Multiple-Dose Non-Linear Regression Analysis Program
Aminoglycoside Dose Prediction

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Summary

The ability of a new multiple-dose non-linear regression analysis program to predict steady-state aminoglycoside peak and trough serum concentrations was evaluated. 30 patients receiving either amikacin (7), gentamicin (10) or tobramycin (13) were studied. A standard method of prediction which requires the collection of 3 or 4 serum samples during a dosing interval and a predictive method which relies upon population-based estimates of pharmacokinetic parameters were compared with the new approach which requires the collection of 2 serum samples. There were no significant differences between the methods which utilised serum concentration data with regard to predictive precision (mean prediction error about 10%). These methods were more precise than the population-based method (p < 0.01, mean prediction error 29.1%). None of the methods produced biased estimates.

These results indicate that when the regression program is employed, valid estimates of pharmacokinetic parameters and prediction of steady-state serum concentrations can be obtained with fewer serum samples than have been recommended.

Individualised optimisation of aminoglycoside therapy using serum concentration data is frequently attempted. The controversies involved in this practice have been thoroughly reviewed (Barza and Lauermann, 1978). If one accepts the desirability of achieving a particular peak and trough steady-state serum concentration in an individual patient, there are several methods which can be used. Hull and Sarubbi (1976) have recommended a method which is based upon the linear relationship of the elimination rate constant (Ke) of aminoglycosides to the estimated creatinine clearance (CLcr) \[ K_e \text{ (in hours}^{-1}) = 0.01 + 0.0024 \times \text{CLcr} \] and which assumes a constant volume of distribution (Vd) of 0.26 L/kg of lean bodyweight. This method does not require measurement of serum aminoglycoside concentrations. Sawchuk and Zaske (1976) have recommended a more rigorous approach whereby Ke and Vd were determined for an individual patient, using 3 or 4 serum concentration values obtained during a dosing interval. They justify this approach by demonstrating marked variation in both Ke and Vd in patients with relatively normal renal function (Zaske et al., 1982). Bootman et al. (1979) have demonstrated a favourable cost-benefit ratio for this approach to
aminoglycoside therapy in burn patients.

It was the purpose of this study to compare predictive performance of these 2 approaches to that of a newly developed multiple-dose non-linear least squares regression analysis program (Koup and Horn, 1983). This program estimates individual patient pharmacokinetic parameters using only 2 serum concentration values collected during the course of routine therapy.

**Methods**

30 non-obese patients aged 51.8 ± 15.2 years (mean ± SD) for whom aminoglycoside pharmacokinetics had been evaluated by 1 of us (L.A.B.) were selected. Patients were chosen in whom good agreement existed between observed steady-state peak and trough concentrations and those predicted by the method of Sawchuk and Zaske (1976). The reason for this arbitrary selection was so we could detect errors that might be attributable to the computer methods we were evaluating (see Discussion). Differences between observed and predicted peak and trough concentrations were 0.57 ± 0.59 µg/ml and 0.31 ± 0.31 µg/ml, respectively. Tobramycin and gentamicin samples were analysed using a homogeneous enzyme immunoassay (EMIT®); amikacin samples were analysed using a fluorescent immunoassay (TDM®). The coefficients of variation observed over a 30-day period were less than 8% for high and low controls.

Seven patients received amikacin, 10 were given gentamicin and 13 received tobramycin. Four serum samples had been collected in each patient during a dosing interval early in the course of aminoglycoside therapy (the interval studied was between the first and the sixth maintenance dose). The dosage interval times varied, depending upon the estimated elimination half-life (Hull and Sarubbi, 1976). An initial sample (C1) was collected just before the study dose and a second (C2) after a 60-minute infusion of the dose. The third and fourth samples (C3 and C4) were collected during the elimination phase. C4 was collected within 30 minutes of the next dose and C3 was collected at a time halfway between C2 and C4. These data were analysed by the standard method of Sawchuk and Zaske (1976) which resulted in estimates of $K_e$ and $V_d$ for the individual patients. The resultant parameter estimates for the study population are shown in figure 1. Table I lists patient dose histories.

The estimated values $K_e$ and $V_d$ were then used to predict steady-state peak ($C_{peak}$) and trough ($C_{trough}$) concentrations according to the following equations:

$$C_{peak} = \frac{(D/T) \left(1 - e^{-K_e T}\right)}{K_e V_d \left(1 - e^{-K_e T}\right)}$$  (Eq. 1)

$$C_{trough} = C_{peak} \cdot e^{-K_e (\tau - T)}$$  (Eq. 2)

where D is the dose, T is the duration of infusion and $\tau$ is the dose interval. This prediction method for steady-state peak and trough concentration is referred to as method A. Actual steady-state peak and trough concentrations were measured in each patient after at least 4 half-lives of maintenance therapy.

Steady-state peak and trough concentrations were also predicted using equations 1 and 2, and $K_e$ and $V_d$ estimates derived for each patient from the relationships proposed by Hull and Sarubbi (1976) [method B]; this method assumes that $K_e$ and $V_d$ are independent parameters. The elimination rate constant ($K_e$) was estimated as follows:

$$K_e (\text{in } h^{-1}) = 0.01 + 0.0024 \times CL_{cr}$$  (Eq. 3)

where $CL_{cr}$ is the estimated creatinine clearance in ml/min. The method of Cockcroft and Gault (1976) was employed to estimate $CL_{cr}$. Vd was assumed to be 0.26 L/kg of ideal bodyweight. Since none of our patients were obese, total bodyweight was employed.

Finally, a multiple-dose modification (Koup and Horn, 1983) of a previously reported (Koepppe and Hamann, 1980) non-linear regression analysis program was used to estimate $V_d$ and aminoglycoside clearance (CL). This program assumes a 1-compartment linear model with a drug administration by periodic intravenous infusion; CL and $V_d$ are treated as independent parameters. The program