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PHARMACOLOGY

Population Pharmacokinetics with Monte Carlo Simulations of Gentamicin in a Population of Severely Ill Adult Patients from Sub-Saharan Africa

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ABSTRACT In sub-Saharan Africa (SSA), gentamicin is commonly used for severe infections in non-intensive-care-unit (ICU) settings, but pharmacokinetic and pharmacodynamic data for this specific population are lacking. We performed a population pharmacokinetic study in an adult Mozambican non-ICU hospital population treated with gentamicin ($n = 48$) and developed a pharmacokinetic model using nonlinear mixed-effects modeling. Simulations showed that non-ICU patient populations in SSA may be at substantial risk for underexposure to gentamicin during routine once-daily dosing.

KEYWORDS aminoglycosides, gentamicin, pharmacodynamics, population pharmacokinetics, severe illness, sub-Saharan Africa

In sub-Saharan Africa (SSA), community-acquired bloodstream infection and sepsis are leading causes of morbidity and mortality among hospitalized adults (1–3). Acute infection-induced pathophysiological changes, such as organ dysfunction, increased capillary permeability, and hypoalbuminemia, are known to lead to alterations in antibiotic volume of distribution (V) and clearance (CL) (4). Pharmacokinetic (PK) changes can give rise to an inability to attain pharmacodynamic (PD) targets, especially among critically ill patients in an intensive care unit (ICU) setting (4, 5). In earlier studies with severely ill non-ICU SSA patients, we found that acute infection in this setting is likely to lead to underexposure to the β-lactams ceftriaxone and benzylpenicillin (6, 7). The specific aims of the current study were to describe the population PK (PPK) of gentamicin in an adult non-ICU SSA hospital population, identify sources of PK parameter variability, and assess the probability of PD target attainment (PTA) of gentamicin for the treatment of infections caused by *Enterobacteriaceae*.

From October 2014 to November 2015, we performed a prospective, observational PPK study of intravenously administered gentamicin among patients aged ≥18 years admitted to the Beira Central Hospital medicine ward (HCB) in Mozambique. The patient population was described previously (6, 7). The study was approved by the Mozambican National Committee for Bioethics in Health (118/CNBS/2013). Participants gave written informed consent. Those unable to read, write, and/or understand Portuguese gave a thumbprint, and an impartial literate witness observed the entire informed-consent process and subsequently cosigned the informed-consent form.

Baseline characteristics and gentamicin dosing information were captured. Any gentamicin dosing regimen prescribed by an HCB physician was accepted. Gentamicin 40-mg/ml solution for injection (Nitin Lifesciences Ltd., Haryana, India) was intravenously administered through bolus injection via a venous catheter in half a minute,

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TABLE 1 Baseline characteristics and dosing schedule of study population

Characteristic[a]	Median baseline value (range)[b]
Female sex (*n* [%])	24 (49)
Age (years)	40 (20–86)
Body weight (kg)	51 (33–76)
Body mass index (kg/m^2)	19.2 (10.4–29.0)
Hemoglobin (g/dl)	10.0 (6.7–14.6)
Albumin (g/liter)	29 (13–40)
GGT (U/liter)	40 (11–372)
ALT (U/liter)	16 (4–116)
AST (U/liter)	33 (12–258)
Creatinine (μmol/liter)	76 (37–1192)
CL_{CR} (ml/min)[c]	74 (4–144)
Gentamicin dosing regimen (*n* [%])	
q24h; dose range, 80–240 mg/kg	29 (60.4)
q12h; dose range, 80–240 mg/kg	16 (33.3)
q8h; dose range, 80–160 mg/kg	3 (6.3)

[a]GGT, γ-glutamyl transferase; ALT, alanine aminotransferase; AST, aspartate aminotransferase.
[b]Results expressed as median (range) unless specified otherwise. $n = 48$.
[c]Estimated with the Cockcroft and Gault equation (8).

according to the physician's prescription. Gentamicin concentration sampling times were predose, 30 to 120 min after intravenous administration, and two random time points during the dosing interval. One sample was used to measure biochemical markers. Creatinine clearance (CL_{CR}) was estimated using the Cockcroft and Gault formula (8). EDTA-anticoagulated blood samples were refrigerated immediately after collection until laboratory processing within 2 h of collection and stored at −80°C until shipment on dry ice to the Netherlands for analysis.

Total gentamicin concentrations were measured using a validated high-performance liquid chromatography-mass spectrometry assay (LC30 UPLC, Shimadzu, Kyoto, Japan; Qtrap 5500 system, Sciex, Framingham, MA). The lower limit of quantification (LLQ) was 0.3 mg/liter and the higher LLQ was 50 mg/liter. Higher concentrations were diluted and reanalyzed.

The PPK analysis was performed using the nonlinear mixed-effects modeling software package NONMEM (7.1.2; Icon Development Solutions, Ellicott City, MD). Gentamicin concentration data that were either not in line with previous concentrations of the same patient (e.g., near LLQ within 2 h after dosing, where previous administrations resulted in concentrations of >3 mg/liter in around the same time span) or not in line with a patient's estimated CL_{CR} (e.g., near LLQ within 3 h after dosing, with a low CL_{CR}) were removed from analysis because they were considered to have resulted from erroneous drug administration and/or data capture. Model building was performed using a stepwise approach (for a full explanation, see Methods in the supplemental material). In brief, first, a structural compartmental PPK model was developed in which the PK of gentamicin was described, including the between-patient variability (BPV) of the PK parameter estimates of *V* and CL. The so-called M3 method was used to handle concentrations below the LLQ (9). In the second step, an effort was made to explain the BPV by building a covariate model in which patient demographics and biochemical markers were tested for their associations with the estimated PK parameters. Improvement of the model by adding a parameter or by introducing a correlation between a covariate and a PK parameter was evaluated using the likelihood ratio test, in which the difference between the minimum objective-function value generated by NONMEM for two hierarchical models was determined. Model performance was also evaluated by visual inspection of diagnostic goodness-of-fit plots (10). In the last step, the robustness and validity of the model resulting from the second step were tested using bootstrap and visual predictive check (VPC) analyses. Using the final model, gentamicin concentration versus time profiles were generated for 1,000 virtual patients by Monte Carlo simulation of the following five dosing regimens: 1.5 mg/kg every 8 h (q8h), which is

TABLE 2 Parameter estimates

Parameter[a]	Structural model		Final model	
	Estimate	Bootstrap estimate (95% CI)[b]	Estimate	Bootstrap estimate (95% CI)[b]
CL (liter/h)	5.5	5.5 (4.0–7.0)	5.7	5.7 (5.2–6.2)
V (liter)	20	21 (16–24)	19	20 (18–21)
BPV				
CL (%CV)	91	90 (49–130)	74	70 (58–89)
V (%CV)	44	47 (2.2–66)	49	48 (38–59)
Correlation between CL and *V* (%)	35	31 (10–56)	46	40 (11–62)
Residual variability				
Proportional error (%)	31	31 (22–41)	32	32 (28–37)
Additive error (mg/liter)	0.095	0.072 (0.035–0.16)	0.056	0.055 (0.023–0.089)
Covariate effect				
CL_{CR} on CL			0.0091	0.0093 (0.0077–0.010)

[a]BPV, between-patient variability; CL, clearance; *V*, volume of distribution; CV, coefficient of variation; CL_{CR}, creatinine clearance; CI, confidence interval.
[b]Minimization was successful for both the structural and the final models, but it failed for the covariance step, yielding no estimates for the relative standard errors of the parameter estimates. Instead, a bootstrap with 1,000 replicates was done for the structural and final models to obtain 95% CIs of the parameter estimates. The shrinkages in the final model in BPV for CL and *V* were 8% and 29%, respectively.

a recommended regimen according to Mozambique's 2007 national formulary (11); 4 mg/kg once daily (q24h), commonly recommended for non-ICU patients; and 5, 6, and 7 mg/kg q24h, commonly recommended as a starting regimen for septic ICU patients. Gentamicin peak (C_{max}) and trough (C_{min}) concentrations were evaluated, with C_{max} defined as the predicted gentamicin concentration 0.5 min after bolus administration of a gentamicin dose and C_{min} as the predicted gentamicin concentration 8 or 24 h after bolus administration for the q8h- and q24h-dosing regimens, respectively. Based on these data, the PTA, i.e., the percentage of patients with a C_{max}/MIC of ≥8,

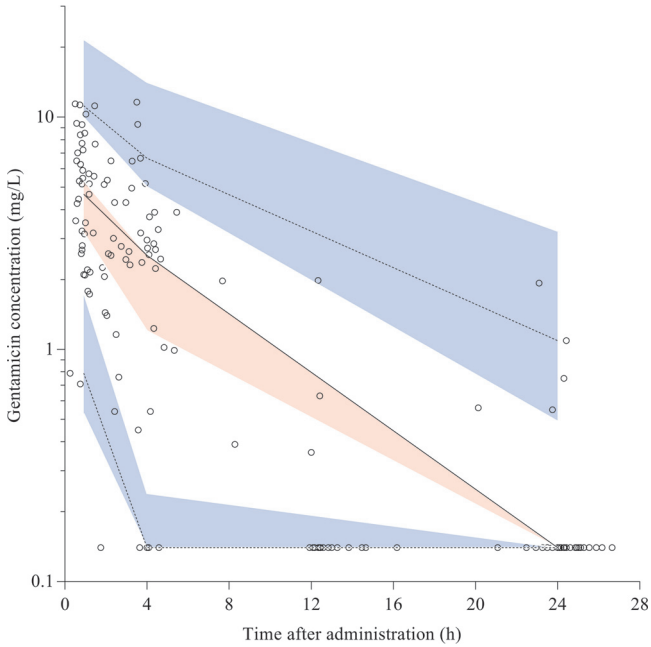

FIG 1 Observed gentamicin concentration-time data and visual predictive check (VPC) of the final model. Open circles are observed concentrations. Solid line is observed median and dashed lines are 5th and 95th percentiles of the observed data. Red shaded area is the 95% confidence interval (CI) of the model-predicted median; blue shaded areas are the 95% CI of the model-predicted 5th and 95th percentiles. In preparing the plot, the observed and simulated concentrations below the LLQ were set to 0.14 mg/liter (0.5 × LLQ) to promote visual inspection of the figure. Solid and dashed lines run within their respective shaded areas, thereby demonstrating adequate fit of the model.

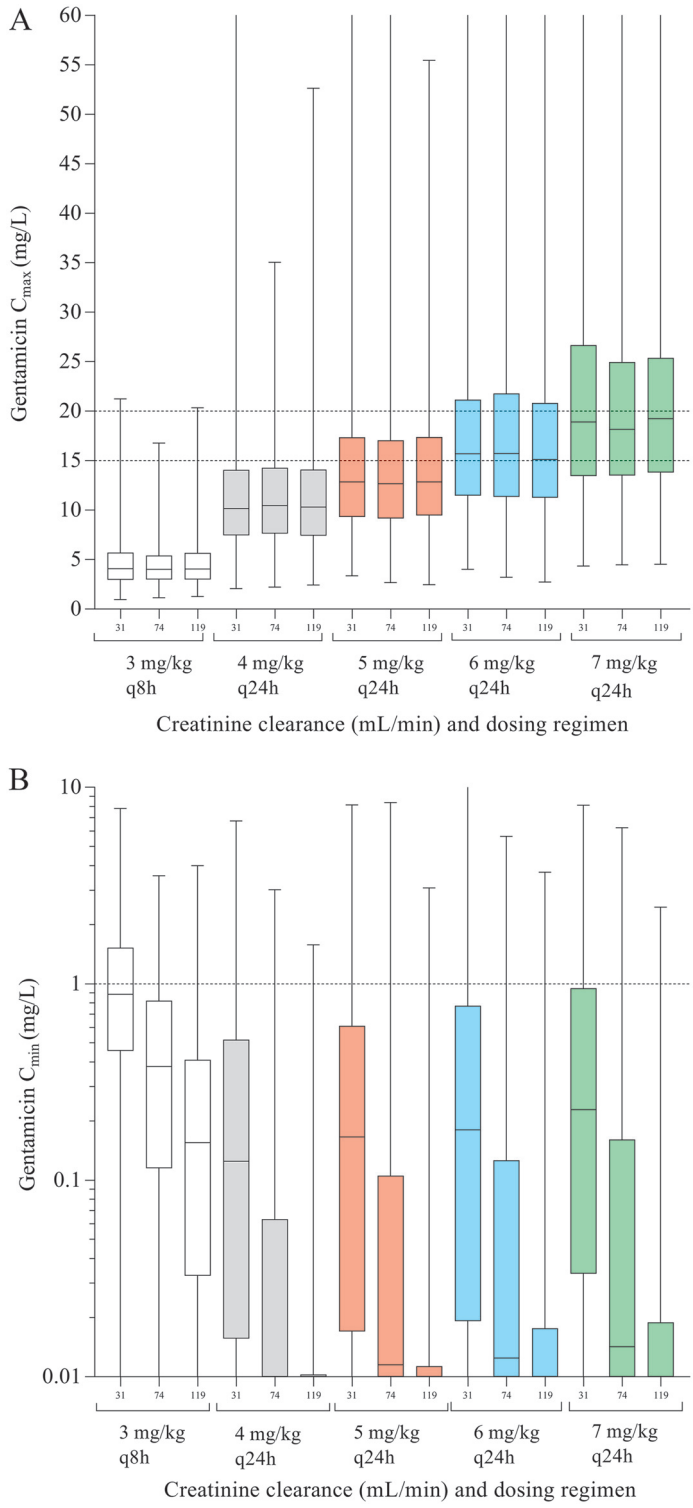

FIG 2 Simulations of gentamicin peak concentrations (A) and trough concentrations (B) for 1,000 virtual patients with all median characteristics of the population but five different dosing schedules (white, 1.5 mg q8h; gray, 4 mg q24h; red, 5 mg q24h; blue, 6 mg q24h; green, 7 mg q24h) and three CL_{CR} levels (10th percentile, 31 ml/min; median, 74 ml/min; and 90th percentile, 119 ml/min).

was calculated (12–14) The choices of target MICs were based on EUCAST clinical breakpoint tables for susceptibility to gentamicin of *Enterobacteriaceae* (MIC clinical susceptibility breakpoint, 2 mg/liter) and on regional reports on antimicrobial susceptibility of *Enterobacteriaceae* obtained from clinical specimens (15–18). The gentamicin

C_{min} was considered adequate for reducing the risk for nephro- and ototoxicity when <1.0 mg/liter (14).

Forty-eight participants yielded 141 gentamicin concentrations (see Fig. S1 in the supplemental material). Patient characteristics and dosing schedules are presented in Table 1. A total of 47 gentamicin samples (33.3%) had concentrations below the LLQ. Twenty samples were removed because they were considered to have resulted from erroneous drug administration and/or data capturing. A one-compartment model best fitted the data, and the estimated BPVs for CL and *V* were 91% and 44%, respectively. Residual variabilities were estimated to be 31% and 0.095 mg/liter, respectively. Parameter estimates from the structural model are summarized in Table 2. The covariate analysis yielded one significant association between gentamicin CL and CL_{CR} (see Fig. S2 in the supplemental material). Incorporation of this linear association in the structural model explained 19% of the BPV. Yet, a substantial part (74%) of the BPV in CL remained unexplained. The final model had an adequate fit (Fig. 1). The bootstrap estimates were similar to the estimates from the structural and final models (Table 2).

All dosing regimens were simulated by using the observed median CL_{CR} (74 ml/min), the 10th percentile (31 ml/min), and the 90th percentile (119 ml/min). Simulations showed that the performance of the 1.5-mg/kg-q8h dosing regimen was poor, with a PTA of 7.5% for patients with the median CL_{CR} and an infection with a susceptible pathogen with an MIC of 1.0 mg/liter, whereas 17.4% of patients were predicted to have a C_{min} of ≥1.0 mg/liter after the first dose (Fig. 2 and Table S1 in the supplemental material). Use of the 4-mg/kg-q24h regimen resulted in PTAs of 71.7% and 17.9% when assuming an infection with a pathogen with MICs of 1.0 and 2.0 mg/liter, respectively. In this scenario, 14.5% of patients with a CL_{CR} of 31 ml/min (observed 10th percentile of CL_{CR}) were predicted to have a C_{min} of ≥1.0 mg/liter after the first dose. The 7-mg/kg-q24h regimen had the highest PTAs, at 96.5% and 61.7% for pathogens with MICs of 1.0 and 2.0 mg/liter, respectively. For patients with a CL_{CR} of 31 ml/min, 24.4% were predicted to have a C_{min} of ≥1.0 mg/liter.

A one-compartment model adequately described gentamicin PK, and comparable to what can be found in septic ICU patients, the estimated *V* and CL in this study's non-ICU population were high, as were the BPVs of these PK parameters (19, 20). Once-daily gentamicin dosing with the commonly recommended initial regimen for non-ICU patients in the SSA setting is likely to lead to insufficient peak concentrations. Higher once-daily dosing regimens of gentamicin, such as those routinely recommended for septic ICU patients, seem to have higher PTAs, but this comes with a substantial risk of toxic through levels, especially for patients with impaired renal function. In the absence of a therapeutic drug-monitoring infrastructure, gentamicin may therefore not be a rational antibiotic choice for severely ill populations in SSA hospital settings.

SUPPLEMENTAL MATERIAL

Supplemental material for this article may be found at https://doi.org/10.1128/AAC.02328-18.

SUPPLEMENTAL FILE 1, PDF file, 1.3 MB.

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J.C.B., R.M., and J.P. designed the study. J.C.B. performed the literature search and obtained ethical approval. J.C.B., M.M., G.N., and M.D. implemented the study, and J.C.B. supervised data collection and study progress on a daily basis. J.C.B. and R.V.H. analyzed the data and drafted the manuscript. J.P. and R.M. critically examined the analysis and findings. We all critically read and commented on draft versions of the report and approved the final version.

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