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Population Pharmacokinetic Characteristics of Amikacin in Suspected Cases of Neonatal Sepsis in a Low-Resource African Setting: A Prospective Nonrandomized Single-Site Study



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ABSTRACT

Background: Amikacin exhibits marked pharmacokinetic (PK) variability and is commonly used in combination with other drugs in the treatment of neonatal sepsis. There is a paucity of amikacin PK information in neonates from low-resource settings.

Objectives: To determine the PK parameters of amikacin, and explore the influence of selected covariates, including coadministration with aminophylline, on amikacin disposition in neonates of African origin.

Methods: Neonates with suspected sepsis admitted to an intensive care unit in Accra, Ghana, and treated with amikacin (15 mg/kg loading followed by 7.5 mg/kg every 12 hours), were recruited. Serum amikacin concentration was measured at specified times after treatment initiation and analyzed using a population PK modeling approach.

Results: A total of 419 serum concentrations were available for 247 neonates. Mean (SD) trough amikacin concentration (from samples collected 30 minutes before the fourth dose) among term (n = 25), and preterm (< 37 weeks' gestation n = 36) neonates were 6.2 (3.4) and 9.2 (5.7) µg/mL, respectively (P = 0.02). A 1-compartment model best fitted amikacin disposition, and birth weight was the most important predictor of amikacin clearance (CL) and distribution (V). The population CL and V of amikacin were related as CL (L/h) = 0.153 (birth weight/2.5)^{1.31}, V (L) = 2.94 (birth weight/2.5)^{1.18}. There was a high between-subject variability (58.9% and 50.7%) in CL and V, respectively. CL and V were 0.058 L/h/kg and 1.15 L/kg, respectively, for a mean birth weight of 2.1 kg, and the mean half-life (based on 1-compartment model), was 13.7 hours.

Conclusions: The V and half-life of amikacin in this cohort varied from that reported in non-African populations, and the high trough and low peak amikacin concentrations in both term and preterm neonates suggest strategies to optimize amikacin dosing are required in this population.

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Introduction

Aminoglycosides in combination with other antibiotics such as beta-lactams, are frequently used to extend the spectrum of

antimicrobial activity for neonatal infection treatment.¹ However, near-ubiquitous resistance of common pathogenic organisms to gentamicin has necessitated the increasing use of amikacin as first-line treatment.² Amikacin exhibits wide interindividual variability in pharmacokinetic (PK) parameters during the neonatal period^{3–6} and with unique PK characteristics among preterm neonates. The wide interindividual variability in amikacin concentrations in heterogeneous neonatal populations require amikacin therapeutic monitoring; however, such data rarely exist in most

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low-resource settings. There is limited information on amikacin PK parameters in neonates of African origin, and there is no consensus on target amikacin concentration ranges in different neonatal populations. This makes it necessary to conduct setting-specific studies to generate information that would improve understanding of amikacin PK characteristics and optimize amikacin dosing in such populations.

The PK characteristics of amikacin may be altered in conditions such as sepsis⁷ and concurrent administration of amikacin with nonsteroidal anti-inflammatory drugs during the first day of life³ result in increased distribution volume (V) and reduced clearance (CL), respectively. Other commonly used drugs in neonatal intensive care settings may also alter aminoglycoside PK characteristics. For example, methylxanthines increase urine output and filtration fraction.⁸ Aminophylline is used for management of apnea of prematurity and is often concurrently administered with amikacin in preterm neonates (<35 weeks' gestation) with suspected sepsis. However, the potential influence of coadministration of aminophylline on the CL of amikacin, which is excreted largely via the renal route (but also with some amount of nonrenal CL), is not known in this population. The aim of this study was to describe the PK characteristics of amikacin in neonates with suspected sepsis in a low-resource sub-Saharan Africa setting where such information is unavailable, and explore the influence of selected clinical and paraclinical parameters as covariates, including aminophylline coadministration, on amikacin PK parameters.

Materials And Methods

Ethical issues

The Ethical and Protocol Review Committee of the University of Ghana School of Medicine and Dentistry approved this study (protocol ID: MS-Et/M.8-P.5.3/2011-2012). Written informed consent was obtained from all parents and/or guardians of recruited neonates.

Study design and site

This was a prospective, nonrandomized single-site study conducted at the neonatal intensive care unit (NICU) of the Department of Child Health, Korle-Bu Teaching Hospital, Accra, Ghana, from November 2013 to June 2014. The NICU is a tertiary referral unit for neonates from health facilities in the southern regions of Ghana. It is a 55-bed unit for preterm and sick neonates and is located in close proximity to the obstetrics and labor wards of Korle-Bu Teaching Hospital. There are about 2000 neonates admitted to the NICU annually, of whom approximately 60% are preterm births. Admission to the NICU is restricted to neonates aged less than 48 hours unless in exceptional circumstances. The unit changed the first-line empirical treatment for neonatal sepsis from gentamicin and ampicillin to amikacin and cloxacillin because of increasing antimicrobial resistance of bloodstream bacterial isolates in recent years.⁹

Study population and inclusion criteria

Hospitalized neonates suspected of having sepsis, and in whom a decision by the attending NICU physician to treat with amikacin, with or without other therapy, were recruited. Neonates who were known to have received any aminoglycoside before admission and those with major congenital anomaly were excluded.

Drug administration

Amikacin (Amikin®- Bristol-Myers Pharmaceuticals, Uxbridge, England) 15 mg/kg body weight was administered as a loading dose, followed by a maintenance dose of 7.5 mg/kg body weight administered every 12 hours. Amikacin was administered in combination with cloxacillin (50 mg/kg body weight every 12 hours) per the NICU dosing guideline at the time of this study. Aminophylline 8 mg/kg body weight was administered as a loading dose followed by a maintenance dose of 3 mg/kg body weight administered every 8 to 12 hours to preterm neonates (<35 weeks' gestation) who required it for management of apnea. The New Ballard Score (0.95 interrater reliability)¹⁰ was used to determine gestational age. All needed drugs and supportive therapy were given per standard NICU guidelines. Amikacin was administered as an intravenous bolus over 2 to 3 minutes.

Blood sampling

Blood was collected via venipuncture from recruited neonates by a study physician before drug administration for the laboratory investigations described below. Blood samples were collected into pediatric culture vials (BACTEC Peds plus/F, Becton-Dickinson, Gauteng, South Africa) for culture and sensitivity, EDTA tubes for full blood count, and serum separator tubes for C-reactive protein (CRP) and procalcitonin (PCT) levels.

For amikacin levels, 1 or 2 blood samples (500 µL per sample) were collected from each neonate into separator tubes, centrifuged, and serum obtained immediately transferred into Eppendorf tubes. Blood samples collected for the purpose of determining peak amikacin levels were collected 1 hour after the third dose, and samples for trough levels were collected 30 minutes before the fourth dose. Other samples (apart from peak or trough) were collected after 2, 4, 6, or 8 hours (full PK screen) following the third amikacin dose.

Laboratory analysis

Blood culture was done using the BACTEC 9240 blood culture system with subsequent biochemical species identification. Serum amikacin concentration was measured by particle-enhanced turbidimetric immunoassay¹¹ using an automated method (Indiko; Thermo Fisher Scientific Inc, Waltham, Massachusetts). The lower limit of quantification of serum amikacin concentration was 0.8 µg/mL and coefficient of variation was <6% over the entire calibration range (1.5–50 µg/mL). CRP assay was performed with a BNII automated system (Dade-Behring Inc, Newark, Delaware). An automated Elecsys (Roche Diagnostics, Rotkreuz, Switzerland) was used to determine serum PCT. All laboratory investigations were done free of charge for all recruited neonates.

PK model building

PK parameters for the study population were estimated by a nonlinear mixed-effects modeling approach using NONMEM version 7.3 (ICON Development Solutions, Dublin, Ireland) and Pirana version 2.8.2 (Pirana Software and Consulting BV). R Software version 3.0.2 and R Package Xpose (R Foundation for Statistical Computing, Vienna, Austria) were used for graphic analysis of model outputs and exploratory covariate analysis. First-order conditional estimation with interaction algorithm was used throughout the model-building process.

The model-building process was done using concentration versus time data after excluding data below the lower limit of quantification. One- and 2-compartment models with linear

Table I
Characteristics of neonates with data for pharmacokinetic modeling (N = 247).

Parameter	Median (range)
Gestational age (wk)	35 (25–44)
Birth weight (kg)	2.3 (0.9–5.2)
Postnatal age (h)	1.23 (0.16–21.75)
Apgar score (5 min)	7 (2–9)
Parameter	n (%)
Preterm (< 37 wk gestation)	131 (53)
Coadministration with aminophylline	93 (38)
Presence of perinatal asphyxia*	52 (21)
Culture positivity†	13 (5)
Sex (M/F)	131/116

* Defined as resuscitation at birth.

† Bacteria isolates include *Streptococcus agalactiae* (n = 3), *Klebsiella pneumoniae* (n = 2), *Escherichia coli* (n = 1), *Serratia odorifera* (n = 1), *Coliform bacillus* (n = 1), *Pantoea sp* (n = 1), *Staphylococcus aureus* (n = 1), *Enterobacter aerogenes* (n = 1), *Streptococcus viridans* (n = 1), and *Burkholderia cepacia* (n = 1).

elimination and zero order input were tested using specific NONMEM subroutines. The 1-compartment model subroutine used was ADVAN1 TRANS2 parameterized as total drug CL and V. The 2-compartment model subroutine used was ADVAN3 TRANS4, parameterized as CL, central compartment volume of distribution (V_1), peripheral compartment volume of distribution (V_2), and intercompartmental CL. A statistical model was developed by assessing between-subject variability (BSV), which was modeled exponentially assuming a log normal distribution. Additive, proportional and combined error models were compared to assess residual error. BSV within the population was assessed by assuming that parameters had a mean of zero and a variance of ω^2 . Residual error was also assumed to have a mean of zero and variance of σ^2 .

The effect of the following covariates, birth weight, gestational age, postnatal age, aminophylline coadministration, gender, blood culture result, presence or otherwise of perinatal asphyxia, and acute phase protein (PCT and CRP) levels on individual PK parameters was assessed by examining parameter-versus-covariate plots. All potential covariates and noncorrelated potential covariates were tested in a linear and power function relationship on the model. Covariates were systematically incorporated into the structural model and retained if they improved fit (backward elimination and forward inclusion).

Initial estimates for variance (ω^2) on BSV (η), and variance (σ^2) on residual errors (ϵ) corresponded to a coefficient of variation of 50%. The main criteria for model comparison were as follows: the likelihood ratio test, represented in NONMEM as a difference in objective function of 3.84, which corresponds to a significance level of < 0.05, decrease in the variance of random effects, goodness of fit plots, and eta-shrinkage.¹²

Table II
Categorization of serum amikacin level in term and preterm neonates after third amikacin dose.*

Neonate	Peak (n = 21)			Trough (n = 25)		
	> 35 $\mu\text{g/mL}$	20–35 $\mu\text{g/mL}$	< 20 $\mu\text{g/mL}$	< 5 $\mu\text{g/mL}$	5–10 $\mu\text{g/mL}$	> 10 $\mu\text{g/mL}$
Term	3/21 (14.3%)	7/21 (33.3%)	11/21 (52.4%)	5/25 (20%)	16/25 (64%)	4/25 (16%)
Preterm	6/28 (21.4%)	10/28 (35.7%)	12/28 (42.9%)	5/36 (13.9%)	22/36 (61.1%)	9/36 (25%)
Comparison of proportions	0.2	0.7	0.2	0.3	0.7	0.1

*P value based on χ^2 test.

* Classification as reported by Sherwin et al.⁴

Model evaluation

The final model was evaluated using goodness of fit plots of observed (DV) versus population-predicted (PRED) and individual-predicted (IPRED) amikacin concentrations. Further evaluation involved use of conditional weighted residuals (CWRES) versus PRED. A bootstrap procedure (n = 1000)¹³ was used to assess the robustness of the final model.

Results

Characteristics of patients

There were 247 neonates of mean (SD) gestational age 35.2 (4.6) weeks, birth weight 2.5 (1.0) kg, and postnatal age 2.01 (2.7) hours, admitted within 24 hours of delivery and whose data (419 concentration time points) were available for inclusion in the PK analysis. Concentrations below the lower limit of quantification (4 time points) were excluded. The treatment period for the recruited neonates ranged from 2 to 7 days. Overall mortality was 8.1%. A summary of patient characteristics is shown in Table I.

Peak and trough amikacin concentration profiles in term versus preterm neonates

The peak amikacin concentration was not statistically different, ($P = 0.5$) between term [17.5 (9.3) $\mu\text{g/mL}$, n = 21] and preterm neonates [19.9 (10.5) $\mu\text{g/mL}$, n = 28]. However, trough amikacin concentration was statistically different between term neonates (n = 25) of mean (SD) gestational age 38.3 (0.9) weeks, and preterm neonates (n = 36) of mean (SD) gestational age of 33.2 (2.5) weeks (6.2 [3.4] vs 9.2 [5.7] $\mu\text{g/mL}$; $P = 0.02$). The trough amikacin serum concentration of 80% of term neonates, and 86.1% of preterm neonates were higher than 5 $\mu\text{g/mL}$. In addition, the peak serum concentration of 52.4% of term neonates, and 42.9% of preterm neonates were lower than 20 $\mu\text{g/mL}$. Proportion of neonates, term and preterm, with peak and trough levels below, within, and above optimal amikacin ranges⁴ is shown in Table II.

Model-building process

The results of PK model development procedure are shown in Table III. The data were best described by a 1-compartment model. PK parameter versus covariate plot showed that birth weight would explain some of the variability in CL and V (Figure 1) and that a power, rather than a linear function of birth weight, correlates better with CL and V. Birth weight as a covariate in the model significantly improved its fit (difference in objective function < 3.84), and the effect of this covariate on CL and V also showed low variance (ω^2) on BSV (Table III). An evaluation of the

Table III
Population pharmacokinetic model development.

Model No.	Model description	Objective function value	Reference Model	Difference in objective function value	Variance in between-subject variability (%) (clearance, volume of distribution)
1	1-compartment (ETA on clearance, volume of distribution)	2232.1	–	–	96.5, 99.7
2	1-compartment, $CL_{TV} = \theta_1 (BW/2.5)^{\theta_2}$	2094.4	1	-137.7	54.6, 92.9
3	1-compartment, $CL_{TV} = \theta_1 (GA/35.3)^{\theta_2}$	2128.6	1	-103.5	64.7, 97
4	1-compartment, $CL_{TV} = \theta_1 (APG5/7.2)^{\theta_2}$	2204.1	1	-27.9	88.6, 90
5	1-compartment, $CL_{TV} = \theta_1$: GRP 0 $CL_{TV} = \theta_2$: GRP1	2161.3	1	-70.8	74.6, 103.5
6	1-compartment, $CL_{TV} = \theta_1$: SEP 0 $CL_{TV} = \theta_2$: SEP 1	2230.8	1	-1.3	96.2, 99.2
7	1-compartment, $CL_{TV} = \theta_1$: ASP 0 $CL_{TV} = \theta_2$: ASP 1	2228.4	1	-3.7	94.3, 100.8
8	1-compartment, $V_{TV} = \theta_1 (BW/2.5)^{\theta_2}$	2148.8	1	-83.3	71.8, 91.9
9	1-compartment, $V_{TV} = \theta_1 (GA/35.3)^{\theta_2}$	2179.0	1	-53.1	101,59.6
10	1-compartment, $V_{TV} = \theta_1 (APG5/7.2)^{\theta_2}$	2217.5	1	-14.6	98.4, 84.1
11	1-compartment, $V_{TV} = \theta_1$: GRP 0 $V_{TV} = \theta_2$: GRP 1	2196.9	1	-35.1	99.1, 81.8
12	1-compartment, $V_{TV} = \theta_1$: SEP 0 $V_{TV} = \theta_2$: SEP 1	2231.7	1	-0.4	96.5, 99.7
13	1-compartment, $V_{TV} = \theta_1$: ASP 0 $V_{TV} = \theta_2$: ASP 1	2229.9	1	-2.1	96.6, 99
14	1-compartment, $CL_{TV} = \theta_1 (BW/2.5)^{\theta_3}$, $V_{TV} = \theta_2 (BW/2.5)^{\theta_4}$	2058.1	2	-36.3	59.5, 54.6
15	1-compartment, $CL_{TV} = \theta_1 (BW/2.5)^{\theta_3}$, $V_{TV} = \theta_2 (BW/2.5)^{\theta_4}$, + Block (η_{CL} , η_V)	2044.4	14	-13.7	58.9, 50.7

θ_1 , θ_2 , θ_3 & θ_4 = Model Parameter Thetas; APG5 = Apgar score at 5 minutes; ASP 0 = no asphyxia; ASP 1 = asphyxia; BW = birth weight; CL_{TV} = Population CL; ETA = variance on between subject variability; GA = gestational age; SEP 0 = negative blood culture; SEP 1 = culture proven pathogenic bacteria; V_{TV} = Population V.

effect of selected clinically important covariates, including gestational age, concurrent administration of amikacin with aminophylline, Apgar score at 5 minutes, gender, results of blood culture (positive or negative), PCT level, CRP level, and presence or otherwise of clinically determined perinatal asphyxia did not significantly improve the model (Table III).

Model 14 compared with the base model (Model 1), showed that the BSV on CL and V reduced by 37% and 45.1%, respectively. Incorporation of a block structure on ω^2 on BSV of CL and V to explain the correlation between these 2 parameters, and the use of proportional error showed a significantly better fit of the model (Model 15).

Model evaluation

Goodness of fit plots, DV versus PRED and IPRED, and CWRES versus PRED, of the final model are shown in Figure 2. Parameter estimates for the final model obtained after bootstrapping are shown in Table IV. From the final model, individual CL (CL_i) and V (V_i) are related by the equations:

$$CL_i = [\theta_1 (BW/2.5)^{\theta_3}] \times \text{EXP}(\eta_{CL_i});$$

$$V_i = [\theta_2 (BW/2.5)^{\theta_4}] \times \text{EXP}(\eta_{V_i})$$

Shrinkage of this final model was 14% for η_{CL} and 30% for η_V .

The mean half-life (pseudo SD) of amikacin based the on 1-compartment open model, obtained as $\ln(2) / CL/V$, was 13.2 (2.2) hours.

Discussion

The study was done to generate data on, and describe the PK of amikacin in, a low-resource setting where amikacin is part of the first-line empirical treatment for suspected neonatal sepsis. The design of the study, characteristics of the population, and therapeutic practice of the setting also allowed an evaluation of the effect of clinically important covariates, including coadministration of aminophylline, a drug that is used in preterm neonates in study settings, on amikacin PK.

The data showed that the trough concentration of the majority of neonates (80% term and 86.1% preterm) were higher than the recommended 5 $\mu\text{g/mL}$, and peak concentrations (52.4% term and 42.9% preterm) were lower than the recommended 20 to 30 $\mu\text{g/mL}$ range suggested as optimal for multiple therapeutic regimens of amikacin.⁴ A drug-monitoring study conducted in term and preterm Singaporean neonates reported relatively higher mean trough serum concentrations: 9.97 (5.67) $\mu\text{g/mL}$ and 14.4 (9.28) $\mu\text{g/mL}$,

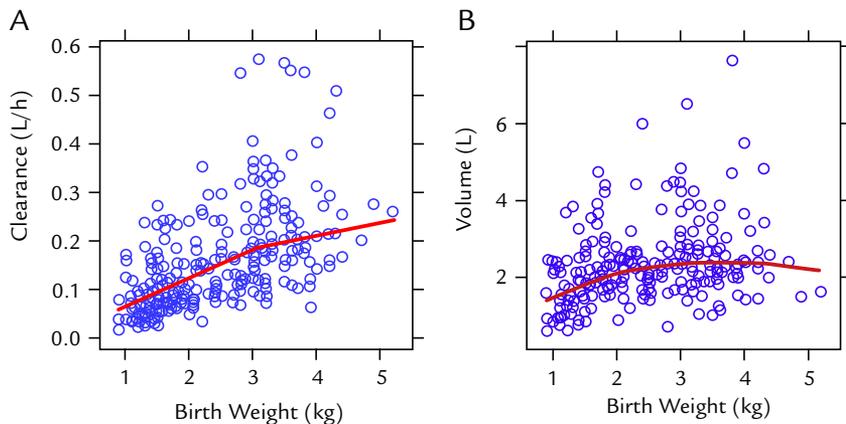


Figure 1. (A) Clearance derived from the base model versus birth weight. (B) Volume derived from the base model versus birth weight.

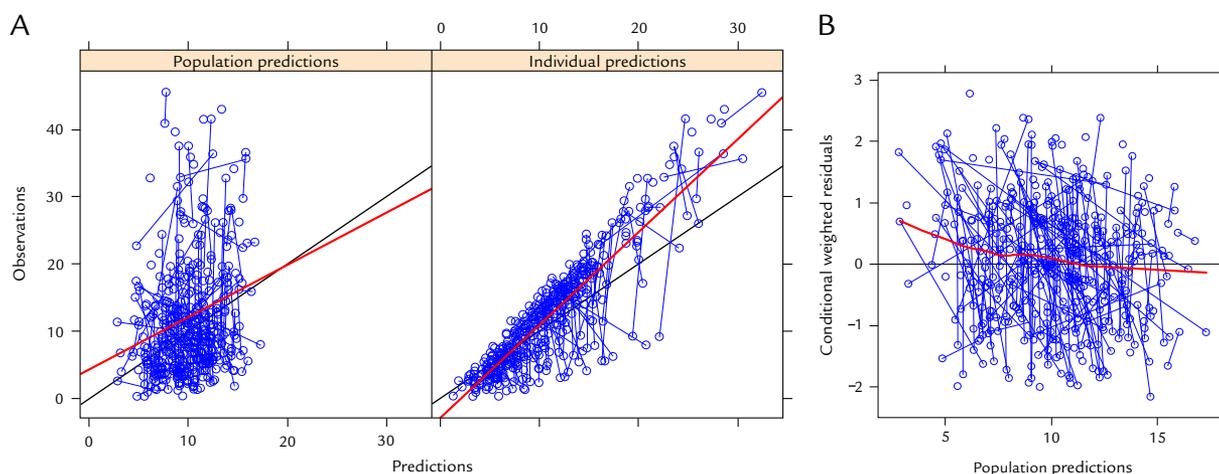


Figure 2. (A) Observed data versus population and individual predictions from the final model. (B) Conditional weighted residuals versus population predictions plot.

respectively.¹⁴ In the current study, neither the optimal peak level nor trough level was reached in a majority of neonates. We were unable to find previous reports on amikacin PK from Ghana or a similar sub-Saharan Africa setting in the published literature. The data obtained from the present study therefore emphasize the need for individualized monitoring of patients on amikacin therapy. In particular, a higher dose (improved peak) and longer intervals (lower trough) may be needed to optimize amikacin dosing in study settings.⁴

The concentration–time data of amikacin among neonates in the current study best fit a 1-compartment model. This is consistent with other studies that have reported a 1-compartment model for amikacin disposition in neonates,^{3–5} but different from others that reported a 2-compartment model for amikacin disposition among neonates.¹⁵ The differences in compartmentalization between the present and other studies may be due to differences in sample schedules or postnatal age differences. Additionally, data from this study showed shrinkage of 14% for η_{CL} and 30% for η_V , which is most likely due to the sparse sampling technique. It has been reported that when shrinkage is higher than 20%, the diagnostic plots based on individual predictions or residuals could be misleading.¹⁶

From the final model obtained in this study, amikacin CL of a population with mean birth weight of 2.1 kg will be 0.058 L/h/kg, which is comparable with the reported CL for a population with a similar body weight profile reported elsewhere (0.048 L/h/kg).⁵ Similarly, amikacin CL of a population with a mean birth weight of 1.38 kg will be 0.85 mL/min/kg, and this is comparable to the CL in the report by Kenyon et al¹⁷ (0.84 mL/min/kg) for a population with a mean body weight of 1.38 kg.

The data from the present study showed birth weight to be the most important determinant of amikacin CL. Aminoglycoside CL correlates well with glomerular filtration rate,¹⁸ whereas body size

(related to weight) and renal maturation (related to gestational age) also correlate with glomerular filtration rate.¹⁹ Introducing birth weight as an explanatory covariate reduced BSV of amikacin CL, and explained approximately 42% of the observed variability. Although unexplained variability could be due to differences in disease state and associated comorbidities (eg, birth asphyxia), these factors did not appear to have an influence on the model when introduced as covariates in this study. Although some studies have reported that gender, postnatal age, and gestational age (reported as postconception age or postmenstrual age in other studies) may influence amikacin CL in neonates,^{4–6} these covariates did not appear to influence CL in the current study. Furthermore, the inclusion of only participants in the first 24 hours of life precludes conclusions being drawn about the effect of postnatal age.

Birth weight was also found to be the only determinant of amikacin V in the current study. This is to be expected because aminoglycosides (being hydrophilic compounds) will generally exhibit a relatively larger V in neonates than in adults,²⁰ partly because of the higher percentage of total body water in neonates. Because aminoglycosides are distributed in extracellular fluid (which positively correlates with total body water), and total body water correlates positively with body weight, the determining effect of birth weight on amikacin distribution found in this study is consistent with these considerations. An effect of gestational age would have been expected because preterm infants have higher percent total body water than term infants, but the lack of improvement of the fit could also be ascribed to the close association between birth weight and gestational age.

The data from the present study suggest that the V of a population of average birth weight of 2.1 kg will equate to 1.15 L/kg. This is relatively large compared with 0.434 L/kg reported by Botha et al⁵ with the same average body weight. This

Table IV

Estimates of final population pharmacokinetic model.

Parameter	Unit	Estimate	Relative standard error (%)	After bootstrap (mean [95% CI])
Population clearance	L/h	0.153	4	0.153 (0.139–0.167)
Population volume	L	2.94	9	2.97 (2.5–3.47)
Power function on weight with clearance		1.31	8	1.32 (1.11–1.55)
Power function on weight with volume		1.18	16	1.18 (0.737–1.53)
Between-subject variability				
Clearance	%	58.9	7	58.0 (47.8–67.9)
Volume of distribution	%	50.7	28	50.8 (31.0–84.2)
Residual variability				
Proportional	%	46.1	4.5	46.1 (41.4–51.0)

variation may be due to postnatal age differences at the start of drug treatment, with a mean postnatal age of 2.01 hours in this study versus 3.1 days in the study by Botha et al.⁵ This finding is also consistent with the possibility of a decrease in V with increasing postnatal age related to the progressive decrease in extracellular fluid volume (postnatal weight loss) within the first few days of life.²¹

The V of neonates obtained from the final model of this study was large (1.14 L/kg) compared with a study with comparable average weight.²² However, the difference could be ascribed to differences in postnatal ages between the 2 studies. Furthermore, the half-life obtained for neonates in the present study for a 2.1 kg mean body weight population, 13.7 hours, was longer than the 6.4 hours reported by Botha et al.⁵ The longer calculated half-life obtained in this study could be a consequence of the large V of amikacin obtained in this population.

Data from this study showed no overall significant effect of coadministration of aminophylline on amikacin PK characteristics. However, neonates who received aminophylline tended toward lower birth weights (and younger gestational ages), and this fact could partly explain the lack of effect, because birth weight explained some variability in amikacin CL and distribution.

Sepsis is characterized by vasodilatation and increased vascular permeability.²³ The resulting increase in permeability is responsible for a fluid shift,²⁴ and may be consistent with a high drug V. Introduction of the covariate positive blood culture (13 out of 247 patients) into the model did not have an influence on the V of amikacin. The lack of effect may be due to variable sensitivity of blood cultures in neonates with sepsis.²⁵

Conclusions

The findings from this study showed low peak and high trough amikacin concentrations among neonates compared with those from other settings. The calculated half-life and V of neonates also differed from those reported in other studies (non-African population). Introduction of aminophylline coadministration as a covariate had no influence on amikacin PK characteristics. These findings suggest that a higher dose and extended interval, would be required to optimize amikacin dosing in this population. Additionally, dosing in infants should incorporate allometric or age-maturational rather than linear functions.

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Conflicts of Interest

The authors have indicated that they have no conflicts of interest regarding the content of this article.

References

- [1] Yurdakok M. Antibiotic use in neonatal sepsis. *Turk J Pediatr.* 1998;40(1):17–33.
- [2] Houghton JL, Green KD, Chen W, et al. The future of aminoglycosides: The end or renaissance? *ChemBiochem.* 2010;11(7):880–902.
- [3] Allegaert K, Anderson BJ, Cossey V, et al. Limited predictability of amikacin clearance in extreme premature neonates at birth. *Br J Clin Pharmacol.* 2006;61(1):39–48.
- [4] Sherwin CMT, Svahn S, Van der Linden A, et al. Individualized dosing of amikacin in neonates: a pharmacokinetic/pharmacodynamic analysis. *Eur J Clin Pharmacol.* 2009;65(7):705–13.
- [5] Botha JH, du Preez MJ, Miller R, Adhikari M. Determination of population pharmacokinetic parameters for amikacin in neonates using mixed-effect models. *Eur J Clin Pharmacol.* 1998;53(5):337–41.
- [6] Treluyer JM, Merle Y, Tonnelier S, Rey E, Pons G. Nonparametric population pharmacokinetic analysis of amikacin in neonates, infants and children. *Antimicrob Agents Chemother.* 2002;46(5):1381–7.
- [7] Rea RS, Capitano B, Beis R, Bigos KL, Smith R, Lee H. Suboptimal aminoglycoside dosing in critically ill patients. *Ther Drug Monit.* 2008;30(6):674–81.
- [8] Osswald H, Schnermann J. Methylxanthines and the kidney. *Handb Exp Pharmacol.* 2011;200:391–412.
- [9] Enweronu-Laryea CC, Newman MJ. Changing pattern of bacterial isolates and antimicrobial susceptibility in neonatal infections in Korle-Bu Teaching Hospital, Ghana. *East Afr Med J.* 2007;84(3):136–40.
- [10] Ballard JL, Khoury JC, Wedig K, Wang L, Eilers-Walsman BL, Lipp R. New Ballard Score, expanded to include extremely premature infants. *J Pediatr.* 1991;119(3):417–23.
- [11] Newman DJ, Henneberry H, Price CP. Particle enhanced light scattering immunoassay. *Ann Clin Biochem.* 1992;29(Part 1):22–42.
- [12] Savic RM, Karlsson MO. Importance of shrinkage in empirical Bayes estimates for diagnostics: problems and solutions. *AAPS J.* 2009;11(3):558–69.
- [13] Bauer RJ. NONMEM Users Guide. Introduction to NONMEM 7.3.0. *Icon Development Solutions, Hanover, MD.* 2014.
- [14] Khan D, Khan F. Therapeutic drug monitoring of amikacin in preterm and term infants. *Singapore Med J.* 2009;50(5):486–9.
- [15] Smits A, De Cock RFW, Allegaert K, et al. Prospective evaluation of a model-based dosing regimen for amikacin in preterm and term neonates in clinical practice. *Antimicrob Agents Chemother.* 2015;59(10):6344–51.
- [16] Mould D, Upton R. Basic concepts in population modeling, simulation, and model-based drug development—part 2: introduction to pharmacokinetic modeling methods. *CPT: Pharmacometrics Syst Pharmacol.* 2013;2:e38.
- [17] Kenyon CF, Knoppert DC, Lee SK, et al. Amikacin pharmacokinetics and suggested dosage modifications for the preterm infant. *Antimicrob Agents Chemother.* 1990;34(2):265–8.
- [18] Koren G, James A, Perlman M. A simple method for the estimation of glomerular filtration rate by gentamicin pharmacokinetics during routine drug monitoring in the newborn. *Clin Pharmacol Ther.* 1985;38(6):680–5.
- [19] Weber W, Kewitz G, Rost KL, et al. Population kinetics of gentamicin in neonates. *Eur J Clin Pharmacol.* 1993;44:523–5.
- [20] Warner A. Drug use in the neonate: interrelationships of pharmacokinetics, toxicity, and biochemical maturity. *Clin Chem.* 1986;32:721–7.
- [21] Bauer K, Vermold H. Postnatal weight loss in preterm neonates less than 1500 g is due to isotonic dehydration of the extracellular volume. *Acta Paediatr Scand.* 1989;360:37–42.
- [22] Sardemann H, Colding H, Hendel J, et al. Kinetics and dose calculations of amikacin in the newborn. *Clin Pharmacol Ther.* 1976;20(1):59–66.
- [23] Hosein S, Udy AA, Lipman J. Physiological changes in the critically ill patient with sepsis. *Curr Pharm Biotechnol.* 2011;12(12):1991–5.
- [24] Gosling P, Sanghera K, Dickson G. Generalized vascular permeability and pulmonary function in patients following serious trauma. *J Trauma.* 1994;36:477–81.
- [25] Brown DR, Kutler D, Rai B, Chan T, Cohen M. Bacterial concentration and blood volume required for a positive blood culture. *J Perinatol.* 1995;15(2):157–9.