CLINICAL INVESTIGATION

Identification of Risk Factors for Elevated Neonatal Gentamicin Trough Concentrations

Jeffrey Gonzalez, PharmD,¹ John Ahern, PharmD,¹ Elizabeth Noyes, PharmD,¹ Michele Corriveau, BScPharm,¹ and Charles Mercier, MD²

¹Pharmacy Services, Vermont Children's Hospital, University of Vermont Medical Center, Burlington, Vermont; ²Neonatal Intensive Care, Vermont Children's Hospital, University of Vermont Medical Center, Burlington, Vermont

OBJECTIVES: The objective of this study was to identify neonatal and maternal characteristics that may be associated with elevated neonatal gentamicin trough concentrations despite application of a previously published gentamicin dosage strategy.

METHODS: Retrospective cohort study of all neonates admitted to University of Vermont Medical Center (562-bed academic teaching hospital, Burlington, VT) receiving gentamicin between June 1, 2009, and August 31, 2013. A total of 205 neonates were included, with 41 cases and 164 controls.

RESULTS: Postmenstrual age (PMA, gestational age plus chronological age) and small-for-gestational age (SGA) status were independently associated with elevated neonatal gentamicin trough concentrations. No maternal risk factor evaluated remained significantly associated in the multivariate analysis.

CONCLUSIONS: The probability of an elevated gentamicin trough concentration increases with lower PMA and is further accentuated in neonates with SGA status. In contrast, the presence of maternal risk factors did not increase the likelihood of elevated gentamicin trough concentrations. Neonates with lower PMA and SGA status may require an individualized dosage and monitoring strategy.

INDEX TERMS: aminoglycosides, drug monitoring, gentamicin, intensive care, neonatal, pediatrics

J Pediatr Pharmacol Ther 2016;21(2):133–139

INTRODUCTION

Sepsis in the neonatal population is a major cause of morbidity and mortality, with mortality rates of up to 50% noted if sepsis is not timely treated.¹ A combination of intravenous ampicillin and intravenous gentamicin comprises standard initial therapy for suspected or documented sepsis in the neonate.² The literature³ suggests that gentamicin trough concentrations of greater than 1.5 mg/L are associated with an increased risk of toxicity. The most commonly reported⁴ toxicities associated with gentamicin use include ototoxicity and nephrotoxicity. Drug accumulation in sensitive organs such as the inner ear and kidney increases with higher plasma concentrations and long durations of exposure. The ability to eliminate the drug from these organs is dependent on diffusion back into the bloodstream. It is for this reason that elevated trough concentrations are

associated with toxicity.⁵ Although the incidence of reported nephrotoxicity and ototoxicity in the neonatal population is relatively low, there are reports of positive correlation with gentamicin concentrations and increased serum creatinine,⁶ as well as an increase in hearing abnormalities associated with gentamicin use.⁷ While evidence of the association between elevated gentamicin troughs and ototoxicity incidence in the neonatal population is limited, the large number of babies receiving aminoglycoside therapy warrants precautionary measures to prevent elevated troughs through appropriate therapeutic drug monitoring.⁸

In 2004, the University of Vermont Medical Center (UVM Medical Center; formerly Fletcher Allen Health Care) implemented a large-dose extended-interval gentamicin dosing strategy (based on weight and postmenstrual age) to reduce the number of gentamicin trough con-

centrations that exceed 1.5 mg/L. As described in a previous report,⁹ this dosage strategy significantly reduced the number of elevated trough concentrations. However, we have continued to observe that a proportion of our neonates (5%-10%) still experience elevated initial trough concentrations with the application of our dosage guidelines. The reasons for this are not clear. The purpose of this follow-up investigation was to identify maternal and neonatal characteristics that may identify neonates who are likely to experience elevated gentamicin trough concentrations despite application of our dosage strategy.

METHODS

This was a retrospective cohort study of all inborn and outborn neonates admitted to the UVM Medical Center, Burlington, Vermont, between June 1, 2009, and August 31, 2013. The UVM Medical Center is a 562-bed academic medical center associated with the University of Vermont and serves a large patient population in Vermont and northeastern New York. It has a total of 58 pediatric beds, with a 20-bed, level-3 neonatal intensive care unit (NICU), a pediatric intensive care unit, and a general pediatric floor. On average, there are over 2200 babies delivered at the UVM Medical Center and 650 admissions to our NICU annually.

The study protocol was approved by the University of Vermont Committees on Human Subjects. Neonates were identified for study inclusion through a query of our laboratory database for recorded gentamicin trough concentrations. An elevated gentamicin trough concentration, as defined by the UVM Medical Center, is ≥ 1.5 mg/L, which was measured using the Advia Centaur XP (Siemens Healthcare Diagnostics, Washington, DC) gentamicin assay with a coefficient variation of 5.5% continually throughout the study period. Neonatal inclusion criteria were 1) age of <28 days; 2) gentamicin administered in accordance with the institution's dosage protocol for treatment of bacterial infections, confirmed sepsis, or empirically to rule out sepsis; and 3) gentamicin peak and trough concentrations drawn after a minimum of 2 doses. Neonates were excluded if there was incomplete documentation of gentamicin administration or serum level collection time or if trough concentration was obtained without an accompanying peak

concentration.

Part of our inclusion criteria required neonates to receive gentamicin in accordance with our dosage protocol: for dosing purposes neonates are divided into preterm versus full-term neonates (full term defined as >37 weeks postmenstrual age [PMA], which is gestational age plus chronological age). Premature neonates of <29 weeks PMA receive 4 mg/kg every 36 hours, premature neonates of ≥ 29 weeks receive 3.5 mg/kg every 24 hours, full-term neonates with a chronological age of ≤ 1 week receive 3.5 mg/kg every 24 hours, and full-term neonates with a chronological age of >1 week receive 2.5 mg/kg every 8 hours. The dose of intravenous gentamicin is delivered over 30 minutes utilizing a syringe pump. To ensure that gentamicin concentrations were measured under steady-state conditions, gentamicin peak and trough concentrations were included in the analysis if they were measured after a minimum of 2 doses. The first recorded gentamicin trough concentration was used along with the accompanying peak concentration to pharmacokinetically derive the true trough concentration (the trough concentration that occurs immediately at the end of the dosage interval). Only initial gentamicin trough concentrations were evaluated; repeated gentamicin trough concentrations were not included. The Adult and Pediatrics Kinetics program (RxKinetics, Plattsburgh, MO) was used to perform the pharmacokinetic extrapolations using the Sawchuk-Zaske method.¹⁰

Neonates were separated into 2 groups based on the extrapolated gentamicin trough concentration: neonates who experienced elevated gentamicin trough concentration (cases) and neonates who did not experience elevated gentamicin trough concentrations (controls). To identify potential risk factors, cases and controls underwent a medical record review by one of the authors (JG). This included a review of demographic factors (neonatal), clinical variables (neonatal and maternal), and concomitant medications (neonatal). The data extracted from each record were validated by a second investigator (JA). All potential risk factors were identified *a priori*.

Statistical Analysis

A sample size calculation was performed to determine the number of patients needed in order for the study to have adequate power to correlate

the preidentified risk factors with the probability of an elevated gentamicin trough concentration. An estimated sample size of 35 neonates with elevated troughs was anticipated for the study period based on preliminary laboratory data. It was calculated that a ratio of 1 neonatal case to 4 neonatal controls would allow an exact chi-square test the ability to detect an associated clinical or demographic variable with a relative risk value of 2.0 with 70% power and 1-sided 5% Type I error level, assuming that the prevalence was 20% for the control neonates.

Summary statistics for clinical and demographic variables were computed for both the neonates with and without troughs that exceeded the current UVM Medical Center limit (≥ 1.5 mg/L). These point estimates were supplemented with 95% confidence intervals. As appropriate, either a chi-square contingency table test or a Fisher's exact test was used to compare the cases and controls for qualitative variables. Continuous or ordinal variables were compared with 2-sample *t*-tests or non-parametric rank tests if data distributions appeared to be of concern. Variables found to be associated with an elevated gentamicin trough concentration in the univariate analysis were included in a logistic regression model to determine if combinations of these variables discriminated between the cases and controls. Statistical significance was defined as a 2-sided *p*-value less than 0.05. Statistical analyses were performed using SYSTAT (version 11, SYSTAT Software Inc, Richmond CA).

RESULTS

During the period of time from June 1, 2009, through August 31, 2013, 41 neonates met the inclusion criteria. One hundred sixty-four controls were randomly selected and enrolled to meet the predetermined case to control ratio. The majority of neonates (202/205) received gentamicin therapy empirically for suspected sepsis. Two neonates (controls) received gentamicin for treatment of pneumonia, and 1 neonate (control) received gentamicin for treatment of necrotizing enterocolitis. Five neonates (1 case and 4 controls) had positive microbiologic cultures that were all from blood (1 from placental vein, 3 drawn peripherally, and 1 location was not indicated). This consisted of coagulase-negative staphylococci in 3 neonates (1 case and 2 controls), *Escherichia coli*

in 1 neonate (control), and *Micrococcus* species in the remaining neonate (control). The mean gentamicin trough concentration in the cases was 1.7 mg/L, with a range of 1.5 to 2.3 mg/L. The mean gentamicin trough concentration for the controls was 0.9 mg/L, with a range of 0.3 to 1.4 mg/L.

The results of the univariate analysis are displayed in the Table. Relative to the controls, cases were significantly younger (33.7 versus 36.6 weeks, $p = 0.001$) and had a lower birth weight (2.147 versus 2.684 kg, $p = 0.005$). In addition, a higher percentage of cases were small for gestational age (SGA) in comparison to the controls (26.8% versus 12.8%); SGA was defined as whether the infant was in the 10th percentile for birth weight, based on the infant's gestational age, maternal race, and infant sex, as computed by either by the Fenton growth chart or on locally derived Vermont hybrid growth curves, which have been previously validated.^{11,12} This difference was marginally significant by the Fisher exact test ($p = 0.051$). Of the maternal variables that were examined, preterm premature rupture of membranes (PPROM) and maternal use of indomethacin (during the same hospitalization prior to neonatal delivery) occurred more commonly in the cases versus the controls (26.8% versus 12.2%, $p = 0.028$, and 17.1% versus 5.5%, $p = 0.022$, respectively). There was no difference between cases and controls in terms of use of neonatal vancomycin, indomethacin, dopamine, or furosemide. Amphotericin B was not used in either cases or controls. One neonate in the control group received dexamethasone for treatment of bronchopulmonary dysplasia (chronic lung disease). No neonates in the study population received therapeutic hypothermia for neonatal encephalopathy.

In the initial logistic regression model, which included PMA, SGA, PPRM, and maternal indomethacin use, only PMA and SGA remained significantly associated with an elevated gentamicin trough concentration. Birth weight was not included in the model because of concerns with collinearity with SGA and PMA. In the final model with PMA and SGA only, the PMA had an adjusted odds ratio of 0.889 with a 95% confidence interval of 0.829 to 0.954 ($p = 0.001$); SGA had an adjusted odds ratio of 2.408 with a 95% confidence interval of 1.031 to 5.625 ($p = 0.042$). Application of the final regression model is illustrated in the Figure.

Table. Univariate and Multivariate Analysis of Factors Associated with Elevated Gentamicin Trough Concentrations (≥ 1.5 mg/L)

	Univariate Analysis			Multivariate Analysis	
	Cases (n = 41)	Controls (n = 164)	p-Value	Odds Ratio (95% Confidence Interval)	p-Value
Neonatal variables					
Males*	21 (51.2)	101 (61.6)	0.286		
Postmenstrual age, wk†, ‡	33.7 $\pm$ 4.5	36.6 $\pm$ 4.8	0.001	0.920 (0.848-0.998)	0.044
Birth weight, kg†	2.147 $\pm$ 1.04	2.684 $\pm$ 1.107	0.005		
Located in NICU*	33 (80.5)	123 (75)	0.193		
APGAR at 5 min†, §	8.1 $\pm$ 1.3	7.9 (1.8)	0.489		
Endotracheal intubation*	15 (36.6)	47 (28.7)	0.345		
Males: hypospadias*, ¶	0 (-)	2 (2)	1		
Single umbilical artery*	1 (2.4)	2 (1.2)	0.49		
Patent ductus arteriosus*	4 (9.8)	7 (4.3)	0.236		
Small for gestational age*	11 (26.8)	21 (12.8)	0.051	2.734 (1.148-6.515)	0.023
Multiple gestation neonate*	7 (17.1)	16 (9.8)	0.265		
Vancomycin*	1 (2.4)	7 (4.3)	1		
Indomethacin*	5 (12.2)	13 (7.9)	0.367		
Dopamine*	0 (-)	3 (1.8)	1		
Furosemide*	0 (-)	2 (1.2)	1		
Amphotericin B*	0 (-)	0 (-)	1		
Corticosteroids*	0 (-)	1 (0.6)	1		
Maternal variables					
Chorioamnionitis*	10 (24.4)	32 (19.5)	0.518		
Preterm premature rupture of membranes*	11 (26.8)	20 (12.2)	0.028	1.854 (0.742-4.636)	0.187
Smoker*,#	10 (24.4)	25 (15.3)	0.172		
Prepregnancy diabetes mellitus*	1 (2.4)	3 (1.8)	1		
Gestational diabetes mellitus*	5 (12.2)	14 (8.5)	0.546		
Maternal hypertension*	9 (22)	19 (11.6)	0.123		
Indomethacin*	7 (17.1)	9 (5.5)	0.022	2.247 (0.695-7.266)	0.176

NICU, neonatal intensive care unit

* n (%)

† mean $\pm$ SD

‡ Postmenstrual age = gestational age + chronological age

§ For 202 patients (40 cases and 162 controls)

¶ Total male population in study was n = 122

For 204 patients (41 cases and 163 controls)

DISCUSSION

This report is a follow-up study to our previous findings that were published in 2004. This investigation used a retrospective case control design to examine whether characteristics of the neonate and its mother were independently associated with elevated neonatal gentamicin

trough concentrations despite application of our current dosage strategy. To our knowledge, this is the first study to evaluate maternal risk factors in addition to neonatal risk factors for elevated gentamicin trough concentrations. In the multivariate model, only neonatal PMA and SGA were found to be independent predictors. Decreasing PMA was associated with an increasing prob-

Figure. The probability of an initial gentamicin trough concentration of ≥ 1.5 mg/L

■ = SGA; □ = not SGA.

SGA, small for gestational age

The probability of an initial gentamicin trough concentration of ≥ 1.5 mg/L as a function of postmenstrual age (PMA) and SGA status, as predicted by the following equation: Probability (elevated trough) = $1/(1 + e^{-(2.564 - 0.117(PMA) + 0.879(SGA))})$. For example, the probability of a neonate having an elevated trough at 33 weeks is approximately 21%. This probability increases to 39% if the neonate is also SGA.

ability of experiencing an elevated gentamicin trough concentration. This finding is physiologically plausible, as neonatal nephrogenesis is not completed until 34 to 36 weeks of gestation.¹³ As a result, neonates born prior to this time will likely have decreased glomerular filtration and, thus, a higher probability of elevated gentamicin trough concentrations. Age has been confirmed¹⁴ to be a risk factor of importance in variability of serum gentamicin concentrations. In neonates who were SGA, the probability of experiencing an elevated trough concentration was approximately two-fold higher compared to that of neonates who were not SGA at every week of PMA. In terms of SGA, Aly et al¹⁵ have recently reported that SGA is associated with an increased risk of renal insufficiency, which can potentially predispose neonates to elevated gentamicin concentrations. To our knowledge, there is only one previous study implicating SGA status as a potential risk factor for decreased gentamicin clearance. The authors concluded that SGA status may need to

be considered in gentamicin dosing regimens due to altered pharmacokinetics secondary to a possible decrease in nephron number and renal organ mass, altered tubular function, and impaired glomerular filtration. In the study's SGA population, gentamicin clearance was decreased, with a prolonged half-life in neonates at postmenstrual ages at or below 32 weeks. In contrast to their findings, we identified that the risk of elevated gentamicin trough concentrations continued to be present in more mature neonates (i.e., those greater than 32 weeks).¹⁶

Other investigators have examined the role of neonatal serum creatinine and urine output and their association with elevated gentamicin trough concentrations. We did not report serum creatinine, as recent data¹⁷ suggest that the correlation between serum creatinine and gentamicin trough concentrations is not clear. In addition, given the potential confounding influence of maternal serum creatinine upon neonatal serum creatinine during the first 24 hours of life, we decided not

to include serum creatinine in our analysis.¹⁸ Urine output can be used to identify neonates at risk for elevated gentamicin trough concentrations.¹⁹ Decreased urine output (<1 mL/kg/hr) has been associated with an increased risk of elevated gentamicin concentrations.²⁰ Given the retrospective nature of this investigation, it was difficult to quantify urine output precisely as it was often reported in combination with stool output. As a result, we did not include this variable in our analysis.

The limitations of this study include the retrospective, case control design, the fact that the investigators were not blinded as to whether the subject was a case or control, the difficulty encountered in retrospectively extracting pertinent factors from the medical record, missing and/or complete documentation, and the fact that clinical outcomes were not correlated with serum drug concentrations. In addition, the necessity of requiring a peak concentration with every trough concentration excluded neonates that only had a trough level drawn. The rationale for requiring a peak concentration was to ensure that all measured trough concentrations were extrapolated to the time that the true trough concentration would occur, which was defined as immediately prior to the next dose. This ensured that the trough concentrations for all subjects were evaluated at the same point in time. The potential limitation with this approach is that it constrained our sample sizes for cases and controls, possibly limiting our ability to identify other risk factors. This study defined an elevated gentamicin trough concentration as ≥ 1.5 mg/L. This is consistent with the work of Davies et al,³ who have associated gentamicin concentrations of ≥ 1.5 mg/L with toxicity. Other investigators have used ≥ 2 mg/L to define elevated gentamicin concentrations. The definitions applied may influence study results. One other potential limitation of this study was the utilization of the birth weight for the characterization of SGA. It is possible that a neonate may be born an appropriate weight for gestational age yet become SGA as a result of excessive weight loss during the hospital stay. These neonates would not be classified as SGA as defined by the study. The generalizability of our study may also be limited as a result of our utilization of an institution-specific dosage protocol.

In summary, the probability of elevated gentamicin trough concentrations increases with more immature neonates. This likelihood is further accentuated in neonates who are also SGA. In contrast, we were not able to identify any maternal characteristics that independently predicted elevated gentamicin trough concentrations. Going forward, our practitioners will need to appreciate that application of our current dosage strategy may not be optimal for neonates with low PMA who are also SGA. In these situations, practitioners will need to develop individualized dosage and monitoring approaches for neonates who possess these characteristics.

Disclosure The authors declare no conflicts or financial interest in any product or service mentioned in the manuscript, including grants, equipment, medication, employment, gifts, and honoraria.

Acknowledgments This report was presented as a platform presentation at the 2014 Eastern States Conference in Hershey, PA, on May 5, 2014. We would also like to acknowledge Dr Taka Ashikaga for his assistance with the statistical analyses of our data.

Abbreviations NICU, neonatal intensive care unit; PMA, postmenstrual age (gestational age plus chronological age); PPROM, preterm premature rupture of membranes; SGA, small for gestational age; UVM Medical Center, University of Vermont Medical Center

Correspondence Jeffrey Gonzalez, PharmD, 111 Colchester Avenue, Mailstop 272BA1, Burlington, VT 05401, email: jeffrey.gonzalez@uvmhealth.org

REFERENCES

1. Stoll BJ, Holman RC, Schuchat A. Decline in sepsis-associated neonatal and infant deaths in the United States, 1979 through 1994. *Pediatrics*. 1998;102(2):e18.
2. Touw DJ, Westerman E, Sprij AJ. Therapeutic drug monitoring of aminoglycosides in neonates. *Clin Pharmacokinet*. 2009;48(2):71-88.
3. Davies MW, Cartwright DW. Gentamicin dosage intervals in neonates: longer dosage interval—less toxicity. *J Paediatr Child Health*. 1998;34(6):577-580.
4. Riff LJ, Jackson GG. Pharmacology of gentamicin in man. *J Infect Dis*. 1971;124(suppl):S98-S105.

5. Darmstadt GL, Miller-Bell M, Batra M, et al. Extended-interval dosing of gentamicin for treatment of neonatal sepsis in developed and developing countries. *J Health Popul Nutr*. 2008;26(2):163-182.
6. Tugay S, Bircan Z, Çağlayan C, et al. Acute effects of gentamicin on glomerular and tubular functions in preterm neonates. *Pediatr Nephrol*. 2006;21(10):1389-1392.
7. Lundergan FS, Glasscock GF, Kim EH, et al. Once-daily gentamicin dosing in newborn infants. *Pediatrics*. 1999;103(6 Pt 1):1228-1234.
8. Kent A, Turner MA, Sharland M, et al. Aminoglycoside toxicity in neonates: something to worry about? *Expert Rev Anti Infect Ther*. 2014;12(3):319-331.
9. Niemic KM, Corriveau MP, Ahern JW. Development of a gentamicin and tobramycin dosing strategy in the neonatal intensive care unit. *J Pediatr Pharmacol Ther*. 2004;9:192-197.
10. Sawchuk RJ, Zaske DE, Cipolle RJ, et al. Kinetic model for gentamicin dosing with the use of individual patient parameters. *Clin Pharmacol Ther*. 1977;21(3):362-369.
11. Bernstein IM, Mohs G, Rucquoi M, et al. The case for “hybrid fetal growth curves”: a population based estimation of normal fetal size across gestational age. *J Matern Fetal Med*. 1996;5:124-127.
12. Fenton TR, Kim JH. A systematic review and meta-analysis to revise the Fenton growth chart for preterm infants. *BMC Pediatr*. 2013;13:59.
13. Fisk K. A review of gentamicin use in neonates. *Neonatal Netw*. 1993;12(7):19-23.
14. Chattopadhyay B. Newborns and gentamicin—how much and how often? *J Antimicrob Chemother*. 2002;49(1):13-16.
15. Aly H, Davies J, El-Dib M, et al. Renal function is impaired in small for gestational age premature infants. *J Matern Fetal Neonatal Med*. 2013;26(4):388-391.
16. Lulic-Botica M, Sheer T, Edwards D, et al. Impact of small-for-gestational (SGA) status on gentamicin pharmacokinetics in neonates. *J Clin Pharmacol*. 2014;54:39-45.
17. Ali AS, Farouq F, Al-Faify K. Pharmacokinetic approach for optimizing gentamicin use in neonates during the first week of life. *Indian J Pharmacol*. 2012;44(1):36-40.
18. Chevalier RL. Developmental renal physiology of the low birth weight pre-term newborn. *J Urol*. 1996;156:714-719.
19. Stach LM, Pallotoo E, Sandritter T. Development of criteria for gentamicin monitoring in a neonatal intensive care unit. *Am J Health-Syst Pharm*. 2012;69:1319-1325.
20. Reimche LD, Rooney ME, Hindmarsh KW, et al. An evaluation of gentamicin dosing according to renal function in neonates with suspected sepsis. *Am J Perinatol*. 1987;4(3):262-265.