An Evaluation of Gentamicin, Tobramycin, and Amikacin Pharmacokinetic/Pharmacodynamic Parameters in HIV-Infected Children

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BACKGROUND The purpose of the study was to calculate gentamicin, tobramycin, and amikacin pharmacokinetic parameters in HIV-infected children and compare conventional multiple daily aminoglycoside dosing to once-daily aminoglycoside (ODA) dosing in attaining peak serum aminoglycoside concentrations (SACs) to minimum inhibitory concentration for 90% of isolates (MIC₉₀) ratios ≥ 8 against selected pathogens.

METHODS Patients (<13yrs) receiving an aminoglycoside (15 patients/drug) in the treatment of gram-negative infection were studied. Intravenous gentamicin/ tobramycin were administered at a dose of 6–7.5 mg/kg/day and amikacin at 20–30 mg/kg/d divided every 8 hrs. Peak and trough serum concentrations were obtained and pharmacokinetic parameters were calculated utilizing a one-compartment steady-state model. SACs for gentamicin/tobramycin dosed at 7.5 mg/kg and amikacin at 22.5 mg/kg once daily were simulated using the calculated pharmacokinetic parameters. Peak SAC:MIC₉₀ ratios were calculated for each dosing method.

RESULTS Mean pharmacokinetic parameters were within 1 standard deviation of reported literature values. Mean peak:MIC₉₀ ratio of ≥ 8 was attained only for *Klebsiella* species (MIC₉₀ 1 μ g/mL) using conventional gentamicin/tobramycin dosing whereas mean amikacin peak:MIC₉₀ ratios ≥ 8 were reached for *Klebsiella*, *Enterobacter*, and *Citrobacter* species (MIC₉₀ 4 μ g/mL). ODA simulations predicted gentamicin/tobramycin peak:MIC₉₀ ratios ≥ 8 in 100% of patients with an organism-MIC₉₀ of 1 μ cg/mL and in 80% of patients with an organism-MIC₉₀ of 2 μ g/mL. Amikacin peak:MIC₉₀ ratio ≥ 8 was predicted for 93% of patients with an organism-MIC₉₀ of 4 μ g/mL but in only 27% if the MIC₉₀ was 8 μ g / mL.

CONCLUSION Optimal peak SAC:MIC₉₀ ratios using conventional aminoglycoside dosing were predicted only for organisms with low MIC₉₀ values. ODA dosing represents an option for improving pharmacodynamic outcomes.

KEYWORDS: aminoglycoside, gentamicin, tobramycin, amikacin, HIV, pharmacokinetics, pharmacodynamics, pediatrics

J Pediatr Pharmacol Ther 2003;8:274-82

Abbreviations

HIVN	HIV Nephropathy
MDA	Multipledaily aminoglycoside
MIC	Minimum Inhibitory Concentration
ODA	Once-daily aminoglycoside
PAE	Post-Antibiotic effect

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INTRODUCTION

Serious bacterial infections are frequently encountered in human immunodeficiency virus (HIV) - infected children. A retrospective review of 680 HIV-infected children from 1980 to 1997 at our institution reported a 10.6% incidence of gram-negative bacillary bacteremia in this population.¹ The most frequently isolated organisms causing gram-negative bacteremia were *Pseudomonas aeruginosa* (26.4%), non-typhoidal

Salmonella (15.3%), *Escherichia coli* (15.3%), *Haemophilus influenzae* (12.5%), *Klebsiella pneumoniae* (9.7%), *Citrobacter freundii* (6.9%), and *Enterobacter* species (5.5%).¹ Similarly, the Pediatric Spectrum of Disease Project reported *Pseudomonas aeruginosa*, *Pseudomonas* (species unspecified), *Klebsiella pneumoniae*, and *Escherichia coli* as the most frequently isolated aerobic gram-negative organisms in pediatric HIV-positive patients.²

The increasing incidence of resistance in nosocomial gram-negative bacilli bacteremia has led to an increased use of aminoglycosides in HIV-infected children at our institution.³ Since a 43% overall case-fatality rate for gram-negative bacillary bacteremia has been reported in HIV-infected children,¹ it is essential to promptly optimize the aminoglycoside regimen when employed in the treatment of a serious gram-negative bacterial infection in this population, especially patients with advanced HIV disease who are profoundly immunosuppressed (Clinical Category C HIV disease and Immunologic Category 3).⁴

The purpose of this study was to calculate aminoglycoside pharmacokinetic parameters and compare the conventional multiple daily aminoglycoside (MDA) administration approach to a once-daily aminoglycoside (ODA) dosing in attaining peak serum aminoglycoside concentrations (SACs) to minimum inhibitory concentration for 90% of isolates (MIC_{90}) ratios ≥ 8 against commonly isolated gram-negative bacilli in HIV-infected children.

MATERIALS AND METHODS

Study patients. The authors evaluated the pharmacokinetic parameters of 45 consecutive HIV-infected children who received an aminoglycoside and who also met inclusion criteria. The study was prospectively performed as part of routine patient care in patients receiving an aminoglycoside (i.e., gentamicin, tobramycin, or amikacin) for suspected or documented serious systemic gram-negative infection. Data were collected and analyzed for the first 15 evaluable patients on each of the three medications. All patients were admitted to the Pediatric Infectious Diseases/Special Immunology Service at the University of Miami/Jackson Children's Hospital.

Patients included in the study met the following criteria: 1) documented HIV-infection, 2) <13 years of age, 3) serum creatinine (SCr) within normal limits for age,⁵ 4) stable renal function as described by <0.3 mg/dL change in SCr from initial normal value for age, and 5) normal fluid status as determined by patient fluid balance, urine specific gravity, weight change, and/or physician clinical impression. Patients were allowed entry into the study for only one treatment course. Exclusion criteria included the following: 1) patient age ≥ 13 years of age, 2) serum creatinine concentration above normal upper limit for age, 3) unstable renal function as defined by a change of ≥ 0.3 mg/dL from baseline normal value for age, 4) patient dehydration or fluid overload as determined by patient fluid balance, urine specific gravity, weight change, and/or physician clinical assessment, 5) serum aminoglycoside concentration drawn prior to third dose of scheduled regimen, 6) incomplete documentation of medication administration time and/or sample collection time, and 7) prior entry into the study.

The University of Miami's Medical Sciences Subcommittee for the Protection of Human Subjects approved the study and informed consent was deemed unnecessary.

Patient Data. Patient demographic data (i.e., age, weight, and gender) were collected for each patient. Each patient's HIV classification, number of concurrent potentially nephrotoxic medications, presence of HIV nephropathy (HIVN), most recent absolute CD4 count and CD4 percent, nutritional status, aminoglycoside dose (mg/kg), and dosing interval were recorded. HIVN was defined as persistent proteinuria. In the absence of a urinary tract infection, persistent proteinuria was defined as a urine dipstick reading of $\geq 1+$ on more than one occasion that was two weeks apart or was identified by a urine protein-creatinine ratio of ≥ 0.2 in a random urine sample.⁶ Patients were classified as growth failure if their nutritional status met the definition of failure to thrive or wasting syndrome.⁴

Serum electrolytes, blood urea nitrogen (BUN), and serum creatinine (SCr) concentrations were evaluated within 72 hours of the collected serum aminoglycoside concentrations (SACs). Serum albumin levels were drawn within 1 week of the SACs.

Dosing and Sample Collection. The aminoglycoside was administered intravenously over 30 minutes via a syringe pump (Medfusion 2001, Medex, Inc., Dublin, OH) at an initial dose of 6–7.5 mg/kg/day divided every 8 hours for gentamicin and tobramycin and 20–30 mg/kg/day divided every 8 hours for amikacin. Steady-state peak and trough SACs were drawn after a minimum of three doses. Peak SACs were obtained 30 minutes after completion of the infusion and trough SACs within 30 minutes of the next scheduled dose. Pharmacokinetic parameters were reported for the first set of evaluable steady-state concentrations. Nurses in-serviced on the study ensured that the standard aminoglycoside administration protocol was followed and that nurses documented the exact dates and times of aminoglycoside administration, infusion duration, and time of serum sample collection on the institution's Therapeutic Drug Monitoring Form. The serum samples were delivered to the laboratory within 30 minutes of collection and were analyzed by fluorescence

$$k_e = \frac{(\ln C_{pk} - \ln C_{tr})}{\Delta t}$$

where k_e = elimination rate constant (h^{-1})

C_{pk} = measured serum peak concentration ($\mu\text{g/mL}$)

C_{tr} = measured serum trough concentration ($\mu\text{g/mL}$)

Δt = time interval between C_{pk} and C_{tr} (h)

$$t_{1/2} = \frac{0.693}{k_e}$$

where $t_{1/2}$ = half-life (h)

$$V_d = \frac{[D] \cdot (1 - e^{(-k_e \cdot t_{inf})}) \cdot e^{(-k_e \cdot t_{pk}^0)}]{(C_{pk})(k_e)(t_{inf})} \cdot [1 - e^{(-k_e \cdot T)}]}$$

where V_d = volume of distribution (L/kg)

D = drug dose (mg/kg)

T = dosing interval (h)

t_{inf} = time of infusion (h)

t_{pk}^0 = time interval between end of infusion and time of C_{pk} sampling (h)

$$CL = k_e \cdot V_d$$

where CL = plasma clearance (L/h/kg)

polarization immunoassay (AxSYM Gentamicin, AxSYM Tobramycin, and TDx/TDxFLx Amikacin, Abbott Laboratories, Abbott Park, IL).

The following equations employing a one-compartment model were utilized in the calculation of the pharmacokinetic parameters.⁷

Utilizing patient-specific pharmacokinetic parameters, simulations were conducted to estimate the serum concentrations attainable by adopting a once-daily aminoglycoside (ODA) dosing strategy. ODA simulations were conducted for gentamicin and tobramycin dosed at 7.5mg/kg and for amikacin at 22.5mg/kg every 24 hours, which is equivalent to the recom-

$$C_{pk}^{Pred} = \frac{[D^{des} \cdot (1 - e^{(-k_e \cdot t_{inf})})]}{(V_d \cdot k_e \cdot t_{inf}) \cdot (1 - e^{(-k_e \cdot T)})}$$

$$C_{tr}^{Pred} = C_{pk}^{Pred} \cdot e^{[-k_e \cdot (T - t_{inf})]}$$

C_{pk}^{Pred} = predicted peak plasma concentration ($\mu\text{g/mL}$)

C_{tr}^{Pred} = predicted trough plasma concentration ($\mu\text{g/mL}$)

D^{des} = desired dose (mg/kg)

mended total daily dose for conventional MDA administration for the respective agents.⁸ Peak SACs (extrapolated to the end of the infusion) and trough SACs (immediately prior to the next dose) were simulated employing the following equations.⁷

The peak SACs to MIC_{90} (minimum inhibitory concentration to inhibit 90% of the isolates) ratio was calculated for the most frequently isolated aerobic gram-negative organisms in pediatric HIV-positive patients. Pharmacodynamic evaluations (i.e., Peak: MIC_{90} ratio) were performed for MDA strategies and ODA simulations.

Data Analysis. Statistical analyses were performed using SAS (SAS Institute, North Carolina). Descriptive statistics were used to characterize the data. In the case of continuous variables, the normality of the distribution was assessed prior to any statistical analysis. Since some of the continuous variables in this study were found to be fairly skewed, both parametric techniques and their non-parametric counterparts were used in the analyses. The Wilcoxon rank test and the t -test were used to compare two groups. Whenever appropriate, means $\pm$ one stan-

Figure 1. Conventional Aminoglycoside Dosing: Ratio of Peak Aminoglycoside Concentration to MIC₉₀ (Peak:MIC₉₀) Value for Commonly Isolated Nosocomial Gram Negative Bacilli in HIV Positive Children

MIC₉₀=Minimum Inhibitory Concentration for 90% of Isolates. Calculated aminoglycoside pharmacokinetic parameters from conventional aminoglycoside dosing are reported on Table 3.

MIC₉₀ values for commonly isolated nosocomial gram-negative bacilli in HIV-infected children are reported on Table 4.

■ = Gentamicin
 ■ = Tobramycin
 □ = Amikacin

dard deviation (SD) are reported. Also, although original data are reported throughout, the stated P values correspond to the most appropriate statistical technique used. A P value <0.05 was considered statistically significant.

RESULTS

Forty-five consecutive patients (15 receiving gentamicin, 15 receiving tobramycin, and 15 receiving amikacin) meeting all entry criteria were included in the study. Overall, 21 of 45 patients were male (46.7%), and 43 of 45 (95.6%) were black. Forty-four of 45 patients were classified as CDC Category C (severe symptoms), and 42 of 45 were in Immunologic Category 3 (profound immunosuppression).⁴ Fourteen of 45 patients carried the diagnosis of HIV-nephropathy (HIVN), and 11 total patients were proteinuric, but not in the nephrotic range. Thirty-nine patients were classified as growth failure (30 failure to thrive, 9 wasting syndrome), and 6 met the definition of normal nutritional status. Table 1 stratifies by gender, racial distri-

Figure 2. Once Daily Aminoglycoside Dosing: Ratio of Peak Aminoglycoside Concentration to MIC₉₀ (Peak:MIC₉₀) Value for Commonly Isolated Nosocomial Gram Negative Bacilli in HIV Positive Children

MIC₉₀= Minimum Inhibitory Concentration for 90% of Isolates. Simulated mean peak concentrations for once-daily aminoglycoside dosing were as follows: gentamicin=21.18 µg/mL; tobramycin= 21.41 µg/mL; amikacin= 59.4 µg/mL. The dose of gentamicin and tobramycin used in the simulations was 7.5 mg/kg IV q 24-hr and amikacin 22.5 mg/kg IV q 24-hr, given as a 30-min infusion.

MIC₉₀ values for commonly isolated nosocomial gram-negative bacilli in HIV-infected children are reported on Table 4.

■ = Gentamicin
 ■ = Tobramycin
 □ = Amikacin

bution, and clinical data in relation to the specific aminoglycoside administered to the patient.

Mean±SD age and weight for all patients were 6.36±3.22 years and 17.01±15.6 kg, with a median of 6 years and 15.6 kg, respectively. Average absolute CD4 count and CD4 percentage were 203 cells/mm³ and 6.4% with corresponding median values of 16.5 cells/mm³ and 2%, respectively. Mean values for blood urea nitrogen (BUN), serum creatinine concentration, serum albumin level, and absolute neutrophil count were within normal limits for age. Patients received an average of 0.69±0.97 (Range 0–4) concurrent nephrotoxic agents. A synopsis of patient demographic and laboratory data stratified per patient group was included in Table 2.

Table 3 summarizes the dosing requirements and pharmacokinetic parameters per patient group in our cohort. The median dosing regimen to achieve SACs in the reference range (i.e., gentamicin/tobramycin peaks=4–12 µg/mL and troughs=0.5–2 µg/mL; amikacin peaks= 20–30

Table 1. Patient Gender, Racial Distribution, and Clinical Data

Characteristic	Patient Group		
	Gentamicin n (%)	Tobramycin n (%)	Amikacin n (%)
Gender (Males)	9 (60)	4 (26.7)	8 (53.3)
Race			
Black	15 (100)	14 (93.3)	14 (93.3)
White		1 (6.7)	1 (6.7)
CDC Classification			
C3	13 (86.7)	13 (86.7)	15 (100)
C2	2 (13.3)	1 (6.67)	
B3		1 (6.67)	
HIV Nephropathy	6 (40)	4 (26.7)	4 (26.7)
Proteinuria	4 (26.7)	2 (13.3)	5 (33.3)
Nutritional Status			
Growth Failure	13 (86.7)	13 (86.7)	13 (86.7)
Normal	2 (13.3)	2 (13.3)	2 (13.3)

µg/mL and troughs <10 µg/mL)⁸ was 2.56, 2.5, and 10 mg/kg/dose every 8 hours for the gentamicin, tobramycin, and amikacin group, respectively, using the conventional MDA approach. The mean values for elimination rate constant (Ke), half-life ($t_{1/2}$), volume of distribution (Vd) and plasma clearance (CL) were within 1 standard deviation of those reported in the literature for other pediatric populations.⁹⁻¹⁴

Specific factors that may affect aminoglycoside clearance were identified and stratified according to the specific aminoglycoside administered.^{6,7} Statistically sig-

nificant differences were not identified for any of the aminoglycosides evaluated upon stratification of pharmacokinetic parameters by patient age groups (patient age > median versus age ≤ median value), growth failure versus nutritionally normal patients, or presence of HIVN as a diagnosis (data not shown); however, the limited number of patients per strata was small, thus limiting comparative value of such analyses. Statistical analyses on continuous variables are limited to the above paragraph. The tables are comprised of simple descriptive statistics.

Table 4 lists the minimum concentrations re-

Table 2. Patient Demographic and Laboratory Data

	Medication Group		
	Gentamicin	Tobramycin	Amikacin
Age (yrs)	5.64±3.46 (5) [0.54–12]	6.97±3.45 (7) [0.5–12]	6.47±2.8 (6) [2–12]
Weight (kg)	15.78±6.78 (14) [4.73–28.9]	18.12±9.03 (15.6) [3.3–42]	17.13± 6.54 (17) [9–35]
Absolute CD4 Count (cells/mm ³)	328 ±679 (10) [2–2,316]	181±381 (42.5) [2–1,406]	101±222 (15) [2–815]
CD4 (%)	6.47±10.5 (2) [1–38]	8.47±10.6 (5) [0–34]	4.27±6.96 (0) [0–26]
BUN (mg/dL)	9.4±6.33 (6) [3–24]	10.07±4.86 (12) [2–20]	8.4±4.12 (8) [4–18]
Serum Creatinine (mg/dL)	0.41±0.12 (0.4) [0.2–0.6]	0.46±0.19 (0.4) [0.3–0.9]	0.39±0.09 (0.4) [0.2–0.5]
Serum Albumin (g/dL)	3.13±0.78 (3.1) [1.4–4.4]	3.21± 0.53 (3.4) [2.1–4]	3.31±0.75 (3.5) [1.7–5]

mean±SD (median) [range]

Table 3. Aminoglycoside Pharmacokinetic Parameters in HIV-Infected Children

	Medication Group		
	Gentamicin (n=15)	Tobramycin (n=15)	Amikacin (n=15)
Dose (mg/kg/dose)	2.74±0.51 (2.56) [1.97–4.2]	2.58±0.52 (2.5) [1.67–4]	10.61±1.78 (10) [8.56–15.93]
Interval (hr)	8.13±1.19 (8) [6–12]	8±0 (8) [8–8]	7.87±0.52 (8) [6–8]
Peak SAC (µg/mL)	8.3±2.43 (7.9) [4.7–12.8]	7.92±2.7 (7.7) [3.9–13.1]	29.12±7.65 (28.4) [17.1–43.8]
Trough SAC (µg/mL)	0.79±0.78 (0.5) [0.1–3]	0.74±0.49 (0.6) 0.2–1.9	1.63±0.88 (1.3) [0.4–3.4]
Ke (hr ⁻¹)	0.37±0.13 (0.35) [0.13–0.62]	0.34±0.09 (0.37) [0.18–0.46]	0.40±0.07 (0.39) [0.31–0.54]
t _{1/2} (hr)	2.21±1.05 (1.97) [1.12–5.17]	2.23±0.71 (1.88) [1.51–3.75]	1.75±0.29 (1.77) [1.29–2.21]
Vd (L/kg)	0.35±0.1 (0.32) [0.23–0.56]	0.36±0.15 (0.32) [0.18–0.76]	0.37±0.12 (0.33) [0.24–0.74]
CL (L/hr/kg)	0.12±0.05 (0.12) [0.04–0.19]	0.11±0.03 (0.11) [0.07–0.17]	0.15±0.04 (0.15) [0.08–0.26]

SAC=serum aminoglycoside concentration; mean±SD (median) [range]

quired to inhibit 90% of the isolates (MIC₉₀) for commonly isolated gram-negative bacilli in HIV-infected children.¹⁵ MIC₉₀ data for *Salmonella* species and *Shigella* species were not reported as National Committee for Clinical Laboratory Standards (NCCLS) guidelines warn against reporting aminoglycosides susceptibilities, stating that this antibiotic class may appear active in vitro but may not be clinically effective against these pathogens.¹⁶ Additionally, MIC₉₀ values for *Haemophilus influenzae* were not reported. Since the introduction of the *Haemophilus influenzae* (Hib) conjugate vaccine in 1990,¹ there has been an absence of invasive disease attributed to this organism in HIV-infected children at our institution.

Figure 1 compares the ratio of mean peak serum aminoglycoside concentration (Table 3) to the reported MIC₉₀ (Table 4) attained by the conventional MDA dosing strategy employed in this study. Using the MDA method, a mean peak:MIC₉₀ ratio of ≥8 was achieved in 47% and 40% of gentamicin and tobramycin recipients, respectively, for organisms with an MIC₉₀ of 1 µg/mL (i.e., *Klebsiella* species). Additionally, only

one third of amikacin recipients in the MDA group attained the target ratio versus organisms with an MIC₉₀ of 4 µg/mL (i.e., *Klebsiella* species, *Enterobacter* species, and *Citrobacter* species).

Utilizing patient-specific pharmacokinetic parameters calculated from the conventional MDA approach, the simulated peak SACs for once-daily aminoglycoside (ODA) dosing method were 21.18±5.35 µg/mL for gentamicin, 21.41±6.96 µg/mL for tobramycin, and 59.4±14.21 µg/mL for amikacin. The predicted trough levels were 0.11±0.34 µg/mL, 0.04±0.06 µg/mL, and 0.01 ± 0.01 µg/mL for gentamicin, tobramycin, and amikacin, respectively.

Figure 2 illustrates the mean peak:MIC₉₀ ratios for the simulated once daily aminoglycoside (ODA) regimens. Utilizing the ODA method, gentamicin and tobramycin peak:MIC₉₀ ratios ≥8 were predicted for 100% of patients infected with organisms with a reported MIC₉₀ value of 1 µg/mL and in 80% when the organisms' MIC₉₀ was 2 µg/mL; however, at the NCCLS susceptibility breakpoint of 4 µg/mL for gentamicin and tobramycin against *E coli*, *P aeruginosa*, *Klebsiella* species, *Citrobacter* species, and *Enterobacter* spe-

Table 4. Minimum antibiotic concentrations required to inhibit 90% of the isolates (MIC₉₀)

Organism	Gentamicin MIC ₉₀ (μ g/mL)	Tobramycin MIC ₉₀ (μ g/mL)	Amikacin MIC ₉₀ (μ g/mL)
Klebsiella sp.	1	1	4
Enterobacter sp.	2	2	4
Citrobacter sp.	2	2	4
Escherichia coli	2	2	8
Pseudomonas aeruginosa	8	2	8

MIC₉₀ data as reported in reference 15

NCCLS susceptibility breakpoints for the above organisms are 4 μ g/mL for gentamicin/tobramycin and 16 μ g/mL for amikacin as reported in reference 16

cies,¹⁶ no gentamicin patient and only 7% of patients on tobramycin were predicted to achieve a ratio ≥ 8 . Similarly, amikacin peak:MIC₉₀ ratio ≥ 8 is predicted for 93% of patients infected with an organism with an MIC₉₀ of 4 μ g/mL but only in 27% of patients if the MIC₉₀ is 8 μ g/mL.

DISCUSSION

HIV-infected children have increased susceptibility to serious bacterial infections caused by gram-negative bacilli, particularly those with severe HIV infection (Category C) and/or profound immunosuppression (Immunologic Category 3).¹ In this population, rapidly optimizing antimicrobial therapy is crucial. Hence, this study evaluated the aminoglycoside pharmacokinetic parameters of HIV-infected children and estimated the dosing requirements necessary to achieve an optimal pharmacodynamic profile.

Although the patients in this study were initiated on conventional, multiple daily aminoglycoside (MDA) dosing, once-daily aminoglycoside (ODA) administration in pediatrics has been increasingly reported.^{9,11,14,17-26} ODA therapy takes advantage of three pharmacodynamic properties of aminoglycosides: 1) concentration-dependent bactericidal activity, 2) postantibiotic effect, and 3) adaptive resistance.²⁷⁻

³⁰ Concentration dependent bactericidal activity means that bacterial eradication increases as the drug concentration rises. A ratio of peak aminoglycoside concentration to minimum inhibitory concentration (MIC) of the organism of at least 8–10 is accepted as optimal.^{27,29,30} Secondly, ODA results in time periods during the

dosing interval whereby the aminoglycoside serum concentration (SAC) falls below the organism's MIC. However, this antibiotic class exhibits a potent post antibiotic effect (PAE), defined as persistent bacterial growth suppression despite antibiotic concentrations below the organism's MIC. PAE is prolonged with increasing SACs.^{27,29,30} Finally, ODA therapy may also prevent the possibility of adaptive resistance. Adaptive resistance refers to a reduction in bacterial killing rate following exposure to a drug, possibly by down regulation of drug uptake by the aminoglycoside-exposed organism. ODA therapy may circumvent adaptive resistance by allowing the organism to revert to its sensitive phenotype during the drug-free period provided by this dosing approach.^{27,29,30}

Concentration-dependent bactericidal activity has been demonstrated in clinical studies. Moore et al. reported that peak serum concentration to MIC ratios exceeding 8–10 are associated with a statistically significant increase in clinical response rate.³¹ Moore's group also demonstrated the association between higher aminoglycoside plasma concentrations and decreased mortality in gram-negative bacteremia as well as a direct correlation between therapeutic response and plasma levels in gram-negative pneumonia.^{32,33} Additionally, several published meta-analyses evaluating ODA in adults have demonstrated increased bactericidal activity and trends toward decreased aminoglycoside toxicity when extended-interval dosing is employed.³⁴⁻⁴³ Although the pediatric literature on ODA is comparatively limited, the published experience in children demonstrates at least equal efficacy and no greater incidence of toxicity when compared to MDA.^{9,11,14,17-26} Other advantages to ODA include reduced costs, resulting from less frequent determinations of serum levels, decreased supply and labor costs, and possibly decreased incidence of nephrotoxicity.

Bass and colleagues reported similar gentamicin pharmacokinetic parameters in children when comparing multiple daily aminoglycoside (MDA) dosing to once daily dosing (ODA) methods.⁹ Our group, therefore, utilized patient-specific pharmacokinetic values calculated from our institution's MDA protocol to estimate the serum aminoglycoside concentrations (SACs) attainable by once-daily dosing (ODA). The pharmacodynamic profiles of MDA and ODA dosing were

subsequently compared. As depicted in Figures 1 and 2, optimal peak:MIC₉₀ ratios against the clinically relevant nosocomial gram-negative bacilli isolated from HIV-positive children were realized with greater frequency when utilizing the ODA regimens.

Our study suggests that a once-daily aminoglycoside (ODA) protocol may result in optimization of pharmacodynamic parameters in HIV-infected children, thus maximizing bacterial killing and possibly reducing toxicity. Successful use ODA in combination with other agents has been reported in immunocompromised pediatric^{14,23-25} as well as in adult^{25,44,45} oncology patients. However, a "one dose fits all" ODA approach may not be optimal (especially in pediatric patients) due to significant inter- and inpatient variability in aminoglycoside pharmacokinetic parameters.⁴⁶ This variability may be more pronounced in HIV-infected children diagnosed with growth failure or HIVN. Even though our study attempted to identify the effect of these factors on patient pharmacokinetic parameters, the limited number of patients per strata was small and thus limited the comparative value of such analyses. Finally, clinical validation of our results is warranted before the switch from MDA to ODA therapy in HIV-infected children becomes the standard of practice.

CONFLICTS OF INTEREST: The authors declare no conflicts of interest or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medications, employment, gifts, and honoraria.

ACKNOWLEDGEMENTS: The authors are grateful for the contributions of Ana Carriedo, RN, Rosy Castro, RN, Alex Machado, RN, Maria Santaella, RN, Lynn Whitt, RN, Isatu Bobb, RN, Gleno James, RN, RN, Lynda Boursiquot, RN, Onya Love, RN, and Yvette Prudent, RN, without whose contributions this study would not have been possible.

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