Prediction of amikacin dose requirements in neutropenic patients with haematological disease

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Abstract **This study reports on the use of an easily applied Bayesian forecasting programme (OPT; Clydesoft) to predict amikacin dose requirements in 10 patients with haematological disease and neutropenic fever. OPT-determined dose adjustment achieved therapeutic drug levels for 80% of the peak and 94% of the trough measurements.**

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Aminoglycosides have a narrow therapeutic index and are potentially nephrotoxic and ototoxic. The achievement of therapeutic serum levels is difficult because of individual kinetic variability.[1] We applied a simple but accurate predictive model to the clinical care of neutropenic patients in whom aminoglycoside kinetics may be significantly altered.[2]

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Patients and methods

Ten consecutive patients with haematological disorders were studied in the Department of Haematology, Groote Schuur Hospital, between 10 June and 27 August 1990. Patients were included in the study if they satisfied criteria for neutropenic fever and required antibiotic therapy according to the standard management protocol.

Amikacin therapy was initiated by the treating physicians who decided on the initial dose. Amikacin sulphate (Amikin; Bristol) was administered intravenously over 30 minutes in 0,9% saline or 5% dextrose water. Blood for amikacin assay was taken 1 hour after commencement of dose administration (peak level) and a second sample at 3 hours in 5 patients, 5 hours in 2 patients, and immediately before the next dose in 3 patients. Peak and trough levels (measured 5 minutes before drug administration) were then measured at least twice weekly or more frequently if impaired renal function developed (a rise in serum creatinine level greater than 40 μmol/l). Specimens were assayed for amikacin within 12 hours of collection by the Abbott TDX Polarised Fluorescent antibody method. The lower limit of sensitivity is 0,8 mg/l and levels below this were recorded as 0,4 mg/l. Amikacin pharmacokinetic parameters were estimated using the OPT version 5.1 soft-

TABLE I.
Prediction performance

Pt	Dose	Peak	PRPK	ME	MAE	RMSE	Trough	PRTR	ME	MAE	RMSE
1	11,9	34,6	28,1	1,2	6,9	7,9	8,7	3,8	4,9	4,9	6,0
2	11,3	29,3	26,6	2,7	4,5	5,5	2,0	1,2	0,8	1,0	1,4
3	9,3	26,0	27,4	–1,4	4,0	4,6	1,3	1,0	0,3	0,7	0,9
4	11,5	30,3	31,8	–1,5	4,3	5,6	1,2	0,6	0,6	0,7	0,8
5	9,1	28,1	34,8	–6,7	6,7	6,9	2,9	3,8	–0,9	1,4	2,4
6	9,1	30,6	22,4	8,2	8,2	8,5	2,4	1,0	1,4	2,3	2,5
7	11,7	36,6	26,2	10,4	10,4	10,8	2,8	1,4	1,5	1,5	1,9
8	8,6	22,3	25,5	–3,1	4,9	6,0	4,3	2,4	1,9	1,9	2,0
9	9,8	31,8	29,1	2,8	8,4	8,8	1,5	0,4	1,7	1,7	1,7
10	12,2	31,3	29,1	2,3	6,7	9,1	2,2	0,8	1,0	1,5	1,8
Average	10,5	30,1	28,1	1,5	6,5	7,4	2,9	1,6	1,3	1,8	2,1

Pt = subject patient number; dose = mean of administered dose of amikacin in mg/kg actual body weight; peak = mean achieved peak drug level in mg/l; PRPK = mean predicted peak level derived from OPT in mg/l; ME = mean error of prediction (achieved — predicted level in mg/l); MAE = mean absolute error; trough = mean achieved trough level in mg/l; PRTR = mean predicted trough level derived from OPT in mg/l.

ware package (Clydesoft)[3] on a personal computer. OPT is based on Bayesian statistical probability theory and assumes a single-compartment kinetic model for amikacin. Individual patient kinetics are initially estimated as follows: age, sex, weight, height and serum creatinine level are entered into a population-based nomogram and these estimates are sequentially modified according to the following data input: dose size, time of administration, serum level and sampling time. Data input is time-weighted and additional significance is attributed to the most recent input.

Derived parameters were then used to predict dose size and the frequency required to achieve peak levels of 30 ± 10 mg/l and trough levels not exceeding 6 mg/l. Appropriate dose changes were made within 24 hours of each serum level assay. The accuracy of this approach was assessed by comparison of the predicted with the achieved results. Bias was measured by calculating mean error (ME) and precision by calculating mean absolute error (MAE) and root mean squared error (RMSE). The method was regarded as unbiased if the 95% confidence interval (CI) for mean error (Thompson's test) included 0 and precise if the MAE and RMSE were < 8 mg/l for peak and < 4 mg/l for trough levels. These criteria are based on those of previously published studies that used gentamicin, tobramycin and netilmicin;[4] a conversion factor of 4 was used to derive the limits for amikacin.

Results (Table I)

There were 10 patients (6 male and 4 female); their mean age was 32 years (range 15 - 60), and their mean minimum neutrophil count during therapy $0{,}05 \times 10^9$/l.

Fifty-one pairs of predicted and achieved levels were evaluated; this required 38 batches of amikacin assays. The mean control value (±SD) was 14,7 ± 0,5 mg/l (range 13,9 - 15,6).

The mean amikacin dose requirement was 10,5 mg/kg/dose (range 9,1 - 12,2). The mean (±SD) of the average amikacin levels achieved for each patient was 30,1 ± 4,1 mg/l for peak and 2,9 ± 2,2 mg/l for trough levels; ME for peak levels = 1,5 mg/l (95% CI –2,6 - 6,5 mg/l), MAE = 6,5 mg/l and RMSE = 7,4 mg/l. Peak level predictions were thus unbiased (95% CI for ME includes 0) and precise (MAE and RMSE < 8 mg/l).

ME of prediction for trough levels = 1,3 (95% CI 0,4 - 1,8). MAE = 1,8 and RMSE = 2,1. Trough level predictions were biased (95% CI did not include 0) but precise (MAE and RMSE < 4 mg/l).

Therapeutic peak levels (20 - 40 mg/l) were achieved for 80% of predictions and non-toxic trough levels (not exceeding 6 mg/l) for 94% of predictions.

Therapeutic peak and trough levels were achieved in 7 patients (70%) after the first kinetic prediction. One patient had toxic peak and trough levels, one had a toxic peak level only and one had sub-therapeutic peak levels.

Discussion

The predictive accuracy achieved in this study compares well with that reported for this method in non-neutropenic patients[4] and with the use of a non-Bayesian method in neutropenic patients.[5] The finding of a biased trough level prediction is probably the result of entry of values of amikacin levels less than 0,8 mg/l as 0,4 mg/l in the predictive model, but appears to be of little clinical significance as 94% of the trough amikacin levels were in the non-toxic range. The three toxic trough levels in this study occurred in a patient with rapidly deteriorating renal failure who subsequently died.

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