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Population pharmacokinetic modelling of gentamicin and vancomycin in patients with unstable renal function following cardiothoracic surgery

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Aims
To describe the population pharmacokinetics of gentamicin and vancomycin in cardiothoracic surgery patients with unstable renal function.

Methods
Data collected during routine care were analyzed using NONMEM. Linear relationships between creatinine clearance (CL_{Cr}) and drug clearance (CL) were identified, and two approaches to modelling changing CL_{Cr} were examined. The first included baseline (BCOV) and difference from baseline (DCOV) effects and the second allowed the influence of CL_{Cr} to vary between individuals. Final model predictive performance was evaluated using independent data. The data sets were then combined and parameters re-estimated.

Results
Model building was performed using data from 96 (gentamicin) and 102 (vancomycin) patients, aged 17–87 years. CL_{Cr} ranged from 9 to 172 ml min^{-1} and changes varied from –76 to 58 ml min^{-1} (gentamicin) and –86 to 93 ml min^{-1} (vancomycin). Inclusion of BCOV and DCOV improved the fit of the gentamicin data but had little effect on that for vancomycin. Inclusion of interindividual variability (IIV) in the influence of CL_{cr} resulted in a poorly characterized model for gentamicin and had no effect on vancomycin modelling. No bias was seen in population compared with individual CL estimates in independent data from 39 (gentamicin) and 37 (vancomycin) patients. Mean (95% CI) differences were 4% (–3, 11%) and 2% (–2, 6%), respectively. Final estimates were: CL_{Gent} (l h^{-1}) = 2.81 × (1 + 0.015 × ($BCOV_{CLCr}$-$BCOV_{CLCrMedian}$) + 0.0174 × $DCOV_{CLCr}$); CL_{Vanc} (l h^{-1}) = 2.97 × (1 + 0.0205 × (CL_{Cr}-$CL_{CrMedian}$)). IIV in CL was 27% for both drugs.

Conclusions
A parameter describing individual changes in CL_{cr} with time improves population pharmacokinetic modelling of gentamicin but not vancomycin in clinically unstable patients.

Introduction

In patients who require cardiothoracic surgery, antibiotic therapy with drugs such as gentamicin and vancomycin may be used to treat or control an underlying condition, for example bacterial endocarditis [1], or to treat other gram positive and gram negative infections that arise following the procedure. Patients may have unstable renal function in association with their clinical condition,

due to nephrotoxicity from prolonged antibiotic therapy, or due to a combination of these factors [2]. Furthermore, renal function may be compromised in the first few days after surgery, and may improve, stabilize or deteriorate thereafter [3, 4]. Previous studies have reported a significant increase (≥35%) in serum creatinine concentrations in 7.7% to 11.4% of patients undergoing cardiac surgery, with a further 3.7% suffering acute renal failure and 1.4% needing postoperative dialysis [3, 5]. Such variability presents a challenge when trying to adjust dosage regimens to maintain target concentrations of gentamicin and vancomycin and may complicate the analysis of population data collected under such circumstances.

Although there are a wealth of data on the identification of covariates to explain variability in pharmacokinetic parameters between individuals, the problem of handling rapidly changing covariates within an individual over time has received limited attention so far. Approaches that have been suggested in the area of population modelling include the use of separate parameters to describe baseline effects and change from baseline effects, and extending the variance model to allow variability in the covariate-parameter relationships between individuals [6, 7].

An additional consideration is finding the best approach for handling changes in covariate values when there are gaps between measurements. Previous techniques that have been recommended for handling missing covariate data include removing individuals with missing data, substituting a mean or median covariate value for the missing data point, multiple imputation and modelling the covariate distribution [8–10].

The pharmacokinetics of both gentamicin and vancomycin have been studied extensively. Population studies using therapeutic drug monitoring (TDM) data collected from relatively stable patients have shown that gentamicin data can be described by a bi-exponential model and that clearance (CL) is closely related to renal function as estimated by creatinine clearance (CL_{Cr}) [11, 12]. Although there is only one previous population study of vancomycin pharmacokinetics in adults [13], other pharmacokinetic studies have consistently found renal function to be the best descriptor of vancomycin CL [14].

The purpose of the present study was to investigate a range of approaches to describe the population pharmacokinetics of gentamicin and vancomycin in patients with unstable renal function.

Methods

Data collection

Data were collected both retrospectively and prospectively from the therapeutic drug monitoring (TDM) files of patients treated within the Cardiothoracic Surgery Unit of the Western Infirmary, Glasgow and from an in house database held within the unit. Dosage and sampling times were recorded by nursing staff on specialized recording sheets and checked by a pharmacist before data were entered into a MAP Bayesian package [15] for interpretation. When dosage and/or sampling times were missing or not clear, the patient or data were excluded from the analysis. Data collected during renal replacement therapy were also excluded. The data used for model building were collected between January 1998 and September 2003 and the test data that were used for predictive performance testing were collected between September 2003 and August 2004. Patients who received gentamicin or vancomycin and had at least one measured serum concentration were eligible for inclusion. The study was approved by the West Ethics Committee of the North Division of NHS Greater Glasgow.

Gentamicin was administered intravenously either by a short infusion over 10–30 min or as a slow bolus over 2–3 min. Vancomycin was administered intravenously by infusion over 0.2 to 4.42 h (median 2 h). Gentamicin therapy was adjusted to achieve peak concentrations (1 h postdose) of 4–6 or 7–10 mg l^{-1} (according to bacteriological advice) and troughs <2 mg l^{-1}. Vancomycin dosage regimens were adjusted to maintain trough concentrations in the range 5–10 mg l^{-1} or 10–15 mg l^{-1} (from 2002 onwards).

The following data were also collected for each patient: gender, weight, age, height and day of therapy. Ideal body weight [16] and body surface area [17] were subsequently calculated. Serial measurements of serum creatinine concentrations (Cr_{Se}) were recorded from TDM and clinical chemistry computer records. CL_{Cr} was estimated by the Cockcroft & Gault equation [18] but Cr_{Se} measurements below the lower limit of the reference range (60 μmol l^{-1}) were set to 60 μmol l^{-1}. This has previously been shown to provide better estimates of drug CL in patients with low creatinine production [11, 12].

Drug analysis

Drug concentrations were analyzed by the Microbiology Department of the Western Infirmary. Gentamicin and vancomycin concentrations were determined using fluorescence polarization immunoassay (TDx™, Abbott Laboratories). The limit of quantification for gentamicin was 0.1 mg l^{-1} and the interassay coefficients of variation were 11% at 1 mg l^{-1}, 7.0% at 4 mg l^{-1} and 4.4% at 8 mg l^{-1}. The limit of quantification for vancomycin was 1.0 mg l^{-1} and the interassay coefficients of variation

were 4.3% at 10.5 mg l^{-1}, 2.1% at 31 mg l^{-1} and 4.2% at 58 mg l^{-1}.

Standard population analysis

Data were analyzed using the population pharmacokinetic package NONMEM® version V 1.1 [19] with a Visual FORTRAN Version 6.0 compiler (DIGITAL™, Digital Equipment Corporation, Maynard, Massachusetts, USA). Post processing of NONMEM® output was undertaken with Xpose (Version 3.007) [20], programmed in the statistics package SPLUS 2000® (Insightful Corporation Seattle, USA).

Preliminary analyses compared single and bi-exponential elimination models. Input was modelled using a zero order function that takes into account the infusion rate and length of infusion for each dose. Inter-individual variability was assumed to be log-normally distributed and covariance between interindividual variabilities in CL and volume of distribution (*V*) was examined. Residual error was modelled using additive, log-normal and combined error structures. All modelling was performed using the First Order Conditional Estimation (FOCE) method with interaction between interindividual and residual variabilities.

The factors that were investigated for an influence on the pharmacokinetics of gentamicin and vancomycin were sex, age, weight, ideal body weight, height, body surface area, day of therapy, Cr_{Se} and CL_{Cr}. Covariates were screened using scatter plots of individual parameter estimates against clinical characteristics and by generalized additive modelling (GAM) using Xpose [20]. Potentially useful covariates were then introduced sequentially into the population model. Models were compared statistically using a likelihood ratio test on the differences in the objective function value (OFV). Statistical significance was set at $P < 0.01$ (a reduction of >6.63 for one degree of freedom). Residual plots, standard errors of parameter estimates and changes in estimates of interindividual and residual variability were also considered.

Extended covariate models

Following identification of the best standard covariate model for each antibiotic, two extended covariate models, previously described by Wählby *et al.* [6], were examined. The first model splits the individual covariate effects into baseline and change from baseline effects, i.e.

$$\text{Ppop} = \theta p \times [1 + \theta_{BCOV} \times (\text{BCOV-BCOVmedian}) + \theta_{DCOV} \times \text{DCOV}]$$

where Ppop is the population parameter estimate, BCOV is the baseline value of the covariate in each individual, BCOVmedian is the median corrected baseline value of the covariate across the population, θp is the typical value of Ppop at the median baseline covariate value and θ_{BCOV} describes the proportional change in Ppop from the typical value as the baseline covariate varies from the median. DCOV are the individual differences between the current covariate value and the baseline covariate value at each time point and θ_{DCOV} is the parameter that describes the influence of this change from baseline on Ppop. Reduced models, in which either θ_{BCOV} or θ_{DCOV} were set to zero, were also fitted to the data.

The second approach included an additional variance parameter ($\eta^{cov,Pi}$) that allowed interindividual variability in the influence of the covariate on the population parameter estimates. Individual estimates of the parameters (Pi) could therefore be described by:

$$\text{Pi} = \theta p \times [1 + \theta cov \times \exp^{\eta cov,Pi} (\text{COV} - \text{COVmedian})] \times \exp^{\eta Pi}$$

Standard and extended covariate models were compared by examining differences in OFV, goodness of fit plots, parameter estimates and standard error estimates.

Analysis of covariate profiles

Although most covariates were stable during therapy, Cr_{Se} concentrations required close monitoring and were typically measured every 1–3 days. Three approaches were used to predict Cr_{Se} and estimate CL_{Cr} on days when results were not available. Method A (daily interpolation) assumed a linear, daily change in Cr_{Se} between measurements. For example, if Cr_{Se} was 90 μmol l^{-1} on day 1 and 120 μmol l^{-1} on day 4, it was estimated to be 100 μmol l^{-1} on day 2 and 110 μmol l^{-1} on day 3. Method B (step forward) assumed Cr_{Se} was stable until a further measurement was available. For example, if Cr_{Se} was measured on days 1 and 4, the day 1 value was used on days 2 and 3. Method C (step backward) used the value from day 4 for days 2 and 3.

All initial model development, and comparison of standard and extended covariate models, was performed using method A. The final population model for each antibiotic was then rerun using estimates derived from methods B and C and the models were compared as before.

Model validation with test data sets

The predictive performances of the final covariate models were evaluated using test data sets collected after the population analysis was complete. Differences between clinical characteristics in the model building and test data sets were examined by calculating the 95% confidence interval (CI) for the difference in proportion, by

Mann–Whitney *U*-test or by Student's *t*-test (as appropriate) with significance level set at $P < 0.05$.

Population predicted concentrations (PRED) were calculated for all patients in the test data sets by running NONMEM after fixing the population parameters to the estimates obtained with the final covariate models. Individual parameter estimates and individual predicted values (IPRED) were then obtained using the 'POSTHOC' command. Observed concentration measurements were compared with population and individual predicted concentrations, and individual CL estimates were compared with population estimates. Prediction errors (PE) were calculated from PRED and IPRED minus observed (OBS) concentrations. Percentage prediction errors (%PE) were calculated from 100 × (PRED-OBS)/PRED and 100 × (IPRED-OBS)/IPRED, then the mean percentage PEs were determined for each patient. This decreases the influence of patients with higher sample numbers. Percentage prediction errors were also calculated for CL. Predictive performances were assessed on the basis of bias (mean prediction error and 95% CI) and imprecision (root mean squared prediction error and 95% CI) [21].

The population covariate models were then run using the test data sets without fixing the parameter estimates. Final population parameter estimates were obtained by running combined data sets comprising both the model building and test data.

Results

There were 96 patients in the gentamicin model building data set and 39 in the test data set. The vancomycin data sets comprised 102 patients (model building data) and 37 patients (test data). Most of the patients received antibiotics for postoperative sepsis. Of the gentamicin recipients, 79% had cardiac surgery, 4% thoracic surgery, 1% a wound infection and 1% native valve endocarditis. Of the vancomycin recipients, 78% had cardiac surgery, 6% thoracic surgery and 2% a wound infection. The reason for admission was not available for 15% of the patients who received gentamicin and 14% who received vancomycin. Both antibiotics were administered to 42 patients.

Information on weight, age, day of therapy, Cr_{Se}, CL_{Cr} and gender was available for all patients (model building and test data sets). Height was missing for 34 patients who received gentamicin and 28 patients who received vancomycin. Ideal body weight for these patients was set at the median value (corrected for gender) of the other individuals. A summary of clinical characteristics of the study patients is presented in Table 1. There were no significant differences between the gentamicin model building and test data sets in terms of gender, age, total body weight, Cr_{Se} and CL_{Cr} estimates, but the median heights and ideal body weights of the patients in the model building set were higher (8 cm and 7 kg, respectively). For vancomycin, small differences were observed in Cr_{Se} (median 107 μmol l^{-1} in the test data set compared with 101 μmol l^{-1} in the model building data set) and in estimated CL_{Cr} (49 ml min^{-1} compared with 60 ml min^{-1}).

Cr_{Se} concentration varied markedly between individuals and also within individuals over time. Creatinine concentrations below 60 μmol l^{-1} occurred in 8 out of 135 patients on gentamicin (1.3% of concentrations) and 9 out of 139 patients on vancomycin (4.5% of concentrations). For the purposes of summarizing the data, a 20% change in Cr_{Se} was assumed to represent a clinically significant change in renal function. On this basis, 39% of patients in the gentamicin model building group had a decline in renal function, 15% an improvement and 4% had changes in both directions. In the test group, 15% of patients had a decline in renal function, 36% an improvement and 8% had both. Similar variability was observed with the vancomycin data sets, such that 25% of patients in the model building group and 11% in the test group had a decline in renal function, 16% of patients in both groups had an improvement, and 5% and 8%, respectively, had changes in both directions. Figure 1 illustrates the patterns of Cr_{Se} concentration within individual patients over time for the combined gentamicin and vancomycin groups.

The model building data sets comprised 365 gentamicin and 408 vancomycin concentration measurements. The number of samples per patient ranged from 1 to 20 (median 2) for gentamicin and 1 to 19 (median 3) for vancomycin. Gentamicin concentrations ranged from 0.1 mg l^{-1} to 11.6 mg l^{-1} and those for vancomycin from 1.3 mg l^{-1} to 43.3 mg l^{-1}. The majority of samples represented trough or random measurements with 66% of gentamicin and 76% of vancomycin samples drawn at least 10 h after the last dose. The test data sets comprised 185 gentamicin and 151 vancomycin concentration measurements with ranges and sampling times that were similar to those observed with the model building data (Table 1).

A mono-exponential elimination model with combined residual error and no covariance between interindividual variability in CL and *V* was adequate as a base for gentamicin. This model yielded a population CL estimate of 2.92 l h^{-1} with an interindividual variability (IIV) of 55% and a *V* of 34.8 l (IIV 55%).

When covariates were added to this model, the best fit was obtained with a linear relationship between drug

Table 1
Characteristics of the gentamicin and vancomycin model building and test data sets. Results are presented as number, or median (range)

	Gentamicin model building	Gentamicin test	Vancomycin model building	Vancomycin test
Demographic data				
Number of patients	96	39	102	37
Males/females	69/27	27/12	71/31	27/10
Age (years)	62 (29, 83)	67 (31, 82)	66 (17, 87)	68 (36, 92)
Weight (kg)	72 (39,138)	72 (47, 119)	74 (44, 110)	69 (47, 112)
Ideal weight (kg)	67 (36, 91)	60 (30, 78)*	66 (36, 91)	60 (42, 85)
Height (m)	1.71 (1.42, 1.98)	1.63 (1.35, 1.83)*	1.7 (1.42, 1.98)	1.64 (1.49, 1.91)
Body surface area (m^2)	1.86 (1.24, 2.40)	1.79 (1.29, 2.38)	1.86 (1.38, 2.31)	1.77 (1.46, 2.40)
Cr_{Se} ($\mu mol\ l^{-1}$)	115 (39, 527)	110 (50, 292)	101 (45, 527)	107 (53, 370)*
CL_{Cr} ($ml\ min^{-1}$)	57 (9, 169)	55 (21, 171)	60 (12, 172)	49 (18, 173)*
Max CL_{Cr} change ($ml\ min^{-1}$)	15.1 (0, 95.1)	18.3 (1.0, 85.6)	11.5 (0, 93.3)	10.6 (0, 84.3)
Pharmacokinetic data				
Number of samples	365	185	408	151
Dose (mg)	120 (60, 300)	160 (40, 300)*	1000 (120, 2000)	1000 (500, 2000)*
Concentration ($mg\ l^{-1}$)	1.8 (0.1, 11.6)	1.5 (0.1, 9.0)*	12.1 (1.3, 43.3)	14.1 (3.6, 31.9)*
Samples per patient	2 (1, 20)	4 (1, 19)*	3 (1, 19)	4 (1, 13)
Time postdose (h)	14.6 (0.5, 95.5)	18.4 (0.6, 65.5)*	16 (3.0, 135)	14.5 (2.7, 67.5)
Follow-up period (days)	4.5 (0.3, 36.9)	7.1 (0.8, 28.9)*	5.6 (0.5, 44.4)	5.7 (0.7, 31.8)

**Significantly different compared with model building data set, $P < 0.05$.*

CL and CL_{Cr}, which reduced the IIV on CL to 31% and the OFV from 536 to 173. However, underestimation of population and individual predicted concentrations was evident at higher gentamicin concentrations and a bi-exponential elimination model was therefore re-tested. This model proved superior based on a lower OFV (–74.9) and an improvement in plots. Removal of IIV in the central compartment volume (*V*1) and intercompartmental clearance (Q) further stabilized the model with no change in OFV. No covariates were found that influenced the volume parameters.

A mono-exponential elimination model with combined residual error and no covariance between interindividual variability in CL and *V* yielded vancomycin population estimates of $3.13\ l\ h^{-1}$ (IIV 61%) for CL and 99.7 l (IIV 47%) for *V*. Similar to gentamicin, the inclusion of CL_{Cr} in the model provided the best fit and reduced both IIV in CL (to 25%) and OFV (from 1752 to 1440). However, in this case, the mono-exponential model remained adequate. Correcting *V* for weight produced a slight improvement in fit but no other covariates were found to influence *V*.

A summary of results for gentamicin and vancomycin clearance models are presented in Table 2.

When the extended covariate models (with bi-exponential elimination) were applied to the gentamicin data set, the inclusion of separate baseline and change from baseline effects of CL_{Cr} on CL produced a fall in OFV of 13.1 and a decrease in IIV in CL from 33% to 27%. Improvement in plots of observed *vs.* population predicted concentrations was evident, and correcting volume for weight produced a further small improvement in fit. The slopes for BCOV and DCOV were well characterized with values of 0.0151 (Relative standard error, RSE 5%) and 0.0174 (RSE 2%), respectively.

The second extended model resulted in an OFV drop of 28.8. However, the additional variance parameter ($\eta^{CLCr,CL}$) had an RSE of 80% and therefore could not be estimated adequately. When both extended models were combined, the additional variance term was again poorly characterized. Therefore, the first extended model was selected for the gentamicin model building data set. The measured, population and individual predicted concentrations from this model are shown in Figures 2a and b.

The extended covariate models had less influence on the vancomycin analysis. Allowing separate baseline

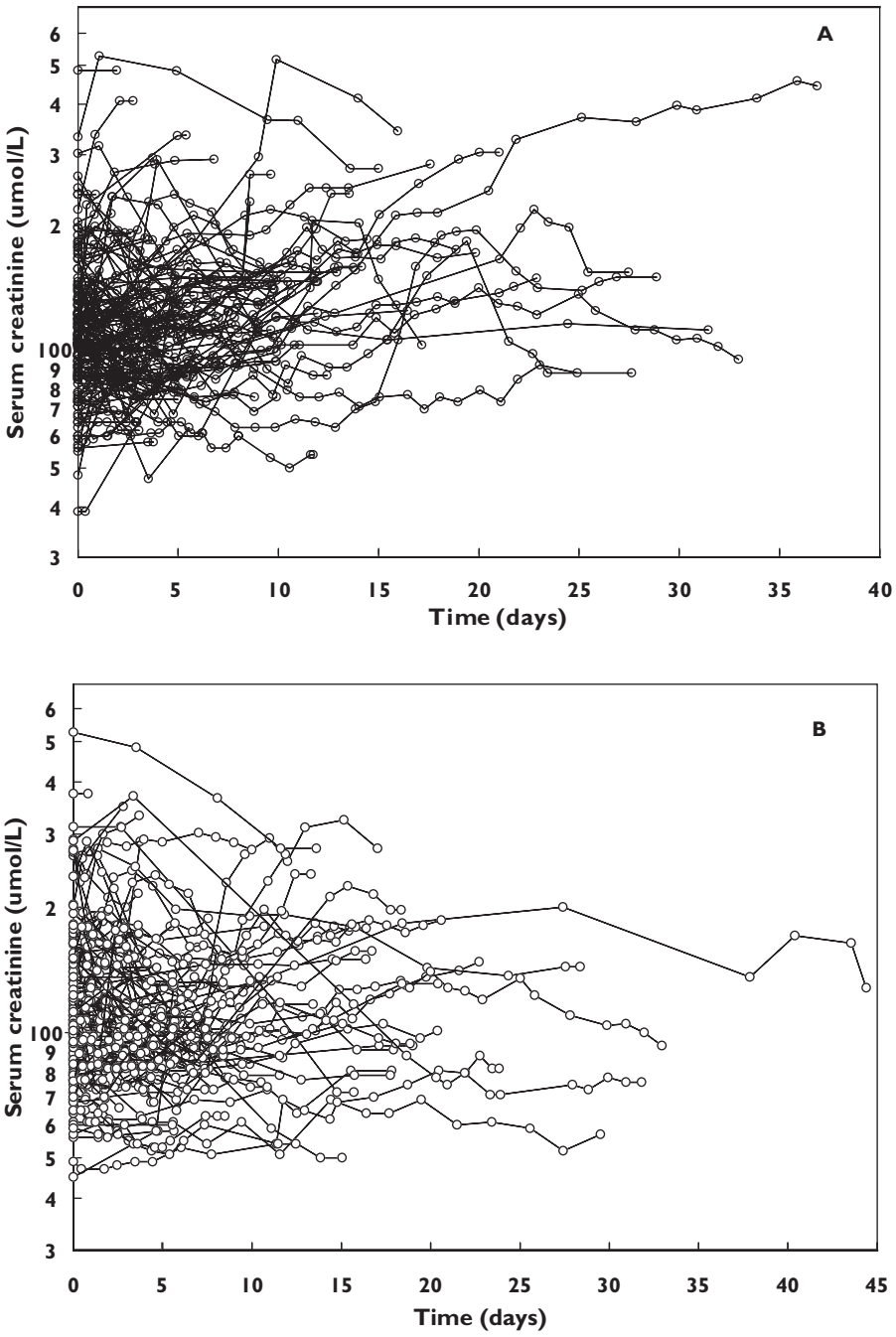

Figure 1
Serum creatinine concentration-time profiles in combined gentamicin (A) and vancomycin (B) data sets

and change from baseline covariate effects produced a fall in OFV of 10.5 but no decrease in IIV of clearance. There was a slight improvement in plots, although this was mainly based on one individual who was particularly unstable. When this patient was removed from the analysis, model improvement was no longer significant. Population and individual predicted concentrations are presented in Figures 2c and d. No improvement in fit was identified with the second extended model or when the extended models were combined.

In the model building groups, Cr_{Se} measurements were missing from 323 of 855 days of gentamicin therapy and from 396 of 987 days of vancomycin therapy. Therefore, the influence on the final population models of different approaches to handling these missing Cr_{Se} measurements was assessed. For gentamicin, there was little difference between the interpolation approach (method A) and the step forwards approach (method B) with OFVs of 84.6 and 80.0, respectively, but method C (step backwards) was less successful (OFV 107.9). For

Table 2
Summary of results for the gentamicin and vancomycin clearance models

	OFV
Gentamicin	
$CL = \theta_1$	378.9
$CL = \theta_1 \times (WT/70)^{0.75}$	379.2
$CL = \theta_1 \times WT$	376.1
$CL = \theta_1 \times WT/Cr_{Se}$	111.9
$CL = \theta_1 \times WT \times (1 + \theta_2 \times (AGE-62))/Cr_{Se}$	99.7
$CL = \theta_1 \times WT \times (1 + \theta_2 \times (AGE-62)) \times (1 + \theta_3 \times SEX)/Cr_{Se}$	99.6
$CL = \theta_1 \times (1 + \theta_2 \times (CL_{Cr}-54))$	97.7
$CL = \theta_1 \times (1 + \theta_2 \times (BCOV-63)) + \theta_3 \times DCOV)$	**84.6**
Vancomycin	
$CL = \theta_1$	1752.5
$CL = \theta_1 \times (WT/70)^{0.75}$	1736.5
$CL = \theta_1 \times WT$	1734.3
$CL = \theta_1 \times WT/Cr_{Se}$	1482.3
$CL = \theta_1 \times WT \times (1 + \theta_2 \times (AGE-62))/Cr_{Se}$	1461.1
$CL = \theta_1 \times WT \times (1 + \theta_2 \times (AGE-62)) \times (1 + \theta_3 \times SEX)/Cr_{Se}$	1455.4
$CL = \theta_1 \times (1 + \theta_2 \times (CL_{Cr}-57))$	**1434.8**

Bold = final model, θ = parameter to be estimated, WT = weight (kg), Cr_{Se} = serum creatinine (μmol l^{-1}), CL_{Cr} = estimated creatinine clearance (ml min^{-1}), BCOV = baseline CL_{Cr}, DCOV = change from baseline CL_{Cr}. N.B. for gentamicin V1 = θ × WT, V2 = θ × WT, Q = θ, for vancomycin V = θ × WT.

vancomycin, the interpolation approach was better than both the step forwards and step backwards approaches with OFVs of 1434.8, 1451.3 and 1452.4 for methods A, B and C, respectively.

Figure 3 illustrates the measured *vs.* (a) population predicted and (b) individual predicted concentrations for the gentamicin test data set, and Table 3 shows the results of the bias and imprecision analysis. Population predictions of concentration measurements were unbiased with a mean difference of –0.1 mg l^{-1} and a mean percentage difference, after obtaining the average for each patient, of –8%. However, imprecision with the population model was relatively high at 0.7 mg l^{-1} for the individual data and 55% when the average percentage errors for each patient were analyzed. Imprecision in the individual predictions was lower at 0.4 mg l^{-1} and 10%, respectively. Figure 4a illustrates the population *vs.* POSTHOC CL estimates for the test data set for gentamicin. No significant bias was identified in the patient averaged mean prediction error of 4%, although a small bias of 0.2 l h^{-1} was observed when all the individual results were considered (Table 3). Imprecision had mean values of 0.7 l h^{-1} (individual results) and 22% (patient averaged results).

Figure 3 illustrates the measured *vs.* (c) population predicted and (d) individual predicted concentrations for the vancomycin test data set. When the number of samples per individual was taken into consideration, there was no significant bias in the percentage prediction error (mean –3%) but a slight positive bias of 1.1 mg l^{-1} was evident when the raw values were examined (Table 3). No bias was observed with individual predictions and imprecision in the patient averaged data. Precision improved from 38% with the population model to 12% when individual predictions were considered. Population *vs.* POSTHOC CL estimates for the test data set are illustrated in Figure 4b. CL estimates were unbiased when both individual and patient averaged data were examined, but imprecision was relatively high with mean values of 0.90 l h^{-1} (individual data) and 25% (patient averaged data).

Table 4 shows that the population parameter estimates obtained with the test and combined data sets were similar to those obtained with the model building data sets for both gentamicin and vancomycin. Figure 5 illustrates measured *vs.* population and individual predicted concentrations from one individual in the (a) gentamicin and (b) vancomycin group in whom Cr_{Se} is changing over time.

Discussion

This study describes the development of population pharmacokinetic models for gentamicin and vancomycin in cardiothoracic surgery patients with unstable renal function. New models designed to cope with time-varying covariates were investigated and were found to improve the fit of the gentamicin data but had little influence on the vancomycin data. Evaluation of the population models with independent data sets confirmed high interindividual variability but individual parameter estimates were found to describe the data well. Although there was no clear advantage in using either previous or interpolated results to replace missing covariate data, interpolated data appeared more reliable.

The preliminary analyses conducted with the model building data sets were unable to characterize the parameters of a bi-exponential elimination model, although there was some evidence of superiority, especially for gentamicin. However, when CL_{Cr} was added to this model as a covariate, bias in the plots indicated that the more complex model was necessary. Interactions between covariate and structural models have pre-

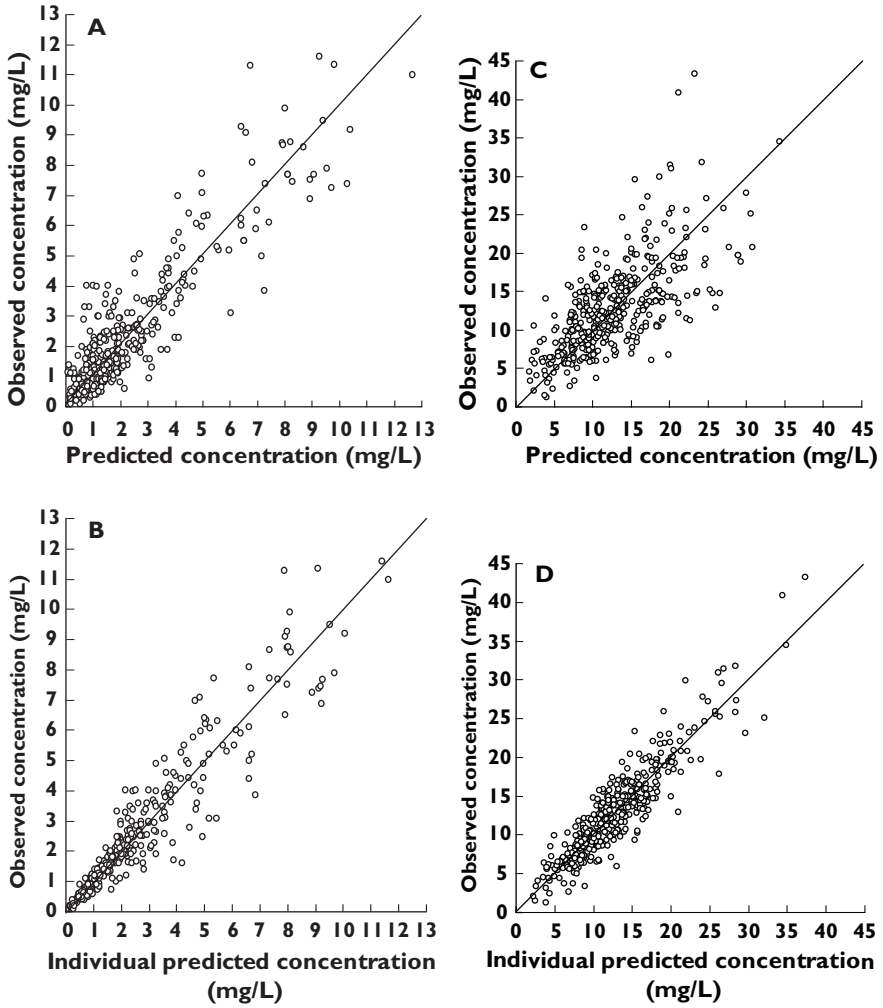

Figure 2
Observed gentamicin concentrations *vs.* population (A) and individual (B) predictions and observed vancomycin concentrations *vs.* population (C) and individual (D) predictions from the model building data sets. The solid line represents the line of identity

viously been identified as important, especially with sparse data [22], and previous studies have indicated that the more complex model is preferable for gentamicin [11, 12]. Similar observations have also been made with vancomycin [14, 23]. However, analysis of peak concentrations is rarely undertaken nowadays since the main concerns are to ensure that trough concentrations are maintained within a range associated with a good clinical response and to avoid excessive drug accumulation. It is likely that this focus on trough concentrations contributed to the difficulties in estimating the parameters of a two compartment model. As expected, estimated CL_{Cr} had a strong influence on the CL of both gentamicin and vancomycin with a change in CL_{Cr} of 10 ml min^{-1} producing alterations in drug CL of around 20%.

Gentamicin median *V*1 and *V*2 estimates (combined data) of 18.1 l (0.25 l kg^{-1}) and 11.0 l (0.15 l kg^{-1}), respectively, are consistent with those observed by Rosario *et al.* [11], but higher than the mono-exponential model value of 17.4 l reported by Kirkpatrick *et al.* [12], who also found that *V* was lower in patients with renal impairment. For vancomycin, a median *V* estimate (combined data) of 90 l (1.24 l kg^{-1}) was again higher than the value of 0.7 l kg^{-1} that has been reported elsewhere [14]. It is possible that the sampling strategy and the influences of critical illness and sepsis [24, 25], may have contributed to the high values observed. However, this result may explain some anecdotal observations of unexpectedly low concentrations in the first 24–48 h of therapy and confirms that our current practice of giving a 'loading dose' of 1000 mg twice daily during this period, even in patients with poor renal function, is appropriate.

Although some degree of biliary excretion has recently been reported for vancomycin [26], both gentamicin and vancomycin are principally cleared by glomerular filtration. However, renal function can vary markedly in cardiac surgery patients due to a range of factors including sepsis [25], infective endocarditis [2] and the adminis-

Table 3
Bias and imprecision of the best final model in the gentamicin and vancomycin test data sets (Results are presented as mean (95% CI))

	Bias	Imprecision
Gentamicin		
PE (mg l^{-1})	–0.1 (–0.3, 0)	0.7 (0.4, 1.1)
Patient averaged %PE	–8 (–26, 9)	55 (8, 103)
IPE (mg l^{-1})	0 (0, 0.1)	0.4 (0.2, 0.7)
Patient averaged %IPE	3 (0, 6)	10 (0, 19)
PE CL (l h^{-1})	0.20 (0.10, 0.29)*	0.70 (0.32, 1.08)
Patient averaged %PE CL	4 (–3, 11)	22 (7, 38)
Vancomycin		
PE (mg l^{-1})	1.1 (0.3–1.9)*	5.0 (2.6, 7.5)
Patient averaged %PE	–3 (–16, 9)	38 (10, 66)
IPE (mg l^{-1})	0.4 (0, 0.7)	2.0 (1.0, 3.0)
Patient averaged %IPE	2 (–2, 5)	12 (1, 23)
PE CL (l h^{-1})	0.02 (–0.12, 0.16)	0.90 (0.40, 1.40)
Patient averaged %PE CL	2 (–2, 6)	25 (13, 37)

**Significantly biased ($P < 0.05$); PE = Predicted (PRED) – Observed (OBS) concentration; %PE = ((PRED – OBS)/PRED) × 100; IPE = Individual predicted (IPRED) – OBS; %IPE = ((IPRED – OBS)/IPRED) × 100; PE CL = Population clearance estimate (CL_{Pop}) – MAP Bayesian clearance estimate (CL_{Bay}); %PE CL = ((CL_{Pop} – CL_{Bay})/CL_{Bay}) × 100.*

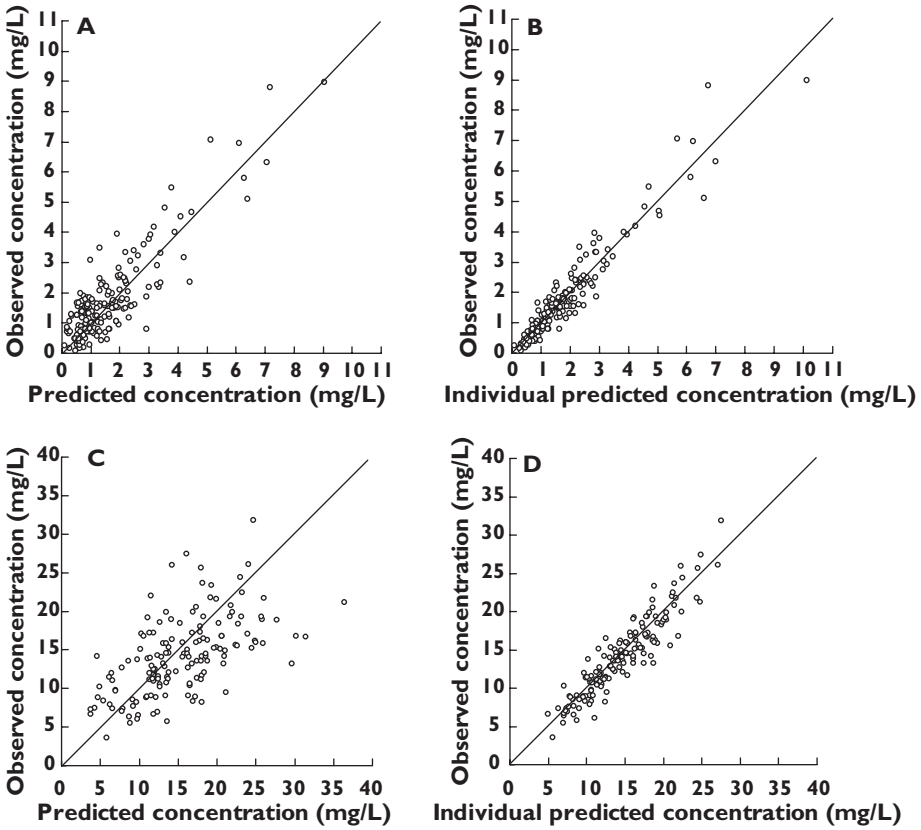

Figure 3
Observed gentamicin concentrations *vs.* population (A) and individual (B) predictions and observed vancomycin concentrations *vs.* population (C) and individual (D) predictions from the predictive performance data sets. The solid line represents the line of identity

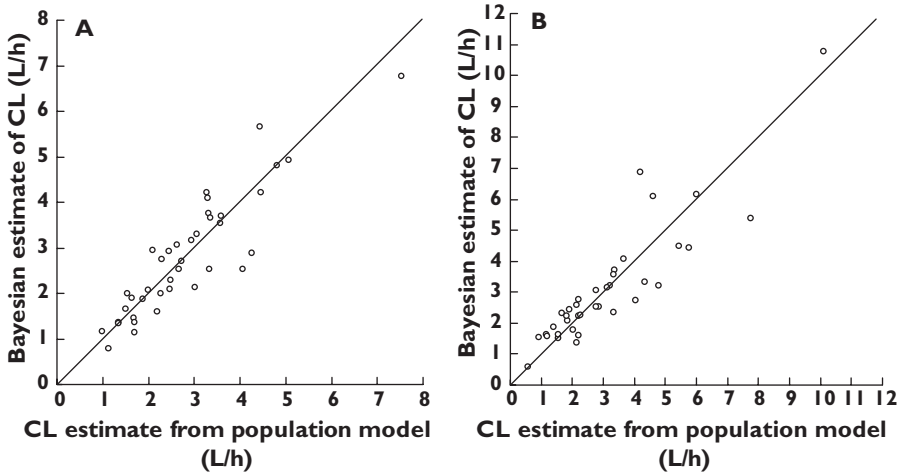

Figure 4
Population *vs.* POSTHOC CL estimates for (A) gentamicin and (B) vancomycin predictive performance data sets. The solid line represents the line of identity

Table 4
Population parameter estimates for the gentamicin and vancomycin, model building, test and combined data sets, using the final model

Parameter	Model building data Estimate (RSE (%))	Test data Estimate (RSE (%))	All data Estimate (RSE (%))
Gentamicin			
CL ($l\ h^{-1}$) = $\theta_1 \times (1 + \theta_2 \times (BCOV_{CLCr} - BCOV_{CLCrMedian}) + \theta_3 \times DCOV_{CLCr})$			
θ_1	2.82 (4%)	2.70 (5%)	2.81 (3%)
θ_2	0.0151 (5%)	0.0143 (8%)	0.0150 (5%)
θ_3	0.0174 (2%)	0.0175 (6%)	0.0174 (2%)
*V*1 ($l\ kg^{-1}$)	0.243 (6%)	0.289 (11%)	0.251 (5%)
*V*2 ($l\ kg^{-1}$)	0.166 (18%)	0.250 (31%)	0.156 (14%)
Q (h^{-1})	1.73 (16%)	0.644 (17%)	1.45 (20%)
η_{CL} (%)	27 (18%)	23 (24%)	27 (17%)
η_{V2} (%)	96 (47%)	110 (67%)	84 (52%)
Add ($mg\ l^{-1}$)	0.08 (45%)	0.20 (30%)	0.13 (23%)
Prop (%)	25 (11%)	19 (16%)	24 (9%)
Vancomycin			
CL ($l\ h^{-1}$) = $\theta_1 \times (1 + \theta_2 \times (CL_{Cr} - CL_{CrMedian})$			
θ_1	2.94 (3%)	3.01 (6%)	2.97 (3%)
θ_2	0.0209 (3%)	0.0203 (5%)	0.0205 (3%)
V ($l\ kg^{-1}$)	1.15 (6%)	1.42 (7%)	1.24 (5%)
η_{CL} (%)	25 (20%)	31 (26%)	27 (16%)
η_V (%)	33 (39%)	33 (26%)	36 (24%)
Add ($mg\ l^{-1}$)	1.7 (19%)	1.4 (27%)	1.6 (18%)
Prop (%)	17 (18%)	10 (22%)	15 (19%)

θ = parameter, CL = clearance, CL_{Cr} = creatinine clearance, BCOV = baseline CL_{Cr}, DCOV = change from baseline CL_{Cr}, V = volume of distribution, V1 = central V, V2 = peripheral V, Q = intercompartmental clearance, η_{CL} = interindividual variability in CL, η_V = interindividual variability in V, Add = additive component of residual random error, Prop = proportional component of residual random error.

tration of potentially nephrotoxic drugs such as gentamicin and penicillins. Cardiac surgery itself is associated with renal dysfunction and three patterns of time-dependent changes in Cr_{Se} concentration have been described [4]. The first involves a rapid rise in Cr_{Se} that resolves over 5–10 days, the second a more prolonged increase to higher values that mirrors impaired cardiac function and may take 2–3 weeks to resolve and the third

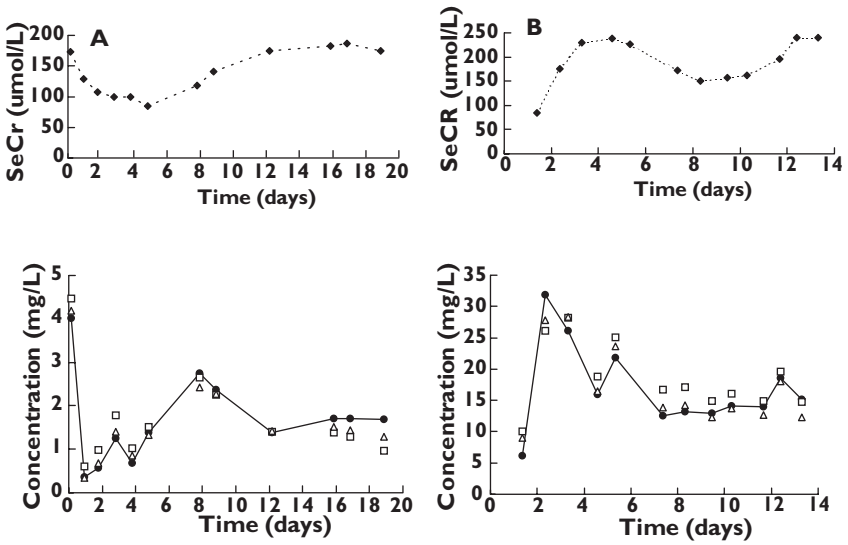

Figure 5
Observed (●) population (PRED) (□) and individual predicted (IPRED) (△) concentrations from one individual *vs.* time in the (A) gentamicin and (B) vancomycin group in whom serum creatinine is changing over time (top panel)

is characterized by a delayed increase associated with persistently poor cardiac function and septic shock. As can be seen in Figure 1, similar patterns in Cr_{Se} over time were observed with the current data set.

These observations of unstable renal function present a challenge when trying to optimize therapy for individual patients. Since elimination half-lives will increase as elimination rate declines, the accumulation of both the Cr_{Se} and drug concentration will lag behind the current estimate of renal function, making interpretation of the results difficult. This issue with respect to gentamicin was investigated by Kirkpatrick *et al.* [27], who demonstrated that changes in gentamicin CL could be detected before changes in Cr_{Se} in patients who developed nephrotoxicity.

The Cockcroft & Gault equation has obvious limitations, since it estimates renal function from serum creatinine concentrations that are assumed to be at steady state. However, other methods, such as the Jelliffe & Jelliffe equation [28, 29] that claim to handle unstable renal function are also based on serum creatinine concentrations. When estimates of creatinine clearance obtained using the Jelliffe equation [29] were compared with those obtained using the Cockcroft & Gault equation [18], the differences were minimal. The mean ± SD) differences at each time point were 0.9 ± 3.6 ml min^{-1} for gentamicin ($n = 853$) and 1.2 ± 4.0 ml min^{-1} for vancomycin ($n = 839$). Since the relationship between the estimates had a coefficient of determination of 0.99 for both drugs, the Cockcroft & Gault equation was used in the analysis, since it is easier to apply.

A first approach to the challenge of analyzing data in the clinically unstable patient is to determine whether such data can be described adequately. Two approaches to this problem were described by Wählby *et al.* [6] and were applied in the present data analysis. Both methods improved the fit of the gentamicin data but although the OFV was lower with the method that included interindividual variability in the relationship between gentamicin CL and CL_{Cr}, the additional parameter was poorly characterized. The alternative approach, in which separate estimates were obtained for the relationships between gentamicin CL and both baseline and change from baseline CL_{Cr} values, was more stable and produced a decrease in interindividual variability in CL. As illustrated in Figures 2a and b and 3a and b, this model provided a good description of both the model building and the test data sets. The final analysis containing all the data produced parameter estimates that were very similar to those obtained with the model building data set alone.

The results obtained with vancomycin suggested that the extended models provided little improvement in the fit, except in the case of one individual who was an outlier with very rapidly declining renal function. Although the change from baseline model produced a statistically significant fall in OFV, there was no improvement in plots or reduction in the interindividual variability in CL. Therefore, it is possible that the longer elimination half-life caused by a larger *V* and lower CL may have meant that changes in renal function took longer to affect vancomycin concentrations and that the estimated CL_{Cr}, rather than the change, was therefore adequate to describe the data. Nevertheless, as with gentamicin, the final model provided a good description of the vancomycin data (as shown in Figures 2b and c and 3b and c) and again the final model and its parameters

were consistent with those obtained with the model building data set.

An additional factor that may have influenced the analysis was the handling of missing Cr_{Se} values. Cr_{Se} is generally measured on a daily basis but samples were sometimes missed over weekends and less frequent sampling tended to occur when creatinine concentrations were stable. Overall, Cr_{Se} data were missing for 34% and 39% of days and Cr_{Se} concentrations were missing on at least 1 day for 87% and 82% of patients in the gentamicin and vancomycin data sets, respectively. However, all patients had at least one Cr_{Se} measurement, and therefore, missing values were not completely unknown, as they were likely to be related to the previous and/or subsequent measurements. Standard methods for dealing with missing covariate data, such as imputing the mean or median of the covariate measurement or multiple imputing methods would therefore not be appropriate.

Missing Cr_{Se} concentrations may have values that show no or minimal change from the previous result, a sharp decrease or increase that was closer to the next result, or have a value somewhere between the two results. These options were explored by substituting missing data with the previous result, the following result or a result based on linear interpolation between the two values. Extrapolating backwards gave the poorest fit to the data for gentamicin, whereas linear interpolation proved best for vancomycin and forward extrapolation was slightly better than interpolation for gentamicin. It is likely that the frequency of covariate measurement, which is usually higher in patients who are clinically unstable, and the rates of change within an individual will influence the outcome of these approaches.

Factors such as comedications and patient hydration status may also affect the pharmacokinetics of gentamicin and vancomycin. Concomitant medication usage (e.g. diuretics) will most likely influence renal function, assessed in this study by monitoring Cr_{Se}. The complexity of concomitant drug and dosage histories and rapid changes in hydration status (with difficulties in quantification) made it impossible to incorporate these factors into the model. Inclusion would also compromise the predictive ability of the model for future patients in whom co-administered drugs and hydration status would be different.

Whether or not a patient undergoes cardiac bypass pumping during their surgery may influence their degree of renal function in the immediate postoperative period. However, one recent study suggests no significant difference in renal function between 'on' and 'off' pump candidates [30]. The majority of patients who were included in this analysis were 'on-bypass'.

The population pharmacokinetic models developed in this study for cardiac surgery patients with unstable renal function can provide initial estimates for maximum a posteriori Bayesian pharmacokinetic packages and an insight into the interpretation of data, and aid intra-individual dosage adjustments. Further investigations are underway to determine if these models can help determine suitable initial doses and individual dosage adjustments (e.g. using NONMEM). The high estimate for the volume of distribution of vancomycin is consistent with anecdotal observations that initial doses of the drug are often inadequate and suggests that a loading regimen over the first 24–48 h may be useful.

In conclusion, this study has used a population approach to describe vancomycin and gentamicin concentration measurements in clinically unstable patients within a cardiothoracic surgery unit. Despite the recognized difficulties of using equations to estimate renal function in this setting, changes in drug handling mirrored changes in estimated creatinine clearance. This observation emphasizes the need to monitor serum creatinine concentrations closely in such patients and to repeatedly adjust the doses of renally cleared drugs. Alternatively, where possible, drug concentrations should be monitored to ensure that excessive or subtherapeutic doses are avoided.

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References

1 Simmons NA, Ball AP, Eykyn SJ, Littler WA, McGowan A, Oakley CM, Shanson DC. Antibiotic treatment of streptococcal, enterococcal and staphylococcal endocarditis. Heart 1998; 79: 207–10.

2 Majumdar A, Chowdhary S, Ferreira MA, Hammond LA, Howie AJ, Lipkin GW, Littler WA. Renal pathological findings in infective endocarditis. Nephrol Dial Transpl 2000; 15: 1782–7.

3 Mangano CM, Diamondstone LS, Ramsay JG, Aggarwal A, Herskowitz A, Mangano DT. Renal dysfunction after myocardial revascularisation. Risk factors, adverse outcomes and hospital resource utilisation. Ann Int Med 1998; 128: 194–203.

4 Myres BD, Moran SM. Haemodynamically mediated acute renal failure. New Engl J Med 1986; 314: 97–105.

5 Zanardo G, Michielson P, Paccagnella A, Rosi P, Calo M, Salandin V, Da Ros A, Michieletto F, Simini G. Acute renal failure in patients undergoing cardiac operation. Prevelance, mortality rate and main risk factors. J Thorac Cardiovasc Surg 1994; 107: 1489–95.

6 Wählby U, Thomson AH, Milligan PA, Karlsson MO. Models for time-varying covariates in population pharmacokinetic-pharmacodynamic analysis. Br J Clin Pharmacol 2004; 58: 367–77.

7 Taright N, Mentré F, Mallet A. Non-stationarity of kinetic parameters in multi-occasion designs. Oral presentation, Sixth PAGE Meeting, Glasgow, 1997.

8 Wu H, Wu L. A multiple imputation method for missing covariates in non-linear mixed-effects models with application to HIV dynamics. Statist Med 2001; 20: 1755–69.

9 Horton NJ, Laird NM. Maximum likelihood analysis of generalised linear models with missing covariates. Statist Meth Med Res 1998; 8: 37–50.

10 Burton A, Altman DG. Missing covariate data within cancer prognostic studies: a review of current reporting and proposed guidelines. Br J Cancer 2004; 91: 4–8.

11 Rosario MC, Thomson AH, Jodrell DI, Sharp CA, Elliott HL. Population pharmacokinetics of gentamicin in patients with cancer. Br J Clin Pharmacol 1998; 46: 229–36.

12 Kirkpatrick CMJ, Duffull SB, Begg EJ. Pharmacokinetics of gentamicin in 957 patients with varying renal function dosed once daily. Br J Clin Pharmacol 1999; 47: 637–43.

13 Yasuhara M, Iga T, Zenda H, Okumura K, Oguma T, Yano Y, Hori R. Population pharmacokinetics of vancomycin in Japanese adult patients. Ther Drug Monit 1998; 20: 139–48.

14 Ducharme MP, Slaughter RL, Edwards DJ. Vancomycin pharmacokinetics in a patient population: effect of age, gender and body weight. Ther Drug Monit 1994; 16: 513–8.

15 Kelman AW, Whiting B, Bryson SM. OPT, a package of computer programs for parameter optimisation in clinical pharmacokinetics. Br J Clin Pharmacol 1982; 14: 247–56.

16 Devine BJ. Gentamicin therapy. Drug Intell Clin Pharm 1974; 8: 650–5.

17 Du Bois D, Du Bois EF. Clinical calorimetry. A formula to estimate the approximate surface area if height and weight be known. Arch Intern Med 1916; 17: 863–71.

18 Cockcroft DW, Gault H. Prediction of creatinine clearance from serum creatinine. Nephron 1976; 16: 31–41.

19 Beal SL, Sheiner LB 1992 NONMEM (User's Guide), Parts 1-VII. Technical Report: University of California, San Francisco.

20 Jonsson N, Karlsson MO. Xpose- an S-PLUS Based population pharmacokinetic/pharmacodynamic model building aid for NONMEM. Comp Meth Prog Biomed 1999; 58: 51–64.

21 Sheiner LB, Beal SL. Some suggestions for measuring predictive performance. J Pharmacokin Biopharm 1981; 9: 503–12.

22 Wade JR, Beal SL, Sambol NC. Interaction between structural, statistical and covariate models in population pharmacokinetic analysis. J Pharmacokin Biopharm 1994; 22: 165–77.

23 Pyrka RD, Rodvold KA, Garrison M, Rotshafer JC. Individualising vancomycin dosage regimens: one versus two-compartment models. Ther Drug Monit 1989; 11: 450–4.

24 Hansen M, Christrup LL, Jarlov JO, Kampmann JP, Bonde J. Gentamicin dosing in critically ill patients. Acta Anaethesiol Scand 2001; 45: 734–40.

25 Buijk SE, Mouton JW, Gyssens IC, Verbrugh HA, Bruining HA. Experience with a once-daily dosing program of aminoglycosides in critically ill patients. Int Care Med 2002; 28: 936–42.

26 Currie BP, Lemos-Filho L. Evidence for biliary excretion of vancomycin into stool during intravenous therapy: potential implications for rectal colonisation with vancomycin-resistant enterococci. Antimicrob Agents Chemother 2004; 48: 4427–9.

27 Kirkpatrick CMJ, Duffull SB, Begg EJ, Frampton C. The use of a change in gentamicin clearance as an early predictor of gentamicin-induced nephrotoxicity. Ther Drug Monit 2003; 25: 623–30.

28 Jelliffe RW, Jelliffe SM. A computer program for estimation of creatinine clearance from unstable serum creatinine levels, age, sex and weight. Math Bioscience 1972; 14: 17–24.

29 Jelliffe R. Estimation of creatinine clearance in patients with unstable renal function, without a urine specimen. Am J Nephrol 2002; 22: 320–4.

30 Asmakopoulos G, Karagounis P, Valencia O, Alexander N, Howlader M, Sarsam MA, Chandrasekaran V. Renal function after cardiac surgery off- versus on-pump coronary artery bypass: Analysis using the Cockroft-Gault formula for estimating creatinine clearance. Ann Thor Surg 2005; 79: 2024–31.