

Population Pharmacokinetic Modeling and Optimal Sampling Strategy for Bayesian Estimation of Amikacin Exposure in Critically Ill Septic Patients

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Abstract: Because the sepsis-induced pharmacokinetic (PK) modifications need to be considered in aminoglycoside dosing, the present study aimed to develop a population PK model for amikacin (AMK) in severe sepsis and to subsequently propose an optimal sampling strategy suitable for Bayesian estimation of the drug PK parameters. Concentration–time profiles for AMK were obtained from 88 critically ill septic patients during the first 24 hours of antibiotic treatment. The population PK model was developed using a nonlinear mixed effects modeling approach. Covariate analysis included demographic data, pathophysiological characteristics, and comedication. Optimal sampling times were selected based on a robust Bayesian design criterion. Taking into account clinical constraints, a two-point sampling approach was investigated. A two-compartment model with first-order elimination best fitted the AMK concentrations. Population PK estimates were 19.2 and 9.34 L for the central and peripheral volume of distribution and 4.31 and 2.21 L/h for the intercompartmental and total body clearance. Creatinine clearance estimated using the Cockcroft-Gault equation was retained in the final model. The two optimal sampling times were 1 hour and 6 hours after onset of the drug infusion. Predictive performance of individual Bayes estimates computed using the proposed optimal sampling strategy was reported: mean prediction errors were less than 5% and root mean square errors were less than 30%. The present study confirmed the significant influence of the creatinine clearance on the PK disposition of AMK during the first hours of treatment in critically ill septic patients. Based on the population estimates, an optimal sampling strategy suitable for Bayesian estimation of the

drug PK parameters was developed, meeting the need of clinical practice.

Key Words: severe sepsis, amikacin, population pharmacokinetics, optimal sampling strategy, Bayesian estimation

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INTRODUCTION

Amikacin (AMK) is an aminoglycoside commonly used in intensive care units (ICUs) for the treatment of patients with life-threatening Gram-negative infections. The drug exhibits a bactericidal effect related to its concentration (ie, concentration-dependent killing) with a prolonged postantibiotic effect and a toxicity related to the total drug exposure.¹ Like other aminoglycosides, AMK displays a narrow range between effective and toxic concentrations, supporting the practice of therapeutic drug monitoring (TDM). Its nephro- and ototoxicities have widely guided attempts to rationalize the drug dosage strategy.^{1,2}

The pharmacokinetic (PK) behavior of the drug is known to be influenced by pathophysiological conditions.³ During severe sepsis and septic shock, AMK disposition is altered by an increased volume of distribution (Vd) and a reduced total body clearance (CL) as a result of leaky capillaries, decreased protein binding, and organ failure.^{4–9} Regrettably, antibiotic dosing regimens used in the ICU rarely take into account the sepsis-induced PK modifications, particularly critical at the early stage of the disease course. In addition, because (patho)physiological changes associated with sepsis determine a wide PK variability,^{10,11} an empiric dosing strategy of AMK is difficult in critically ill septic patients, reinforcing the role of TDM. It is therefore of interest to explore all approaches allowing to predict and control PK variability of the drug in this patient population to propose individualized dosing regimens. To date, several (patho)physiological factors are reported to account for PK variability of AMK in ICU patients with sepsis: body weight, oxygen extraction ratio, serum albumin, and sepsis severity (estimated by the Acute Physiology And Chronic Health Evaluation [APACHE] II score) for the Vd variability, creatinine clearance, positive end-expiratory pressure, and catecholamine administration for the CL variability.^{11–15}

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Among PK-based dosing methods dedicated to the aminoglycoside TDM, the Bayesian maximum a posteriori approach appears attractive for ICU patients. Unlike non-Bayesian methods (eg, nomogram, non-Bayesian least-squares method), the maximum a posteriori estimation displays better predictive performance for individualized drug dosage, because it incorporates some prior information (ie, covariates, PK model, residual error model, prior distributions).^{16,17} In addition, the Bayesian estimation can be performed using a limited number of concentrations, as is usually the case in ICU patients. However, such a method depends on the quality of the population estimates.¹⁸ In addition, the relative lack of suitable population data may limit the success of the Bayesian approach. To date, some population models have been described for AMK PK in critically ill septic patients at steady state,^{11–14,18} but none has been developed in the early phase of the septic process.

The objectives of the present study were 1) to characterize the population PK of AMK in 88 critically ill septic patients during the first 24 hours of antibiotic treatment; 2) to assess and model the effect of demographic and pathophysiological factors on the PK of the drug using a nonlinear mixed effects modeling approach; and 3) to develop an optimal sampling strategy suitable for Bayesian estimation taking into account clinical constraints.

MATERIAL AND METHODS

Patients and Sampling

Patients with a diagnosis of severe sepsis or septic shock fulfilling the standard criteria¹⁹ were included. Severe sepsis was defined as sepsis associated with organ dysfunction assessed by the Sepsis-related Organ Failure Assessment score.²⁰ Septic shock was defined as an acute circulatory failure characterized by persistent arterial hypotension needing vasopressor drugs. The study was observational and was conducted in ICUs of four Belgian university hospitals (Cliniques universitaires St-Luc, Hôpital Erasme and Universitair Ziekenhuis Brussel in Brussels and Clinique St-Pierre in Ottignies) after approval by the respective Ethics Committees. Written consent was obtained from patients or their legal representatives. Patients aged younger than 18 years or older than 90 years with chronic renal failure requiring dialysis previously treated (or having developed allergy) with any investigated drugs during the week before inclusion were excluded as well as pregnant and breastfeeding females.

All data from routine clinical care were recorded before onset of antibiotic treatment, ie, demographic data, complete blood count and routine biochemistry markers, admission diagnoses, APACHE II scores, and Sepsis-related Organ Failure Assessment scores.^{21,22}

Patients were treated with a first dose of AMK (25 mg/kg) combined with a broad-spectrum β -lactam (piperacillin, ceftazidime, cefepime, or meropenem), selected according to local clinical practice. The combination was given by two separate intravenous lines as a 30-minute infusion. The study period was limited to the first 24 hours of antibiotic therapy, considered as the most critical period in the

management of patients with severe sepsis or septic shock. Next, doses of AMK were determined according to the local TDM practice (involving trough and peak concentrations to assess toxicity and efficacy, respectively). Furthermore, β -lactam administration was based on standard dosing regimens and adapted to renal function.

Blood samples were drawn without anticoagulant immediately before and 1, 1.5, 4.5, 6 or 8, and 24 hours after onset of the first infusion. The exact sampling times were recorded by the nursing or medical staff. After centrifugation, serum samples were stored at -70°C until shipment in dry ice to the reference laboratory for analysis.

Analytical Assay

All drug analyses were performed in the laboratory of Cliniques universitaires St-Luc, Brussels. The serum samples were analyzed for AMK by fluorescence polarization immunoassay (TDx; Abbott Laboratories, Abbott Park, IL)^{23,24} according to the manufacturer's recommendation with a limit of quantification of 0.8 mg/L. Quality control samples at 5, 15, and 30 mg/L were assayed once daily. The method displayed a between-run imprecision ranging from 3% to 8%.

Population Pharmacokinetic Analysis

PK analysis was carried out using the nonlinear mixed effects modeling program NONMEM Version VI (double precision; ICON Development Solutions, LLC, Ellicott City, MD). A G77 Fortran was used to compile and execute NONMEM. The program was run with the Perl-speaks-NONMEM (PsN) tool kit and Xpose (Version 4), for statistical and graphic model evaluation.^{25,26}

Population Parameter Estimation

The first-order conditional estimation with interaction method was used to assess population characteristics of AMK parameters (fixed and random effects). The interindividual variability (η) was described by an exponential model:

$$\theta_i = \theta_{\text{pop}} \cdot \exp(\eta_i) \quad [1]$$

where θ_i is the value of the PK parameter θ in the i^{th} individual, θ_{pop} is the typical value of θ in the population, and η_i quantifies the deviation of θ_i from θ_{pop} . η is assumed to be a normal random variable with a mean of 0 and a variance of ω^2 .

The residual variability (ε) was described by an additive, proportional, or a combined proportional and additive error model:

$$C_{\text{obs}} = C_{\text{pred}} + \varepsilon_{\text{add}} \quad [2]$$

$$C_{\text{obs}} = C_{\text{pred}} \cdot (1 + \varepsilon_{\text{prop}}) \quad [3]$$

$$C_{\text{obs}} = C_{\text{pred}} \cdot (1 + \varepsilon_{\text{prop}}) + \varepsilon_{\text{add}} \quad [4]$$

where C_{obs} is the observed concentration, C_{pred} is the predicted concentration, and $\varepsilon_{\text{prop}}$ (proportional component) and ε_{add} (additive component) quantify the deviation of C_{obs} from C_{pred} . ε is assumed to be a normal random variable with a mean of 0 and a variance of σ^2 .

Both one- and two-compartment models with first-order elimination were tested. Initial estimates of parameters for

NONMEM modeling were obtained from previous PK analyses using WinNonlin software (Version 5.0.1; Pharsight Corporation, Mountain View, CA).^{27,28} Model building was guided by the NONMEM objective function value, the precision of estimates, and basic goodness-of-fit plots (ie, observed versus predicted concentrations, conditional weighted residuals versus predicted concentrations, and conditional weighted residuals versus time after dose).²⁹

Covariate Model Building

The following patient-specific covariates were tested for influence on PK parameter estimates: three demographic data (sex, age, and body weight), four renal function markers (creatinine, urea and creatinine clearance [CL_{CR}] estimated either from the Cockcroft-Gault equation,³⁰ or from the simplified Modification of Diet in Renal Disease formula³¹), nine hepatic function markers (albumin, total protein, total bilirubin, aspartate aminotransferase, alanine aminotransferase, gamma-glutamyl transpeptidase, alkaline phosphatase, prothrombin time, activated partial thromboplastin time), two disease severity scores (APACHE II and Sepsis-related Organ Failure Assessment) and each of the associated (patho)physiological variables (eg, potassium, hematocrit, white blood count, arterial oxygen tension/fractional inspired oxygen ratio),^{20,21} four hemodynamic characteristics (presence of septic shock, mechanical ventilation, positive end-expiratory pressure, catecholamine administration), one inflammatory marker (C-reactive protein), two types of resuscitation fluids (crystalloid and colloid solutions), and the coadministered β-lactam (piperacillin, ceftazidime, cefepime, or meropenem). Missing values (less than 3% on all data) were replaced by the respective median or mode of the population. Individual Bayes estimates of PK parameters were generated, and covariate–PK parameter relationships were visually inspected and investigated in NONMEM. The final model was built using a two-stage approach:

1. In the first step, continuous covariates were centered to their median and separately added to the structural model in a linear or nonlinear way:

$$\theta_{\text{pop}} = \theta_1 + (\theta_2 \cdot \text{cov}) \quad [5]$$

$$\theta_{\text{pop}} = \theta_1 + \text{cov}^{\theta_2} \quad [6]$$

where θ_1 is the typical value of the PK parameter and θ_2 is the fractional change on θ_1 resulting from the covariate (cov).

Categorical covariates were coded as dichotomous variables (cov = 1 if present, cov = 0 if absent) and tested for influence on PK parameter estimates according to the Equation 5. A decrease in objective function value 6.64 or greater (χ^2 distribution, $P \leq 0.01$, degree of freedom = 1) from the structural model was considered statistically significant.

2. In the second step, a full model was built, including all covariates that showed significant influence on PK parameters. Starting from the full model, a backward selection was performed: covariates which on deletion resulted in an increase in objective function value 10.83 or greater (χ^2 distribution, $P \leq 0.001$, degree of freedom = 1) were retained in the final model.

Model Validation

Evaluation of the final model was conducted using a nonparametric bootstrap procedure, case-deletion diagnostics, and visual predictive check.^{25,32,33} For the bootstrap analysis, 1000 replicates of parameter estimates were generated from the original patient data, and the medians and the 2.5th and 97.5th percentiles of the bootstrap distributions were compared with the final model estimates. For the case-deletion diagnostics, a Cook score and a covariance ratio were computed for each individual; patients with a Cook score greater than 1 combined with a covariance ratio less than 0.5 were considered as influential individuals. For the visual predictive check, 1000 subjects were simulated from the final model estimates, and the 95% prediction interval was compared with the time course of observed concentrations.

Optimal Sampling Strategy

The optimal sampling strategy was performed using PopED software (Version 2.10; <http://poped.sourceforge.net>), written in high-performance language for MATLAB software and provided with a Graphical User Interface for Windows users.^{34,35} Optimization was performed over sampling times using a Bayesian optimal design criterion. Based on the determinant of the robust Bayesian information matrix,³⁶ this criterion was computed on the individual level, as previously reported.³⁷ Optimal sampling times were selected using a stochastic gradient algorithm, as proposed by Pronzato and Walter.³⁸ Prior information of the AMK parameter distribution was obtained from the population PK analysis. Taking into account clinical constraints, a two-point sampling strategy was investigated with a total sampling period of 1 to 6 hours after start of the drug infusion. Indeed, a blood sampling timeframe of 0 to 6 hours would allow most likely the involvement of the same nursing staff and a combined samples shipment to the laboratory.

RESULTS

Patients

Eighty-eight adult patients with severe sepsis or septic shock were enrolled in the study over a period of 20 months. Twenty-eight patients were reported to be comedicated with piperacillin, 19 with ceftazidime, 20 with cefepime, and 21 with meropenem. Five hundred seven blood samples were collected with a number of samples varying from four to six per patient. Four percent of samples were missing for clinical reasons (eg, surgery, medical tests). Individual concentration–time profiles are given in Figure 1 and revealed, as expected, a large variability in AMK concentrations. Table 1 presents a summary of the patient characteristics.

Population Pharmacokinetic Analysis

A two-compartment model with first-order elimination best fitted the AMK concentrations. The model was parameterized in terms of central volume of distribution (V1), peripheral volume of distribution (V2), intercompartmental clearance (Q), and CL. A combined proportional and additive model adequately described residual variability. The population PK estimates of the structural model (ie, without

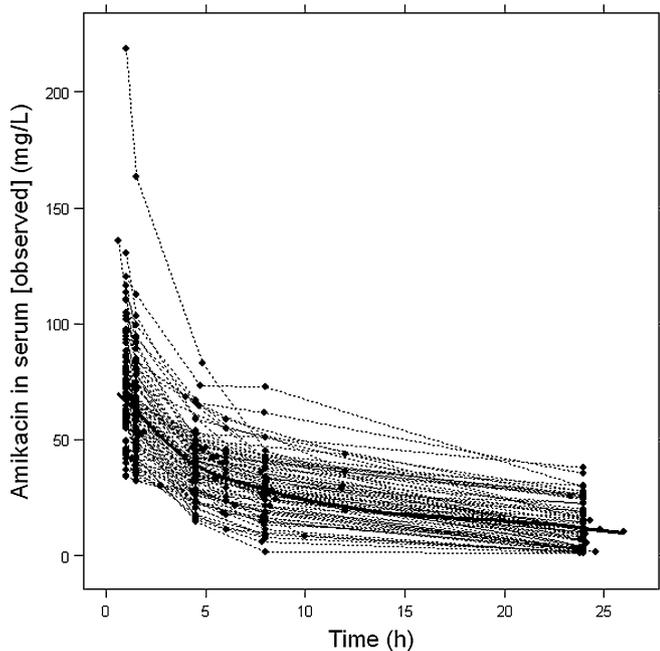


FIGURE 1. Individual concentration–time profiles in critically ill septic patients (n = 88) after administration of a first dose of amikacin (25 mg/kg) infused in 30 minutes.

covariates) are reported in Table 2. Interindividual variability could be assessed for V1 (39%), V2 (44%), Q (16.5%), and CL (71.9%). Parameter uncertainty was expressed as the relative standard error of estimates (RSE) and was small for

TABLE 1. Characteristics (median values [range]) of 88 Critically Ill Septic Patients Before the Start of Antibiotic Treatment (25 mg/kg amikacin combined with a broad-spectrum β-lactam)

Demographic, Clinical, and Biologic Data		
Male/female	%	65/35
Age	years	65 (22–89)
Body weight	kg	70 (38–125)
Severe sepsis/septic shock	%	29/71
APACHE II score		20 (6–45)
SOFA score		8 (1–19)
Mechanical ventilation	%	52
Catecholamine administration	%	53
Resuscitation fluids		
Infused crystalloid solution	mL	2800 (200–7445)
Infused colloid solution	mL	1000 (0*–3379)
C-reactive protein	mg/L	16.6 (0.13–299.9)
Creatinine	mg/dL	1.2 (0.2–6.6)
Urea	mg/dL	69 (13–236)
Creatinine clearance†	mL/min	55.5 (12.3–408.3)
Albumin	g/dL	1.8 (0.8–4.9)
Total protein	g/dL	4.2 (1.1–8)
Bilirubin	mg/dL	0.9 (0.1–59)

*Reported for 12 patients.

†Estimated using the Cockcroft-Gault equation.

APACHE, Acute Physiology And Chronic Health Evaluation; SOFA, Sepsis-related Organ Failure Assessment.

fixed-effect parameters (5%–8%, except for Q) and higher for random-effect parameters (10%–34%, except for the interindividual variability in Q).

The full model included, in a linear way, sex and weight as significant covariates on V1 and weight, APACHE II score, and CL_{CR} estimated by the Cockcroft-Gault and Modification of Diet in Renal Disease formula equations as significant covariates on CL. Only the CL_{CR} calculated using the Cockcroft-Gault formula was retained in the final model after backward elimination. Table 2 presents the final population PK estimates with their respective RSE. Introduction of the significant covariate reduced the interindividual variability in CL from 71.9% to 59.2%.

Basic goodness-of-fit plots for the final model of AMK are displayed in Figure 2 and did not reveal obvious model misspecification. Predicted concentrations were closely and symmetrically scattered around the line of identity (Fig. 2A–B), and the conditional weighted residuals were centered to zero and marked no trend over time (Fig. 2C–D). Table 2 lists the results of 1000 bootstrap replicates, presented as medians with 2.5th and 97.5th percentiles. Bootstrap median values closely agreed with the population estimates of the final model. Figure 3 illustrates the visual predictive check plot and revealed a substantial overlap of the simulated distributions with the observations. A total of 94.3% observed concentrations fell within the 95% prediction interval (2.1% observed concentrations were outside the lower limit and 3.6% observed concentrations were outside the upper limit of the 95% prediction interval) and were symmetrically distributed around the median. Case-deletion diagnostics revealed no patient substantially influencing any of the estimates (ie, no patients with a Cook score greater than 1 combined with a covariance ratio less than 0.5).

Optimal Sampling Strategy

The optimal sampling times for Bayesian estimation of the AMK PK, obtained using PopED software, were 1 and 6 hours after onset of the drug infusion. Because the optimal times actually corresponded to sampling times of the clinical study, predictive performance of the optimal sampling strategy was investigated. For this purpose, individual Bayes estimates were firstly computed within NONMEM (POSTHOC option with MAXEVAL = 0) using, separately:

1. All the sampling time points of the clinical study; and
2. One and 6 hours after onset of the infusion.

Second, predictive performance of individual Bayes estimates computed using the optimal sampling times was assessed by the relative mean prediction error (MPE%) as a measure of bias and the relative root mean square prediction error (RMSE%) as a measure of precision³⁹:

$$MPE\% = \frac{\sum_{i=1}^n PE_i}{n} \cdot 100\% \quad [7]$$

TABLE 2. Population Parameter Estimates of Amikacin During the First 24 Hours of Treatment in Critically Ill Septic Patients and Bootstrap Validation

Parameter	Unit	Structural Model Estimate (RSE)	Final Model Estimate (RSE)	Bootstrap (n = 1000) Median (2.5th–97.5th percentiles)
Pharmacokinetic parameter				
V1	L	19.2 (5.42%)	19.2 (5.31%)	18.7 (16.6–20.7)
V2	L	9.34 (7.10%)	9.38 (7.15%)	9.59 (8.3–11.1)
Q	L/h	4.31 (19.1%)	4.38 (18.3%)	4.72 (3.55–6.93)
CL	L/h	2.21 (7.96%)	0.77 (28.4%)	0.78 (0.3–1.18)
Covariate				
$\theta_{CL-CLCR}$	mL/min	NA	1.42 (18.4%)	1.4 (0.95–1.97)
Interindividual variability				
V1 (CV)	%	39 (18.8%)	39.1 (18.8%)	38.6 (32.2–46.1)
V2 (CV)	%	44 (33.5%)	43.6 (31.7%)	41.5 (30.7–54.4)
Q (CV)	%	16.5 (224%)	16.7 (202%)	20.9 (2.97–43.4)
CL (CV)	%	71.9 (12.6%)	59.2 (14.8%)	58.3 (50.2–68.4)
Residual variability				
Proportional error (CV)	%	26.8 (10.2%)	26.8 (10.2%)	26.2 (21.4–28.5)
Additive error (SD)	mg/L	1.02 (30.4%)	1.03 (29.7%)	1.01 (0.69–1.41)
OFV		2127	2095	2075

RSE, relative standard error of estimates; V1, central volume of distribution; V2, peripheral volume of distribution; Q, intercompartmental clearance; CL, total body clearance; $\theta_{CL-CLCR}$, fractional change on CL resulting from creatinine clearance (CL_{CR}); CV, coefficient of variation; SD, standard deviation; OFV, objective function value; NA, not applicable.

$$RMSE\% = \sqrt{\frac{\sum_{i=1}^n (PE_i)^2}{n}} \cdot 100\% \quad [8]$$

where PE is the prediction error, defined as [reference value – predicted value], and n is the number of PK parameter pairs (ie, reference and predicted values). PK parameters estimated using all the sampling time points of the clinical study were investigated in the equations as reference values, whereas those estimated using the optimal sampling times were investigated as predicted values.

Predictive performance of individual Bayes estimates computed using the optimal sampling strategy is summarized in Table 3; MPE% and RMSE% were, respectively, less 1.1% and less than 9% for both V1 and Q and less than 4.6% and less than 29.1% for both V2 and CL.

DISCUSSION

Several population PK models have been developed for aminoglycosides in patients with altered PK behavior, including ICU patients. However, few models have been described for AMK in critically ill septic patients.^{11–14,18} Moreover, to our knowledge, no clinical study has focused on the critical period in the management of these patients (ie, first hours of treatment). In the present study, a population PK model has been developed based on AMK concentrations of 88 critically ill septic patients during the first 24 hours of antibiotic treatment (25 mg/kg AMK once daily combined with a broad-spectrum β -lactam). Typical parameters, their corresponding interindividual variability, and residual variability have been used to design an optimal sampling strategy

to develop suitable Bayesian estimators taking into account clinical practice.

During nonlinear mixed effects modeling, time profiles of AMK concentrations were described by a two-compartment model with first-order elimination. Population PK estimates of the drug confirmed the sepsis-induced PK modifications (ie, increased Vd and decreased CL)^{4–9} and were consistent with most reported values for critically ill septic patients.^{11–15,18} As expected, patients were characterized by a wide interindividual variability in the AMK PK disposition, particularly in the elimination of the drug (71.9%). Although (patho)physiological changes associated to sepsis determine a wide PK variability,^{10,11} only CL_{CR} (estimated by the Cockcroft-Gault) was found to significantly influence the AMK elimination. Linear dependence between CL_{CR} and AMK CL was not surprising, because the drug is eliminated through the renal route. However, no other covariate was retained in the final population model such as demographic data (body weight), biologic markers (albumin), clinical characteristics (eg, APACHE II score, positive end-expiratory pressure) as reported in previous population PK studies.^{11–15} A possible explanation is that the present study was focused on the early phase of the septic process, unlike other studies, which were conducted at steady state. Nevertheless, although critically ill septic patients receive larger quantities of intravenous resuscitation fluids early in the disease course,⁴⁰ neither infused crystalloid or colloid volume nor cumulative total volume of both fluids was found to explain the interindividual variability in the AMK Vd.

Fixed-effect parameters of the final population model were estimated with small RSE, suggesting high precision in their estimation (Table 2). In contrast, RSE of random-effect parameters was greater, although less than 32% for all

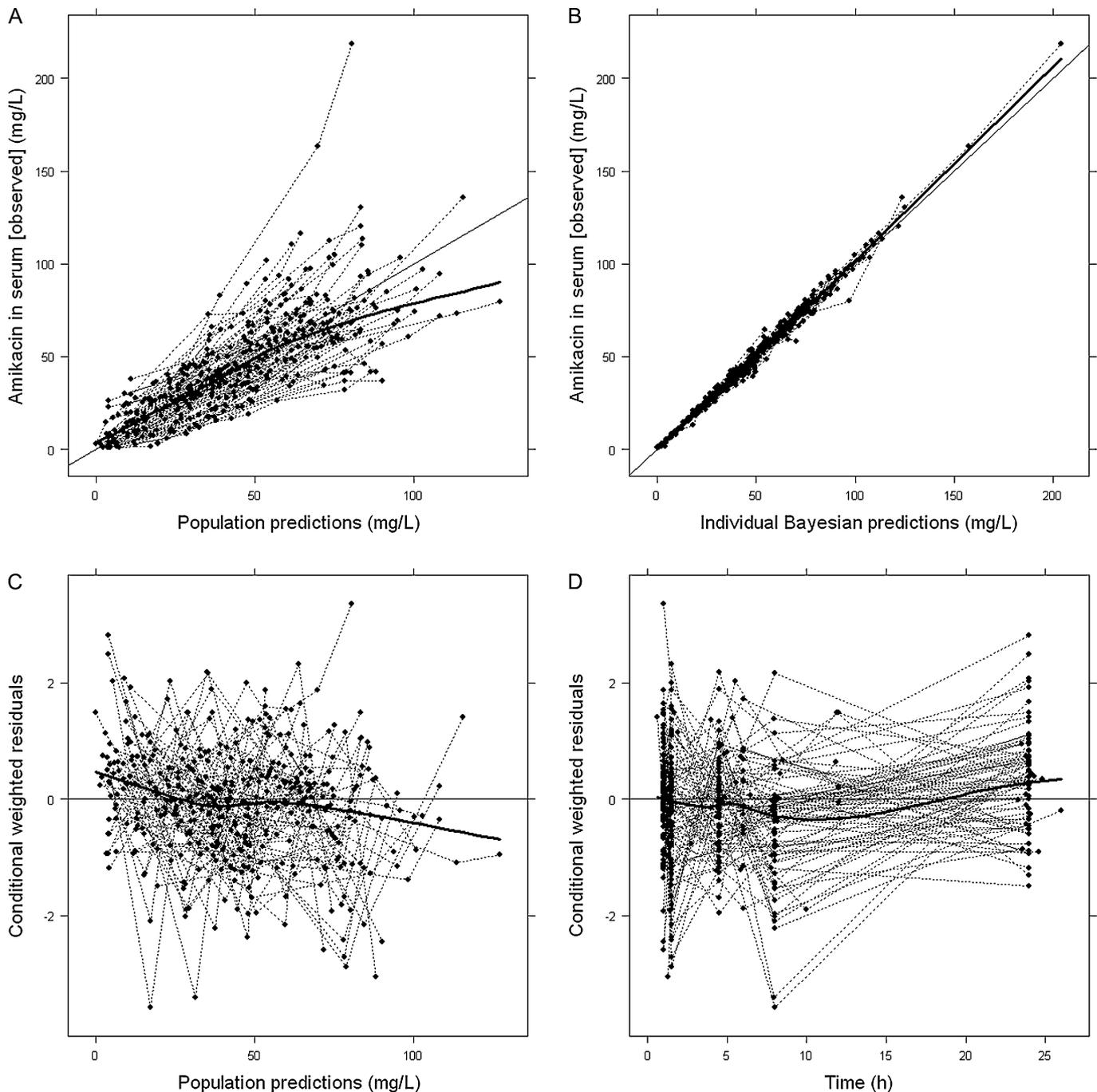


FIGURE 2. Basic goodness-of-fit plots for the final model of amikacin in critically ill septic patients: (A) observed concentrations vs. population predicted concentrations; (B) observed concentrations versus individual predicted concentrations; (C) conditional weighted residuals versus population predicted concentrations; (D) conditional weighted residuals versus time. The line $x = y$ is the identity line. The bold line is the LOESS smooth.

estimates (except for the interindividual variability in Q). Moreover, the final model was found to adequately fit the AMK data; no obvious bias or model misspecification was identified (Fig. 2), and the model was found to be stable, robust (Table 2) and accurate (Fig. 3).

Traditionally, peak and trough concentration values are used to perform Bayesian estimation of the aminoglycoside

PK parameters¹⁷ without identifying the most informative times according to the optimal sampling theory. For the first time, a two-point Bayesian method was developed, based on a robust design criterion, to propose a practical and convenient sampling strategy for AMK in critically ill septic patients. Although attractive, the robust optimality approach has not been widely used in population PK/pharmacodynamics. To

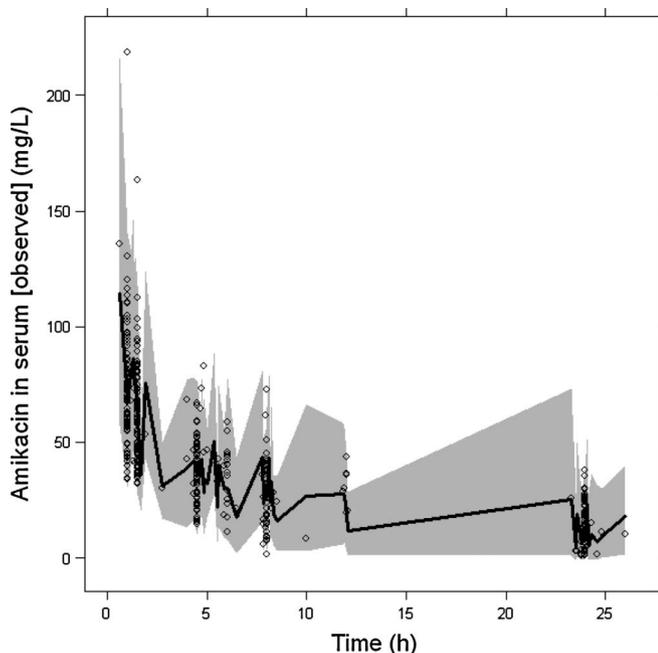


FIGURE 3. Visual predictive check plot of the final population model for amikacin. The gray field covers the 95% prediction interval for simulated data (n = 1000), and the dark line depicts the predicted median. The dots are the observed concentrations.

our knowledge, robust criteria for Bayesian design have been implemented in OSP-Fit, PopED and POPT software packages.^{34,41,42} In the present study, optimal sampling times were obtained using PopED software^{34,35} based on the determinant of the robust Bayesian information matrix³⁶; the two optimal times were found to be at 1 and 6 hours after onset of the drug infusion. Predictive performance of this sampling design was satisfactory, because accuracies were less than 5% and precisions were less than 29.1% (Table 3).

To cover more potential patients, a further optimal sampling strategy was similarly performed based on the determinant of the robust Bayesian information matrix with, in addition, consideration of uncertainty around the population parameters. When considering uncertainty, optimal times

TABLE 3. Predictive Performance of a Two-Point Bayesian Sampling Strategy Based on a Robust Design Criterion in Critically Ill Septic Patients Treated With Amikacin (25 mg/kg)

PK Parameter	Optimal Sampling Times 1 and 6 Hours After Start of Infusion	
	MPE%	RMSE%
V1	1.04	8.96
V2	-0.61	29.09
Q	1.09	2.88
CL	-4.59	28.78

V1, central volume of distribution; V2, peripheral volume of distribution; Q, intercompartmental clearance; CL, total body clearance; MPE%, relative mean prediction error; RMSE%, relative root mean square prediction error.

consisted in two replicates at 6 hours after onset of the drug infusion. Practical meaning of replications has been addressed in a previous paper by Merlé and Mentré; according to the main source of experimental error (analytics, contaminations, etc), replications can be performed either by splitting the collected sample into two parts before drug measurement or by drawing two samples at the same time from two different sites.⁴³ Because the last option appears unrealistic in routine practice, a single sample drawn at 6 hours and split into two parts before dosing could be preferred for obvious nursing reasons. Because, in the present study, only a single measurement at 6 hours was available from the database, predictive performance of the sampling strategy using replications could not be assessed. A prospective validation of the sampling design should be performed using replications at 6 hours after onset of the first drug infusion as well as using 1 and 6 hours.

The study highlighted the significant influence of the Cockcroft-Gault CL_{CR} on the PK disposition of AMK in critically ill septic patients during the early phase of the disease process. Using developed population estimates of the drug, an optimal two-point sampling strategy was proposed for this patient population based on a robust Bayesian design criterion.

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