JPP Journal of Pharmacy and Pharmacology

JPP 2009, 61: 759–766

Received November 17, 2008
Accepted March 02, 2009
DOI 10.1211/jpp/61.06.0008
ISSN 0022-3573

Research Paper

Evaluation of population pharmacokinetic models for amikacin dosage individualization in critically ill patients

María del Mar Fernández de Gatta[a], Silvia Romano Moreno[b], María Victoria Calvo[c], Ramón Ardanuy[d], Alfonso Domínguez-Gil[a,c] and José M. Lanao[a]

[a]Department of Pharmaceutical Technology, Faculty of Pharmacy, University of Salamanca, Spain; [b]Department of Pharmacy, Autonomous University of San Luis Potosi, Mexico; [c]Pharmacy Service, University Hospital of Salamanca, Spain and; [d]Department of Statistics Faculty of Sciences, University of Salamanca, Spain

Abstract

Objectives The aim of this study was to evaluate the reliability for dosage individualization and Bayesian adaptive control of several literature-retrieved amikacin population pharmacokinetic models in patients who were critically ill.

Methods Four population pharmacokinetic models, three of them customized for critically-ill patients, were applied using pharmacokinetic software to fifty-one adult patients on conventional amikacin therapy admitted to the intensive care unit. An estimation of patient-specific pharmacokinetic parameters for each model was obtained by retrospective analysis of the amikacin serum concentrations measured ($n = 162$) and different clinical covariates. The model performance for a priori estimation of the area under the serum concentration–time curve (AUC) and maximum serum drug concentration (C_{max}) targets was obtained.

Key findings Our results provided valuable confirmation of the clinical importance of the choice of population pharmacokinetic models when selecting amikacin dosages for patients who are critically ill. Significant differences in model performance were especially evident when only information concerning clinical covariates was used for dosage individualization and over the two most critical determinants of clinical efficacy of amikacin i.e. the AUC and C_{max} values.

Conclusions Only a single amikacin serum level seemed necessary to diminish the influence of population model on dosage individualization.

Keywords amikacin; Bayes theorem; dosage individualization; population pharmacokinetics

Introduction

Population pharmacokinetics provides a quantitative view of the effect of several pathophysiological and/or clinical factors, on the pharmacokinetic profile of drugs. So, population pharmacokinetic models allow patients to be treated as individuals by expressing each model parameter based on individual covariates.[1,2] Accordingly, customized models for well-defined patient categories (critically ill, oncologic, cystic fibrosis) could lead to more precise dosage individualization. In antibiotherapy, such models have increasingly used Monte Carlo simulation to evaluate the probability of attaining targeted pharmacodynamic exposures against pathogens of interest. However, as a tool to assist clinicians to design rational empirical dosages, such an approach must be rigorously validated. In the clinical setting, model reliability may be impaired by several issues: drug administration or blood sampling errors; insufficient or incorrect patient data; failure to consider patient covariates, or intra-individual variability. External validation (i.e. application of the model developed to a new data set from another study) addresses the broader issue of the generalization of the model, although its applicability may be unclear.[3] When pharmacokinetic models are developed for clinical predictive purposes, determining whether model deficiencies have a noticeable effect on the substantive inferences is the key question. It is also necessary to show whether other approaches yield

Correspondence: Silvia Romano Moreno, Department of Pharmacy, Autonomous University of San Luis Potosi, Av. Manuel Nava No. 6 Zona Universitaria, San Luis Potosí, S.L.P. México.
E-mail: srm@uaslp.mx

similar or better estimates. Population model validation studies are scarce in the literature, especially for old drugs and they are sometimes selected on the basis of arbitrary and subjective criteria. However, calculating a dosage regimen without any patient data only relies on the model chosen and, as a recent example illustrates, the choice of a particular population pharmacokinetic model proved to be critical for dose adjustment by therapeutic drug monitoring.[4]

For aminoglycoside therapy, Bayesian methods offer rapid and accurate tools for dosage individualization in patients with diverse pharmacokinetic behaviour.[5–8] The population parameter estimates used range from the literature values to classical population studies using NONMEM.[9–12] When such models are obtained from specific cohorts (e.g. oncology or intensive care unit (ICU)), a more precise estimation of dosage requirements is achieved.[11–14] In fact, one drawback of the Bayesian approach for dosage individualization is its dependence on the quality of the population pharmacokinetic information used.[15,16] However, it is not widely appreciated how well Bayesian methods perform in the task of model comparison.[17–19] Bayesian probability theory provides a unifying framework for data modelling. The overall aims are to find models that are matched to the data and to use these models to make optimal predictions. To evaluate the plausibility of alternative models in the light of the available data, Bayesian methodology relates this plausibility to the predictions made by models about the data and the prior plausibility of such models.[18]

Accordingly, this study was designed to evaluate the reliability of four population pharmacokinetic models of amikacin in critically ill patients, using both conventional and Bayesian methodology. This evaluation, made using alternative models, should indicate whether they were reliable predictors of amikacin concentrations in such target populations and hence their clinical suitability for dosage individualization.

Materials and Methods

Patient characteristics

Fifty-one patients prescribed amikacin therapy admitted to the medical ICU at the University Hospital in Salamanca were included in the study. These patients were selected retrospectively if at least three criteria were fulfilled. These were: availability of $n \geq 1$ amikacin post-infusion serum concentrations, obtained from routine therapeutic drug monitoring; age ≥ 16 years; and knowledge of the clinical diagnosis and other patient data needed to implement population pharmacokinetic models, as well as the times of dosage administration and blood sampling.

Patients were not excluded on the basis of concurrent disease states or drug therapy, except for solid or haematological malignancies or when extracorporeal removal techniques were used.

The previous patient data as well as the data pertaining to amikacin serum concentration monitoring were collected from the records of the Clinical Pharmacokinetic Service in conjunction with a review of the patient's clinical history if necessary. In accordance with ethical guidelines, the data were presented anonymously. Since the study involved retrospective collection of routine clinical data and required no additional blood samples other than those ordinarily requested by the Clinical Pharmacokinetic Service, informed consent was not obtained. However, approval was obtained from the Institutional Review Board of the University Hospital. Therefore, no formal guidelines were required for amikacin dosage regimens. The usual amikacin therapeutic drug monitoring practice in the ICU involved collection of predose and postdose serum samples at the start of therapy (24–48 h). Additional serum levels were obtained depending on the clinical evolution of the patient: trough or peak levels to evaluate toxicity or efficacy, respectively.

Table 1 Patient characteristics

Number (male/female)	51 (36/15)
Age (years)	58.9 ± 15.4
Total body weight (kg)	70.7 ± 14.9
Height (cm)	166.1 ± 7.6
Serum creatinine (mg/dl)	1.20 ± 0.55
Initial amikacin dosage (mg/kg per day)	12.7 ± 5.5
Number of amikacin serum concentrations per patient	3.2 ± 1.4
Mean serum amikacin concentration (mg/l)	11.5 ± 9.7
Apache II[a] score	18.3 ± 8.1
Positive end-expiratory pressure (cm H_2O)	6.4 ± 3.5
Administration of catecholamines (yes/none)	10/41

[a]Acute physiology and chronic health evaluation.[20]

Patient characteristics and amikacin-related data are summarized in Table 1. The most prevalent clinical diagnoses of the patients were sepsis ($n = 25$), pneumonia ($n = 14$) and multiple trauma ($n = 4$).

Dosage administration and sampling times

All patients received initial amikacin dosage regimens chosen by attending physicians and 40.3% of patients were initially treated on conventional 500 mg two- or three-times daily regimens. All doses were administered over 30–60 min as intermittent intravenous infusions. Serum samples were mainly obtained at the steady-state situation and only six samples were obtained after the first and second doses. The amikacin serum concentrations really obtained ($n = 162$) were trough ($n = 83$), collected within 60 min before the next infusion, peak ($n = 67$), collected within 30–180 min post-infusion, and other sampling times ($n = 12$). Serum amikacin concentrations were measured by a fluorescence polarization immunoassay method (TDx analyzer, Abbott Laboratories, Abbott Park, IL, USA). The intraday and interday coefficients of variation for the assay were <5% and 9%, respectively.

Population pharmacokinetic models

The amikacin serum concentrations measured were compared with those predicted by four population pharmacokinetic models retrieved from the literature, shown in Table 2.[21–24] All these models assumed as the structural model the one-compartment kinetic model. The basic pharmacokinetic parameters of this structural kinetic model were clearance (CL) and volume of distribution (Vd) that allowed for the

Table 2 Summary of population pharmacokinetic models

Model	Equations	Variability (CV%)	
		Between patients	Assay
1[22]	Vd = 0.25 l/kg	0.3	0.15
	CL (ml/min per kg) = 0.0417 + 0.815 CL_{CR}[b]	0.25, 0.4[a]	
2[13]	Vd (l) = 0.39 W × (1 + 0.24 Sepsis)	0.23	NA
	CL (ml/min) = 0.93 CL_{CR}[b] × (1 + 0.22 Trauma)	0.28	
3[10]	Vd (l) = 1.5 × Apache II score	0.29	NA
	CL (ml/min) = 44.5 + 0.67 CL_{CR}[b] – 1.29 PEEP – 8.34 Cat	0.41	
4[21]	Vd = 0.35 l/kg	0.32	0.15
	CL (ml/min per kg) = 0.0417 + 0.815 CL_{CR}[b]	0.25, 0.4[a]	

Cat, use of catecholamines; CL, clearance; CL_{CR}, creatinine clearance; CV, coefficient of variation; NA, not applicable; PEEP, positive end-expiratory pressure; Vd, volume of distribution; W, total body weight. [a]For intercept and slope, respectively. [b]Method of estimation of CL_{CR}: Cockroft-Gault[23] for models 1 and 4, Jeliffe[24] for models 2 and 3.

prediction of the amikacin serum concentrations for different dosing and sampling schedules.

The selection of population pharmacokinetic models was based on the availability in our patients in the ICU of clinical information about the covariates required for the different models: age, height, gender, body weight, serum creatinine, acute physiology and chronic health evaluation (Apache II) score,[20] level of positive end-expiratory pressure (PEEP) and catecholamine administration.

These models were applied to all patients to compare predictive performance and the estimated values of the pharmacokinetic parameters. For this purpose, all models were incorporated in a computerized pharmacokinetic system (Abbottbase Pharmacokinetic Systems, Abbott Park, IL, USA), except model 1, which came provided with such software.[22] This software allowed the choice of several pharmacokinetic models and used different methods for the estimation of individual pharmacokinetic parameters, including Bayesian methodology. When residual error models were not available, the default in Abbottbase software was used.

Dosing weight defined as ((total body weight – ideal body weight)0.4 + ideal body weight) was used for all the calculations.[25] Creatinine clearance (CL_{CR}) used for the predictions was that corresponding to the last serum creatinine concentration obtained. The estimation of CL_{CR} was done using the specific formulas used by the authors in the original models.

We performed a priori (without serum concentration data) and Bayesian (with only the first trough serum level measured) forecasting of amikacin pharmacokinetic parameters and serum concentrations by repeated analysis of each patient data for the four population models considered. A priori predictions involve only population information, whereas Bayesian predictions are the predictions of that individual patient's subsequent serum concentrations after using the population model and then fitting the patient's own earlier data. Equal weighting of the variances in the measured serum concentrations to the variances in the population pharmacokinetic model parameters were used.

To further assess the clinical utility of population models for dose individualization based on area under serum concentration–time curve (AUC) values, this parameter was obtained retrospectively in each patient as daily dose divided by clearance (CL). The amikacin dosage was fixed at a hypothetical 1000 mg/day as standard daily dose and individual clearance was estimated with a maximum a posteriori (MAP) Bayesian approach, using all the serum data available per patient as individual information. Since another usual pharmacodynamic index for aminoglycoside therapy is the maximum serum concentration (C_{max}) vs minimum inhibitory concentration (MIC) ratio, (C_{max}/MIC), the corresponding a priori C_{max} value for the same dose and using all of the individual information was also estimated to compare the population models evaluated. Peaks predicted at 0.5 h post-infusion were used as an approach of C_{max} value, considering that in aminoglycoside therapeutic drug monitoring 0.5–1 h is the usual sampling time.

To extend the clinical utility of our study, estimation of the mean daily dose for the extended dosage interval regimen approach, aiming to achieve a target $C_{max} \approx 45$ μg/ml and $C_{min} < 1$ μg/ml, was done using the best predictive population pharmacokinetic model.[26]

Predictive performance of models

The predictive performance of population models for a priori and Bayesian amikacin serum concentration predictions was assessed using the following criteria. Firstly, linear regression analysis of the correlation between measured and predicted amikacin serum concentrations. Secondly, proportion of measured serum concentrations predicted accurately, defined as being centred on the predicted concentration ±20%; and prediction error analysis as proposed by Sheiner and Beal.[27] Bias was estimated from the mean prediction error (MPE), which was calculated as the sum of the predicted minus the observed values, divided by the number of pairs of data points. Precision was estimated from the mean absolute prediction error (MAE) calculated as Σ[MPE]/n. Finally, statistical comparison of standardized prediction errors, where standard deviation in the predicted values was a normalization factor. The standard deviation was obtained from the residual error variances used by the Abbottbase software.

Bayesian inference

To make a comparison of the four models via Bayesian inference, the following development was considered:

Let §(j) be the prior probability of model j, i = 1, 2, 3, 4, and ε(i) the error with that model defined by: ε(j) = observed – estimated.

This error has two components: one for Vd and the other for CL. If the correct model is j, then the errors have a two-dimensional normal distribution with a mean of zero:

$\varepsilon(j) \ldots N_2\ (0, \Sigma(j))$ such that the likelihood is:

$$L(j) = \exp\ \{-n/2\ \mathrm{Tr}\,[\textstyle\sum(j)^{-1}\, M(j)]\}/(2\pi)^{2n}\ \det\ (\textstyle\sum(j))^{n/2}$$

where M(j) is the matrix of second-order sample moments of the errors, which is an estimator of Σ(j), and hence the likelihood can be estimated by:

$$\begin{aligned} \hat{L}(j) &= \exp\ \{-n/2\ \mathrm{Tr}\,[M(j)^{-1}\ M(j)]\}/(2\pi)^{2n}\ \det\ (M(j))^{n/2} \\ &= \exp(-n/2.2)/(2\pi)^{2n}\ \det\ (M(j))^{n/2} \\ &= e^{-n}/(2\pi)^{2n}\ \det\ (M(j))^{n/2}. \end{aligned}$$

In these equations Tr is the transpose matrix, n is the number of cases and det the determinant.

The a posteriori possibilities (§^) are proportional to the initial ones multiplied by the likelihoods. Thus:

$$(\hat{\S}) \propto \S(j)\ Lj \approx \S(j)\ \hat{L}(j) \propto \S(j)/\det\ (M(j))^{n/2}.$$

Since §(j) = 1/4 we finally have:

$$(\hat{\S}) \propto 1/\det\ (M(j))^{n/2}$$

and the model achieving the highest value would be the most suitable.

To compare the four models we considered that the a posteriori probabilities of models were proportional to the initial ones multiplied by the likelihoods. The model that achieved the highest value would be the most suitable.[19]

Statistical analysis

Statistical analyses were performed using the 11.0 version of the SPSS software (SPSS Inc Headquarters, Chicago, IL, USA). Statistical significance was defined a priori as a *P* value of less than or equal to 0.05. For multiple comparisons, the Kruskal–Wallis and the Bonferroni tests were selected owing to the homoscedasticity of the data.

Results

Amikacin pharmacokinetic parameters and serum concentrations were predicted from the four population pharmacokinetic models evaluated in our cohort of 51 patients in the intensive care unit. All patients had at least one amikacin serum concentration measured but additional concentrations available per patient were one, two, three or more for nineteen, eight, thirteen and eight patients, respectively. Thus, 162 amikacin serum concentrations were predicted a priori, whereas for Bayesian prediction this figure was 111.

The regression analyses between predicted and measured amikacin concentrations for all models are shown graphically in Figure 1 whilst the correlation analyses are shown in Table 3. The proportion of measured concentrations predicted accurately, defined as being centred on the predicted concentration ±20%, was 15.4, 27.7, 19.7 and 22.8% respectively for models 1–4 considered with respect to a priori prediction. The values, in similar ranking, were 14.4, 46.8, 34.2 and 36.9% for Bayesian prediction.

The conventional metrics for the evaluation of the predictive performance of population pharmacokinetic models were prediction errors, both normal and standardized. The former were globally depicted by box plotting (Figure 2), whereas the latter have been summarized in Table 4. From visual inspection of the MPE, variations in the predictive performance of the population models were evident, model 2 appearing as the one best centred around the desired zero value. Analysis of the standardized prediction errors revealed that all pharmacokinetic population models performed best in the a priori prediction of peak amikacin concentrations, whereas trough concentrations were more biased and imprecisely predicted. Also, the statistical differences among the models evaluated were very apparent for peak concentrations.

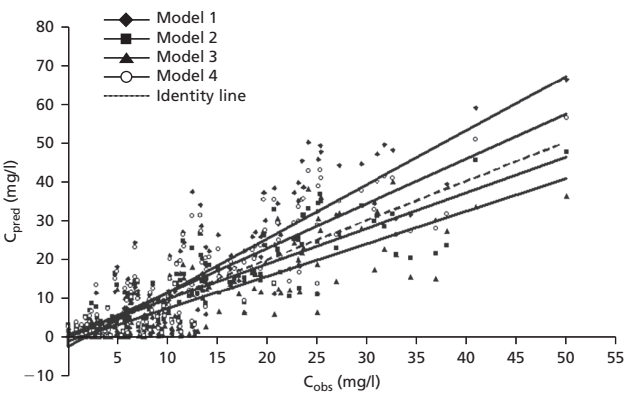

Figure 1 Linear regression analysis between measured and predicted amikacin serum concentrations for four population models. C_{obs}, measured serum concentrations; C_{pred}, predicted serum concentrations. See Table 3 for correlation analysis.

Table 3 Correlation analysis for the four population models

Correlation analysis	Model 1	Model 2	Model 3	Model 4
r	0.87	0.86	0.82	0.86
Intercept (confidence interval)	–2.45 (–4.28, –0.61)	0.52 (–0.75, 1.80)	–1.03 (–2.38, 0.31)	–0.24 (–1.78, 1.30)
Slope (confidence interval)	1.39 (1.27, 1.51)	0.91 (0.83, 1.00)	0.83 (0.74, 0.92)	1.15 (1.04, 1.25)

See Figure 1.

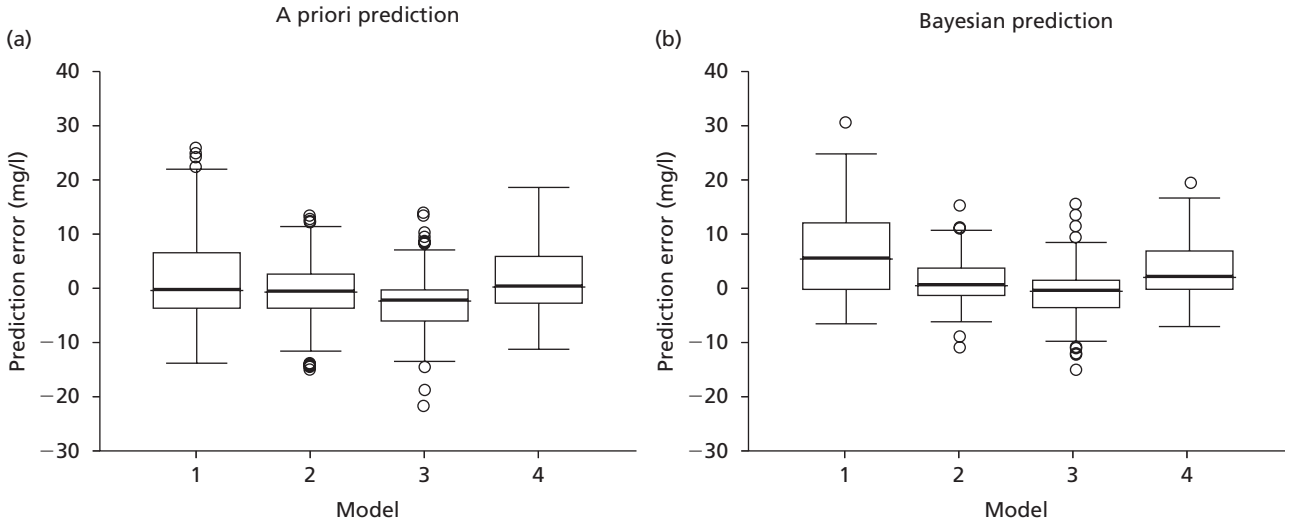

Figure 2 Mean prediction errors obtained from population pharmacokinetic models of amikacin serum concentrations in the whole population. The two models used were (a) a priori prediction and (b) Bayesian prediction. The box–whisker plot represents the median, 25th and 75th percentiles, respectively. The circles represent outliers.

The a priori vs Bayesian prediction for trough concentrations was: –2.79 ± 3.9 vs –0.62 ± 3.8, –1.16 ± 4.0 vs –0.93 ± 2.3, –3.73 ± 4.0 vs –1.23 ± 2.4 and –1.31 ± 4.1 vs –0.97 ± 2.6 μg/ml for the MPE of models 1–4, respectively. Also, the mean values of MAE were reduced from 3.6 ± 3.0 for the a priori to 1.9 ± 2.0 for Bayesian prediction.

The possible influence of a diagnosis of sepsis in predictive performance was examined. Nearly 50% of our patients had this diagnosis and one of the population pharmacokinetic models evaluated was specifically designed in that subpopulation. Table 5 summarizes the performance of the models in septic patients, similar findings to those obtained for the analysis of the global population being observed. Model comparison by Bayesian inference reaffirmed model 2 as more suitable owing to the higher value obtained for posteriori possibility: 0.99 vs 1.3 exp –25, 3.9 exp –9 and 2.2 exp –12 for the other models.

The comparison of the models in terms of AUC showed the following mean ± SD AUC values for a priori vs Bayesian estimation: 319.8 ± 142.8 vs 322.5 ± 181.3, 339.6 ± 148.0 vs 316.4 ± 141.6, 212.5 ± 56.4 vs 244.6 ± 118.2 and 319.8 ± 142.8 vs 304.6 ± 167.3 mg h/l for models 1, 2, 3 and 4, respectively. The estimated a priori C_{max}, expressed as mean ± SD values, were 58.2 ± 12.9, 36.4 ± 8.2, 41.2 ± 13.7 and 43.8 ± 9.8 mg/l for models 1–4, respectively. These AUC and C_{max} values could be interpreted further by taking into account some published MIC data concerning important pathogens in the ICU environment, thus allowing their use as surrogates to predict clinical success.

For an extended dosage interval regimen of amikacin, and according to the best predictive population model, the mean ± SD (range) dose obtained was 1453 ± 370 (750–2750) mg, which must be administered each 24, 48 and 72 h for the 62, 28 and 8% of patients, respectively.

Discussion

Despite continued progress toward anti-infective dosage selection based on pharmacodynamic characteristics, antibiotic dosage regimens should be further individualized by linking pharmacodynamic criteria with patient- and/or institution-specific MIC values and pharmacokinetic

Table 4 Predictive performance in the whole population

Model used	Standardized mean prediction error ± SD			
	A priori prediction		Bayesian prediction*	
	C_{peak} (n = 67)[a]	C_{trough} (n = 83)[b]	C_{peak} (n = 66)[c]	C_{trough} (n = 34)[d]
Model 1	0.93 ± 1.0	–4.20 ± 8.3	2.18 ± 1.0	–1.76 ± 3.1
Model 2	–0.08 ± 1.7[e]	–1.46 ± 2.8	0.66 ± 1.9	–1.58 ± 2.7
Model 3	–1.06 ± 3.0	–10.6 ± 15.7	–1.04 ± 3.4	–1.79 ± 2.4
Model 4	0.66 ± 1.0	–1.18 ± 2.2	1.32 ± 1.1	–1.36 ± 2.3

*Using one measured concentration as feedback. [a]Significant differences ($P < 0.05$) among models except 1 vs 4 and 2 vs 3. [b]Significant differences ($P < 0.05$) among models except 2 vs 4. [c]Significant differences ($P < 0.05$) among models except 2 vs 4. [d]No significant differences among models. [e]Confidence interval 95% comprised zero value.

Table 5 Predictive performance in patients with sepsis

Model used	Standardized mean prediction error ± SD			
	A priori prediction		Bayesian prediction*	
	C_{peak} (n = 33)[a]	C_{trough} (n = 40)[b]	C_{peak} (n = 33)[c]	C_{trough} (n = 16)[d]
Model 1	0.88 ± 0.8	−5.36 ± 10.1	2.08 ± 0.9	−1.99 ± 3.0
Model 2	−0.46 ± 1.6[e]	−1.54 ± 2.6	0.01 ± 0.7	−1.87 ± 3.3
Model 3	−1.28 ± 2.3	−14.7 ± 22.6	−1.53 ± 3.5	−2.48 ± 2.4
Model 4	0.50 ± 0.9	−1.74 ± 2.7	1.18 ± 1.0	−1.61 ± 2.7

*Using one measured concentration as feedback. [a]Significant differences ($P < 0.05$) among models except 1 vs 4 and 2 vs 3. [b]No significant differences ($P < 0.05$) among models except 2 vs 3 and 3 vs 4. [c]Significant differences ($P < 0.05$) among models except 2 vs 3. [d]No significant differences among models. [e]Confidence interval 95% comprised zero value.

parameters.[28,29] The rate of optimal serum aminoglycoside profiles obtained after dosage adjustment by Bayesian feedback techniques is remarkable, but the large proportion of patients seen to have sub-therapeutic peak concentrations before dosage individualization emphasizes the need for therapeutic drug monitoring and better initial dosing strategies.[30–32] Good population pharmacokinetic models would help to optimize the appropriate dose since the initiation of aminoglycoside therapy, irrespective of the multidose or once-daily dosage schedules used.

Although the first intended application of the pharmacokinetic models we evaluated here was initial selection of the amikacin dosage in ICU patients, the predictive performance of the corresponding serum concentrations was the usual surrogate.[5] The performance of the models was first evaluated when they were used as a nomogram before the availability of any amikacin concentrations (a priori prediction) and then using the minimum collected data as individual or feedback information (Bayesian prediction). Since the prior data e.g. the expected values of the pharmacokinetic parameters for any given patient, were adjusted differently for each model, the predicted concentrations must differ among models. However, in this study it was apparent that for both a priori and Bayesian prediction statistically significant differences ($P < 0.05$) in prediction errors were only seen for the peak amikacin concentrations. The most important determinant of peak concentrations was the volume of distribution (Vd), and hence it was pertinent to conclude that discrepancies in this parameter for population models may have been be more critical. However, another additional factor could be the error in the measurement of peak concentrations. A study of 36 patients in the ICU reported that interpatient variability in amikacin pharmacokinetics may have been more than moderate for Vd.[33] The models assuming Vd as only a function of body weight yielded a significant bias in predicting a priori and Bayesian peak amikacin concentrations (8.9 ± 8.3 and 11.1 ± 7.7 μg/ml, respectively, for model 1; 5.5 ± 7.0 and 5.7 ± 5.5 μg/ml, respectively, for model 4). In contrast, models 2 and 3, which took into account relevant descriptors of critically ill patients for the estimation of Vd as sepsis diagnosis or Apache II score, allowed a more accurate prediction of peak amikacin concentrations, even if the model did not include feedback. In fact, the means ± SD of MPE for a priori peak amikacin prediction of such models were not significantly different from zero. These results may have implications for clinical efficacy because the C_{max}/MIC ratio could be used as a pharmacodynamic target for dosage adjustment.[34–36] Bacopolou *et al.*[33] have suggested that individualized once-daily amikacin dosing to target peaks of 45 μg/ml may be a safe and effective strategy for patients in the ICU.

Predictive performance is the most indicative test of a predictor because it considers bias as well as systematic error with repeated use. However, under the assumption of unbiased population parameter estimates a more appropriate test is that the mean value of the standardized prediction errors should not be significantly different from zero.[2,3] In this respect, model 2 performed the best in a priori and Bayesian predictions of peak values for the whole population and also in patients with sepsis. Moreover, the therapeutic precision seemed to be increased for this model owing to the greater ability to reach a clinically acceptable range (±20%) of target serum concentrations and a better degree of association between the observed and predicted amikacin concentrations. The final pharmacokinetic values from model 2 were in very good agreement with the a priori distribution of model parameter estimates, also confirming it, via Bayesian inference, as the best overall population model.

Despite the evident reliability of model 2 in critically ill patients, it is worth noticing that Bayesian prediction improved predictive performance irrespective of the population model used. Therefore only a single amikacin serum sample was needed for an acceptable Bayesian prediction of the individual pharmacokinetic profile, regardless of the population information used. However, a more precise and optimal prediction could be made if a higher number of samples could be obtained.

While all the models were negatively biased for trough amikacin concentrations, the relationship between amikacin clearance (CL) and patient covariates could be more complex or variable than those defined in the population models considered here. Moreover, in this study the patients had a moderate renal insufficiency. This fact eventually could influence the predictive performance of the models if patients with severe renal impairment, where amikacin pharmacokinetics may be significantly modified, were considered. Intra-individual variations related to the pathological characteristics of critically ill patients could lead to outliers in

amikacin concentrations, which could feasibly explain the observed precision and bias. However, when the same approach was used for the adaptive control of aminoglycoside therapy in other patient populations, predictive performance was similar.[7–10,15,21,31,32,37,38]

Methods that rely on the estimation of Vd and CL would appear preferable in patients with variable pharmacokinetics, such as critically ill patients. However, methods based on the use of target AUC have been advocated since the increasing prevalence of once-daily aminoglycoside dosing.[35–38] This clinical scenario and the unavailability of amikacin nomograms specifically based on ICU patients prompted us to assess the a priori predictability of the AUC in this specific patient population. The influence of the population model in this estimation was clear from the statistically significant differences ($P < 0.05$) observed among the models. The ranges (50–920) and variation coefficients (45.2–55.5%) of the AUC values obtained underscored the idea that pharmacokinetic behaviour in critically ill patients was too variable and that individual pharmacokinetic monitoring was warranted to attain a narrower range for such targets.

Population model-based Bayesian approaches with extended-interval dosing have not been formally studied for amikacin in patients who are critically ill. According to the best predictive population model an initial amikacin dosage of 1500 mg or equivalent 20 mg/kg/day is likely used for this selected population. Figure 3 depicts model influence on serum profiles for such an initial dosage. However, other considerations should be taken into account for decision making in patients in intensive care, such as wide intra- and interpatient variability and the need of further dosage interval adaptation. These uncertainties as well as model-dependence could be minimized from only one concentration measurement as a part of the routine clinical care of the patient. This approach would have definitive advantages over nomogram or population pharmacokinetic models for amikacin dosing in the environment of the ICU, although other appropriate methods of dosage design may be used in this setting.[39]

We believe that clinicians should be aware of the differences among published population models when selecting dosages, especially for patients who are critically ill and who seldom tolerate sub-optimal therapy. Although our results consistently pointed to the potential importance of this fact, the retrospective design of our study and the fact that the clinical outcomes were not evaluated support the need for supplementary prospective and comparative clinical trials to confirm what the optimum amikacin model is for this heterogeneous population.

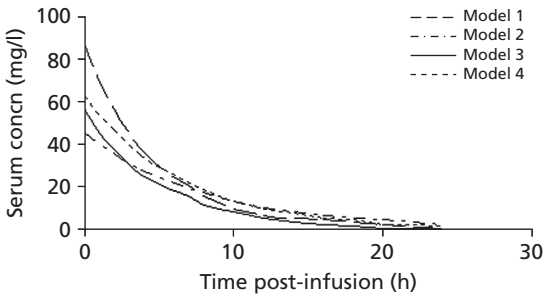

Figure 3 Simulated serum concentration profile of amikacin. The four models tested used an initial once-daily amikacin dose of 1500 mg/day.

Conclusions

For patients in the ICU the use of specific covariates such as sepsis diagnosis or Apache II score in population pharmacokinetic models was shown to be decisive in the a priori optimum choice of amikacin dosage based on the C_{max}/MIC ratio. These specific models might be used as a starting dosing nomogram for this patient population and only one serum measurement individually obtained seems to neglect the model influence on dosage individualization. However, given the interpatient pharmacokinetic variability associated with critical illness it is unlikely that even highly predictive models would provide the level of clinical confidence necessary to replace this minimum individual information.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

Funding

This research was supported by the project GR207 for Excellent Research Groups. JCyL. 2008.

References

1. Sheiner LB *et al*. Estimation of population characteristics of pharmacokinetic parameters from routine clinical data. *J Pharmacokinet Biopharm* 1977; 5: 445–479.
2. Mandema JW *et al*. Building population pharmacokinetic-pharmacodynamic models. I. Models for covariate effects. *J Pharmacokinet Biopharm* 1992; 20: 511–528.
3. Ette EI *et al*. Model appropriateness and population pharmacokinetic modelling. *J Clin Pharmacol* 2003; 43: 610–623.
4. Neef C *et al*. Pitfalls in TDM of antibiotic drugs: analytical and modelling issues. *Ther Drug Monit* 2006; 28: 686–689.
5. Sun H *et al*. Population pharmacokinetics. A regulatory perspective. *Clin Pharmacokinet* 1999; 37: 41–58.
6. Thomson AH, Whiting B. Bayesian parameter estimation and population pharmacokinetics. *Clin Pharmacokinet* 1992; 22: 447–467.
7. Duffull SB *et al*. Comparison of two Bayesian approaches to dose-individualization for once-daily aminoglycoside regimens. *Br J Clin Pharmacol* 1997; 43: 125–135.
8. Joubert P *et al*. Population approach to the forecasting of amikacin plasma and urinary levels using a prescribed dosage regimen. *Eur J Drug Metab Pharmacokinet* 1999; 24: 39–46.
9. Gauthier T *et al*. Predictive performance of two software packages (USC*PACK PC and Abbott PKS system) for the individualization of amikacin dosage in intensive care unit patients. *Int J Biomed Comput* 1994; 36: 131–134.
10. Lugo Goytia G, Castañeda-Hernández G. Bayesian approach to control of amikacin serum concentrations in critically ill patients with sepsis. *Ann Pharmacother* 2000; 34: 1389–1394.
11. Debord J *et al*. Population pharmacokinetic parameters for Bayesian monitoring of amikacin therapy in intensive care unit patients. *Eur J Clin Pharmacol* 1992; 43: 435–436.

12. Lugo Goytia G, Castañeda-Hernández G. Amikacin Bayesian forecasting in critically ill patients with sepsis and cirrhosis. *Ther Drug Monit* 1997; 19: 271–276.
13. Romano S *et al*. Influence of clinical diagnosis in the population pharmacokinetics of amikacin in intensive care unit patients. *Clin Drug Invest* 1998; 15: 435–444.
14. Radomski KM *et al*. General versus subpopulation values in Bayesian prediction of aminoglycoside pharmacokinetics in haematology-oncology patients. *Am J Health-Syst Pharm* 1997; 54: 542–544.
15. McClellan SD, Farringer JA. Bayesian forecasting of aminoglycoside dosing requirements in obese patients: influence of subpopulation versus general population pharmacokinetic parameters as internal estimates. *Ther Drug Monitor* 1989; 11: 431–436.
16. Fernández de Gatta MM *et al*. Bayesian forecasting in paediatric populations. *Clin Pharmacokinet* 1996; 31: 325–330.
17. Goodman SN. Toward evidence-based medical statistics. 2: The Bayes Factor. *Ann Inter Med* 1999; 130: 1005–1013.
18. MacKay DJC. *Information Theory, Inference and Algorithms*. Cambridge: University Press, 2003.
19. Zellner A. *An Introduction to Bayesian Inference in Econometrics*. New York: Wiley and Sons, 1971.
20. Knaus WA *et al*. Apache II: a severity of disease classification system. *Crit Care Med* 1985; 13: 818–830.
21. Lacarelle B *et al*. Evaluation of a Bayesian Method of amikacin dosing in Intensive Care Unit patients with normal or impaired renal function. *Ther Drug Monitor* 1987; 9: 154–160.
22. Abbott Laboratories, Diagnostics Division. Abbottbase pharmacokinetic systems operations manual. Abbott Park, Abbott Laboratories, USA, 1993.
23. Cockroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976; 16: 31–41.
24. Jelliffe RW. Creatinine clearance: bedside estimate. *Ann Intern Med* 1973; 79: 604–605.
25. Bauer IA *et al*. Influence of weight on aminoglycoside pharmacokinetics in normal weight and morbidly obese patients. *Eur J Clin Pharmacol* 1983; 24: 643–647.
26. Alvarez-Lerma F *et al*. Recomendaciones para la monitorización de antibióticos en pacientes críticos ingresados en UCI. *Enferm Infecc Microbiol Clin* 2008; 26: 230–239.
27. Sheiner LB, Beal SL. Some suggestions for measuring predictive performance. *J Pharmacokinet Biopharm* 1981; 9: 503–512.
28. Craig WA. Does the dose matter? *Clin Infect Dis* 2001; 33 (Suppl. 3): 233–237.
29. Goldberg J, Owens RC. Optimizing antimicrobial dosing in the critically ill patient. *Curr Opin Crit Care* 2002; 8: 435–440.
30. Bartal C *et al*. Pharmacokinetic dosing of aminoglycosides: a controlled trial. *Am J Med* 2003; 114: 194–198.
31. Kaufmann GR *et al*. Safety and efficacy of two–compartment Bayesian feedback program for therapeutic tobramycin monitoring in the daily clinical use and comparison with a non-Bayesian one-compartment model. *Ther Drug Monit* 1998; 20: 172–180.
32. Böttger H *et al*. Use of aminoglycosides in critically ill patients: individualization of dosage using Bayesian statistics and pharmacokinetic principles. *Ther Drug Monitor* 1988; 10: 280–286.
33. Bacopolou F *et al*. A study of once-daily amikacin with low peak target concentrations in intensive care unit patients: pharmacokinetics and associated outcomes. *J Crit Care* 2003; 18: 107–113.
34. Kashuba AD *et al*. Optimizing aminoglycoside therapy for nosocomial pneumonia caused by Gram-negative bacteria. *Antimicrob Agents Chemother* 1999; 43: 623–629.
35. Turnidge J. Pharmacodynamics and dosing of aminoglycosides. *Infect Dis Clin North Am* 2003; 17: 503–528.
36. Conil JM *et al*. Increased amikacin dosage requirements in burn patients receiving a once-daily regimen. *Int J Antimicrob Agents* 2006; 28: 226–230.
37. Bresolle F *et al*. Population pharmacokinetics of amikacin in critically ill patients. *Antimicrob Agents Chemother* 1996; 40: 1682–1689.
38. Barclay ML *et al*. Once daily aminoglycoside therapy. Is it less toxic than multiple daily doses and how should it be monitored? *Clin Pharmacokinet* 1999; 36: 89–98.
39. Macdonald I *et al*. Evaluation and comparison of simple multiple model, richer data multiple model and sequential interacting multiple model (IMM) Bayesian analyses of gentamicin and vancomycin data collected from patients undergoing cardiothoracic surgery. *Ther Drug Monit* 2008; 30: 67–74.