Comparison of Amikacin Pharmacokinetics in Neonates Following Implementation of a New Dosage Protocol

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OBJECTIVES The primary aim was to compare attainment of goal serum amikacin concentrations using two dosage regimens in patients admitted to a neonatal intensive care unit. Secondary objectives included comparison of percentages of supratherapeutic trough concentrations, and subtherapeutic and supratherapeutic peak concentrations.

METHODS This was an Institutional Review Board–approved, retrospective study of neonates receiving amikacin during January–December 2013 (group 1) and January–December 2014 (group 2). Group 1 received amikacin dosage consistent with published recommendations, whereas group 2 was dosed using a modified protocol that was based on postmenstrual and postnatal age. Goal serum amikacin peak concentration was defined as 20 to 35 mg/L; hence, subtherapeutic and supratherapeutic peak concentrations were defined as <20 mg/L and >35 mg/L, respectively. Supratherapeutic trough concentrations were >8 mg/L. Between-group analysis was performed using Wilcoxon-Mann-Whitney test, Student *t*-test or χ^2 , or Fisher exact analysis as appropriate with a *p* value <0.05.

RESULTS A total of 278 neonates were included (group 1: *n* = 144; group 2: *n* = 134). Most patients were male (60%) and were admitted for prematurity or respiratory distress (77%). The median gestational age in group 1 was 34.4 weeks (range, 30.0–37.9 weeks) versus group 2 at 36.9 weeks (range, 31.4–38.9 weeks), whereas the postnatal age was similar between both groups at 4 days. There was a significant increase in attaining goal peak amikacin concentrations between groups 1 and 2, 34% versus 84%, *p* < 0.001, and decrease in supratherapeutic peak concentrations, 65% versus 12%, *p* < 0.001. There was no significant difference in subtherapeutic peak or supratherapeutic trough concentrations.

CONCLUSIONS A modified neonatal amikacin dosage protocol resulted in increased peak amikacin serum concentration compared with published dosage recommendations. Future research should focus on determination of the optimal dosage regimen in neonates.

ABBREVIATIONS AKI, acute kidney injury; CI, confidence interval; NICU, neonatal intensive care unit; PMA, postmenstrual age; PNA, postnatal age; SCr, serum creatinine; Vd, volume of distribution

KEYWORDS amikacin; aminoglycosides; antibiotic; dosage; neonate; pharmacokinetics; safety; therapeutic drug monitoring

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Introduction

Aminoglycosides are bactericidal agents that inhibit protein synthesis by binding to the 30S ribosomal subunit.¹ They are almost exclusively eliminated renally, with a highly variable elimination half-life that is prolonged in neonates compared with children and adults.^{2,3} In combination with ampicillin, an aminoglycoside is often initiated as empiric antibiotic therapy for neonatal early-onset sepsis, or sepsis occurring within the first 3 days of life. In addition, aminoglycosides are also often initiated with vancomycin in neonatal late-onset sepsis, or sepsis occurring after the first 3 days of life.⁴ Although aminoglycosides are widely used in the neonatal intensive care unit (NICU), there remains much discussion

on optimal dosage, safety, and efficacy.

In the NICU, gentamicin is the most commonly prescribed aminoglycoside.⁵ However, there has been an increase in resistance of *Escherichia coli* to gentamicin and tobramycin.^{6,7} In 2011, our institution-specific susceptibilities to gentamicin and tobramycin were 90% and 91%, respectively. Because of decreased susceptibility rates with gentamicin and tobramycin, prescribers have opted to change the aminoglycoside of choice for neonatal sepsis to amikacin, with an *E coli* 99% susceptibility rate in our NICU. Although our institution has seen an increase in amikacin use, there remains no consensus on an optimal dosage regimen. Commonly used drug references recommend a conventional dosage method that consist of a 10 mg/

Table 1. Neonatal Intensive Care Unit Amikacin Dosage Protocol

Postmenstrual age, wk	Postnatal age, days	Subgroup	Amikacin Dose	
			Group 1 (Prior to January 2014)	Group 2 (January 2014-Present)
≤29	0-7	1	18 mg/kg every 48 hr	14 mg/kg every 48 hr
	8-28	2	15 mg/kg every 36 hr	12 mg/kg every 36 hr
	≥29	3	15 mg/kg every 24 hr	12 mg/kg every 24 hr
30-34	0-7	4	18 mg/kg every 36 hr	12 mg/kg every 36 hr
	≥8	5	15 mg/kg every 24 hr	12 mg/kg every 24 hr
≥35	All	6	15 mg/kg every 24 hr	12 mg/kg every 24 hr

kg intravenous load followed by 5 to 7.5 mg/kg every 8 to 12 hours for a maximum daily dose of 15 mg/kg/day.^{8,9} However, more recently, extended-interval dosage strategies (e.g., 15-18 mg/kg every 24-48 hours) employing either fixed dosage or individualized dosage based on postmenstrual age (PMA) and postnatal age (PNA) have been studied in the NICU population.¹⁰⁻¹² Extended-interval dosage increases prevalence of peak and trough concentrations within therapeutic range and is theorized to minimize nephrotoxicity associated with supratherapeutic trough concentrations.¹³⁻¹⁵ Amikacin and the other aminoglycosides have been associated with ototoxicity as well, although incidence cannot be predicted by serum drug concentrations.¹⁶

At the study institution, amikacin dosage in 2012 was based on extended-interval dosage recommendations published in NeoFax.¹⁰ Because of observed supratherapeutic peak concentrations, in January 2014 we implemented a new dosage protocol based on pharmacokinetic data in a sample population collected during a medication use evaluation (Table 1). The primary aim of this study was to evaluate the attainment of goal amikacin concentrations before and after implementation of this new dosage protocol.

Materials and Methods

Study Design

This was an Institutional Review Board–approved, retrospective study of NICU patients receiving amikacin during two different time periods: January-December 2013 (group 1) and January-December 2014 (group 2). Group 1 included patients who received an amikacin dose consistent with recommendations from NeoFax,¹⁰ and group 2 included patients who received a dosage from the modified protocol (Table 1).

Patients receiving amikacin were identified for inclusion using the institution's electronic medical record, Meditech (Meditech Information Technology Inc, Westwood, MA). Patients were included if they had an amikacin peak and trough serum concentration drawn while receiving appropriate amikacin therapy based on the dosage recommendations of the respective year. Amikacin peak and trough serum concentrations were

defined as a concentration collected 30 minutes after completion of the infusion and 30 to 60 minutes before the next scheduled dose, respectively. Generally only one set of concentrations was used for each dosage recommendation per patient; however, patients who received a second round of amikacin therapy were eligible for inclusion again if the patient met criteria for dosage that used a different age subgroup. For concentrations not meeting the above collection time criteria, peak and trough concentrations were extrapolated with the use of pharmacokinetic equations. Goal peak and trough concentrations for this study were defined as 20 to 35 mg/L and <8 mg/L, respectively. Concentrations were excluded if they were drawn prior to administration of the second dose of amikacin or were identified as an erroneous drug concentration. An erroneous concentration was defined as a calculated volume of distribution (Vd) that was ±30% of 0.4 to 0.6 L/kg, the expected neonatal population Vd.⁸

Patients were excluded if they had acute kidney injury (AKI), defined as a reduction in urine output to less than 0.5 mL/kg/hr for longer than 8 hours, an absolute increase in serum creatinine (SCr) by 0.3 mg/dL, or an increase in SCr greater than 50% from baseline prior to receiving amikacin therapy.¹⁷ Patients receiving extracorporeal membrane oxygenation, who had congenital anomalies of the kidney or ear, or who were diagnosed with cytomegalovirus infection were also excluded from this study.

Study Objectives and Data Collection

Demographic data, including age, weight, length, sex, and ethnicity, were gathered from the patient's electronic medical record. Baseline characteristics of Apgar scores and the presence of intrauterine growth restriction, congenital heart disease, and diagnosis of cytomegalovirus were collected. Data on presence of congenital heart disease, defined as a cyanotic heart defect or acyanotic heart defect (e.g., atrial septal defect), requiring surgical intervention prior to or during amikacin therapy, were collected. Concomitant use of nephrotoxic (i.e., acyclovir, amphotericin, ibuprofen, indomethacin, and vancomycin) or ototoxic (furosemide,

Figure 1. Patient enrollment. ECMO, extracorporeal membrane oxygenator; Vd, volume of distribution.

vancomycin) agents, and administration of an inotrope or vasopressor therapy were noted. Microbiology results and positive cultures were assessed. Hearing screen results and renal function markers, including serum creatinine and urine output at baseline and during amikacin therapy were recorded. Pharmacokinetic parameters were calculated based on the measured/extrapolated amikacin peak and trough serum concentrations and included elimination rate constant, half-life ($T_{1/2}$), and Vd.

The primary objective was to compare the percentage of goal amikacin peak serum concentration attainment between groups 1 and 2. Secondary objectives included comparison of percentages of supratherapeutic troughs (>8 mg/L) and subtherapeutic (<20

mg/L) and supratherapeutic (>35 mg/L) peak serum concentrations between groups 1 and 2 and subgroups based on PMA and PNA. In addition, a safety analysis was performed and compared the incidence of AKI and ototoxicity between groups 1 and 2. After patients were screened using this definition, a panel of pediatric pharmacotherapy specialists further reviewed the patients to determine if patients met this criteria. Ototoxicity was defined as failure of the newborn hearing screen in one or both ears at any time during hospitalization after amikacin therapy was received. Additionally, pharmacokinetic parameters were compared between groups 1 and 2, and subgroup analyses were performed based on PMA, PNA, and presence of congenital heart disease.

Statistical Methods

Descriptive statistics were computed for all demographic and clinical variables. Categorical variables, including the primary objective, were compared by the χ^2 test. Interval and continuous variables were assessed for normality using the Shapiro-Wilk test and compared using the Student *t*-test or the Wilcoxon-Mann-Whitney test, when appropriate. An *a priori* power calculation was performed for the primary outcome. A total of 78 patients were needed in each group to detect a 30% increase in goal peak attainment with 80% power and 5% type 1 error.

Additionally, two logistic regression analyses were performed to assess the independent effect of the new dosage on AKI and ototoxicity. For AKI, the confounding variables included in the regression model were PMA, PNA, sex, duration of amikacin, nephrotoxic agents, and inotropes/vasopressors. The confounding variables included in the regression analysis assessing ototoxicity included duration of amikacin, time between completion of amikacin therapy and hearing screens, vancomycin, and furosemide. The *a priori* level of significance was <0.05.

Results

Figure 1 includes an overview of patients included in the study. A total of 243 potential peak and trough concentration pairs were identified in group 1, representing 226 patients. A total of 95 potential pairs were excluded, leaving 148 paired serum concentrations available for analysis, representing 144 patients (Figure 1). There were 226 potential concentration pairs identified in group 2, representing 199 patients. A total of 87 potential pairs were excluded, leaving 139 pairs, representing 134 patients.

Table 2 contains a comparison of baseline demographics between groups. Most patients were white males admitted for prematurity or respiratory distress (Table 2). There was a non-significant difference ($p = 0.08$) in the median gestational age of group 1 (34.3

Table 2. Baseline Demographics

Variable	Group 1 (n = 148)	Group 2 (n = 139)	p Value
Demographics			
Male, n (%)	87 (58.8)	80 (57.6)	0.83
White, n (%)	78 (52.7)	97 (69.8)	0.06
Gestational age, wk, median (IQR)	34.3 (30.0-37.9)	36.9 (30.1-38.9)	0.08
Postnatal age, days, median (IQR)	1 (0-2)	1 (0-2)	0.89
Postmenstrual age, wk, median (IQR)	35.0 (30.0-38.0)	37.0 (33.0-39.0)	0.03
Weight, kg, median (IQR)	2.20 (1.48-3.04)	2.68 (1.67-3.40)	0.04
Length, cm, median (IQR)	45.0 (39.5-50.0); n = 145	47.0 (40.5-51.0); n = 136	0.08
Reason for admission, n (%)			<0.01
Prematurity	77 (53.5)	45 (33.6)	
Respiratory distress	38 (26.4)	53 (40.0)	
Surgical	10 (6.9)	16 (11.9)	
Infectious	6 (4.2)	5 (3.7)	
Cardiac	1 (0.7)	10 (7.5)	
Other	12 (8.3)	5 (3.7)	
Apgar score			
At 1 min, median (IQR)	6 (3-8); n = 145	6 (3-8); n = 136	0.66
At 5 min, median (IQR)	8 (6-9); (n = 146)	8 (6-9); n = 137	0.81
At 10 min, median (IQR)	7 (6-8); n = 55	7 (7-8); n = 47	0.59
Intrauterine growth restriction, n (%)	11 (7.5)	9 (6.5)	0.74
Congenital heart disease, n (%)	15 (10.1)	23 (16.6)	0.11
Positive culture, n (%)	16 (11.0); n = 145	21 (16.41); n = 128	0.20

IQR, interquartile range

weeks) versus group 2 (36.9 weeks). However, there was a statically significant difference in the median PMA between group 1 and group 2, 35.0 versus 37.0 weeks, respectively, $p = 0.03$. There was also a statistically significant difference ($p = 0.04$) in the median weight between group 1 (2.2 kg) and group 2 (2.68 kg). The only other significant difference in baseline characteristics was reason for admission ($p < 0.001$); more neonates were admitted for prematurity in group 2 versus group 1. All other baseline demographics, and duration of amikacin therapy with a median of 6 days, were similar among groups.

Amikacin Serum Concentrations

Figure 2 contains the breakdown of amikacin serum peak and trough concentrations between the two groups. There was a statistically significant difference in the overall mean peak concentrations between groups 1 and 2: 37.7 ± 7.3 mg/L versus 28.5 ± 5.8 mg/L, $p < 0.01$ (Table 3). There was a significant difference in the number of patients with a goal peak concentration between groups 1 and 2: 50 (34%) versus 117 (84%), $p < 0.01$. This corresponded with a significant decrease in supratherapeutic peak concentrations between groups 1 and 2: 97 (65%) versus 16 (12%), $p < 0.01$. There were

no differences in the number of patients with subtherapeutic peak concentrations or supratherapeutic trough concentrations.

Two trough serum concentrations were excluded in group 2 because of an erroneous value, leaving a total of 137 concentrations available for analysis. For the overall trough concentrations, there was no significant difference between groups 1 and 2: 2.3 ± 1.6 versus 2.0 ± 1.7 mg/L, $p = 0.77$.

Table 3 provides the mean peak concentrations in groups 1 and 2 for 6 different subgroups based on PMA and PNA (Table 1). Between the two groups, there were statistically significant differences in 5 of the 6 subgroups in the mean peak serum concentrations. Analysis was not performed for subgroup 3 because of the small sample size. Figure 3 contains a comparison of the number of patients in groups 1 and 2 who attained goal peak serum concentrations in these subgroups. There was a significant difference between the number of patients in 3 of the 5 subgroups who achieved the goal peak concentrations when comparing groups 1 and 2 (Table 3).

Pharmacokinetic Analysis

Table 4 provides the pharmacokinetic parameters

Figure 2. Amikacin concentration results based on dosage regimen.

for the 6 subgroups. The half-lives varied according to PMA and PNA and ranged from 4.93 to 11.0 hours. The Vd of the groups ranged from 0.353 to 0.472 L/kg. Separate variables were also calculated for patients with congenital heart disease. Statistical analysis was not performed between those with congenital heart disease and those without, because of inadequate sample size between groups.

Safety Analysis

A total of 8 patients (5.4%) in group 1 and 14 patients (10.0%) in group 2 experienced potential AKI during amikacin therapy. The odds of AKI were approximately 1.9 times greater in group 2 versus group 1, but this difference was not significant when controlling for other covariates, adjusted odds ratio 0.52 (95% confidence interval [CI], 0.21-1.3). All of these patients had an increase in SCr, but none met the criteria of urine output <0.5 mL/kg/hr. Most (90.1%) of these patients were included in the PMA ≤29 weeks and PNA 0 to 7 days subgroup (n = 13), followed by the PMA ≥35 weeks subgroup (n = 7). In the regression analysis, PMA was independently associated with a 1.2 greater odds of AKI, with more premature infants being at greater risk, adjusted odds ratio 0.82 (95% CI, 0.75 - 0.89). The duration of amikacin therapy in these patients ranged from 4 to 12 days. Of the 22 patients with AKI, none had

a supratherapeutic trough concentration, although 4 patients had a trough concentration >4 mg/L. There was no observed difference in the number of concomitant nephrotoxic medications in those who developed AKI versus those who did not (p = 0.32).

Hearing screens were documented in 134 patients in group 1 and 122 in group 2. Sixteen patients developed ototoxicity, including 8 (6.0%) in group 1 and 8 (6.6%) in group 2. One half of these patients had a supratherapeutic trough concentration, including 6 patients in group 1 with a peak concentration >40 mg/L. The odds of ototoxicity were approximately 1.03 times greater in group 2 versus group 1, but this difference was not significant when controlling for other covariates, adjusted odds ratio 0.976 (95% CI, 0.34 - 2.8).

Discussion

This is the largest study to date evaluating amikacin in neonates, including pharmacokinetic data from 278 neonates in a variety of age groups. Although several of our subgroups had small numbers, we were able to assess pharmacokinetic parameters across 6 different dosage subgroups based on PMA and PNA. Our study did include a large number of neonates with a PNA of 0 to 7 days and varying PMA; these data are noteworthy considering that these neonates would be the most likely to receive aminoglycoside therapy for early-onset sepsis.

Ten previous studies have assessed the pharmacokinetics and/or dosage regimens of amikacin in neonates.^{2,3,11,12,15,18-22} Many of these studies were conducted in the 1980s to the 1990s. With advances in neonatology, the makeup of NICU patients is significantly different. The largest and most recent study of these was performed by An and colleagues.¹⁹ These investigators conducted a retrospective study evaluating pharmacokinetics and dosage in 181 Korean neonates. Similar to our study, An et al¹⁹ compared amikacin pharmacokinetics between a predosage and postdosage protocol change. Their mean gestational age was younger than the median age of our population, approximately 33 weeks versus 34 to 37 weeks. It should be noted though that their population was divided into 4 subgroups with

Table 3. Subgroup Peak Concentration Analysis

Subgroup	PMA, wk	PNA, days	Group 1 (n = 148)	Group 1 Peak, mg/L*	Group 2 (n = 139)	Group 2 Peak, mg/L*	p Value
1	≤29	0-7	23	40.5 ± 6.76	18	32.8 ± 4.52	<0.01
2	≤29	8-28	4	38.0 ± 2.10	5	25.7 ± 6.53	<0.01
3	≤29	≥29	1	44.4	1	28.1	—
4	30-34	0-7	37	40.9 ± 7.82	12	25.1 ± 5.13	<0.01
5	30-34	≥8	7	35.1 ± 6.95	9	25.9 ± 3.90	<0.01
6	≥35	ALL	76	35.5 ± 6.75	94	28.5 ± 5.88	<0.01

*Mean ± SD

Figure 3. Amikacin concentration results subgroup analysis.

Group 1; group 2. Subgroup 1 = PMA $\leq$ 29 weeks, PNA 0 to 7 days; subgroup 2 = PMA $\leq$ 29 weeks, PNA 8 to 28 days; subgroup 3 = PMA $\leq$ 29 weeks, PNA $\geq$ 29 days; subgroup 4 = PMA 30 to 34 weeks, PNA 0 to 7 days; subgroup 5 = PMA 30 to 34 weeks, PNA $\geq$ 8 days; subgroup 6 = PMA $\geq$ 35 weeks. PMA, postmenstrual age; PNA, postnatal age.

■ Group 1: 2013; ■ Group 1: 2014

different divisions based on PMA and PNA. The investigators reported Vd ranged from 0.47 to 0.61 L/kg and half-life from 4.4 to 17.6 hours. Our Vd ranged from 0.35 to 0.47 L/kg and half-life from 4.9 to 11.0 hours. It is difficult to make significant conclusions when comparing these data. First, this study was conducted in Korean neonates, whereas most patients in our study were white; at this time it is unclear if pharmacokinetics is varied based on race. Second, there were differences in how their subgroup populations were divided, making it difficult to determine the impact that PNA and PMA had on Vd and half-life when comparing the results.

Based on the pharmacokinetic analysis, An and colleagues¹⁹ supported the use of their postdosage protocol. Their dosage regimen was 13 mg/kg per dose with a dose frequency of every 12 to 48 hours depending on PNA and PMA. With this dosage, they found that their mean amikacin peak concentration was 25.8 ± 4.9 mg/L. Approximately 81.3% achieved an amikacin peak concentration of 20 to 30 mg/L, an increase of 30% from the predosage protocol change group. Power calculations for our study were based on this increase. Their mean trough concentration was 2.7 ± 2.3 mg/L. In comparison, our mean peak and trough concentrations with our postdosage protocol group were 28.5 ± 5.8 mg/L and 2.0 ± 1.7 mg/L, respectively. It should be noted that An and colleagues were targeting an amikacin peak concentration between 20 and 30 mg/L, which contributed to their lower mean peak concentration compared with our revised protocol.

Based on the findings in this study, the revised dosage protocol resulted in a greater number of peak concentrations within our targeted range of 20 to 35 mg/L. A number of published sources provide a wide

range of doses of amikacin in neonates.⁸⁻¹⁰ Our data would suggest that using these published sources will result in supratherapeutic peak concentrations (>35 mg/L) for subgroups 1 (PMA $\leq$ 29 weeks, PNA 0-7 days), 4 (PMA 30-34 weeks, PNA 0-7 days), and 6 (PMA $\geq$ 35 weeks, all PNA).

In the present study, 6 different subgroups based on PNA and PMA were included. Because of the retrospective design, not all subgroups had an equal distribution of patients, making it difficult to perform statistical analyses. For example, subgroup 3 only included 1 patient in group 1 and group 2. Excluding this subgroup, the Vd ranged from 0.414 to 0.472 L/kg. As expected, the half-life varied according to PNA. In addition, we also assessed the pharmacokinetics of neonates with congenital heart disease. Only 2 studies have evaluated the pharmacokinetics of aminoglycosides in neonates with congenital heart disease.^{23,24} Moffett and colleagues evaluated the pharmacokinetics of gentamicin in 48 children with congenital heart disease.²³ They evaluated the pharmacokinetics in 4 neonates and found that the Vd was 0.33 ± 0.08 L/kg and half-life was 5.3 ± 3.3 hours. Given that tobramycin, gentamicin, and amikacin have a similar Vd, these findings are in contrast to the present study.²⁵ We found that the mean Vd was 0.449 L/kg, with a comparable half-life of 6.97 hours. It is possible that this difference in Vd is likely related to a smaller sample size. In addition, Moffett and colleagues do not provide details on the PNA and PMA of the neonates included in their study, making it difficult to provide additional insight.

To date, studies evaluating aminoglycoside-related AKI in neonates have been limited because of small sample sizes.^{11,12,15} The number of neonates with AKI based on our definition was 5.4% to 10.0%, which is similar to the range of 1.2% to 5.9% of infants and children reported elsewhere.²⁶ For the purposes of this study, we used a definition that evaluated both SCr and urine output that has been used previously to evaluate the safety of indomethacin and ibuprofen in neonates.^{17,27} However, the definition of AKI in the neonate is still undefined, with renal function dependent on factors including the patient's gestational age and PNA.²⁸ It is unclear why the incidence of AKI was higher in group 2 versus group 1. Despite this, our logistic regression found an adjusted odds ratio of 0.52 (95% CI, 0.21-1.3), suggesting that there is no association between dosage groups and AKI when controlling for other covariates. Not surprisingly, the only variable significantly associated with development of AKI was PNA.

Previous studies have noted a wide range in the incidence of aminoglycoside-related ototoxicity by audiometry, with anywhere from 2% to 25% in infants and children.²⁶ Based on our definition, we included neonates who failed at least one hearing screen prior to discharge from the NICU following receipt of amikacin. Our overall incidence of ototoxicity was 6% to 6.6%. It

Table 4. Subgroup Pharmacokinetic Analysis

Subgroup	PMA, wk	PNA, days	No. (n = 287)	k_e , hr ⁻¹ *	$T_{1/2}$, hr*	V_d , L/kg*
1	≤29	0-7	41	0.065	11.00	0.414
2	≤29	8-28	9	0.075	9.64	0.472
3	≤29	≥29	2	0.141	4.93	0.353
4	30-34	0-7	49	0.089	7.96	0.462
5	30-34	≥8	16	0.116	6.20	0.454
6	≥35	All	170	0.116	6.21	0.433
Congenital heart disease			38	0.107	6.97	0.449

k_e , elimination constant; PMA, postmenstrual age; PNA, postnatal age; $T_{1/2}$, half-life; V_d , volume of distribution

*Mean

is feasible that our incidence of ototoxicity may be underestimated. Although we controlled for time between amikacin therapy and hearing screen, we may have missed delayed-onset ototoxicity because aminoglycosides progressively accumulate in the inner ear, with a prolonged half-life compared with plasma.^{17,18} Furthermore, we could not account for vestibular toxicity that would manifest as vertigo or gait imbalances because there is no objective measure of these symptoms in a neonate. Based on our logistic regression, no variables, including dosage groups, were significantly associated with the development of ototoxicity.

There are several limitations to our study. First, our study was retrospective, limiting the availability of data to the electronic medical record. Also, the retrospective nature of our study did not allow us to control for all variables affecting amikacin pharmacokinetics or prove causality of AKI or ototoxicity. As noted, the definition of AKI in neonates is not widely agreed upon, although we used a previously published definition.¹⁷ Future studies should continue to work to establish a more consistent definition of AKI in this population. Third, the goal peak for amikacin is not universally accepted. We targeted a peak concentration of 20 to 35 mg/L. Some have suggested targeting higher peak concentrations of up to 40 mg/L for life-threatening infections.⁸⁻¹⁰ Our study did not evaluate clinical outcomes, so it is difficult to determine if neonates with higher peak concentrations achieved improved efficacy. Last, the design of this study did not allow us to include an equal number of neonates in our subgroups. As a result, it is difficult for us to make significant recommendations based on the small sample sizes. Future studies should focus specifically on these smaller subgroups, including the congenital heart disease population.

Conclusion

Our revised amikacin dosage protocol resulted in more frequent attainment of desired peak concentrations of 20 to 35 mg/L compared with published dosage guidelines. Our study showed this revised protocol increased attainment of goal peak concentrations by

50%. Future research should focus on determination of the optimal amikacin peak and trough concentrations needed to achieve adequate efficacy with less toxicity. In addition, future research should also focus on evaluating the dosage and pharmacokinetics of subgroups, including neonates with congenital heart disease with varying PNA and PMA.

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