Comparison of Sawchuk-Zaske and Bayesian forecasting for aminoglycosides in seriously ill patients

CHARLES P. DENARO & PETER J. RAVENSCROFT

Department of Clinical Pharmacology, Princess Alexandra Hospital, Ipswich Road, Woolloongabba, Brisbane, Queensland, Australia 4102

1 Individual pharmacokinetic parameters and predicted steady-state serum concentrations of aminoglycosides were calculated by Sawchuk-Zaske (SZ) and Bayesian methods.

2 Predicted concentrations were compared with observed steady-state concentrations for 36 seriously ill patients with systemic infections. Four aminoglycoside concentrations were used for the SZ method. Differing numbers of serum aminoglycoside samples were used in the Bayesian parameter estimation: one sample Bayesian used one post-infusion concentration, two sample Bayesian used a trough plus one post-infusion concentrations and four sample Bayesian used a trough plus three post-infusion concentrations.

3 79% of the SZ predictions were within $\pm 2 \text{ mg l}^{-1}$ of the observed peak concentrations, and 72% of the two sample Bayesian predictions were within the same range. 82% of SZ and the two sample Bayesian predictions were within $\pm 1 \text{ mg l}^{-1}$ of the observed trough concentrations.

4 A confidence interval comparison of estimated pharmacokinetic parameters and precision for the predicted concentrations showed no important differences between the SZ and the two sample Bayesian. The four sample Bayesian was the most precise method.

5 We conclude that the Bayesian forecasting method utilizing a trough plus one post-infusion concentrations is as useful as the SZ method which requires three to four serum concentrations in individualizing aminoglycoside therapy for seriously ill patients.

Keywords aminoglycosides pharmacokinetics

Introduction

The wide interpatient variation in aminoglycoside pharmacokinetics (Barza *et al.*, 1975; Zaske *et al.*, 1982a) has led to a number of methods being used to individualize therapy (Chan *et al.*, 1972; Hull & Sarubbi, 1976; Sawchuk *et al.*, 1977; Burton *et al.*, 1985). Aminoglycoside pharmacokinetic parameters may be greatly changed in patients who are seriously ill with septicaemia and/or have large fluctuations in their extra-cellular fluid volume (Pennington *et al.*, 1975; Zaske *et al.*, 1976; Denaro & Ravenscroft, 1987; Lacarelle *et al.*, 1987). The importance of the correlation

between peak serum aminoglycoside concentrations and clinical outcome is now widely accepted (Jackson & Riff, 1971; Noone *et al.*, 1974; Moore *et al.*, 1984a,b). Methods used to individualize therapy must (1) accurately estimate volume of distribution (*V*) and clearance (*CL*), so that desired peak drug concentrations are attained, (2) have the ability to predict changes in aminoglycoside pharmacokinetic parameters that occur with disease, (3) be easily implemented and (4) be cost effective.

The least squares regression or Sawchuk-Zaske (SZ) method (Sawchuk & Zaske, 1976)

Table 1 Patient characteristics

Age (years)	47.7 (16.7) (17–69)
Sex	M 24 (66%) F 12 (33%)
Weight ^b (kg)	66.4 (13.3) (45–93.6)
Serum creatinine ^{b1} (mg%)	1.02 (0.34) (0.57–1.81)
Estimate CL _{Cr} ^{b1} (ml min ⁻¹ kg ⁻¹)	1.41 (0.51) (0.51–1.92)
Temperature ^b (°C)	38 (0.8) (37–40)
Aminoglycoside:	
Gentamicin	24 (66%)
Tobramycin	12 (33%)

^a Results expressed as mean, (s.d.), (range).

^b At the start of aminoglycoside therapy.

¹ seven patients above normal range.

² Creatinine clearance (CL_{Cr}) calculated by Cockcroft-Gault formula. Eight patients below 1 ml min⁻¹ kg⁻¹.

has been widely used to individualize aminoglycoside therapy. This has been shown to be far superior to empirical dosing schedules, nomograms and physician intuition for aminoglycoside therapy (Lesar *et al.*, 1982; Platt *et al.*, 1982; Begg *et al.*, 1985). Bayesian statistical methods have also been used in dose prediction (Sheiner *et al.*, 1975; Vozeh *et al.*, 1981; Burton *et al.*, 1985; Iliadis *et al.*, 1985). This method has a number of potential advantages over the SZ method including the possibility that it may require fewer serum drug concentrations for adequate forecasting.

The aim of this study was to compare the predictive ability of the SZ and Bayesian methods for aminoglycoside therapy in seriously ill patients, using a protocol which would identify the minimum number of serum drug concentrations that would give accurate pharmacokinetic forecasting.

Methods

Patients

Thirty-six patients were evaluated by both methods (Table 1). Three patients had two separate evaluations. Twenty-eight patients were febrile and six had mild impairment of renal function. The diagnoses of these seriously ill patients are listed in Table 2. Forty-two per cent came from the Intensive Care Ward, 39% from

Table 2 Patient diagnoses

Neutropenia and sepsis	14 (39%)
Chest infection	10 (28%)
Peritonitis	4 (11%)
Cholangitis/liver abscess	3 (8%)
Burns	2 (6%)
Others	3 (8%)

the Haematology/Oncology Unit and the remainder from general medical and surgical wards.

Pharmacokinetic prediction methods

(a) *Sawchuk-Zaske (SZ) method:* The rate constant of disposition (*k*) is estimated from a least squares regression of three post-infusion concentrations (Sawchuk & Zaske, 1976). *V* and *CL* are then calculated from one compartment model equations. A desired peak concentration of 8 mg l⁻¹ and a desired trough concentration of 1.5 mg l⁻¹ were selected as treatment goals. These concentrations are generally accepted to be therapeutic and nontoxic (Wenk *et al.*, 1984). The dose and dosing intervals to provide these concentrations were then calculated using the estimated pharmacokinetic parameters. A computer program written in BASIC was used to perform these tasks. The new dosing regimen was instituted on the same day as the dose was given.

(b) *Bayesian method:* This was based on the method of Sheiner *et al.* (1972, 1979) and Sheiner & Beal (1982). The program requires height, weight, serum creatinine, age and sex of the patient. A computer program designed by Abbott Diagnostics which runs on IBM compatible microcomputers was used for the calculations (Abbott Pharmacokinetic Systems Aminoglycoside Program Operations Manual Version 1, 1986, Abbott Laboratories Diagnostic Division, PO Box 152020, Irving, Texas, 75015). The initial parameters used for the Bayesian prediction were: Slope 0.815 (s.d., 0.326); non-renal clearance 0.0417 (s.d., 0.0104); volume of distribution 0.25 (s.d., 0.075).

Sampling procedure

A dose of gentamicin or tobramycin was given by infusion over 30 min to minimize the initial distribution phase of the drug. This procedure was either supervised by the attending nurse to ensure that the infusion was constant or given by an infusion pump. The times when the

infusion began and finished were recorded. The giving set was flushed through at the end of the infusion. Three post-infusion blood samples were taken over at least one and often two-three half-lives. The average duration over which the concentrations were taken was 1.4 half-lives. If the patient had been receiving an aminoglycoside prior to the administration of this dose, a pre-infusion (trough) blood sample was also taken. Eighty-one per cent of patients had this dose within 48 h of the commencement of their aminoglycoside therapy.

To monitor the therapy and to assess the predictability of the SZ method, peak (30 min after the end of the infusion) and trough concentrations were measured 24 h after the new dosing regimen had commenced. These were steady-state concentrations taken four-five half-lives after the commencement of the new predicted dosing regimen.

The patient data and serum drug concentrations used for the SZ method were also used in the Bayesian program. However three differing combinations of concentrations were used to estimate the parameters: one sample Bayesian used only the second post-infusion concentration, two sample Bayesian used the trough plus the second post-infusion concentration and four sample Bayesian used the trough plus all three post-infusion concentrations. We chose the second post-infusion concentration which was taken on average 2.2 h after the infusion (range 1.5 to 3.5) because the sampling time for this concentration was convenient with respect to ward routine. Each combination of the serum drug concentrations used in the Bayesian program was used for separate calculations of the pharmacokinetic parameters V and CL . The dosing regimen which was actually given to the patients was then used in the dose-estimator section of the Bayesian program which in turn used the calculated values of V and CL . Thus, the program would predict the resulting peak and trough steady-state concentrations from the administered dosing regimen. These predicted concentrations could then be compared with the observed steady-state concentrations. Four series of estimates were compared—one SZ and three sets of Bayesian estimates using different combinations of serum concentrations.

Assay

Aminoglycoside concentrations were measured by fluorescence polarization immunoassay (TDX, Abbott) (Jolly *et al.*, 1981) which had an interday coefficient of variation of 4.5%.

Statistical analysis

The analysis suggested by Sheiner & Beal (1981) was used. The bias or mean error (ME) and precision or mean square error (MSE) were calculated for the predicted concentrations. These data and the pharmacokinetic parameters were tested for normality using the Shapiro-Wilk test (Zar, 1984). Depending on the results, a parametric two way analysis of variance (ANOVA) or nonparametric two way ANOVA (Friedmans test), in association with a corresponding Tukey multiple comparison test, was used to analyse differences (Zar, 1984). Only differences between the chosen 'standard' method and all other methods were recorded.

The confidence interval analysis used a log ratio method (Bolton, 1984). The difference between methods was expressed as a percentage difference from the 'standard' method. For the pharmacokinetic parameters the SZ method has been chosen as the standard. If the population mean difference was 20% or greater between any two methods, it was classified as an important difference. The confidence interval was calculated for 95% confidence and used the log error mean square as an estimate of the variance.

Since ME and MSE contain negative or zero values the log ratio method of calculating confidence intervals is not possible. We compared the predicted concentrations directly to assess the mean population difference between all other methods and the most precise method.

Results

Table 3 displays the estimated pharmacokinetic parameters for all methods. There was a wide variation in these parameters as expected in seriously ill patients. As calculated by SZ, the V ranged from 0.16 to 0.47 l kg⁻¹, a three-fold difference. CL ranged from 0.04 to 0.15 l kg⁻¹ h⁻¹, a four-fold difference (Denaro & Ravenscroft, 1987). There were statistically significant differences in Bayesian estimates of V and CL when compared with SZ, but the confidence interval analysis showed that all those differences were less than 20%.

The mean errors in the Bayesian methods for estimating peak concentration were statistically different from SZ, which had the smallest mean error (Table 4). However, the most precise method for peak concentrations was the four sample Bayesian and only the one sample Bayesian was statistically different (Table 5).

Table 3 Pharmacokinetic parameter estimates using Sawchuk-Zaske and Bayesian forecasting. Results expressed as mean (s.d.)

Method	V ($l\text{ kg}^{-1}$) ¹	CL ($l\text{ h}^{-1}\text{ kg}^{-1}$) ¹	$t_{1/2}$ (h) ¹
SZ	0.29 (0.08)	0.09 (0.03)	2.41 (0.92)
1B	0.25 (0.01)*	0.09 (0.03)	2.18 (0.78)*
2B	0.29 (0.04)	0.08 (0.02)*	2.72 (0.97)*#
4B	0.29 (0.04)	0.08 (0.02)*	2.58 (0.97)

SZ Sawchuk-Zaske method.

1B One sample Bayesian method.

2B Two sample Bayesian method.

4B Four sample Bayesian method.

¹ Analysis of variance shows significant differences between methods.

* Significantly different from Sawchuk-Zaske method by Tukey test at 0.05 level.

Mean population difference is = or > 20% compared with Sawchuk-Zaske method using 95% confidence intervals.

Table 4 Mean error (bias) of Sawchuk-Zaske and Bayesian methods^a comparison based on the smallest mean error

Method	Peak (mg l^{-1}) ¹	Trough (mg l^{-1}) ¹
SZ	0.29 (1.64)	-0.50 (0.57)*
1B	1.70 (1.30)*	-0.40 (0.67)*
2B	1.36 (1.23)*	0.16 (0.84)
4B	1.04 (1.15)*	-0.08 (0.66)

^a Results expressed as mean.

¹ Analysis of variance shows significant differences between methods.

* Significantly different from lowest mean error, i.e. SZ for peak and 4B for trough by Tukey test at 0.05 level.

Table 6 lists the possible mean population differences for predicted peak concentrations between all other methods and the most precise method, the four sample Bayesian. There was no method where the possible mean difference could be > 10% worse (95% confidence) than the four sample Bayesian for peak concentrations.

For trough concentrations the least biased method was the four sample Bayesian. SZ, and the one sample Bayesian were statistically inferior. There were no statistical differences between methods for trough MSE. However the confidence interval analysis suggested that all other methods (SZ, the one sample Bayesian and the two sample Bayesian) were inferior predictors of trough concentrations compared with the four sample Bayesian, i.e. a large difference (> or = to 20%) from the four sample Bayesian is possible.

These results are summarised in part by Table 7 which tabulates the accuracy of the

Table 5 Mean squared error (precision) of Sawchuk-Zaske and Bayesian methods. Comparison based on the smallest mean square error

Method	Peak ¹	Trough	Total ¹
SZ	2.66	0.54	3.20
1B	4.54*	0.60	5.14*
2B	3.22	0.71	3.93
4B	2.38	0.44	2.82

¹ Analysis of variance shows significant differences between methods.

* Significantly different from lowest score, i.e. 4B for peak and trough by Tukey test at 0.05 level.

prediction i.e. whether a method's predicted concentration was within ± 1 or $\pm 2\text{ mg l}^{-1}$ of the observed peak or ± 0.5 or $\pm 1\text{ mg l}^{-1}$ of the observed trough concentration for each patient. Table 7 shows that the two sample Bayesian and SZ offer similar performance in predicting concentrations.

Table 6 Comparison using confidence intervals to determine the mean population difference between predicted concentrations using method with smallest mean square error as standard. The difference is expressed as a ratio.

<i>Method</i>	<i>Peak concentration mean difference</i>	<i>Trough concentration mean difference</i>
SZ/4B	0.88 – 0.96	0.75 – 0.94#
1B/4B	1.02 – 1.10	0.68 – 0.86#
2B/4B	0.99 – 1.07	0.97 – 1.22#

Ratio is = or > 20% different from 1.0, i.e. numerator could be > or = to 20% different from the denominator (standard method – 4B).

Table 7 Accuracy of prediction by each method.

<i>Method</i>	<i>SZ</i>	<i>1B</i>	<i>2B</i>	<i>4B</i>
% prediction of peak $\pm 1 \text{ mg l}^{-1}$	38%	28%	36%	51%
% prediction of peak $\pm 2 \text{ mg l}^{-1}$	79%	59%	72%	79%
% prediction of trough $\pm 0.5 \text{ mg l}^{-1}$	51%	54%	51%	62%
% prediction of trough $\pm 1 \text{ mg l}^{-1}$	82%	82%	82%	85%

Discussion

The two methods, SZ and Bayesian, were rigorously tested when one considers the wide range in pharmacokinetic parameters and the change in individual parameters within 24 h in this group of patients (Denaro & Ravenscroft, 1987). Comparing the pharmacokinetic variables for each method is useful but it is the final predicted concentrations that have the most meaning. We agree with Sheiner & Beal (1981) that linear regression between predicted and observed concentrations with its associated correlation coefficient can be misleading and often yields overly optimistic assessments. Therefore the bias and precision of the predicted concentrations are more useful.

Hypothesis testing has been used to compare the pharmacokinetic parameters, bias and precision. This method does not measure the difference between two groups and therefore does not tell us whether the statistical significance is clinically relevant. Calculating how large the difference could be allows rational decisions about which of the forecasting methods are clinically comparable with the most precise method. On the other hand not finding statistical difference may be due to having inadequate numbers of subjects in the study. One other study has compared Sawchuk-

Zaske and Bayesian forecasting. The 17 patients in this study were selected to exclude those with altered *V*. The authors found no statistically significant difference between these methods although they did not calculate the power of the analysis to obtain a significant difference (Burton *et al.*, 1986).

Confidence intervals were used because they display the range where the mean population difference lies. We used a log ratio analysis to express the possible range of differences as a percentage of the standard or best method. When confronted with a number of statistical differences as shown in Tables 3 to 5, this analysis allows one to decide which are the clinically important differences. With the log ratio analysis, a value of 1.0 indicates that the population means of the two methods in question coincide and this was used to compare the pharmacokinetic parameters. For precision or accuracy we compared the predicted concentrations themselves, our tenet being that if there was a large difference between predicted concentrations of one method compared to a method which had the lowest MSE (i.e. the method with the closest precision with the observed concentrations) it would be an inferior forecasting method. We have decided on practical grounds that if a possible difference is 20% or greater, then it is an inferior predictor.

Attainment of 20% around an ideal peak concentration of 8 mg l^{-1} (therefore ± 1.6) and a trough concentration of 2 mg l^{-1} (± 0.4), would seem to be a reasonable goal in aminoglycoside forecasting.

The SZ method requires a trough and three post-infusion concentrations taken preferably over two half-lives. Therefore routine implementation of this method is expensive and difficult in practice. This method underestimates trough concentrations (Sawchuk *et al.*, 1977; Denaro & Ravenscroft, 1987) and it cannot predict changes in pharmacokinetic parameters. It also relies solely on serum concentrations for parameter estimation. The Bayesian method uses population data as well as serum concentrations and our primary aim was to assess the performance of Bayesian forecasting using only two aminoglycoside concentrations.

For V , only the one sample Bayesian was statistically different from SZ. The confidence interval analysis reveals the mean population difference between the one sample Bayesian and SZ to be less than 20%. For CV there are statistical differences between SZ and the two sample Bayesian and the four sample Bayesian. It is likely that SZ has overestimated CL as will be explained below. The confidence intervals suggest that the possible mean difference will not be large.

The four sample Bayesian was the most precise predictor of resultant steady-state peak concentrations. SZ and the two sample Bayesian were not as good, but were statistically indistinguishable from the four sample Bayesian. Confidence interval analysis also indicated that the two sample Bayesian and SZ could offer comparable performance in predicting peak concentrations as the four sample Bayesian. The one sample Bayesian is statistically different from the four sample Bayesian and even though the possible mean differences from the four sample Bayesian are not large they are slightly greater than for the two sample Bayesian. Table 7 shows the reduced accuracy for predicting peak concentrations.

There were statistical differences in mean error for peak concentrations between SZ and Bayesian methods (Table 4). This is the result of slight underestimation of V and CL by the Bayesian methods. Usually peak concentrations are considered to be largely determined by V , however in this case the observed steady-state peak concentrations were taken 30 min after the end of a 30 min infusion, and therefore a significant amount of aminoglycoside would be cleared by the time peak concentrations were collected.

This underestimation of V and CL is not surprising considering that these patients were seriously ill and their pharmacokinetic parameters often deviated considerably from the initial population parameters. Most patients were febrile which has been shown to lower serum concentrations (Pennington *et al.*, 1975). V increases in critically ill patients (Beckhouse *et al.*, 1985) and some had peritonitis, ascites or burns, which affect V and CL (Zaske *et al.*, 1976; Gill & Kern, 1979). Also a few were severely ill with widespread endothelial damage from endotoxaemia resulting in an expanded extracellular volume.

The most precise predictor of trough concentrations was the four sample Bayesian. There were no statistical differences between the methods but the confidence intervals for trough concentration comparison with the four sample Bayesian are wide for SZ, the one and two sample Bayesian and the mean differences could be greater than 20%. This indicates that we did not have sufficient numbers to distinguish among these methods statistically and that SZ, the one and two sample Bayesian are likely to be inferior predictors of trough concentrations. At least the one and two sample Bayesian are similar to SZ in predicting trough concentrations (Table 7).

The SZ method underestimates true steady-state trough concentrations. This can be inferred from the statistical difference in the mean error as compared with the two and four sample Bayesian. This is likely to be due to overestimation of the true clearance and suggests that the use of a one compartment model equation to calculate aminoglycoside CL is not optimum. We conclude that in these seriously ill patients we can satisfactorily achieve the performance of SZ which requires four concentrations with two routine (a peak and trough) aminoglycoside concentrations using the Abbott Bayesian program. The use of this method with only one concentration gives inferior but still clinically useful performance. The Bayesian program also offers other advantages over SZ. Patient data are stored on floppy disc and further information such as recent aminoglycoside concentrations and changes to the serum creatinine can be added to update the estimates of the pharmacokinetic parameters. The program also has a graphics module which can quickly illustrate the result of a particular dosing regimen and is very useful for teaching.

The Bayesian methodology, however, is not foolproof and requires an experienced person to interpret the estimated parameters and dosing regimens. Up to 30% of peak and 20% of

trough concentrations will not be estimated accurately by one prediction. The program cannot predict future changes in the pharmacokinetic parameters of an individual patient. Often there are falls in both V and CL when the patient improves (Pennington *et al.*, 1975; Siber *et al.*, 1975; Beckhouse *et al.*, 1985; Denaro & Ravenscroft, 1987). Similarly, worsening of clinical status may also change the parameters. It has been our experience that patients who develop septicaemic shock may have large changes in their V and CL . Obviously patients with ascites would demonstrate a fall in V as they improve. This program does not take into account the third or deep compartment of aminoglycosides.

Meticulous attention to practical issues is required. These include recording the infusion time and flushing the drug from the giving set at the end of the infusion as well as accurate recording of the sample collection times. This program requires weight to be measured and this may be difficult to obtain in seriously ill

patients. Thus experience is important and fine-tuning the regimen with regular peak and trough monitoring is mandatory.

The use of these methods to individualize aminoglycoside therapy has led to the attainment of optimal concentrations from the start of therapy. This often involves the safe use of large doses of aminoglycosides in the first few critical days in the course of sepsis. Frequently the doses required initially are 1.5 to 3 times the normal recommended dosage (Zaske *et al.*, 1982a; Denaro & Ravenscroft, 1987). Retrospective studies have suggested an improved survival with such a stratagem (Noone *et al.*, 1974; Zaske *et al.*, 1982b; Moore *et al.*, 1984a,b).

We would like to acknowledge Abbott Diagnostics and in particular Dr Randolph Miller and his team for designing the Abbott Bayesian Programs and allowing us early use for their appraisal. We would also like to thank Dr Carl Peck for his advice and guidance. This study was supported by the Merck, Sharpe and Dohme Research Fellowship in Clinical Pharmacology.

References

- Barza, M., Brown, R. B., Shen, D., Gibaldi, N. & Weinstein, L. (1975). Predictability of blood levels of gentamicin in man. *J. infect. Dis.*, **132**, 165–174.
- Beckhouse, M. J., Whyte, I. N., Byth, P., Napier, J. C. & Smith, A. J. (1985). Aminoglycosides in the intensive care unit. A study of altered pharmacokinetics in the critically ill. *Annual Scientific Meeting of the Australian Society of Clinical and Experimental Pharmacologists*, Abstract No. 101.
- Begg, E. J., Atkinson, H. A., Jeffrey, M. & Taylor, N. (1985). Comparison of computerized prediction of aminoglycoside dosage with dosage based on physician intuition. *Annual Scientific Meeting of the Australian Society of Clinical and Experimental Pharmacologists*, Abstract No. 99.
- Bolton, S. (1984). *Pharmaceutical statistics. Practical and clinical applications*, p. 289. New York: Marcel Dekker.
- Burton, M. E., Brater, D. C., Chen, P. S., Day, R. B., Huber, P. J. & Vasco, M. R. (1985). A Bayesian feedback method of aminoglycoside dosing. *Clin. Pharmac. Ther.*, **37**, 349–357.
- Burton, M. E., Chow, M. S. S., Platt, D. R., Day, B., Brater, D. C. & Vasco, M. R. (1986). Accuracy of Bayesian and Sawchuk-Zaske dosing methods for gentamicin. *Clin. Pharm.*, **5**, 143–149.
- Chan, R. A., Benner, E. J. & Hoepfick, P. D. (1972). Gentamicin therapy in renal failure; a nomogram for dosage. *Ann. int. Med.*, **76**, 773–778.
- Denaro, C. P. & Ravenscroft, P. J. (1987). Usefulness of estimating individual pharmacokinetic data for aminoglycoside therapy in seriously ill patients. *Aust. N.Z. J. Med.*, **17**, 526–531.
- Gill, M. A. & Kern, J. W. (1979). Altered gentamicin distribution in ascites. *Am. J. hosp. Pharm.*, **36**, 1704–1706.
- Hull, J. H. & Sarubbi, F. A. (1976). Gentamicin serum concentrations: Pharmacokinetic predictions. *Ann. Int. Med.*, **85**, 183–189.
- Iliadis, A., Bachir-Raho, M., Bruno, R. & Favre, R. (1985). Bayesian estimation and prediction of clearance in high dose methotrexate infusions. *J. Pharmacokin. Biopharm.*, **30**, 101–115.
- Jackson, G. G. & Riff, L. J. (1971). Pseudomonas bacteraemia: Pharmacologic and other bases for failure of treatment with Gentamicin. *J. infect. Dis.*, **124** (Suppl), S185–S191.
- Jolly, M. E., Stroupe, S. D., Wang, C. J., Panas, H. N., Keegan, C. L., Schmidt, R. L. & Schwenzer, K. S. (1981). Fluorescence polarization immunoassay I. Monitoring aminoglycoside antibiotics in serum and plasma. *Clin. Chem.*, **27**, 1190–1197.
- Lacarelle, B., Granthil, C., Manelli, J. C., Bruder, N., Francois, G. & Cano, J. P. (1987). Evaluation of a Bayesian method of amikacin dosing in intensive care unit patients with normal or impaired renal function. *Ther. Drug Monit.*, **9**, 154–160.
- Lesar, P. S., Rotschafer, J. C., Strand, L. M., Solem, L. D. & Zaske, D. E. (1982). Gentamicin dosing errors with four commonly used nomograms. *J. Am. med. Ass.*, **248**, 1190–1193.
- Moore, R. D., Smith, C. R. & Lietman, P. S. (1984a). Association of aminoglycoside plasma levels with therapeutic outcome in gram-negative pneumonia. *Am. J. Med.*, **77**, 657–662.
- Moore, R. D., Smith, C. R. & Lietman, P. S. (1984b). The association of aminoglycoside plasma levels with mortality in patients with gram-negative

- bacteremia. *J. infect. Dis.*, **149**, 443–448.
- Noone, P., Parsons, T. M. C., Pattison, J. R., Slack, R. C. B., Garfield-Davies, D. & Hughes, K. (1974). Experience in monitoring gentamicin therapy during treatment of serious gram-negative sepsis. *Br. med. J.*, **1**, 477–481.
- Pennington, J. E., Dale, D. C., Reynolds, H. Y. & MacLowry, J. D. (1975). Gentamicin sulphate pharmacokinetics: low levels of gentamicin in blood during fever. *J. infect. Dis.*, **132**, 270–275.
- Platt, D. R., Matthews, S. J., Sevka, M. J., Forthcomer, J. B., Quintiliani, R., Cunha, B. A., Nightingale, C. H. & Chow, M. S. S. (1982). Comparison of four methods of predicting serum gentamicin concentrations in adults with impaired renal function. *Clin. Pharm.*, **1**, 361–365.
- Sawchuk, R. J. & Zaske, D. E. (1976). Pharmacokinetics of dosing regimens which utilize multiple intravenous infusions: Gentamicin in burn patients. *J. Pharmacokin. Biopharm.*, **4**, 183–195.
- Sawchuk, R. J., Zaske, D. E., Cipolle, R. J., Wargin, W. A. & Strate, R. G. (1977). Kinetic model for gentamicin dosing with the use of individual patient parameters. *Clin. Pharmac. Ther.*, **21**, 362–369.
- Sheiner, L. B. & Beal, S. L. (1981). Some suggestions for measuring predictive performance. *J. Pharmacokin. Biopharm.*, **9**, 503–512.
- Sheiner, L. B. & Beal, S. L. (1982). Bayesian individualization of pharmacokinetics: Simple implementation in comparison with non-Bayesian methods. *J. pharm. Sci.*, **71**, 1344–1348.
- Sheiner, L. B., Beal, S., Rosenberg, B. & Marathe, V. V. (1979). Forecasting individual pharmacokinetics. *Clin. Pharmac. Ther.*, **36**, 294–305.
- Sheiner, L. B., Halkin, H., Peck, C., Rosenberg, B. & Melmon, K. L. (1975). Improved computer-assisted digoxin therapy. A method using feedback of measured serum digoxin concentrations. *Ann. Int. Med.*, **82**, 619–627.
- Sheiner, L. B., Rosenberg, B. & Melmon, K. L. (1972). Modelling of individual pharmacokinetics for computer-aided drug dosage. *Comput. Biomed. Res.*, **5**, 441–459.
- Siber, G. R., Echeverria, P., Smith, A. L., Paisley, J. W. & Smith, D. H. (1975). Pharmacokinetics of Gentamicin in children and adults. *J. infect. Dis.*, **132**, 637–651.
- Vozech, S., Muir, K. P., Sheiner, L. B. & Follath, F. (1981). Predicting individual Phenytoin dosage. *J. Pharmacokin. Biopharm.*, **9**, 131–146.
- Wenk, M., Vozech, S. & Follath, F. (1984). Serum level monitoring of antibacterial drugs. *Clin. Pharmacokin.*, **9**, 457–492.
- Zar, J. H. (1984). *Biostatistical analysis*, pp. 88–222. Englewood Cliffs N.J.: Prentice-Hall Inc.
- Zaske, D. E., Bootman, J. L., Solem, L. B. & Strate, R. G. (1982b). Increased burn patient survival with individualized dosages of gentamicin. *Surgery*, **91**, 142–149.
- Zaske, D. E., Cipolle, R. J., Rotshaefer, J. C., Solem, L. D., Moser, N. R. & Strate, R. G. (1982a). Gentamicin pharmacokinetics in 1,640 patients: method for control of serum concentrations. *Antimicrob. Agents Chemother.*, **21**, 407–411.
- Zaske, D. E., Sawchuk, R. J., Gerding, G. N. & Strate, R. G. (1976). Increased dosage requirements of Gentamicin in burns patients. *J. Trauma*, **16**, 824–828.

(Received 9 May 1988,
accepted 16 January 1989)