Teicoplanin Population Pharmacokinetic Analysis in Hospitalized Patients

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Abstract: The goal of this study was to build a population pharmacokinetic (PK) model to characterize the population PK parameters in our hospitalized patients. Teicoplanin serum concentrations from clinical routine were used. Antibiotic dose history and blood collection times were recorded and analyzed with NONMEM-V. Demographic and biologic data creatinine clearance (CL_{cr}), weight (WT), and albumin (Alb) were tested for inclusion as covariates in the basic model. Intraindividual and residual variability were modeled. One hundred seven sparse samples (mainly trough levels), from 79 patients, were included. A 2-compartment PK model characterized by clearance (CL), central compartment volume of distribution (V_c), intercompartment clearance, and steady-state volume of distribution (V_{SS}) with first-order elimination adequately described the data. CL_{cr} and WT significantly influenced teicoplanin CL (CL = 0.57[0.15]*(1 + 0.0048[0.39]*(CL_{cr} − averageCL_{cr})*WT) L/h). V_{SS} was not affected by any covariate (V_{SS} = 50.2[0.13]L). A negative trend between Alb and individual V_{SS} estimates was observed without statistical significance. In a new data set, bias and precision resulted in mean values of −3.24% and 9.42%, respectively. In conclusion, CL_{cr} and WT are significant covariates on teicoplanin CL. Results from predictive accuracy and precision show the usefulness of this model for implementation in a therapeutic drug monitoring program in the near future.

Key Words: population pharmacokinetics, teicoplanin, therapeutic drug monitoring

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INTRODUCTION

The rising prevalence of Gram-positive infections over recent years has led to an increased consumption of glycopeptides such as vancomycin or teicoplanin. Both antimicrobials are similar in terms of antibacterial spectrum and efficacy, but the latter shows fewer adverse effects.[1–4]

Teicoplanin is a glycopeptide antimicrobial drug, which interferes with the cell wall synthesis by inhibiting polymerization of peptidoglycan.[5,6] The different pharmacokinetic features of teicoplanin (with longer elimination half-life compared with vancomycin[7]) allow its administration once a day by intravenous or intramuscular route, which is a real benefit in surgery prophylaxis.[8]

Because the bactericidal activity of teicoplanin is time-dependent, microbiologic and clinical efficacy are maximal when antibiotic concentration remains approximately 4 times over the minimal inhibitory concentration of the pathogen.[9] Several reports describe optimal bacterial killing when trough serum concentrations, at equilibrium (steady-state conditions), attain values within 10 to 20 mg/L with the exception of endocarditis and bone or prosthetic infections in which the recommended therapeutic range is 20 to 25 mg/L.[10–12] Therapeutic drug monitoring (TDM) of vancomycin combined with a Bayesian approach to optimize dose regimens has been performed for many years.[13–15] However, teicoplanin TDM still remains under discussion. It is accepted that TDM is useful when 1) a good correlation between blood drug concentration and pharmacologic response is seen, 2) blood concentrations of the drug are a better predictor than is dose, and 3) high inter- and intraindividual variability in dose against response is present. To date, there is some evidence that efficacy and toxicity are related to teicoplanin plasma concentrations and specifically to trough drug levels during treatment.[16] Moreover, a high interindividual variability in teicoplanin disposition has been described and, up to now, some studies, including demographic or biologic covariates to quantify and better explain this variability, have been reported.[17–20] Consequently, TDM of teicoplanin may be considered.[21] In addition, Pea et al have reported, in some special populations, the value of TDM in individualizing the dosage selection to optimize antibiotic treatment.[22,23]

Population pharmacokinetic (PK) parameters obtained from a population PK analysis are often used as empirical prior information for a Bayesian analysis of sparse PK data from new individuals.[24,25] Subsequently, the estimated individual PK parameters can be used for dosing advice in clinical practice.

In this study, we have retrospectively analyzed teicoplanin serum concentrations obtained from inpatients who required teicoplanin. The main goal was to build a population PK model to characterize the population PK parameters in hospitalized patients as a starting point for future teicoplanin dosage optimization in clinical routine.

PATIENTS AND METHODS

Teicoplanin Dosage

In our setting, teicoplanin is integrated as a first-line treatment in the guidelines for 1) antibiotic prophylaxis in

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surgical procedures such as hepatic transplantation, thoracic surgery, major gastrointestinal surgery, and further treatment if needed as a result of Gram-positive infection disease; and 2) Gram-positive infections in patients with severe acute renal impairment (creatinine clearance [CL_{cr}] lower than 20 mL/min).

The initial dosage of teicoplanin was prescribed in all cases in accordance with the literature.[26] Patients were scheduled to receive 3 loading intravenous doses of 400 mg/12 hours followed by a maintenance intravenous dose of 400 mg once daily every 48 hours or every 72 hours according to their renal function.

Patients and Blood Samples

From 2001 to 2004, serum teicoplanin concentrations from inpatients treated with intravenous teicoplanin (Targocid; Aventis Pharma, S.A., Spain) were studied (index data set). These samples were scheduled to be obtained at the end of the interval between 2 consecutive doses (trough concentrations) and at steady-state conditions (SS) defined as the situation in which the rate of drug administration is equal to the rate of drug elimination so that the plasma drug concentration remains constant. Serum drug concentrations from patients undergoing extracorporeal depurative techniques such as hemodialysis or continuous hemofiltration were excluded from the study.

For each patient, 1) demographic data such as age, gender, and weight; 2) routine clinical biochemistry data: serum creatinine (Cr), creatinine clearance (CL_{cr}) calculated by the formula of Cockcroft-Gault,[27] total serum bilirubin (Bil), serum albumin (Alb), and blood urea nitrogen (BUN); 3) teicoplanin dose history (both amount and administration time); and 4) the time at which the blood samples were drawn, were recorded. Sampling and dosing times were obtained from the routine TDM history records, which were recorded throughout the period of the study. Demographic and clinical biochemistry data were obtained from the clinical history records.

From January to August 2005, data from new inpatients (validation data set), treated with teicoplanin in the same conditions as those previously used in the analysis, were recorded and used to validate the population PK model.

Ethical committee approval and patient consent were not requested because they are not compulsory for TDM data use.

Pharmacokinetic Study and Model Building

Serum drug concentrations versus time data (from the index data set) were analyzed on the basis of the population approach using the nonlinear mixed-effect program NONMEM version V[28] and applying the 3-step strategy: 1) basic population model selection, 2) exploring parameter versus covariate relationships outside of NONMEM, and 3) covariate and final model selection.

Regarding the structural population PK model, 2 options: one- versus 2-compartment PK model with intravascular administration and first-order elimination, were tested. The population PK parameters (P) of the selected model were characterized and interindividual variability in these parameters was modeled as log normally distributed. Consider for a generic PK parameter, the following model:

$$P = \mu_P \exp(\eta_P) \quad (1)$$

in which μ_P is the population mean of P (P = CL, V_c, Q, V_{SS}) and η_P is a normally distributed random effect [$N \sim (0, \omega^2_P)$] capturing the interindividual variability of P. The random effects for different parameters may be correlated. A mean parameter μ_P may be further modeled as a function of covariates as follows:

$$\mu_P = \theta_{P1} * [1 + \theta_{P2}(CT - {}_{av}CT)] \quad (2)$$

$$\mu_P = \theta_{P1} * (CT/{}_{av}CT)^{\theta P2} \quad (3)$$

$$\mu_P = \theta_{P1} * [(1 - CG) + \theta_{P2} * CG] \quad (4)$$

in which, θ_{Pj} (j = 1,2,…) represents elements of a vector of population fixed-effect parameters, CT is the continuous covariate value of the patient, ${}_{av}CT$ is the mean covariate value along the studied population, and CG is a categorical covariate coded in the data set as 0 or 1. Additive, proportional, and combined error models were tested for residual variance on drug concentrations. The first-order conditional estimation method was applied for parameter estimation.

Subsequently, demographic factors and biologic data were tested for inclusion as covariates in the basic population PK model to explain interindividual variability. A standard graphic method was used plotting each covariate against individual estimates of PK parameters under the basic population PK model. Each covariate was then investigated in NONMEM and retained if it led to a significant improved fit. Improvements to the model were evaluated by: 1) graphic displays based on the agreement between the observed and predicted drug concentrations, 2) plots of predictions versus residuals and weighted residuals, 3) the uniformity of the distribution of the residuals, and 4) the log-likelihood ratio test, which is the difference in NONMEM objective functions (OFV) between 2-nested models. The difference in minus twice the log-likelihood between a full model (with covariate) and a reduced model (without covariate) is asymptotically χ^2-distributed with degrees of freedom equal to the difference in number of parameters between the 2 compared models. Covariates were kept in the model if they yielded $P < 0.05$ according to this test. Subsequently, all the covariates found to be significant were added simultaneously to the model to test for significance again. As a last step, the final model was assessed by a backward-deletion strategy and each covariate was removed in turn from it. An increase in OFV greater than at least 5 units was required to consider the covariate as significant.

Model Validation

An internal validation of the population PK model was performed in NONMEM V by simulating 1000 teicoplanin plasma profiles taking into account the covariates included in the final population PK model. Mean and 95% confidence interval were calculated for each experiment. Statistics were performed using S-Plus 6.1.[29]

The predictive performance of the PK model previously described was assessed by analyzing data from new individuals (validation data set) treated with teicoplanin in similar

conditions to the study population (index data set).[30] Individual predicted teicoplanin concentrations for all sampling times were obtained by Bayesian estimation ("*posthoc*" subroutine of NONMEM without the estimation step) setting population PK parameter values (mean PK parameters, interindividual and residual variability) to population values previously obtained in the index data set. The performance of the Bayesian analysis was evaluated by comparison of the observed (OBS) concentrations with the population predicted (PRED) and individual predicted (IPRED) concentration values. Bias and precision were calculated and expressed in terms of percentage prediction error (PE%) and absolute percentage prediction error (APE%), respectively,[31] as follows:

$$\begin{aligned} \text{IPE}\% &= [(\text{OBS} - \text{IPRED})/\text{IPRED}] * 100 \\ \text{PPE}\% &= [(\text{OBS} - \text{PRED})/\text{PRED}] * 100 \end{aligned} \quad (5)$$

$$\begin{aligned} \text{IAPE}\% &= [|(\text{OBS} - \text{IPRED})/\text{IPRED}|] * 100 \\ \text{PAPE}\% &= [|(\text{OBS} - \text{PRED})/\text{PRED}|] * 100 \end{aligned} \quad (6)$$

Dosage Regimen Simulations

Population mean and interindividual variability of the PK parameters were used to simulate 500 PK responses to different teicoplanin dosing schemes for: 1) an average 73-kg patient and low, median, and high CL_{cr} values; and 2) an average patient with CL_{cr} = 63.3 mL/min and low, median, and high weight. Based on that, in each case, the dose to be given once daily to reach a target trough concentration of 15 mg/L or 25 mg/L was estimated.

RESULTS

Subjects and Samples

One hundred seven serum teicoplanin concentrations, from 79 patients ranging from 3.7 to 82.1 mg/L, were used during the analysis (Table 1: index data set). The lower value corresponds to a 12-hour concentration after the first dose (400 mg teicoplanin) in a patient with impaired renal function (CL_{cr} = 20 mL/min). The highest value (82.1 mg/L) is a peak concentration obtained 1 hour after teicoplanin administration in a patient with mild renal function impairment (CL_{cr} = 63.3 mL/min).

Patients' age and weight ranged from 21 to 83 years (mean, 59 years) and 40 to 160 kg (mean, 73 kg), respectively. In all cases, Gram-positive infection (87% of cases resulting from *Staphylococcus* sp.) was documented by microbiologic cultures (teicoplanin susceptibility breakpoint ≤8 mg/L). The enrolled population consisted of adult patients presenting with bone or prosthetic infections (N = 3), endocarditis (N = 8), catheter-related bacteremia or primary bacteremia (N = 25), pneumonia (N = 12), and gastrointestinal infections (N = 30).

Mean (±standard deviation) CL_{cr} was 63.3 ± 40.5 mL/min. Ninety-seven percent of the patients received an initial teicoplanin dose of 400 mg. In only 2 subjects, an initial reduced dose of 200 mg was mistakenly prescribed.

TABLE 1. Therapeutic Drug Monitoring (TDM) Samples and Patients' Characteristics for Both Groups of Patients: the Index Data Set and the Validation Data Set

	Index Data Set	Validation Data Set
Total TDM samples	107	22
Serum concentrations range (mg/L)	3.7–82.1	4.9–35.1
No. (females/males)	79 (50/29)	15 (10/5)
TDM samples per subject	1.4	1.5
No. with more than one sample (%)	25 (32%)	5 (33%)
Age (years)	59.2 ± 12.9	67.2 ± 7.4
Weight (kg)	73.2 ± 21.5	66.1 ± 11.7
Cr (mg/dL)	1.7 ± 1.0	2.0 ± 0.9
CL_{cr} (mL/min)	63.2 ± 40.5	51.4 ± 21.8
BUN (mg/dL)	46.9 ± 32.6	49.3 ± 33.4
Alb (mg/dL)	28.4 ± 5.3	29.5 ± 4.2

Cr, serum creatinine; CL_{cr}, creatinine clearance; BUN, blood urea nitrogen; Alb, serum albumin.

After checking the sampling times of the studied serum specimens, data showed that some of them were drawn at random times within the interdose interval (range, 2–109 hours after last dose administration). Nevertheless, most of them were taken in steady-state conditions (75%) and just before a drug dose administration (68% of trough concentrations). Sixty-three of all 79 patients (80%) had been receiving therapy with teicoplanin for at least 6 days when TDM was performed. Twenty-five per cent of samples were obtained before reaching steady-state conditions, mainly from patients with a certain degree of renal impairment. Sixteen of 79 patients (20%) initially showed values of creatinine clearance lower than 20 mL/min. In these patients, the acute renal impairment episode was caused by a combination of several factors such as: 1) low blood renal flow after surgery, 2) age (usually older than 70 years), and 3) concomitant nephrotoxic drugs: aminoglycosides, or frusemide; but in none of these cases was the use of renal replacement procedures needed and renal function improved to normal values within the period of the study.

Population Pharmacokinetic Model

The results obtained with the different population PK models tested in this study are displayed in Table 2. A basic 2-compartment PK model, described by population clearance (CL), population volume of distribution of the central compartment (V_c), population intercompartment clearance (Q), and population volume of distribution at steady-state (V_{SS}), with intravenous administration and first-order elimination adequately explained the data. However, the available data neither supported the estimation of Q nor the interindividual variability of V_c and Q. Thus, Q was set to a fixed value obtained from the literature,[18,32] and interindividual variability was only incorporated in CL and V_{SS}. Correlation between random effects was also incorporated. Residual variability consisted of a proportional error of 28%.

First, all covariates were tested separately for their effect on the PK parameters before being included in the model.

TABLE 2. Comparison of the Different Models Tested for Modeling Teicoplanin PK

Model	PK Model	OFV	Δ (OFV)
1	One-compartment model first-order elimination	617.221	—
2	Two-compartment model first-order elimination (basic model)	608.475	8.742*
3	Model 2 + CL_{cr} on CL	601.860	6.619*
4	Model 2 + weight on CL	602.163	6.312*
5	Model 3 + Alb on CL	601.737	0.123
6	Model 3 + Alb on V_{SS}	598.929	2.931
7	Model 3 + age on CL	599.991	1.869
8	Model 3 + age on V_{SS}	598.732	3.128
9	Model 3 + gender on CL	600.908	0.912
10	Model 3 + gender on V_{SS}	601.147	0.713
11	Model 3 + weight on CL (final model)	596.622	5.238*
12	Model 11 + weight on V_{SS}	599.619	0.003

*$P < 0.05$.

OFV, objective function value; Δ (OFV), difference in OFV between 2 nested models; CL_{cr}, creatinine clearance; CL, teicoplanin clearance; VC, teicoplanin central volume of distribution; VSS, teicoplanin steady-state volume of distribution; Alb, serum albumin (mg/dL).

Second, combinations of them were investigated. The results showed that CL_{cr} and weight significantly influenced teicoplanin CL (reduction of the NONMEM objective function value ($P < 0.05$; Table 2), whereas age, gender, Alb, and BUN did not. Results from these negative runs (age, albumin, and gender in CL in the basic model) are not shown in Table 2. Maximum a posteriori (MAP) CL estimates from the basic model against CL_{cr} are displayed in Figure 1.

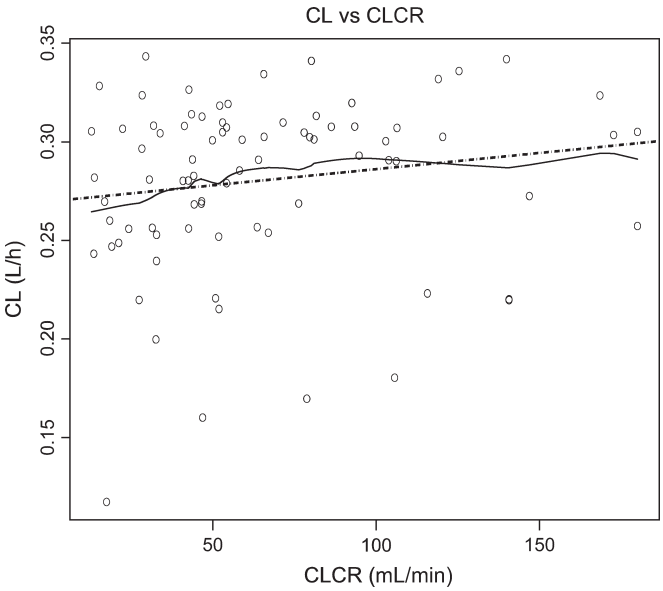

FIGURE 1. Plot of individual maximum a posteriori teicoplanin clearance estimates (CL) obtained from the basic model against creatinine clearance (CL_{cr}). Open circles, observations; solid line, line indicating the general data trend; dash line, linear regression. X-axis: CL_{cr} in mL/min; y-axis: teicoplanin CL in L/h.

Including both covariables (CL_{cr} and weight on CL) in the final population model, a 7% and 10% reduction in unexplained interindividual variability was found for CL and V_{SS}, respectively. Regarding the goodness-of-fit plots, a good accordance between observed and predicted concentrations is observed. Furthermore, the weighted residual values are uniformly distributed and within an acceptable range (−2 and +4), and no changes over time take place over the time course of the study as shown by the WRES versus time plot (Fig. 2). Therefore, the basic model was modified to include the effect of weight and CL_{cr} on CL.

The estimated PK parameters of the final model are summarized in Table 3.

Validation

Results from the internal validation showed that practically all observations dropped into the 95% CI for each experiment: 1) low, mean, or high creatinine clearance values; and 2) weight of 50, 73, or 90 kg.

Regarding the predictive performance of the model, the validation data set included 15 new patients (5 males and 10 females) whose demographic and clinical characteristics are displayed in Table 1. Mean bias and precision for the MAP Bayesian estimates (IPRED) resulted in −3.24% and 9.42%, respectively, both around the expected value of 0 and better than those values obtained from the population PK-model based estimates (PRED), which were −8.45% and 11.15%, respectively (Fig. 3).

Simulations

Results from simulations are displayed in Tables 4 and 5. The usual daily dose of 400 mg seems to be enough to attain the target concentration of 15 mg/L in all patients with normal renal function except for those heavy individuals (weight of 90 kg or more), for whom a higher dose of 600 mg/24 hours might be considered. In patients with CL_{cr} lower than 30 mL/min and weight around 50 kg or less, the dose should be decreased to 200 mg every 24 hours or, alternatively, the interval between doses might be extended to 48 or 72 hours while maintaining the usual dose of 400 mg.

If a target level of 25 mg/L is required, according to our model, a dosage regimen of 600 mg/24 hours is recommended in patients with normal renal function and mean weight, because the usual daily dose of 400 mg results in mean (±standard deviation) trough concentrations just above the target (25.1 ± 14.0 mg/L).

DISCUSSION

In this study, we retrospectively evaluate serum teicoplanin samples obtained in our institution during a 4-year period. We approach this analysis on the basis of a population PK study to obtain population PK data that would be used, subsequently, in a Bayesian forecast program to predict the individual PK behavior to optimize therapy.

In this study, the basic population PK model finally selected was a 2-exponential model with first-order elimination (Table 2), and the teicoplanin PK parameters obtained are in good agreement with those published up to that time by

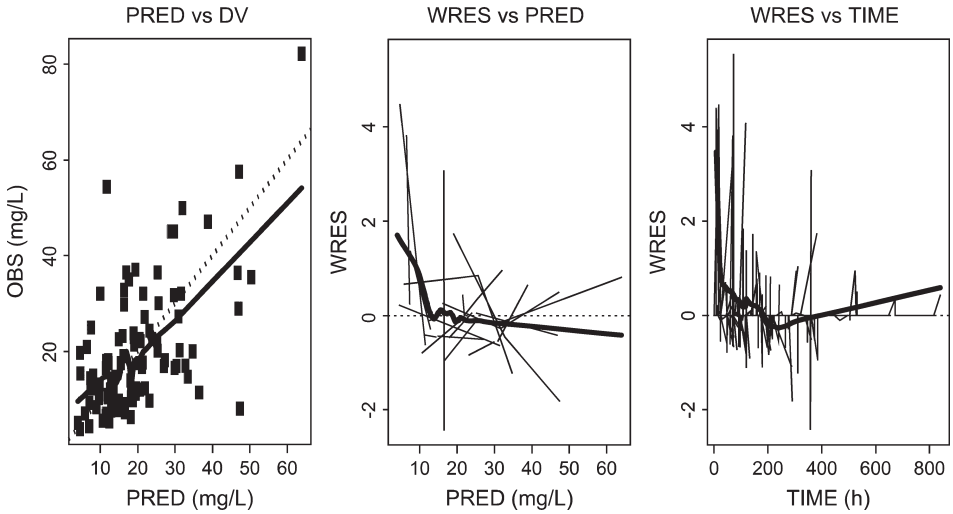

FIGURE 2. Goodness-of-fit plots for the final population PK model. A Plot of population predictions (PRED) versus observed teicoplanin concentrations (OBS); dashed line, line of identity; thick line, line indicating the general data trend. B Plot of population residuals (WRES) versus population predictions (PRED); thick line, line indicating the general data trend. C population residuals (WRES) versus time; thick line, line indicating the general data trend. Concentrations (OBS and PRED) are in milligrams per liter; time is in hours.

other authors.[7,33] From our results, a terminal drug half-life of approximately 61 hours can be estimated, which is similar to the one reported earlier.

Our results suggest that appropriate therapy with teicoplanin is feasible when both patients' creatinine clearance and weight are taken into account. As expected, patients' renal function influences the total drug clearance, because teicoplanin is mainly excreted by the kidneys.[2] Development of renal impairment is often seen in special populations such as critically ill patients or postsurgery patients. Thus, maintenance doses have then been adjusted according to CL_{cr} and TDM is clearly advisable.[34]

A statistically significant association between weight and MAP CL estimates was also observed. Although a slight positive trend between weight and V_{SS} was detected, its inclusion in the population PK model did not improve the fit (Table 2) in contrast with the results obtained by Yu et al, who described a significant influence of patient body weight on both systemic CL and volume of distribution of the central compartment.[17] We have no explanation for this discrepancy, but we can speculate that the lack of a statistically significant association between V_{SS} and the covariates tested could be explained by the limited number of informative blood samples at early times after drug administration in too few patients experiencing similar clinical conditions/infections.

TABLE 3. Final Estimates of the Population PK Parameters for Teicoplanin

Parameter	Estimate	Parameter	Estimate
θ_{CL1} (L/h)	0.57 (15)	θ_{CL3}	1.00 (39)
θ_{Vc} (L)	3.10 (21)	CV_{CL} (%)	35 (37)
θ_{Q} (L/h)	4 FIX	$CV_{CL\text{-}Vss}$ (%)	35 (75)
θ_{Vss} (L)	50.20 (13)	CV_{Vss} (%)	67 (26)
θ_{CL2}	0.0048 (39)	CV_{res} (%)	28 (40)

θ_{CL1}, teicoplanin clearance for an individual with average creatinine clearance; θ_{Vc}, volume of distribution of the central compartment; θ_{CL2}, multiplier of teicoplanin clearance for the difference (CL_{cr} – average CL_{cr}); θ_{CL3}, power of weight in power function predicting teicoplanin clearance; θ_{Vss}, volume of distribution in steady-state conditions; CV_p, coefficient of interindividual variation (P = CL, V_{SS}); CV_{res}, coefficient of residual variation. Precision (standard error: %) of the estimates is expressed (in parentheses).

Final population PK equation: $CL = 0.57*(1 + 0.0048(CL_{cr} - \text{average}CL_{cr})*WT$.

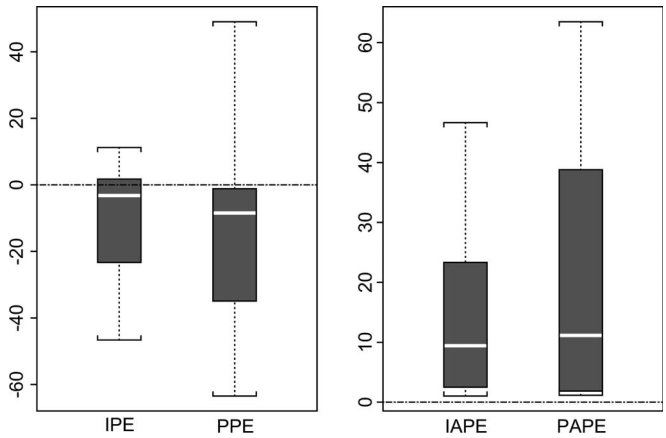

FIGURE 3. Box plots of percentage error (IPE, from maximum a posteriori [MAP] Bayesian estimated concentrations; PPE, from population estimated concentrations) and absolute percentage error (IAPE, from MAP Bayesian estimated concentrations; PAPE, from population estimated concentrations) of the validation data set. Ordinate in percentage. The white band in each error box marks the 50th percentile; the box boundaries are at the 25th and 75th percentiles, and the limits of the whiskers are at the 10th and 90th percentiles. Other horizontal lines are ''outliers,'' ie, values outside the 10th to 90th percentile range. Dashed line, horizontal line at 0 (target value).

TABLE 4. Trough Serum Teicoplanin Concentrations in mg/L (expressed as Mean ± Standard Deviation) at Steady-state Conditions Resulting After Simulating 1000 PK Profiles for Different Dosing Schemes and for an Average 73-kg Patient

	CL_{cr} = 30 mL/min	CL_{cr} = 63 mL/min	CL_{cr} = 120 mL/min
200 mg	15.7 ± 8.9 *(55) †(87)	12.6 ± 7.2 *(69) †(94)	9.1 ± 4.9 *(88) †(99)
400 mg	30.2 ± 15.6 *(14) †(44)	25.1 ± 14.0 *(25) †(58)	17.8 ± 9.2 *(44) †(80)
600 mg	45.9 ± 22.1 *(3) †(17)	36.5 ± 19.4 *(7) †(33)	27.6 ± 16.1 *(19) †(55)

Percentage of patients below the target (trough values of *15 mg/L or †25 mg/L) are shown between parentheses.

We are aware that a limitation of the study could be the deficient number of random samples along the whole study. Certainly, a large number of randomly drawn samples in a large number of patients would provide more conclusive results.

None of the other covariates studied (BUN, Alb, age, and gender) showed any influence on the drug volume of distribution. Although negative trends between Alb against individual V_{SS} and CL estimates were observed, neither achieve statistical significance. It is not surprising to note the influence of serum Alb levels on PK parameters because teicoplanin presents a high albumin binding degree[35] (close to 91%). A negative relationship between serum Alb levels and apparent CL of teicoplanin was described by Barbor et al mainly in heavily hypoalbuminemic patients (cutoff point of 20 g/L).[8] In our study, serum Alb levels below 23 g/L were not observed because they were corrected by administering albumin supplements to our patients. We suppose this may have been a major reason for the failure to detect any influence of Alb on CL or V_{SS}. However, we believe it is worth taking into account the tendency observed, and patients with altered serum Alb concentrations such as individuals presenting with cirrhosis, critically ill patients, burn patients, or neutropenic subjects might benefit from TDM.

A relationship between age and PK features was sought by including the former as a covariate affecting the population PK parameters. No significant association was seen in our study, which is in accordance with the results obtained by Yu et al in a population of patients with endocarditis,[17] but contrary to what was found by Lortholary et al[18] who reported a significant variation of V_{SS}, which increased with age. A difference between our data and theirs was the range of age in the studied population, which was broader in their patients compared with ours. We presume this may explain our negative results.

Individualizing dosage regimens is not an easy task for those drugs that show a high variability between subjects. This is the case of teicoplanin. In a population of neutropenic patients, Lortholary et al[18] reported values of CL and V_{SS} variability (expressed as coefficient of variation in percentage) of 43% and 51%, respectively. They linked these high values of variability to creatinine clearance values and ages of patients. Previously, Rybak et al[36] have found significantly greater and more highly variable values of total and renal clearances of teicoplanin in a group of intravenous drug abusers with bacterial endocarditis when compared with healthy volunteers. They also assume that it may be related to a higher drug glomerular filtration rate. In our study, both inter- and intraindividual variability were characterized (Table 3) and resulted in values within the range of those previously described.

Before carrying out any simulation to assist us in selecting an optimal initial dosage regimen, it should be previously established that the described population PK model is predictive.[30] An appropriate way to do this is to forecast drug concentrations of new patients (treated in the same manner as those included in the study) according to the PK model and compare them with the concentrations observed. In a separate group of 15 patients (validation data set), bias and precision showed values within acceptable limits (−3.24% and 9.42%, respectively), supporting the validity and the further use of the proposed population PK model. Subsequently, a dosage regimen simulation study was performed. It resulted that in an average 73-kg patient with normal renal function, a dose of 400 mg once daily leads to borderline trough drug concentrations (mean value, 17.8 mg/L). Similarly, values around 18.6 mg/L were predicted in a heavy patient (90 kg or more) with a mean CL_{cr} of 63 mL/min. In both scenarios, our simulations show that a higher dose (ie, 600 mg) may be considered, which is similar to the results obtained in a recent study conducted in critically ill patients by Whitehouse et al.[32] On the other hand, in patients with CL_{cr} lower than 30 mL/min, teicoplanin could easily accumulate and lower doses or

TABLE 5. Trough Serum Teicoplanin Concentrations in mg/L (expressed as Mean ± Standard Deviation) at Steady-state Conditions Resulting After Simulating 1000 PK Profiles for Different Dosing Schemes and for an Average Patient With CL_{cr} = 63 mL/min

	Weight = 50 kg	Weight = 73 kg	Weight = 90 kg
200 mg	19.8 ± 11.1 *(38) †(75)	12.6 ± 7.2 *(69) †(94)	9.5 ± 5.1 *(86) †(99)
400 mg	38.3 ± 19.4 *(7) †(27)	25.1 ± 14.0 *(25) †(58)	18.6 ± 9.6 *(40) †(76)
600 mg	58.2 ± 27.6 *(1) †(8)	36.5 ± 19.4 *(7) †(33)	28.9 ± 16.8 *(17) †(57)

Percentage of patients below the target (trough values of *15 mg/L or †25 mg/L) are shown between parentheses.

extended interdose intervals (to 48–72 hours) might be appropriate to attain the recommended drug concentrations. As previously reported, it is critical to achieve higher serum drug concentrations, around 20 to 25 mg/L, for the effective use of teicoplanin in patients presenting with endocarditis, osteomyelitis, or septic arthritis.[10–12] According to our simulations, only dosage regimens of 600 mg would be satisfactory for all patients presenting with one of these pathologies except for those light patients with a moderate renal impairment for whom a 400 mg of teicoplanin every 24 hours would be sufficient.

In summary, we developed a model to describe the population PK of teicoplanin in hospitalized patients. Results from this study could be a starting point for the implementation of the Bayesian adaptive control approach to optimize teicoplanin dosage regimens in our routine TDM program. Despite the lack of definitive evidence that teicoplanin TDM improves patient outcomes, we believe individualized pharmacokinetic dosing adjustment would be advisable to guarantee serum drug concentrations within the recommended therapeutic range. However, to confirm our results, further population PK studies in a large number of patients are needed.

REFERENCES

1. Glupczynski Y, Lagast H, Van der Auwera P, et al. Clinical evaluation of teicoplanin for therapy of severe infections caused by Gram-positive bacteria. *Antimicrob Agents Chemother*. 1986;29:52–57.
2. Brogden RN, Peters DH. Teicoplanin. A reappraisal of its antimicrobial activity, pharmacokinetic properties and therapeutic efficacy. *Drugs*. 1994;47:823–854.
3. Murphy S, Pinney RJ. Teicoplanin or vancomycin in the treatment of Gram-positive infections? *J Clin Pharmacol Ther*. 1995;20:5–11.
4. Wilson AP. Comparative safety of teicoplanin and vancomycin. *Int J Antimicrob Agents*. 1998;10:143–152.
5. Heydorn A, Petersen BO, Duus JO, et al. Biosynthetic studies of the glycopeptide teicoplanin by (1)H and (13)C NMR. *J Biol Chem*. 2000; 275:6201–6206.
6. Sun B, Chen Z, Eggert US, et al. Hybrid glycopeptide antibiotics. *J Am Chem Soc*. 2001;123:12722–12723.
7. Rowland M. Clinical pharmacokinetics of teicoplanin. *Clin Pharmacokinet*. 1990;18:184–209.
8. Barbot A, Venisse N, Rayeh F, et al. Pharmacokinetics and pharmacodynamics of sequential intravenous and subcutaneous teicoplanin in critically ill patients without vasopressors. *Intensive Care Med*. 2003; 29:1528–1534.
9. Craig WA. Basic pharmacodynamics of antibacterials with clinical applications to the use of beta-lactams, glycopeptides, and linezolid. *Infect Dis Clin North Am*. 2003;17:479–501.
10. Wilson AP, Shankar S, Felmingham D, et al. Serum and tissue levels of teicoplanin during cardiac surgery: the effect of a high dose regimen. *J Antimicrob Chemother*. 1989;23:613–617.
11. Wilson AP, Gaya H. Treatment of endocarditis with teicoplanin: a retrospective analysis of 104 cases. *J Antimicrob Chemother*. 1996; 38:507–521.
12. Schaison G, Graninger W, Bouza E. Teicoplanin in the treatment of serious infection. *J Chemother*. 2000;12(Suppl 5):26–33.
13. Rice TL. Simplified dosing and monitoring of vancomycin for the burn care clinician. *Burns*. 1992;18:355–361.
14. Leader WG, Chandler MH, Castiglia M. Pharmacokinetic optimisation of vancomycin therapy. *Clin Pharmacokinet*. 1995;28:327–342.
15. Pea F, Porreca L, Baraldo M, et al. High vancomycin dosage regimens required by intensive care unit patients cotreated with drugs to improve haemodynamics following cardiac surgical procedures. *J Antimicrob Chemother*. 2000;45:329–335.
16. Chambers HF, Kennedy S. Effects of dosage, peak and trough concentrations in serum, protein binding, and bactericidal rate on efficacy of teicoplanin in a rabbit model of endocarditis. *Antimicrob Agents Chemother*. 1990;34:510–514.
17. Yu DK, Nordbrock E, Hutcheson SJ, et al. Population pharmacokinetics of teicoplanin in patients with endocarditis. *J Pharmacokinet Biopharm*. 1995;23:25–39.
18. Lortholary O, Tod M, Rizzo N, et al. Population pharmacokinetic study of teicoplanin in severely neutropenic patients. *Antimicrob Agents Chemother*. 1996;40:1242–1247.
19. Tod M, Alet P, Lortholary O, et al. Implementation and evaluation of a stochastic control strategy for individualizing teicoplanin dosage regimen. *J Pharmacokinet Biopharm*. 1997;25:695–712.
20. Lamont E, Thomson AH, Dawber M, et al. *Population Pharmacokinetics of Teicoplanin in Outpatient Home Parenteral Antibiotic Therapy (OHPAT)* [Abstract]. Uppsala, Sweden: Population Approach Group in Europe, June 16–18, 2004.
21. MacGowan AP. Pharmacodynamics, pharmacokinetics, and therapeutic drug monitoring of glycopeptides. *Ther Drug Monit*. 1998;20:473–477.
22. Pea F, Brollo L, Lugano M, et al. Therapeutic drug monitoring-guided high teicoplanin dosage regimen required to treat a hypoalbuminemic renal transplant patient undergoing continuous venovenous hemofiltration. *Ther Drug Monit*. 2001;23:587–588.
23. Pea F, Viale P, Candoni A, et al. Teicoplanin in patients with acute leukaemia and febrile neutropenia: a special population benefiting from higher dosages. *Clin Pharmacokinet*. 2004;43:405–415.
24. Vozeh S, Hillman R, Wandell M, et al. Computer-assisted drug assay interpretation based on Bayesian estimation of individual pharmacokinetics: application to lidocaine. *Ther Drug Monit*. 1985;7:66–73.
25. Jelliffe RW, Schumitzky A, Van Guilder M, et al. Individualizing drug dosage regimens: roles of population pharmacokinetic and dynamic models, Bayesian fitting, and adaptive control. *Ther Drug Monit*. 1993;15: 380–393.
26. Chow AW, Azar RM. Glycopeptides and nephrotoxicity. *Intensive Care Med*. 1994;20(Suppl 4):S23–S29.
27. Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31–41.
28. Beal SL, Sheiner LB, eds. *NONMEM Users Guides*. MD: GloboMax, LLC, Maryland, 1989–1998.
29. *S-plus 6.1 for Windows Supplement*. Seattle: Insightful Corp, 2002.
30. Ette EI, Williams PJ, Kim YH, et al. Model appropriateness and population pharmacokinetic modeling. *J Clin Pharmacol*. 2003;43:610–623.
31. Sheiner LB, Beal SL. Some suggestions for measuring predictive performance. *Journal of Pharmacokinetics and Biopharmaceutics*. 1981; 9:503–512.
32. Whitehouse T, Cepeda JA, Shulman R, et al. Pharmacokinetic studies of linezolid and teicoplanin in the critically ill. *J Antimicrob Chemother*. 2005;55:333–340.
33. Smithers JA, Kulmala HK, Thompson GA, et al. Pharmacokinetics of teicoplanin upon multiple-dose intravenous administration of 3, 12, and 30 milligrams per kilogram of body weight to healthy male volunteers. *Antimicrob Agents Chemother*. 1992;36:115–120.
34. Pea F, Brollo L, Viale P, et al. Teicoplanin therapeutic drug monitoring in critically ill patients: a retrospective study emphasizing the importance of a loading dose. *J Antimicrob Chemother*. 2003;51:971–975.
35. Bailey EM, Rybak MJ, Kaatz GW. Comparative effect of protein binding on the killing activities of teicoplanin and vancomycin. *Antimicrob Agents Chemother*. 1991;35:1089–1092.
36. Rybak MJ, Lerner SA, Levine DP, et al. Teicoplanin pharmacokinetics in intravenous drug abusers being treated for bacterial endocarditis. *Antimicrob Agents Chemother*. 1991;35:696–700.