALCULATED FROM COMPUTER-SIMULATED CURVES WHERE AN AVERAGE TARGET INTRA-OCULAR CONCENTRATION OF 10 μg/ml GENTAMICIN AND THE DOSE INTERVAL ARE SET (FIG. 3)

	Dose interval (h)		
	24	12	8
Peak concentration (μg/ml)	40,41	21,08	15,46
Minimum concentration (μg/ml)	0,14	2,07	4,45
Maintenance dose (mg)	49,17	24,59	16,39
Time to peak concentration (h)	1,84	1,81	1,74

Discussion

Normally the pharmacokinetic behaviour of a drug is determined by using concentration-time relationships obtained from a series of samples from one individual. Data of this nature can, however, not be obtained from the eyes of human patients. We therefore used a sample of individual patients to obtain analysable data.

To test the linearity of the system, three different doses were employed. The simplest models providing acceptable fitting were open, single-compartment models with first-order elimination kinetics (Fig. 2, Table I).

The computer-simulated curves for multiple-dose regimens (Fig. 3) assume that the elimination kinetics of gentamicin remain first order. This is a reasonable assumption within the limits of the doses calculated to obtain the maximum average target concentration of 10 μg/ml because it is well known that the aminoglycosides are excreted largely in unaltered form.[2] However, selective distribution and attainment of equilibrium of the antibiotic in different tissues of the eye may alter the model with time into a multicompartment one. It has, for instance, been shown that retrobulbar injection of gentamicin resulted in lower concentrations in the cornea of rabbit eyes than the subconjunctival route.[10]

We feel that the simulations of multiple-dose regimens are of clinical value as they provide guidelines for the concentrations that can be expected in the aqueous humour bearing in mind that the minimum inhibitory concentration of gentamicin ranges from 2 μg/ml to 10 μg/ml for different bacteria.[15]

Fig. 4 illustrates that the first-order character of the pharmacokinetic model results in a linear relationship between the dose and the average target intra-ocular concentrations for different dosage schedules. The choice of dosage schedule is dictated by the accepted difference between maximum (peak) and minimum (trough) concentrations (Fig. 3). The smallest difference is obtained using an 8-hour dosage regimen, while the 24-hour dosage schedule allows the gentamicin levels to fall below the minimum inhibitory concentration for most bacteria (Table II). These considerations together with the use
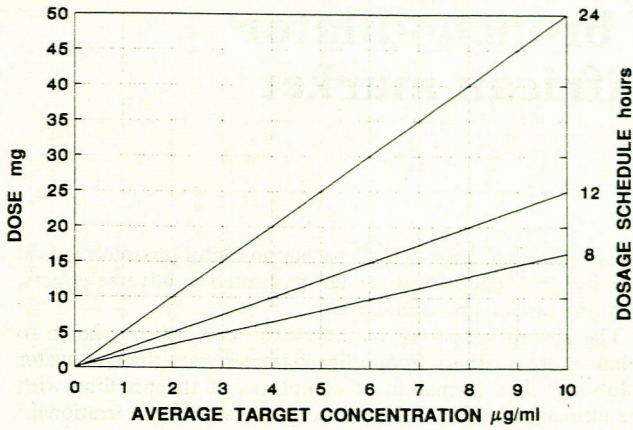
Fig. 4. Relationships between average target intra-ocular concentration and dose for 8, 12 and 24-hourly dosage schedules of subconjunctivally injected gentamicin.

of Fig. 4 as a simple nomogram to determine the dose needed for a specified aqueous humour concentration for a fixed dosage schedule should be of value to clinicians in deciding on an appropriate treatment for different bacterial infections.

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