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ORIGINAL ARTICLE

Should gentamicin trough levels be routinely obtained in term neonates?

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OBJECTIVE: Gentamicin is a common antibiotic used to treat sepsis in neonates. We hypothesize that obtaining routine gentamicin trough levels may not be necessary in low-risk, term infants.

STUDY DESIGN: We performed a retrospective cohort study of term infants ($n = 346$) treated with gentamicin in a single level III neonatal intensive care unit (NICU). The results of gentamicin trough levels and the correlation with risk factors and potential side effects were recorded. In addition, we conducted a survey of 75 academic NICUs across the United States regarding their gentamicin monitoring practice.

RESULTS: Routine trough levels did not predict potential gentamicin toxicity in neonates with low risk factors. Regression analysis demonstrated a positive correlation between gentamicin trough levels and serum creatinine. The survey of the NICUs in the United States demonstrated significant inconsistency in gentamicin monitoring practice.

CONCLUSION: Obtaining gentamicin trough levels guided by risk factors is more appropriate than obtaining routine trough levels in low-risk term neonates.

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INTRODUCTION

Gentamicin is one of the most commonly used antibiotics to treat sepsis in the neonatal period. The mechanism of action is bactericidal inhibition of protein synthesis.[1,2] Because of the potential for ototoxicity and nephrotoxicity, routine serum trough levels are often drawn to reassure clinicians that levels are maintained below the safe level (< 2 μg/ml).[2–9]

Preterm infants are more prone to toxic trough levels, likely because of the immaturity of their renal function.[10–12] Although monitoring gentamicin serum levels is indicated in preterm infants, there is paucity of data regarding such need in term low-risk infants. Studies have shown that since extended dosing intervals have been adopted, trough levels are much more predictable.[13–18] Two meta-analyses demonstrated that extended dosing intervals of gentamicin in neonates achieved desired safe serum concentrations (defined as trough < 2 μg/ml and peak > 5 μg/ml).[1,19] However, despite wide adaptation of this new dosing schedule, monitoring and dose adjustments based on trough levels remain varied among clinicians across the country. This inconsistency occurs not only among institutions but also among different physicians in the same practice. This can cause considerable confusion and prohibits a standardized approach to gentamicin serum level monitoring practice.

We hypothesized that the definition of toxic gentamicin trough level is not standardized in clinical practice across the United States. Furthermore, we hypothesized that obtaining routine gentamicin trough levels in low-risk term infants is not clinically necessary. The present study was conducted to answer these two hypotheses.

MATERIALS AND METHODS

We conducted a phone survey of 75 academic level III/IV neonatal intensive care units (NICUs) that have neonatal fellowship programs from across the United States regarding gentamicin serum level monitoring practice. Two phone calls were attempted to either the NICU charge nurse/director or the neonatal fellow. The phone survey was composed of the following questions:

1. *Which antibiotics do you use in treating sepsis/presumed sepsis in full-term neonates?*
2. *If gentamicin is used, what is the dose/interval?*
3. *When is a gentamicin trough level drawn?*
4. *What is considered an abnormal trough level?*
5. *Who decides the cutoff for an abnormal gentamicin trough level?*

The answers were recorded and stratified based on the responses given.

To determine the occurrence of abnormal trough levels in term neonates (⩾2 μg/ml) and the clinical correlation with potential risk factors and adverse effects, we performed a retrospective study of the charts of 346 full-term neonates admitted to the NICU at Winthrop University Hospital, a designated New York state Regional Perinatal Center. The inclusion criteria were: (1) term infants > 37 weeks of gestation, (2) < 1 week of age, (3) receiving gentamicin for presumed sepsis (7-day course) and (4) having trough levels drawn before the third dose. Our unit uses extended dosing interval of 4 mg kg^{-1} per day and the gentamicin trough level is routinely obtained before the third dose. This study was approved by our institutional review board as an expedited protocol. Gestational age, birth weight, dosage given, hearing screen results, concomitant administration of nephrotoxic drugs (vancomycin, indomethacin, furosemide or amphotericin) as well as serum creatinine levels when available (if obtained before the trough level was drawn) were recorded.

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Table 1. Survey of 75 academic neonatal intensive care units (NICUs) across the United States demonstrated significant variability regarding gentamicin use; however, the majority of NICUs used ampicillin and gentamicin as the antibiotics of choice to treat neonatal sepsis in the first week of life (90%), prescribed gentamicin at a dose of 4 mg kg− 1 per day (84%) and sampled gentamicin trough levels before the third dose (58%)

Question 1: Which antibiotics do you use in treating sepsis/ presumed sepsis in full-term neonates?	Ampicillin/gentamicin (90%)	Vancomycin/gentamicin (4%)	Ampicillin/gentamicin/ vancomycin (4%)	Vancomycin/ cefotaxime (2%)
Question 2: If gentamicin is used, what is the dose/ interval?	4 mg kg^{-1} per day (84%)	5 mg kg^{-1} per day (9%)	3.5 mg kg^{-1} per day (5%)	4.5 mg kg^{-1} per day (2%)
Question 3: When is the gentamicin trough level drawn?	Before third dose (58%)	Before fourth dose (30%)	Before second dose (12%)	

Descriptive statistics were presented using means and proportions as appropriate. Normality of the variables 'gentamicin trough levels' and 'creatinine' was examined using Kolmogorov–Smirnov test. Spearman's correlation coefficient and scatter plot were used to evaluate relationship between creatinine and gentamicin trough level. A linear regression model was used to determine the effect of creatinine on the trough level. SAS 9.4 (SAS Institute Inc., Cary, NC, USA) was used to perform the analyses and *P*-value of < 0.05 was considered statistically significant.

RESULTS

Definition of gentamicin toxic trough levels across academic NICU institutions in the United States

The phone survey of the academic NICUs demonstrated significant inconsistencies. Of the 75 NICUs contacted, 55 (73%) responded with full answers to questions asked. As shown in Table 1, the answers for the first three questions demonstrated that the majority of NICUs use ampicillin and gentamicin to treat neonatal sepsis in the first week of life (90%), gentamicin dose of 4 mg kg^{-1} per day (84%) and obtain gentamicin trough levels before the third dose (58%). Although differences existed between institutions, most of the variability was related to questions 4 and 5 (What is considered an abnormal gentamicin trough level? and Who decides the cutoff for such level?). Out of the 55 NICUs that responded to our survey (Figure 1), 35 NICUs (64%) stated that they have a fixed cutoff value that defines toxic trough gentamicin levels, 18 (33%) defined toxic gentamicin level as $\geqslant 2$ μg/ml and 17 (31%) defined toxic gentamicin level as $\geqslant 1$ μg/ml. As shown in (Figure 1), 20 NICUs (36%) did not have a fixed cutoff value to define toxic trough gentamicin levels but rather this level was determined by either the medical team for 9 NICUs (16%) or pharmacy staff for 11 NICUs (20%).

The incidence of high gentamicin trough levels in term neonates and its correlation with risk factors and potential side effects

A population of 346 patients met our inclusion criteria. The mean gestational age was 40.4 weeks and mean birth weight was 3.315 kg. Table 2 depicts the incidence of trough levels in term neonates < 1, 1 to 1.9 and $\geqslant 2$ μg/ml, as well as its correlation with risk factors and potential adverse effects. Gentamicin serum trough level < 1 μg/ml was reported in 57% of neonates, whereas 42% had a level between 1 and 1.9 μg/ml. Only 2 patients (0.6%) had elevated trough levels of 2 and 2.1 μg/ml. Both patients had a history of low urine output, defined as < 1 ml $kg^{-1}h^{-1}$ or at least two dry diapers in the 24 h period before the gentamicin trough level was drawn. There were 7 neonates who had abnormal hearing screens but none had trough levels of $\geqslant 2$ μg/ml (3 with trough levels < 1 μg/ml and 4 with trough levels 1 to 1.9 μg/ml). We had 3 patients with concomitant use of nephrotoxic drugs, but none had gentamicin trough levels of $\geqslant 2$ μg/ml. None of our patients had serum creatinine levels of > 1 mg dl^{-1}. Spearman's correlation analysis demonstrated a positive correlation between gentamicin trough levels and serum creatinine (Figure 2). An unadjusted linear regression model was developed for gentamicin trough level using creatinine as the independent variable ($R^2 = 0.10$, regression coefficient = 0.51, s.e. = 0.11, F = 22.89, $P < 0.0001$). Hence, we can interpret the regression coefficient that for every 1 mg dl^{-1} increase in creatinine, gentamicin trough level would increase by 0.51 μg/ml.

DISCUSSION

Our study demonstrates the wide variability among clinical practitioners regarding the definition of a toxic gentamicin trough level. Furthermore, the results from our NICU demonstrated the low yield of elevated gentamicin serum trough levels in term, low-risk neonates (with normal urine output and normal serum creatinine).

Aminoglycosides along with β-lactam antibiotics remain the most widely adopted antibiotics in many NICUs, with gentamicin being the most commonly used aminoglycoside. Drawbacks to the use of aminoglycosides in neonates include their narrow therapeutic index causing a greater potential for ototoxicity and nephrotoxicity. Extended dosing intervals were adopted by many NICUs to improve gentamicin's pharmacodynamic profile, consisting of a larger gentamicin dose given over a prolonged dosing interval of 24 h while maintaining drug safety.[20–24] Dosing regimens range from 2 to 5 mg kg^{-1} per dose, administered every 8 to 36 h with target trough concentrations from 0.5 to 2 μg/ml.[25] In most cases, this antibiotic regimen is used in neonates at high risk for infection as an empirical therapy to rule out suspected sepsis, rather than to actually treat proven sepsis. Such courses are only used for 48 h (until cultures are negative) with no need to obtain trough levels. However, if the regimen course exceeds 48 h, most NICUs will monitor the gentamicin trough level and that might dictate change in dosing and/or interval. A study conducted by Boyle *et al.*[26] in 2006 attempted to develop a nomogram similar to the adult nomogram used for evaluation of gentamicin doses 4–16 h after administration. The study was unable to construct a single, clinically valid nomogram to predict aminoglycoside concentrations for infants of varying ages, using the once daily gentamicin dosing.[26] In a retrospective study done by Stach *et al.*,[4] factors associated with an increased risk of supratherapeutic trough levels included inappropriate dosing, elevated serum creatinine concentrations, low urine output and shock. Contrary to our focus on term infants, the mean gestational age for this study subjects was 35 weeks (range 23–41 weeks) and the incidence of inappropriate gentamicin doses given was 18%. Nevertheless, their conclusion is in agreement with our results that frequent monitoring of gentamicin serum levels may not be necessary in low-risk neonates if standard correct doses are used.[4] The wide variability observed in

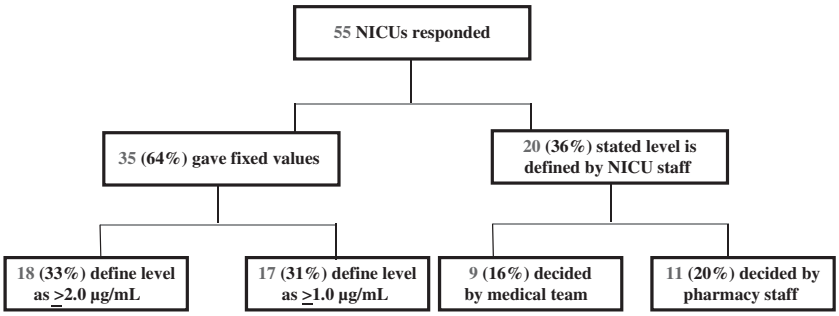

Figure 1. Phone survey results show inconsistency regarding gentamicin trough level monitoring practice. Of all 55 neonatal intensive care units (NICUs) surveyed, toxic trough level was defined as ⩾2.0 µg/ml (33% of all NICUs) or ⩾1.0 µg/ml (31% of all NICUs); however, 36% of the 55 NICUs deferred the definition of toxic trough levels to the NICU staff on a case-by-case basis.

Table 2. Results of data stratified by trough level ranges showing the incidence of gentamicin trough levels and its correlation with risk factors and potential side effects

Gentamicin levels	*< 1.0 µg/ml*	*1.0–1.9 µg/ml*	*⩾2.0 µg/ml*
Incidence	198/346 (57.2%)	146/346 (42.2%)	2/346 (0.6%)
Birth weight (mean)	3.574 kg	3.438 kg	3.330 kg
Birth weight < 2.5 kg	5/198 (2.5%)	7/146 (4.8%)	0
Low urine output	19/198 (9.5%)	12/146 (8.2%)	2/2 (100%)
Abnormal hearing screen	3/198 (1.5%)	4/146 (2.7%)	0
Nephrotoxic meds	2/198 (1.0%)	1/146 (0.7%)	0
Creatinine serum levels (mean)	0.4 mg dl^{-1}	0.5 mg dl^{-1}	0.7 mg dl^{-1}

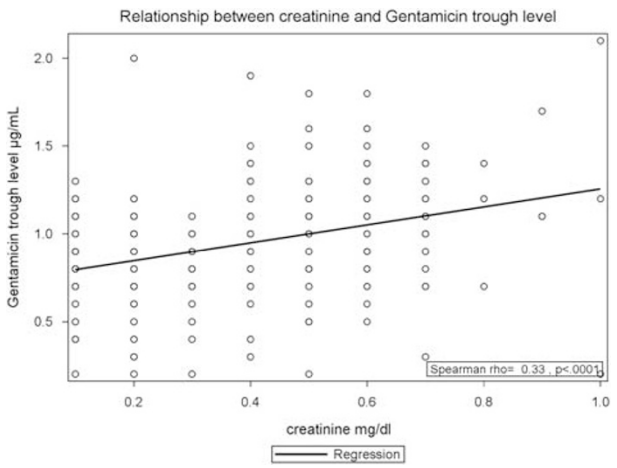

Figure 2. Scatter plot with a linear regression line depicting positive relationship between serum creatinine and gentamicin trough levels.

our survey among academic NICUs regarding the definition of toxic gentamicin trough level was surprising. A possible explanation is that a widely used drug reference, 'Neofax', lists the toxic gentamicin trough level as >1 µg/ml, but other references list toxic levels as ⩾2 µg/ml.[27–30] Review of the Neofax references did not provide evidence to justify the definition of toxic gentamicin trough level as >1 µg/ml in term neonates. Our survey demonstrated that 20% of the NICUs do not use any fixed reference value for gentamicin to adjust doses but rather depend on pediatric pharmacy staff that adjust doses based on calculated pharmacokinetics. Such practice would require resources that might not be available for all NICUs, hence another reason for practice variability.

Some of the limitations of our study include the inherent disadvantages of performing a retrospective study. Another possible limitation is that urine output, serum creatinine and gentamicin serum levels were recorded on day 3 of therapy and not throughout the 7-day course. In addition, the phone survey used NICU staff self-reporting, allowing for possible recall bias and potentially incomplete information.

To our knowledge, this is the largest study to date ($n = 346$) addressing the range of gentamicin trough levels in term neonates treated for >48 h using extended dosing interval administration. Our results confirm what previous studies have alluded to regarding the poor yield of routine checking of gentamicin trough levels in low risk neonates, defined as full term neonates with adequate urine output, no clinical or laboratory evidence of renal impairments and/or concomitant use of nephrotoxic drugs.[4,31] Based on our study we recommend monitoring gentamicin trough levels if neonatal serum creatinine level is above the known normal ranges for neonates and/or urine output is not adequate. On the other hand, some of these neonates with high creatinine levels might not need monitoring of gentamicin levels as serum creatinine in the first week of neonatal life is mostly reflective of maternal serum creatinine rather than neonatal kidney disease; however, it will be difficult to distinguish between both in routine practice.

We propose an alternative paradigm in favor of a focused approach of obtaining gentamicin trough levels only in the presence of clinical or laboratory evidence of renal impairments or concomitant use of nephrotoxic drugs. This will result in significant cost savings, less blood work performed and reduced nurse-tasking time.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

1 Rao SC, Srinivasjois R, Hagan MA. One dose per day compared to multiple doses per day of gentamicin for treatment of suspected or proven sepsis in neonates. *Cochrane Database Syst Rev* 2011; **11**: 1–36.
2 Brunton LB, Chabner BA, Knollmann BC. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 12th edn. McGraw-Hill: New York, 2011.
3 Reynolds L, Mailman T, McMillan D. Gentamicin in neonates at risk for sepsis - peak serum concentrations are not necessary. *Paediatr Child Health* 2012; **17**: 310–312.
4 Stach L, Pallotto E, Sandritter T. Development of criteria for gentamicin monitoring in a neonatal intensive care unit. *Am J Health Syst Pharm* 2012; **69**: 1319–1325.
5 Miron D. Once daily dosing of gentamicin in infants and children. *Pediatr Infect Dis J* 2001; **20**: 1169–1173.
6 Thureen PJ, Reiter PD, Gresores A, Stolpman N, Kawato K, Hall DM. Once- versus twice-daily gentamicin dosing in neonates $\geqslant$ 34 weeks' gestation: cost-effectiveness analyses. *Pediatrics* 1999; **103**: 594–598.
7 Krishnamoorthy S, Nair A, Furness J, Sanderson J. Gentamicin use in neonates: should we have a change of practice? *Scott Med J* 2013; **58**: 241–245.
8 Agarwal G, Rastogi A, Pyati S, Wilks A, Pildes RS. Comparison of once-daily versus twice-daily gentamicin dosing regimens in infants $>$ or = 2500 g. *J Perinatol* 2002; **22**: 268–274.
9 Koren K. Therapeutic drug monitoring principles in the neonate. *Clin Chem* 1997; **43**: 222–227.
10 Knight J, Davis E, Manouilov K, Hoie E. The effect of postnatal age on gentamicin pharmacokinetics in neonates. *Pharmacotherapy* 2003; **23**: 992–996.
11 Williams BS, Ransom JL, Gal P, Carlos RQ, Smith M, Schall SA. Gentamicin pharmacokinetics in neonates with patent ductus arteriosus. *Crit Care Med* 1997; **25**: 273–275.
12 Valitalo P, Van den Anker J, Allegaert K, De Cock R, De Hoog M, Simons S *et al.* Novel model-based dosing guidelines for gentamicin and tobramycin in preterm and term neonates. *J Antimicrob Chemother* 2015; **70**: 2074–2077.
13 Begg EJ, Vella-Brincat JW, Robertshawe B, McMurtrie MJ, Kirkptrick CM, Darlow B. Eight years' experience of an extended-interval dosing protocol for gentamicin in neonates. *J Antimicrob Chemother* 2009; **63**: 1043–1049.
14 Dersch-Mills D, Aikerman A, Alshaikh B, Sundaram A, Yusuf K. Performance of a dosage individualization table for extended interval gentamicin in neonates beyond the first week of life. *J Matern Fetal Neonatal Med* 2016; **29**: 1451–6.
15 Smith C, Lee KR, Phelps SJ. Is gentamicin monitoring necessary in infants 3 months of age or younger. *J Pediatr Pharmacol Ther* 2004; **9**: 144.
16 Nielsen EI, Sandström M, Honoré PH, Ewald U, Friberg LE. Developmental pharmacokinetics of gentamicin in preterm and term neonates: population modelling of a prospective study. *Clin Pharmacokinet* 2009; **48**: 253–263.
17 Pacifici GM. Clinical pharmacokinetics of aminoglycosides in the neonate: a review. *Eur J Clin Pharmacol* 2009; **65**: 419–427.
18 Bajaj M, Palmer K. Gentamicin usage in newborns--a simple and practical regime. *Pharm World Sci* 2004; **26**: 242–244.
19 Nestaas E, Bangstad HJ, Sandvik L, Wathne K. Aminoglycoside extended interval dosing in neonates is safe and effective: a meta-analysis. *Arch Dis Child Fetal Neonatal Ed* 2005; **90**: F294–F300.
20 Hansen A, Forbes P, Arnold A, O'Rourke E. Once daily gentamicin dosing for the preterm and term newborn: proposal for a simple regimen that achieves target levels. *J Perinatol* 2003; **23**: 635–639.
21 DiCenzo R, Forrest A, Slish JC, Cole C, Guillet R. A gentamicin pharmacokinetic population model and once-daily dosing algorithm for neonates. *Pharmacotherapy* 2003; **23**: 585–591.
22 Lundergan F, Glasscock G, Lundergan FS, Glasscock GF, Kim EH, Cohen RS. Once-daily gentamicin dosing in newborn infants. *Pediatrics* 1999; **103**: 1228–1234.
23 Murphy JE, Austin ML, Frye RF. Evaluation of gentamicin pharmacokinetics and dosing protocols in 195 neonates. *Am J Health Syst Pharm* 1998; **55**: 2280.
24 Contopoulos D, Giotis N, Baliatsa D, Ioannidis J. Extended-interval aminoglycoside administration for children: a meta-analysis. *Pediatrics* 2004; **114**: e111–e118.
25 Dersch-Mills D, Akierman A, Alshaikh B, Yusuf K. Validation of a dosage individualization table for extended-interval gentamicin in neonates. *Ann Pharmacother* 2012; **46**: 935–942.
26 Boyle E, Brookes I, Nye K, Watkinson M, Riordan A. "Random" gentamicin concentrations do not predict trough levels in neonates receiving once daily fixed dose regimens. *BMC Pediatr* 2006; **6**: 8.
27 Stolk L, Degraeuwe P, Nieman F, De Wolf MC, Boer A. Population pharmacokinetics and relationship between demographic and clinical variables and pharmacokinetics of gentamicin in neonates. *Ther Drug Monit* 2002; **24**: 527–531.
28 Giapros V, Andronikou S, Cholevas C, Papadopoulou Z. Renal function in premature infants during aminoglycoside therapy. *Pediatr Nephrol* 1995; **9**: 163–166.
29 Contopoulos-Ioannidis DG, Giotis ND, Baliatsa DV, Ioannidis JP. Extended-interval aminoglycoside administration for children: a meta-analysis. *Pediatrics* 2004; **114**: e111–e118.
30 Andronikou S, Giapros V. Effect of aminoglycoside therapy on renal function in fullterm infants. *Pediatr Nephrol* 1996; **10**: 766–768.
31 Murphy JE. Prediction of gentamicin peak and trough concentrations from six extended-interval dosing protocols for neonates. *Am J Health Syst Pharm* 2005; **62**: 823–827.