



Published in final edited form as:

*J Perinatol.* 2013 October ; 33(10): 778–782. doi:10.1038/jp.2013.59.

## Every 36-hour Gentamicin Dosing in Neonates with Hypoxic Ischemic Encephalopathy Receiving Hypothermia

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### Abstract

**Objective**—To examine the impact of a change in the empiric gentamicin dose from 5 mg/kg every 24h to 5 mg/kg every 36h on target drug concentration achievement in neonates with hypoxic ischemic encephalopathy (HIE) receiving therapeutic hypothermia.

**Study Design**—Gentamicin drug concentrations in neonates with HIE receiving therapeutic hypothermia were examined during two time periods in a retrospective chart review. During the initial treatment period (November 2007 to March 2010; n=29), neonates received gentamicin 5 mg/kg every 24h (Q24h period). During the second treatment period (January 2011 to May 2012; n=23), the dose was changed to 5 mg/kg every 36h (Q36h period). Cooling criteria and protocol remained the same between treatment periods. Gentamicin drug concentrations including achievement of target trough concentrations (<2 mg/L) were compared between treatment periods. Individual Bayesian estimates of gentamicin clearance were also compared.

**Result**—Neonates with an elevated trough concentration >2 mg/L decreased from 38% to 4% with implementation of a Q36h dosing interval (P<0.007). The mean gentamicin trough concentration was 2.0 ± 0.8 mg/L during the Q24h period and 0.9 ± 0.4 mg/L during the Q36h period (P<0.001). Peak concentrations were minimally impacted (Q24h 11.4 ± 2.3 mg/L vs. Q36h

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#### Conflicts of Interest

The authors have no conflict of interest, real or perceived, to report. There was no study sponsor.

#### Previously Presented

- 1) Data from the Q24h period were used for a published population pharmacokinetic analysis and formed the basis for the every 36h gentamicin dose change under study.
- 2) Preliminary findings of this work in part will be presented as abstract and poster for the Pediatric Academic Societies Annual Meeting, Washington, DC, May 4–7, 2013.

10.0 ± 1.9 mg/L; P=0.05). The change in gentamicin trough concentration could not be accounted for by differences in gentamicin clearance between treatment periods (P=0.9).

**Conclusion**—A 5 mg/kg every 36h gentamicin dosing strategy in neonates with HIE receiving therapeutic hypothermia improved achievement of target trough concentration <2 mg/L while still providing high peak concentration exposure.

### Keywords

gentamicin; neonates; pharmacokinetics; hypothermia; hypoxic ischemic encephalopathy

## INTRODUCTION

Current understanding on the pharmacokinetics of drugs in neonates with hypoxic ischemic encephalopathy (HIE) is limited. In addition to brain injury, global hypoxic insult often results in acute liver and kidney injury that can impact drug clearance.(1–5) In addition, therapeutic hypothermia is recommended for moderate to severe HIE(6) with the potential to alter drug pharmacokinetics through changes in organ physiology and blood flow.(7) Considering these factors, drug pharmacokinetics must be evaluated in neonates with HIE receiving hypothermia.(7).

Gentamicin is commonly used in neonates with HIE for the empiric treatment of presumptive infection.(7) A previous study demonstrated no impact of hypothermia on trough concentrations in HIE neonates.(8) However, in this same study a gentamicin dose of 4–5 mg/kg every 24h resulted in elevated trough concentrations, i.e. >2 mg/L in 36% of hypothermic and 44% of normothermic neonates. A population pharmacokinetic analysis of gentamicin in neonates with HIE receiving hypothermia also reported frequent elevations in trough concentrations using a similar dosing scheme.(9) A dosing interval of every 36 hours was predicted to be needed to allow for adequate drug clearance and achieve target trough concentrations <2 mg/L. Accordingly, our institution recently changed the empiric dose of gentamicin for neonates with HIE receiving hypothermia from 5 mg/kg every 24h to 5 mg/kg every 36h. The goal of the present study was to evaluate the impact of this change in dosing frequency on target drug concentration achievement.

## METHODS

This study was approved by the UCSF Committee on Human Research. In January 2011, the neonatal intensive care unit (NICU; a fifty-bed level III unit located in a tertiary care, academic medical center) at the University of California San Francisco (UCSF) adopted a revised empirical gentamicin dose of 5 mg/kg IV every 36h for neonates with HIE receiving therapeutic hypothermia. Prior to this time, the recommended gentamicin dose was 5 mg/kg IV every 24h. Using retrospective chart review, the initial gentamicin peak and trough concentrations in the study population (neonates with HIE treated with whole-body therapeutic hypothermia (33.5°C)) pre and post implementation of the every 36H dosing regimen were evaluated. The evaluation time periods were the following: November 2007 to March 2010 (gentamicin 5 mg/kg IV every 24h; Q24h period) and January 2011 to May 2012 (gentamicin 5 mg/kg IV every 36h; Q36h period).

Cooling criteria and protocol remained the same between the two treatment periods.(10) All neonates were started on gentamicin for a ‘rule-out’ sepsis as part of the cooling protocol. Gentamicin dosing guidelines are disseminated at UCSF using an antimicrobial dosing card distributed to all residents, clinical pharmacists and faculty physicians. Dose recommendations are reinforced by clinical pharmacists via daily review. As part of standard therapeutic drug monitoring (TDM), a trough concentration was recommended after the 2nd or 3rd dose during both treatment periods. Peak concentrations were not recommended during the Q24h period but were recommended during the Q36h period due to the inexperience with the new dose. In those instances associated with acute renal failure (i.e. elevated or rapidly rising serum creatinine), TDM was occasionally measured earlier than usually recommended. Gentamicin peak concentrations were drawn 30 minutes after the end of a 30-minute infusion, and trough concentrations were drawn just prior to the next dose.

Clinical and laboratory data, including the complete gentamicin dosing and drug concentration history, were collected. Neonates were excluded if the gentamicin dose or drug concentration history were not available or incomplete, ECMO was required, or with the presence of concomitant congenital heart disease or kidney disease. The target trough concentration was <2 mg/L. Gentamicin concentrations were measured using a competitive immunoassay with a reportable range of 0.2 mg/L to 24 mg/L (ADVIA Centaur Gentamicin assay, Bayer Diagnostics, Deerfield, IL).

### Pharmacokinetic and Statistical Analysis

Differences in peak and trough concentrations between treatment periods were compared using Student’s t-test. The percentage of neonates achieving target trough concentrations was compared using Fisher-exact test. To examine if gentamicin clearance (CL) was similar between treatment periods and not confounding drug concentration achievement, an empirical Bayesian estimate of CL was calculated for each neonate implementing our published population pharmacokinetic model(9) in the nonlinear mixed-effects modeling program NONMEM (Version VII, Icon Development Solutions, Ellicott City, MD). In the pharmacokinetic model gentamicin CL was predicted by birthweight and serum creatinine (Cr) on day of life 2 as defined by the following equation:

$$CL(L/h)=0.111 \times \left( \frac{Birthweight}{3.3 \text{ kg}} \right)^{0.75} \times \left( \frac{1}{Cr_{,mg/dl}} \right)^{0.566}$$

The inter-individual variability of CL followed an exponential error model with a coefficient of variation of 16.1%. Utilizing each neonate’s birthweight, serum creatinine, and gentamicin dosing and concentration history, individual empirical Bayesian estimates of CL were calculated using the MAXEVAL=0 POSTHOC estimation routine in NONMEM. The estimated gentamicin clearance was then scaled using the allometric 3/4 power model to a 70kg adult(11) and log-transformed before comparison by Student’s t-test. All statistical analyses were performed using R (Version 2.12.0; R Foundation for Statistical Computing,

Vienna, Austria). Continuous data are reported as mean  $\pm$  SD, and categorical data are reported as counts (%). A P value  $<0.05$  was considered significant.

## RESULTS

Thirty-four neonates with HIE receiving therapeutic hypothermia in the Q24 period and 27 neonates with HIE receiving therapeutic hypothermia in the Q36h period had gentamicin concentration data available. Five neonates were excluded from the Q24h period: three required ECMO, one was diagnosed with cardiomyopathy, and one had incomplete dose records. Four neonates were excluded from the Q36h period: one required ECMO, two had incomplete dose records, and one had only a random drug level. Therefore, a total of 29 neonates in the Q24h period and 23 neonates in the Q36h period were evaluated. All neonates had gentamicin trough concentrations available. Eighteen (62%) neonates in the Q24h period and twenty (87%) neonates in the Q36h period had peak concentrations.

Neonates were generally comparable between the two treatment periods; however, neonates in the Q24h period had a slightly lower gestational age, lower 5-minute APGAR, higher base deficit, and higher mortality rate (Table 1). Five neonates died after redirection of care for severe brain injury that was detected by neurologic exam and confirmed with EEG and/or Head Ultrasound and MRI. One neonate died after redirection of care for moderate-severe brain injury and severe end-organ dysfunction represented by persistent coagulopathy requiring ongoing transfusions, elevated liver enzymes, and acute renal failure. There were no differences in birthweight and serum creatinine between treatment periods - two major predictors of gentamicin clearance.

The mean gentamicin dose was  $4.9 \pm 0.3$  mg/kg every 24 hours and  $5.0 \pm 0.1$  mg/kg every 36 hours during the Q24h and Q36h period, respectively. The time of initial gentamicin drug level measurement increased from  $2.2 \pm 1.1$  days in the Q24 period to  $3.2 \pm 0.9$  days in the Q36 period ( $P=0.001$ ). This increase coincides with the difference in timing of a 3rd gentamicin dose using an every 24h versus an every 36h regimen. Gentamicin peak and trough concentrations achieved during both treatment periods are shown in Figure 1. The mean trough concentration decreased from  $2.0 \pm 0.8$  mg/L in the Q24h period to  $0.9 \pm 0.4$  mg/L in the Q36h period ( $P<0.001$ ). The percentage of neonates with an elevated trough concentration  $>2$  mg/L decreased from 38% (11 of 29) to 4% (1 of 23) with implementation of a Q36h dosing interval ( $P<0.007$ ). There was a trend toward lower peak concentrations (Q24h  $11.4 \pm 2.3$  mg/L vs. Q36h  $10.0 \pm 1.9$  mg/L;  $P=0.05$ ). The lowest peak concentration was 7.5 mg/L and 7.4 mg/L in the Q24H and Q36h periods, respectively.

Gentamicin clearance was similar in both treatment periods (Q24h  $1.17 \pm 0.24$  L/h/70kg vs. Q36h  $1.15 \pm 0.19$  L/h/70kg;  $P=0.9$ ). Serum creatinine on the second day of life correlated with trough concentration (Q24h  $r^2 = 0.54$ ; Q36h  $r^2 = 0.14$ ) and gentamicin clearance (combined  $r^2 = 0.48$ ) (Figure 2). During the Q24 period, 4 of the 6 neonates who ultimately died had an elevated trough concentration  $>2$  mg/L; the serum creatinine was 1.2 mg/dl in three of these four neonates. In the two neonates who died but had a normal trough concentration, the serum creatinine was 0.9 mg/dl on the second day of life. The one

neonate who did not achieve target trough concentration in the Q36h period had a serum creatinine of 1.3 mg/dl on the second day of life.

## DISCUSSION

This study examined the impact of implementing a new empiric gentamicin dose of 5 mg/kg every 36h on drug concentrations in neonates with HIE receiving hypothermia. The major study finding was that every 36h dosing significantly improved achievement of target trough concentration with 96% achieving a concentration <2 mg/L. In addition, high peak concentrations were still maintained with this dosing strategy.

Neonates with HIE are a critically ill population often with multi-organ system morbidity. (3,4) Therapeutic hypothermia for 72 hours is an effective treatment modality in neonates with moderate to severe HIE(12) and is now the standard of care.(6) As the treatment for neonates with HIE evolves and specialized neonatal neurocritical care models are developed,(13) understanding the therapeutic use of drugs in this population and their unique clinical pharmacologic needs will be essential.

Gentamicin is a common antibiotic used in neonates to treat suspected sepsis.(14) A standard dose of 4–5 mg/kg every 24h regularly achieves target drug concentrations in full-term neonates.(15) However, a previous clinical study in neonates with HIE showed a high rate of elevated trough concentrations >2 mg/L for both hypothermic and normothermic subjects when this standard dose was used.(8) To help develop a customized gentamicin dose strategy for neonates with HIE receiving hypothermia, we previously evaluated gentamicin pharmacokinetics.(9) Gentamicin clearance was reduced in neonates with HIE receiving hypothermia, and birthweight and serum creatinine were significant predictors of gentamicin clearance. Monte Carlo simulations predicted a gentamicin dose of 5 mg/kg every 36h would achieve trough concentrations <2 mg/L in 90% of neonates. Post-implementation of this gentamicin dose, achievement of target trough concentrations in neonates with HIE receiving hypothermia was similar to the model predictions. In addition, this dosing strategy still benefits from higher peak concentrations associated with extended interval aminoglycoside dosing that are desirable given the concentration-dependent killing of gentamicin.(16) While larger, multi-center studies would provide further validation, the current evidence supports an empiric gentamicin dose of 5 mg/kg every 36h in neonates with HIE receiving hypothermia to achieve trough concentrations <2 mg/L.

Gentamicin is eliminated from the body by glomerular filtration,(17) and gentamicin clearance was lower in neonates with reduced kidney function as measured by serum creatinine on DOL 2 (Figure 2). This is in agreement with previous pharmacokinetic studies in neonates,(18–20) however the relationship between serum creatinine and gentamicin clearance in neonates has been inconsistent.(21) This inconsistency is likely due to the confounding of serum creatinine in the first 24 to 48 hours after birth with maternal kidney function due placental transfer. But, neonates with HIE who develop acute kidney injury have been documented to have elevation in serum creatinine as soon as DOL 1,(22) which could explain its predictive ability found in our study. However, even for a given serum creatinine interpatient variation in gentamicin clearance remained. Therefore, TDM at the

3rd gentamicin dose is still necessary to help guide more long-term dosing. Due to the poor sensitivity of serum creatinine in detecting mild and moderate acute kidney injury,(23) newer urinary biomarkers such as neutrophil gelatinase-associated lipocalin (NGAL) that are potentially more sensitive and specific predictors of acute kidney injury warrant further study in the HIE population.(24–26)

We focused on gentamicin dosing in the context of hypothermia since all neonates with HIE in our study were cooled. Animal studies have shown a decrease in gentamicin clearance during severe (29°C)(27) but not moderate (35°C) hypothermia.(28) A previous clinical study reported similar gentamicin trough concentrations in normothermic and hypothermic (33.5°C) neonates.(8) A similar lack of effect of hypothermia on drug clearance in neonates with HIE has been reported for phenobarbital, a drug primarily dependent upon hepatic metabolism.(29,30) However, the power to detect small to modest effects of hypothermia on phenobarbital pharmacokinetics was likely low given study design limitations inherent to the HIE population, including small sample size, limited concentration sampling, concomitant medications, and large variation in pathophysiology. In addition, an already reduced drug clearance in neonates with HIE(31) likely makes the detection of further alterations from hypothermia challenging. Hypothermia is now standard of care in neonates with HIE,(6) and this creates a complexity moving forward in studying the specific effect of hypothermia on drug pharmacokinetics. Whether future studies will be able to adequately address the hypothermic effect on drug pharmacokinetics in neonates is unclear. Nonetheless, understanding drug pharmacokinetics and drug dose needs in neonates with HIE while receiving hypothermia is still valuable clinically.

Limitations to our study include potential differences in neonates between the two study periods. The institution's cooling protocol criteria did not differ between treatment periods and therefore provided some consistency in population selection. Nonetheless, a few measured patient characteristics that could indicate a sicker population were different (see Table 1). Most evident, death was more common in the Q24 period (6 of 29) versus the Q36h period (0 of 23). However, death was due to redirection of care for brain injury and not end-organ dysfunction in all but one neonate. In addition, the similarity in birthweight and serum creatinine between treatment periods was reassuring since these were found to be two predictors of gentamicin clearance in neonates with HIE receiving hypothermia,(9) and the calculated gentamicin clearance was the same between treatment periods. Since gentamicin clearance is the fundamental pharmacokinetic parameter influencing trough concentrations, the neonates were comparable from a pharmacologic perspective. Furthermore, in the neonates who ultimately died, the serum creatinine was still helpful in predicting gentamicin clearance and helped differentiate the patients from a pharmacologic perspective. Further limitations to the study include the retrospective design, small sample size and the availability of a convenience sample of drug level data collected as part of routine care. Additionally, the study lacked power to directly evaluate the impact of the dose change on clinical outcomes, including treatment effectiveness or toxicity. Every 36h and 48h dosing intervals have previously been described for other neonatal populations with reduced gentamicin clearance such as the preterm neonate.(32,33)



## Conclusions

Compared to a 5 mg/kg every 24h dose, an empiric gentamicin dose of 5 mg/kg every 36h improved achievement of trough concentrations <2 mg/L in neonates with HIE receiving hypothermia. Due to the variation and frequent acute kidney injury in neonates with HIE, routine TDM is recommended to help guide dosing. Focused clinical pharmacology studies for other medications commonly used in neonates with HIE receiving hypothermia are warranted.

## Acknowledgments

### Authorship

Adam Frymoyer wrote the first draft of the manuscript and NO honorarium, grant, or other form of payment was given to anyone to produce the manuscript. Each author listed on the manuscript has seen and approved the submission of this version of the manuscript and takes full responsibility for the manuscript. Each author clearly meets authorship criteria as described at <http://www.icmje.org>.

**Sources of support:** A.F. received support in part by the National Institutes of Health grant R01 AI50587, D.V. received support in part by National Institutes of Health grant R01 AI50587, R01 GM26696, S.L.B. received support by the National Center for Advancing Translational Sciences, National Institutes of Health through UCSF-CTSI Grant KL2TR000143.

We would like to thank Susan Peloquin, RN, MS, Clinical Coordinator of the UCSF Neuro-Intensive Care Nursery and members of the UCSF Neuro-Intensive Care Nursery leadership and nursing teams for helping support this project. A.F. received support in part by the National Institutes of Health grant R01 AI50587, D.V. received support in part by National Institutes of Health grant R01 AI50587, GM26696. S.L.B. received support by the National Center for Advancing Translational Sciences, National Institutes of Health through UCSF-CTSI Grant KL2TR000143.

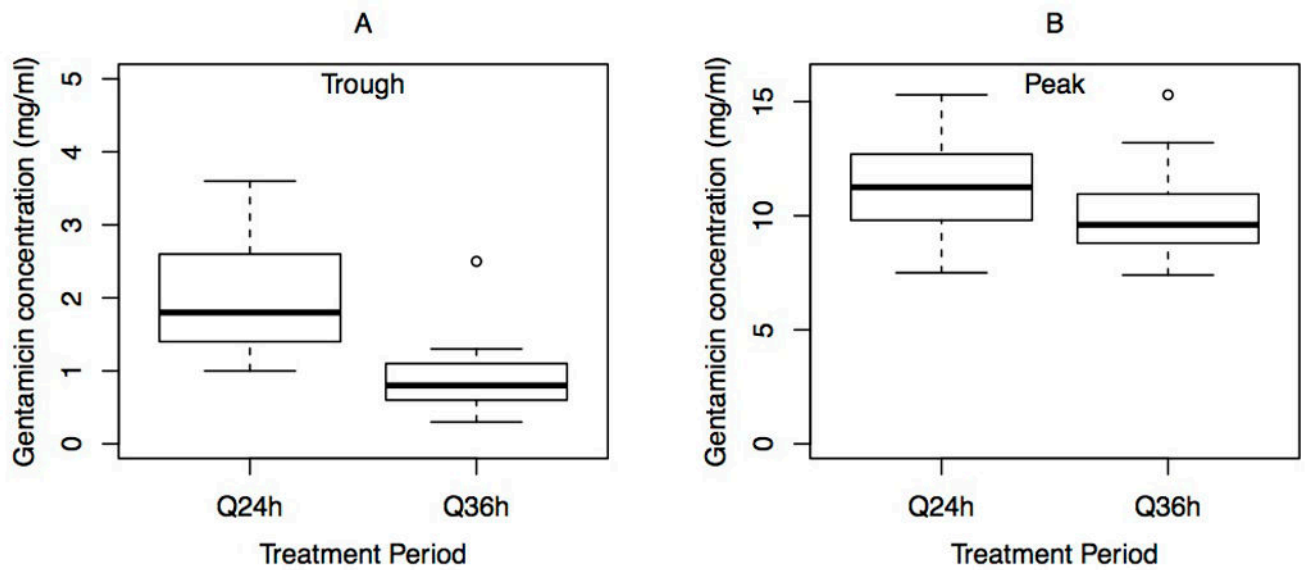
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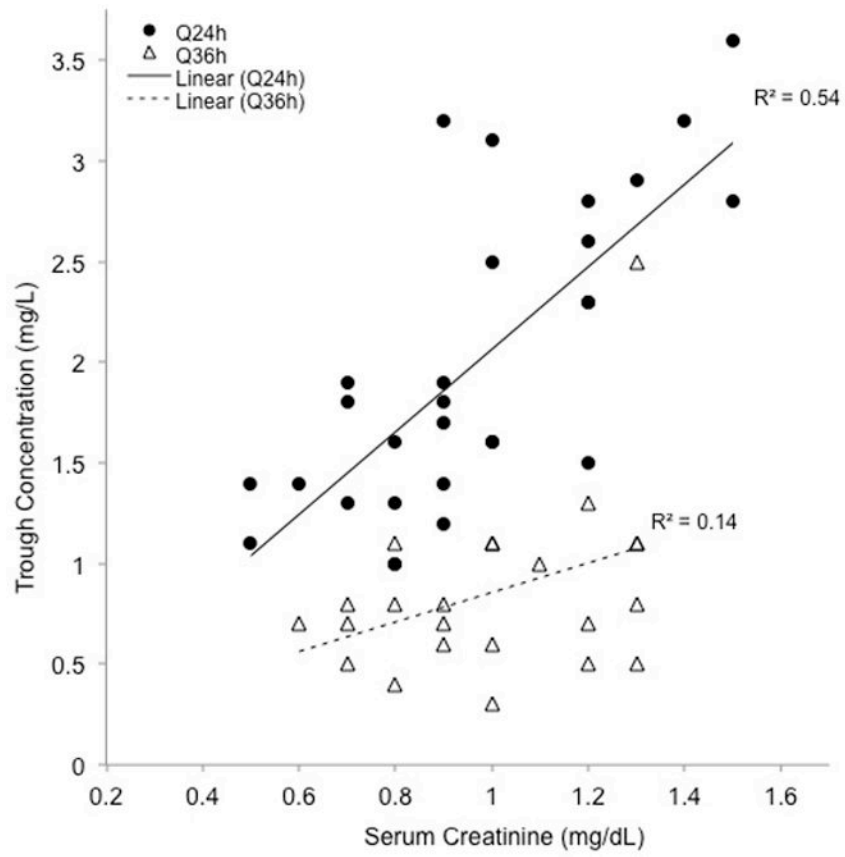
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**Figure 1.** Gentamicin trough (A) and peak (B) concentrations in neonates with HIE receiving therapeutic hypothermia. Neonates received 5 mg/kg every 24 hours during the Q24h period and 5 mg/kg every 36 hours during the Q36h period. Box plot whiskers represent  $\pm 1.5 \times$  inner quartile range. (Trough: Q24h n=29, Q36h n=23; Peak: Q24h n=18, Q36h n=20)

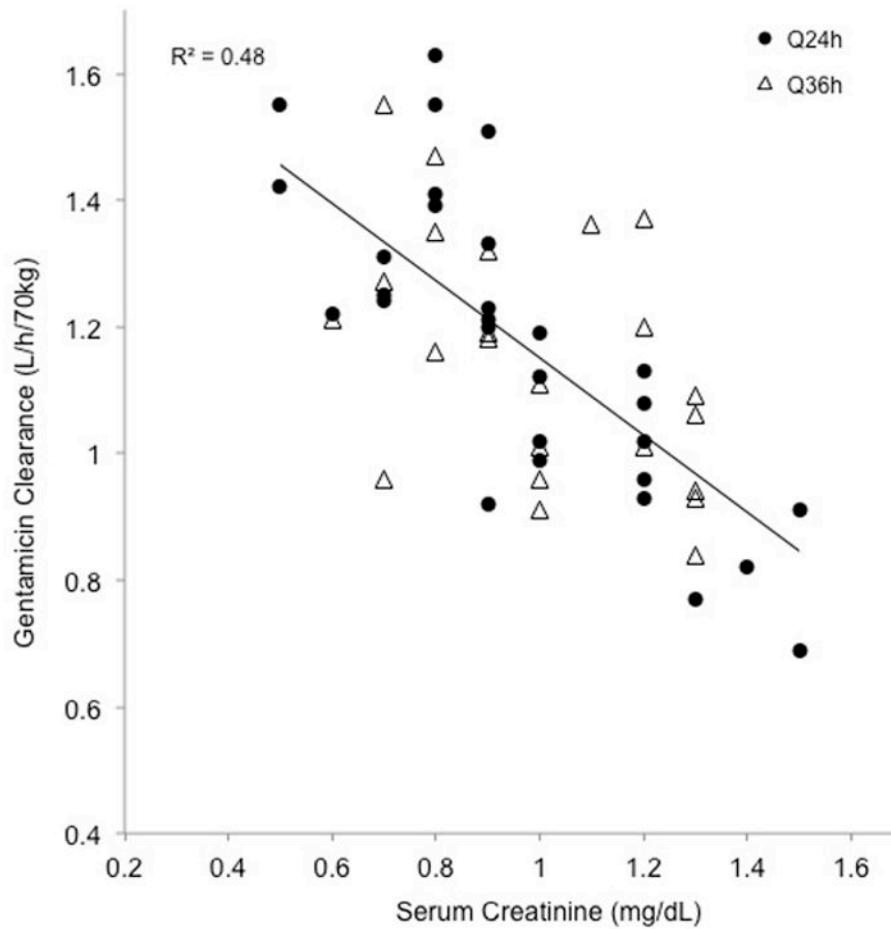


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**Figure 2.**

Relationship of trough concentration (A) and gentamicin clearance (B) with serum creatinine in neonates with HIE receiving hypothermia. Bayesian estimates of gentamicin clearance were calculated for each neonate (see Methods for details). Serum creatinine was measured on the second day of life. Neonates received gentamicin 5 mg/kg every 24 hours during the Q24h period and 5 mg/kg every 36 hours during the Q36h period. Line represents linear regression line for neonates by period (A) or for all neonates combined (B).

Table 1

## Patient Demographics

	Q24h Period (n = 29)		Q36h Period (n = 23)		p- value**
	Mean $\pm$ SD	Min, Max	Mean $\pm$ SD	Min, Max	
Gestational Age, wks	39.3 $\pm$ 1.9	35.7, 42.3	40.2 $\pm$ 1.1	37.6, 41.9	0.048
Birthweight, kg	3.26 $\pm$ 0.58	2.23, 4.83	3.45 $\pm$ 0.57	1.87, 4.64	0.3
APGAR					
5 min	3 $\pm$ 2	0, 7	4 $\pm$ 2	0, 9	0.03
10 min	5 $\pm$ 2	0, 9	5 $\pm$ 2	0, 10	0.3
First umbilical or arterial pH	7.0 $\pm$ 0.2	6.5, 7.3	7.0 $\pm$ 0.2	6.7, 7.2	0.6
Base Deficit, mmol/L	-20 $\pm$ 8	-4, -35	-15 $\pm$ 6	-3, -24	<0.001
Serum creatinine*, mg/dL	1.0 $\pm$ 0.3	0.5, 1.5	1.0 $\pm$ 0.2	0.6, 1.3	0.6
Assisted Ventilation, n (%)	24 (83%)	-	17 (74%)	-	0.5
Seizures, n (%)	16 (55%)	-	10 (43%)	-	0.6
Dopamine, n (%)	18 (62%)	-	12 (52%)	-	0.6
Death prior to discharge, n (%)	6 (21%)	-	0 (0%)	-	0.028

\* On day of life two; Three patients in Q24h group did not have serum creatinine.

\*\* t-test or Fischer-exact