Population Pharmacokinetics of Gentamicin in Mexican Children With Severe Malnutrition

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Background: To develop a population pharmacokinetic model of gentamicin in children with complicated severe malnutrition and to study the influence of covariates (weight and age) on pharmacokinetic indices. In addition, we use the model to perform Monte Carlo simulations to explore the efficacy of several dosage regimens.

Methods: Twenty-six children with severe complicated malnutrition were studied. Ninety-six samples of gentamicin plasma concentrations, obtained from 0.5 to 8 hours after intravenous dosing, were analyzed. Population pharmacokinetic models were built using the program Monolix 4.2 (Lixoft, Antony, France). Monte Carlo simulations were performed to evaluate optimal dosage regimens, using the final pharmacokinetic model, based on the probability of pharmacokinetic–pharmacodynamic target attainment.

Results: The concentration–time data were fitted best to 1-compartment model. The estimated population clearance was 1.1 L/h, and the volume of distribution was 2.23 L, with an interindividual variability of 47.2% and 35.6%, respectively. The final models for the clearance and volume of distribution were as follows: CL (L/h) = CL = 1.15 (age/median age)$^{0.321}$ and V (L) = 2.33 (weight/median weight)$^{0.743}$. In Monte Carlo simulations, gentamicin given in dosages of 7.5 to 15 mg/kg optical density was effective in achieving the pharmacodynamic target C_{max}:minimal inhibitory concentration >10 for minimal inhibitory concentrations ≤2.5 mg/L, with a probability lower than 1% for C_{min} >1 mg/L.

Conclusions: Based on the available evidence, an intravenous dose of 7.5 to 15 mg/kg once daily in children with complicated severe malnutrition and normal renal function ensures high probability of efficacy and low risk of nephrotoxicity, which gives further support to the recommendations issued by the World Health Organization treatment for this patient population.

Key Words: population pharmacokinetics, gentamicin, malnutrition, Mexican children

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Severe malnutrition, defined by the World Health Organization (WHO) as a weight-for-height Z-score of ≤−3, remains to have a high prevalence in less developed countries. Malnutrition is associated with a high incidence of infections and with a higher mortality as compared with well-nourished children.[1] Therefore, early administration of an appropriate antimicrobial regimen and obtaining therapeutic concentrations are important in this population to reduce mortality risk.[2]

Ampicillin and gentamicin are the first-line antibiotics recommended by WHO in children with severe malnutrition and sepsis.[3] Gentamicin is an aminoglycoside antibiotic that is distributed into the extracellular fluid and is eliminated by the kidneys. Its effectiveness is determined by the relationship between the peak concentration and the bacterial minimal inhibitory concentration (MIC).[4] However, the body and physiologic changes associated with severe malnutrition may alter the pharmacokinetics of antibiotics, so the standard dose may result in subtherapeutic or toxic concentrations.[5] Therefore, having a specific pharmacokinetic model for this patient population may allow the design of dosage regimens that achieve with higher probability the pharmacodynamic targets.

Despite the high global burden of malnutrition and its association with high mortality because of infection, to our knowledge there are only 5 publications on the pharmacokinetics of gentamicin in this population.[6–10] Therefore, the objective of this study was to develop a population pharmacokinetic model of gentamicin in children with complicated severe malnutrition (CSM) and to study the influence of covariates (weight and age) on pharmacokinetic indices. In addition, we use the model to perform Monte Carlo simulations to explore the efficacy of several dosage regimens.

MATERIAL AND METHODS

Study Design and Patient Population

With the scientific and ethical committee approval and parental consent, the gentamicin serum concentrations and the clinical data obtained in a prospective series of patients with CSM were analyzed retrospectively. All the patients were treated with ampicillin and gentamicin according to the WHO recommendations.[3] Gentamicin was administered intravenously in a bolus infusion over 30 minutes (2.5 mg/kg every 8 hours). A sampling scheme was randomly assigned to each patient to ensure a similar number of points for different times throughout the dosing interval. Each patient contributed to 3 to 4 samples obtained at steady state at the following postinfusion times: 0.5, 1, 2, 4, 6 and 8 hours postinfusion. Patients with abnormal kidney function or hemodynamic instability were not included in the analysis. Abnormal renal function was considered as a creatinine level higher than the normal value for age (serum creatinine, 17.7 to 44.2 μmol/L for infants and children aged to 2 weeks to 5 years and serum creatinine to 26.5 to 88.4 μmol/L for children aged to 5 to 10 years).

Gentamicin Determination Concentrations

Samples were analyzed in the laboratory of pharmacology, and gentamicin plasma concentrations were measured by fluorescence polarization immunoassay (TDX System; Abbott Laboratories, Dallas, TX). The quantification limit was 0.1 mg/L and the interassay and intraassay coefficients of variation were 4.8% over the entire calibration range.

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Population Pharmacokinetic Analysis

A population pharmacokinetic approach using a nonlinear mixed-effect model was implemented by means of the software program Monolix version 4.2, which combines the stochastic-expectation maximization algorithm and a Markov Chain Monte Carlo procedure for likelihood maximization. The iteration kernels, k1 and k2, were set to perform a great number of iterations with the purpose to obtain the best convergence. Markov Chain Monte Carlo chains were fixed to 10, and simulated annealing was used to improve the convergence toward the global maximum of the likelihood.

Model Building

Structural Model

The gentamicin concentration–time data were described using compartmental pharmacokinetic modelling. One- and two-compartment models with zero order input were analyzed. The log-likelihood, the Akaike information criterion and the Bayesian information criterion were used to test hypothesis to select the final model. Visual inspection of the model's fit was performed by generating diagnostic plots, including observed versus population predicted gentamicin concentrations and observed versus individual predicted concentrations (Fig. 1). Models were further selected on the basis of the precision of the parameter estimates, measures of variability and the objective function value. A reduction in the OFV of more than 3.84 (-2 log likelihood difference) was considered to be significant with 1 degree of freedom and a $P < 0.05$.

Interindividual and Error Models

Interindividual variability in pharmacokinetic parameters were ascribed to an exponential model according to the equation: $\theta_j = \theta_p \times \exp(\varsigma j)$, where θ_j is the estimate for a pharmacokinetic parameter in the j_{th} patient as predicted by the model, θ_p is the typical population pharmacokinetic parameter value and ς is a random variable from a normal distribution with zero mean and variance ω^2. Residual variability, which includes intraindividual variability, measurement errors and model misspecification, was estimated using additive and proportional error models; $C_{ij} = C_j + \varepsilon_{add}$ and $C_{ij} = C_j(1 + \varepsilon_p)$, where C_{ij} and C_j are the observed and predicted concentrations of gentamicin for the j_{th} patient at the time i, respectively, and ε is the error, a random variable with a normal distribution with zero mean and variance $\acute{o}^2$.

Selection of Covariates

Once the basic model was determined, the relevance of the covariates age and weight was explored. Allometric models based on previous recommendations for analyzing data in pediatric patients,[11] as well as simple linear models, were investigated. Each of the potential covariates was incorporated into the basic model after a stepwise inclusion process to obtain the final model. The covariates were added to the model until the objective function does not show a further decrease. Then, covariates were removed from the model by applying the stepwise backward method. Covariates were retained in the model if they were associated with a significant increase in the value of the objective function.

Model Evaluation

The accuracy and precision of the model were assessed by applying the nonparametric bootstrap method. One thousand random samples with replacement were derived from the original database, and then the standard errors for the estimated population parameters were calculated. A model was considered stable if less than 10% of the simulations fell outside the confidence intervals of 90% of the measured concentrations of gentamicin. The 10th, 90th and 50th percentiles of the simulated concentrations were plotted and superimposed on the observed concentrations.

Monte Carlo Simulation

A Monte Carlo simulation of 1000 patients was conducted to determine the probability of target attainment (PTA) the pharmacokinetic/pharmacodynamic target in a population of patients with CSM aged from 3 to 50 months for the following gentamicin dosing regimens: 2.5 mg/kg every 8 hours, 7.5 mg/kg every 24 hours, 10 mg/kg every 24 hours and 15 mg/kg every 24 hours. All dosing regimens were simulated using an infusion time of 0.5 hour. The C_{max}/MIC ratio for MICs range from 0.03 to 8 μg/mL was estimated for each patient. The PTA was calculated using a pharmacokinetic/pharmacodynamic target C_{max}/MIC ≥ 10. A PTA > 90% was defined as optimal.

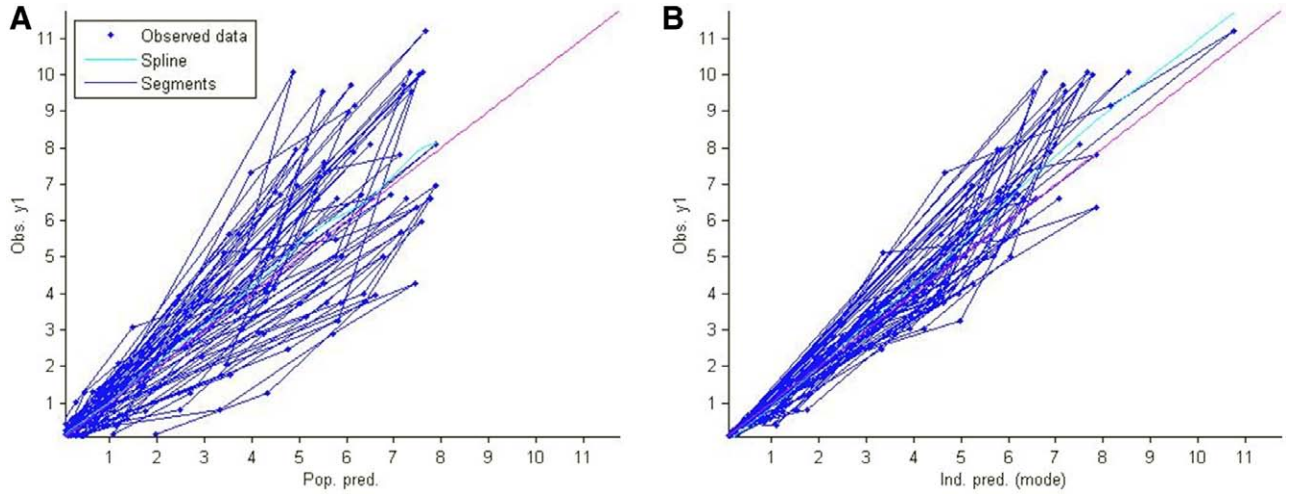

FIGURE 1. Diagnostic plots for the final 1-compartment model. (A) Observed versus population predicted gentamicin concentrations (mg/L). (B) Observed versus individual Bayesian predicted gentamicin concentrations (mg/L). full color online

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TABLE 1. Demographic and Clinical Characteristics of the Patients

Characteristics	
Gender % (M/F)	77/23
Body weight (kg)	7.1 ± 2.4
Height (cm)	70.9 ± 7.6
Age (mo)	20.7 ± 16
Z scores weight for age	–3.4 ± 0.8
Type of malnutrition% (marasmic/kwashiorkor)	70/30
Albumin (g/dL)	2.2 ± 0.3
Creatinine (μmol/L)	66 ± 5
Diagnosis	
Diarrhea (%)	70
Pneumonia (%)	20
Septicemia (%)	15

Creatinine normal values for age: (1) 2 wk to 5 yr: 17.7 to 44.2 μmol/L and (2) 5 to 10 yr: 26.5 to 88.4 μmol/L.

RESULTS

Patient Population

Twenty-six children with severe malnutrition, according to the definition of the WHO, were studied. The characteristics of the population are summarized in Table 1. The mean (±SD) age and weight were 20.7 ± 16 months and 7.1 ± 2.4 kg, respectively. The mean (±SD) serum creatinine was 66 ± 5 μmol/L. Marasmic malnutrition was diagnosed in 70% and Kwashiorkor malnutrition in 30%. Diarrhea, pneumonia and septicemia were the main diagnoses. In all patients, the infection process was controlled and they remained hospitalized for several weeks until their nutritional recovery was obtained.

Population Pharmacokinetics

A total of 96 samples were collected prospectively from 26 patients aged between 3 months and 5 years. The concentration–time data were fitted best for a 1-compartment model with parameters CL and V, with its associated variability modeled exponentially. The estimated CL was 1.1 L/h with a coefficient of interindividual variability of 47.2%, and the estimated V was 2.2 L with a coefficient of interindividual variability of 35.6%.

A 2-compartment model was not better than the 1-compartment model to describe the data, the variability of the estimates were higher and diagnostic graphs showed no evidence of improvement.

Graphs of individual determinations of pharmacokinetic parameters against clinical and demographic data confirm age and weight as potential covariates. Table 2 summarizes the values of the population parameters for the basic model, allometric and no-allometric scaling models. The model with the greatest reduction in the objective function was selected as the final model. The final population pharmacokinetic model parameters are shown in Table 3, along with the parameter estimates from 100 bootstrap runs. Clearance and volume of distribution of gentamicin were best described by the following allometric models: CL (L/h) = CL = 1.15 (age/median age)$^{0.321}$ and V (L) = 2.33 (weight/median weight)$^{0.743}$.

The diagnostics to evaluate the final model are shown in Figures 2 and 3. The normalized prediction distribution error values are distributed randomly with a normal distribution. The results of visual predictive check of the model were based on 200 simulations. The majority of the observed values lie within the 5% and 95% percentiles, and less than 10% of the observations were outside these percentiles.

Monte Carlo Simulations

The percentage of simulated patients who achieved a C_{max}/MIC ratio >10 at each MIC value with the standard and the extended gentamicin dosage regimens is presented in Figure 4. With a dose of 2.5 mg/kg every 8 hours, only 30% of patients would be expected to achieved the target C_{max}/MIC ratio >10 if the bacterial MIC was ≤1 mg/L. However, with once a day dose of 7.5 mg/kg, the percentage increased to 99%. With a dose of 10 mg/kg optical density (OD), 90% of patients would be expected to achieve a C_{max}/MIC ratio >10 for bacteria with a MIC ≤2.5 mg/L. With a dose of 15 mg/kg OD, 90% of patients would be expected to achieve a C_{max}/MIC ratio >10 for bacteria with a MIC ≤3.5 mg/L. Therefore, the pharmacokinetic/pharmacodynamic breakpoint for aerobic Gram-negative organisms was ≤0.125 for thrice-daily dosage regimen, ≤1 for 7.5 mg/kg OD, ≤2.5 for 10 mg/kg OD and ≤3.5 for 15 mg/kg OD regimen dosage. The probability of a C_{min} higher than 1 mg/L was 9.8% for a regimen of 2.5 mg/kg every 8 hours, whereas for all OD regimens dosage, the probabilities were kept less than 1%.

DISCUSSION

In this study, we used a population approach to determine the pharmacokinetic parameters of gentamicin in Mexican children with CSM along with their interindividual and intraindividual variability, using a nonlinear mixed-effects model implemented in the program software Monolix version 4.2.

The pharmacokinetics of gentamicin was appropriately described by a 1-compartment model with the estimated parameters:

TABLE 2. Comparison of the Objective Function for Basic and Final Models

Model	–2 × LL	AIC	BIC	ω_V	ω_{CL}
Basic model V = 2.21 CL = 1.1	403	413	420	0.356	0.472
Allometric model V = 2.33 (weight/weight*)$^{0.743}$ CL = 1.15 (age/†age)$^{0.321}$	360	376	388	0.244	0.349
No-allometric model V = 1.02 $\theta_{v(weight, kg)}$ = 0.103 CL = 0.748 $\theta_{CL(age, mo)}$ = 0.017	376	390	400	0.252	0.366

*Median weight = 7.6 kg.
†Median age = 19 mo.
AIC indicates Akaike information criterion; BIC, Bayesian Information criterion; CL, clearance in L/h; LL, log likelihood; V, volume of distribution in liters.

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TABLE 3. Final Model Pharmacokinetic Parameters Estimates And Bootstrap Replicates

Parameters	Mean	RSE (%)	Bootstrap Estimate	Bootstrap, 95% confidence interval
V (L)	2.33	5	2.32	2.22–2.41
θ_{wV}	0.743	22	0.753	0.723–0.782
CL (L/h)	1.15	7	1.15	1.10–1.19
θ_{ageCL}	0.321	22	0.335	0.315–0.354
ω_{V}	0.244	18	0.249	0.238–0.258
ω_{CL}	0.349	14	0.350	0.336–0.363
Proportional residual variability (ϵ)	0.240	7	0.244	0.234–0.253

volume of distribution and clearance. We evaluated different models, selecting the one that showed the best fit based on the reduction of the objective function value and interindividual variability. An allometric scaling model was selected; the model included age as covariate that significantly influence the clearance, and weight as covariate that influences the volume of distribution of gentamicin in our population of patients with CSM.

Pharmacokinetics of gentamicin in children with malnutrition has been scarcely studied, although it is part of the first-line antimicrobial therapy recommended by WHO for children with severe complicated malnutrition.[4] Bravo et al[7] studied the pharmacokinetics of gentamicin, after a dose of 3.5 mg/kg intravenously, in children with marasmus malnutrition and eutrophic children aged between 4 and 10 months. Fitting the data to a 2-compartment model, the results showed no difference in the pharmacokinetic parameters between the 2 groups, except for the volume of distribution that it was 18.3% higher in children with marasmus (0.46 vs. 0.39 L/kg). Applying our model to the data of their population, the average volume of distribution predicted by our model is 32% smaller (0.31 vs. 0.46 L/kg). This difference could be explained by the age-related changes in body water percentage,[11] because of differences in age distribution between the 2 populations.

More recently, Seaton et al[6] studied the pharmacokinetics of gentamicin in 34 children with ages between 6 and 120 months and severe malnutrition; 62% with marasmus and 38% with kwashiorkor. Gentamicin was administered at doses of 7.5 mg/kg once a day intramuscularly. Applying a population analysis, a structural pharmacokinetic model of 2 compartments was selected. The interindividual variability was 42% for clearance (CL/F), 32% for the central volume of distribution (V1/F) and 64% for peripheral volume of distribution (V2/F). The covariates, weight, base deficit, temperature and creatinine were included in the final model, reducing the CL/F interindividual variability to 26%. Weight was included as a covariate for central distribution volume in the final model, the interindividual variability was not reduced (32% vs. 33%). Base deficit was the only covariate associated with V2/F; inter-individual variability was reduced to 55%. The estimated median CL/F was 0.10 L/h/kg, similar to that observed in our patients. The median of the volume steady state (V1 + V2) was 0.66 L/kg, far exceeding the volume of distribution estimated in our patients. The use of a 2-compartment model and the route of administration may explain the differences in distribution volumes obtained, although it is difficult to rule out the effect of nutritional status and severity of infection.

Aminoglycosides have a concentration-dependent bactericidal activity, which means that as the concentration increases, the rate of bacterial clearance is greater. Thus, the goal of therapy is to use the highest possible dose and that at the same time to be consistent with a low risk of toxicity.[12,13] Therefore, the administration of high dose once a day, unlike lower doses at short intervals, has a rational justification and clinical evidence that supports it.[14–16] A recent metanalysis support the efficacy and safety of once-daily aminoglycoside dosing in children; however, none of the studies analyzed were in children with malnutrition.[17] To

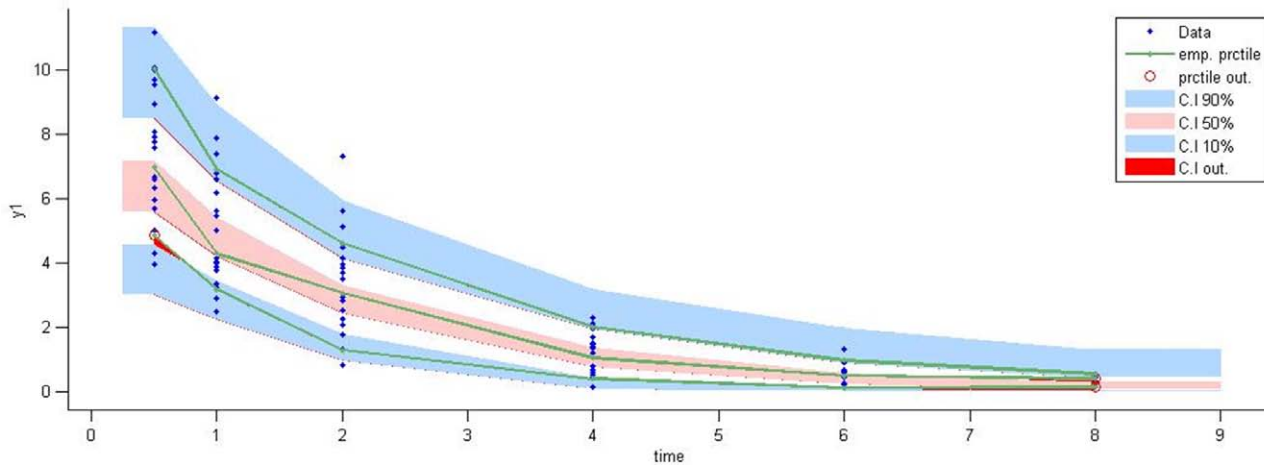

FIGURE 2. Prediction-corrected visual predictive check for gentamicin concentrations (mg/L) versus time (hours). The green lines show the 10th, 50th and 90th percentiles of observed data; the areas represent the 90% confidence interval around the simulated percentiles. full color online

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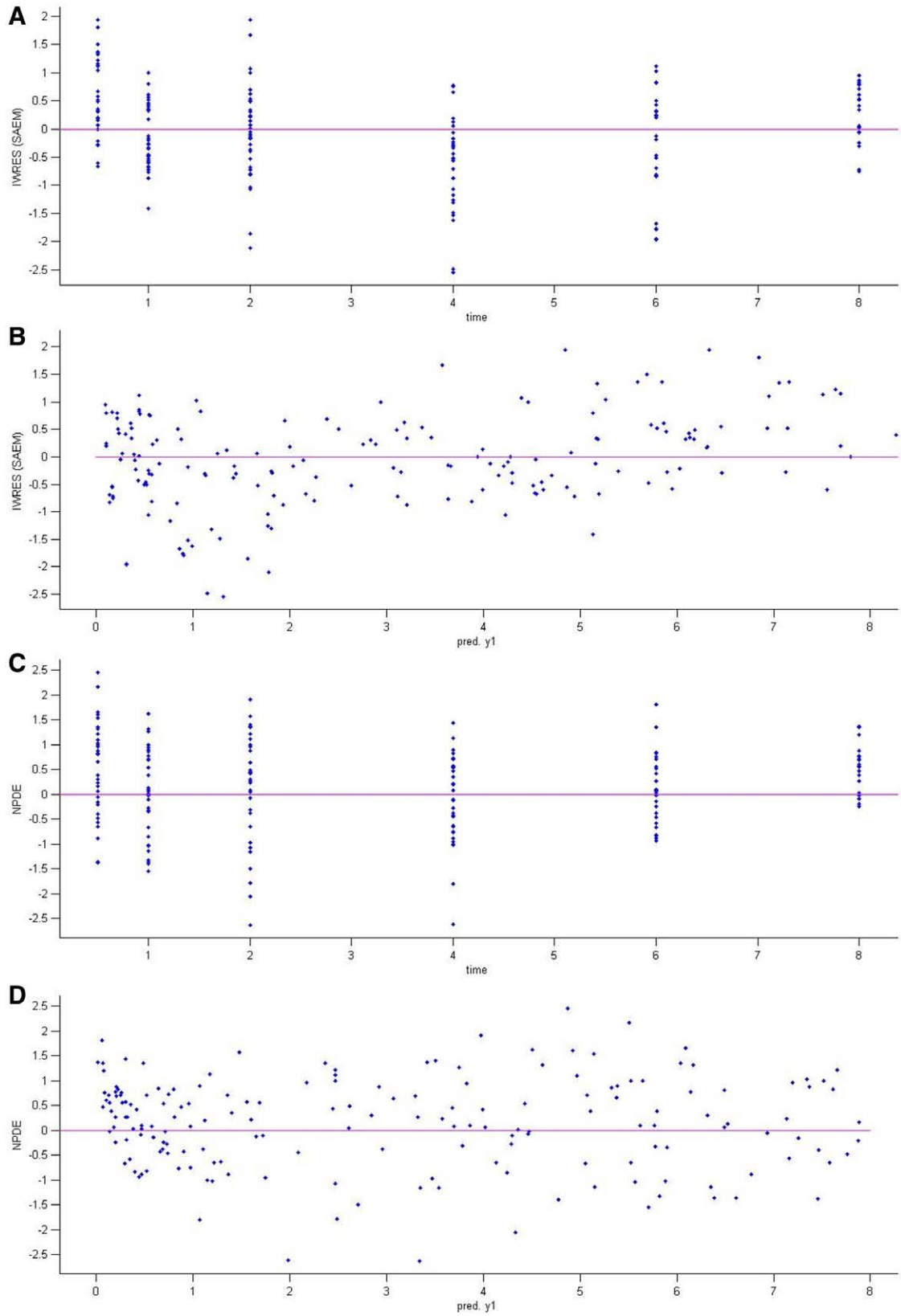

FIGURE 3. Diagnostic plots: population-weighted residuals (WRES; A and B) and normalized prediction distribution error (NPDE; C and D) as a function of time (A and C) and population prediction (B and D). SAEM indicates stochastic-expectation maximization algorithm; NPDE, normalized prediction distribution error. full color online

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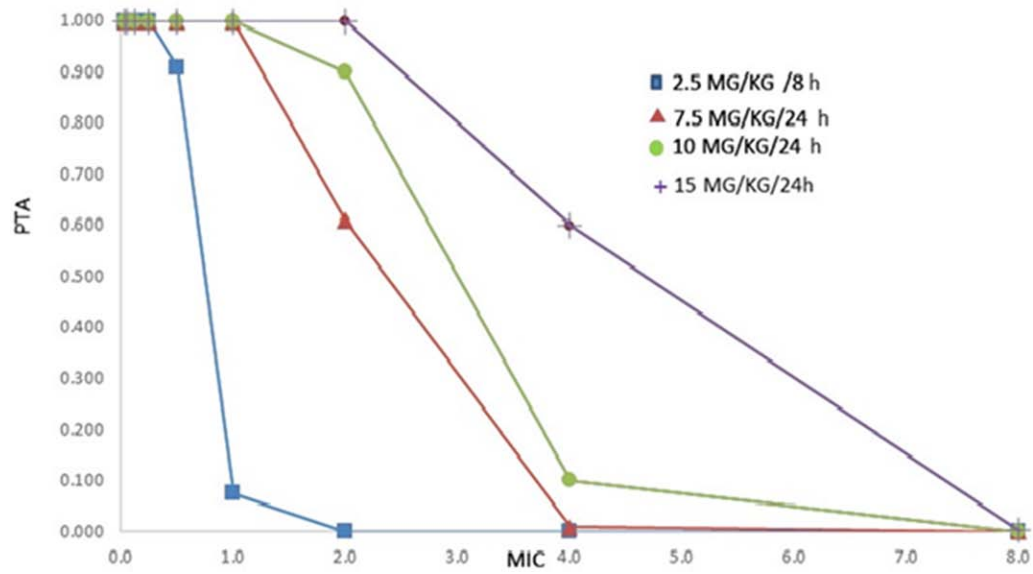

FIGURE 4. Probability of achieving a target C_{max}/MIC ≥10 for different gentamicin dosage regimens: 2.5 mg/kg every 8 hours, 7.5, 10 and 15 mg/kg every 24 hours. A PTA ≥90% was considered as optimal. full color online

our knowledge, only 2 studies had been published on once-daily gentamicin dosage in malnourished children. Khan et al[8] studied 310 children of both sexes aged between 6 months and 5 years with malnutrition to compare the efficacy, safety and pharmacokinetics of gentamicin administered intramuscularly as once-daily dose (ODD) or as conventional thrice-daily dosing. The same total daily dose (5 mg/kg/d) was administered in both groups. There was no difference in the percentage of patients who had a partial or good clinical response. However, the peak serum gentamicin concentrations in the ODD group were significantly higher in comparison to the peak serum concentrations in the thrice-daily dosing group (11.7 ± 4.1 vs. 4.7 ± 1.8 mg/L). The study by Seaton et al[6] in 34 children with severe malnutrition, although it is not a study designed to demonstrate efficacy and safety, shows that ODD allows to achieve concentrations greater to 8 mg/L in all patients and above to 12 mg/L up to 76%. Ninety-eight percent of the concentrations obtained after 20 hours were <1 mg/L. Moore et al[4] demonstrated a dose–effect relationship between the pharmacodynamics of aminoglycosides (C_{max}/MIC) and clinical response, and a C_{max}/MIC ratio 8:1 to 10:1 was suggested as a target to optimize the bactericidal effect and minimize resistance to aminoglycosides. According to the European Committee on Antimicrobial Susceptibility Testing report (version 5.0, 2015)[18] the MIC cutoff points for *Enterobacteriaceae* responsible for most infections in children with malnutrition are within the range of 1 to 4 mg/L for gentamicin. Thus, peak concentrations of 10 to 40 mg/L should be required to obtain a C_{max}/MIC ratio >10. Lopez et al[19] determined the population gentamicin pharmacokinetics in critically ill children, and through Monte Carlo simulations, it was estimated that ODD of 8 mg/kg was necessary to reach a peak concentration >16 mg/L and C_{max}/MIC ratio ≥8, assuming a MIC up to 2 mg/L for *Escherichia coli* and *Pseudomonas aeruginosa*, in 100% of the patients aged from 1 day to 16 years. Applying a C_{max}/MIC ratio ≥10, our model predicts that ODD of 7.5 to 10 mg/kg is necessary to secure the elimination of Gram-negative enterobacteria with MICs up to 2.5 mg/L with a low probability of trough concentrations above 1 mg/L. Therefore, knowing the population pharmacokinetics for a specific population of malnourished children allows us to estimate the dose to obtain, with less uncertainty, the numerator of the C_{max}/MIC ratio to optimize the efficacy of gentamicin. However, the denominator of this ratio requires knowledge of the distribution of MICs for the most prevalent Gram-negative bacteria in each health institution.

Our model, however, has limitations because of the small sample size and because it did not have an external validation. While it was validated internally, external validation is important for dosage recommendations.[20] However, our recommendations based on the model and Monte Carlo simulations coincide with those obtained by other authors and the recommendations of the WHO. Prospective studies are needed to determine the efficacy and safety of these dosing schedules in patients with CSM. Finally, another apparent limitation is the fact that because there is limited access to the equipment necessary to provide intravenous therapy in many hospitals in developing countries, it is often necessary to administer antibiotics by the intramuscular route. However, aminoglycoside pharmacokinetic studies have shown that the peak concentrations obtained after intramuscular injection are similar to those obtained at the end of a 30-minute infusion intravenously.[21,22] Thus, the suggested intravenous dosing regimens can be extrapolated to the intramuscular route, which is the route used most frequently in hospitals with limited resources.

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