ORIGINAL ARTICLE

# Pharmacokinetics of Gentamicin in Newborns with Moderate-to-Severe Hypoxic-Ischemic Encephalopathy Undergoing Therapeutic Hypothermia

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## Abstract

*Objective* To investigate gentamicin pharmacokinetics in neonates with moderate-to-severe hypoxic-ischemic encephalopathy (HIE) who underwent therapeutic hypothermia (TH). *Methods* Data were collected retrospectively from infants admitted between January 2007 and February 2011. Gentamicin was given at 2.5 mg/kg/dose q12h intravenously. Infants not eligible for TH underwent therapeutic normothermia (TN). After reviewing the data which showed >85 % of infants undergoing TH had gentamicin trough concentration >2 µg/ml at steady state, the gentamicin level monitoring protocol was modified since March 2011. *Results* In the initial retrospective study, 15 TN infants were compared with 19 TH infants. There was significant difference in median gentamicin half-life (7.01 *vs.* 9.57 h). A higher proportion of infants in the TH group required dosage adjustment (8/15 *vs.* 17/19). After March 2011, gentamicin level taken 12-h post 1st dose was measured routinely and 18/22 infants had trough gentamicin levels >2 µg/ml. Their dosing intervals were extended to Q18h or beyond. *Conclusions* Infants with moderate-to-severe HIE who undergo TH may exhibit changes in the pharmacokinetic properties of gentamicin compared to infants who undergo TN. By measuring gentamicin level at 12-h after the first dose of 2.5 mg/kg/dose, appropriate dosing interval can be determined and the duration of exposure to toxic gentamicin level can be reduced.

**Keywords** Hypothermia · Neonates · Encephalopathy · Gentamicin

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## Introduction

Based on a better understanding of the pathogenesis of tissue damage following perinatal hypoxic-ischemia from the past 15 years' research, modest brain cooling has been used to attenuate the cascade of events that contributes to brain injury. Large randomized controlled trials have demonstrated the benefits of therapeutic hypothermia (TH) in newborns with moderate to severe hypoxic-ischemic encephalopathy (HIE) after perinatal asphyxia [1–4]. However, knowledge on TH effects on other physiological functions, more specifically its effects on drug elimination, is limited.

Gentamicin has been one of the most commonly prescribed aminoglycosides for the treatment of neonates with suspected or documented early onset sepsis because of its broad spectrum of activity and extensive experience with its use [5]. Potential side effects include nephrotoxicity and ototoxicity [5–9]. Previous studies have evaluated extended-interval gentamicin dosing in neonates [10–14]. A recent meta-analysis had shown that therapeutic serum concentrations are achieved more often with extended interval dosing than with the traditional dosing, but there was no significant difference in clinical cure rate or toxicity [15].

Aminoglycosides are excreted unchanged by kidneys, with less than 1 % eliminated in feces. Compared to adults, glomerular filtration rate (GFR) is lower in newborns and is significantly lowered during the immediate post-asphyxial stage [16, 17] . In a retrospective clinical study, using a once daily gentamicin dosing protocol (4–5 mg/kg/dose), serum gentamicin concentrations in HIE infants undergoing TH were not significantly different from TN [18]. However, other studies revealed reduced gentamicin clearance in this group of infants [19, 20].

The aims of the present study were (i) to characterize the pharmacokinetic properties of gentamicin in neonates with HIE

who underwent TN and TH, and (ii) to evaluate the impact of revised gentamicin level monitoring regimes on minimizing potential toxic drug exposure in these vulnerable infants.

## Material and Methods

Data were collected retrospectively from infants admitted to the Level III Neonatal Intensive Care Unit at Children's and Women's Health Centre in Vancouver, Canada between January 2007 and February 2011. Eligible infants had moderate-to-severe HIE (Sarnat stage 2 or 3) and participated in the Infant Cooling Evaluation (ICE) study or fulfilled the clinical criteria for TH, as standard care, after 2008. The inclusion criteria for TH included: (i) gestational age ≥ 35 wk, (ii) moderate or severe encephalopathy as defined by the presence of seizures or the presence of signs in at least three of six categories defined in the Abbreviated Encephalopathy Table, and (iii) evidence of perinatal asphyxia by at least one of the following: (a) 5-min Apgar score of <5, (b) ongoing ventilation at 10 min of age, (c) pH<7.00, base deficit >12 or lactate >5 mmol/L in cord arterial or arterial/venous/capillary gases within the 60 min of birth (d) within 6 h (before 2009) or 8 h of age (since 2009). Infants who underwent TN were infants in the control arm of the ICE study or those not eligible for TH because TH could not be started within 6 h (before 2009) or 8 h of age (from 2009 onwards). Blood cultures were taken and ampicillin and gentamicin were given on admission as empirical treatment for possible early-onset sepsis. Gentamicin dose was 2.5 mg/kg at 12 h intervals and infused as gentamicin 10 mg/ml (Sandoz Canada, Inc., Quebec, Canada), over 0.5 h.

Blood samples for measuring gentamicin concentrations were routinely collected within 0.5 h before and 0.5 h after the third dose. However, if impaired renal function was suspected, for pharmacokinetic analysis, two samples separated by at least 10 h were collected within a dosing interval. Gentamicin concentrations were measured using the Abbott AxSYM system, utilizing fluorescence polarization immunoassay technology (Abbott Laboratories Diagnostics Division, Abbott Park, IL, USA). Sawchuk and Zaske's method was used to estimate the volume of distribution (Vd), elimination rate constant (Ke), half-life ($t_{1/2}$), clearance (Cl), and peak concentration ($C_{max}$) and trough concentration ($C_{min}$) after 1st dose [21].

Basic demographic characteristics, including gestational age, birth weight, gender, 5-min Apgar score and birthplace, were extracted. Highest values of creatinine measured between 48 and 72 h of life were reported. Based on measured gentamicin trough and peak levels around the third dose which were considered as the steady state Cmax and Cmin., gentamicin $t_{1/2}$, Vd, Ke, weight normalized Cl (L/h/kg), $C_{max}$ & $C_{min}$ after the first dose were calculated, and the need for dose adjustment due to elevated drug levels were recorded.

Post infusion gentamicin peak level was not measured in three TH infants, therefore estimates of Vd and Cl were not available for these three infants, but their $t_{1/2}$ and Ke were calculated, based on at least two measurements, separated by at least 10 h. In addition, the use of any inotropes during the first 72-h treatment period was recorded.

In the initial retrospective study from 2007 to February 2011, data revealed an unacceptable high proportion of infants undergoing TH had elevated gentamicin levels for a longer time period than those undergoing TN. The authors decided to have closer monitoring of gentamicin levels among these HIE infants. Since March 2011, blood samples for measuring gentamicin concentrations were collected at 12 h after the first dose. Based on this, if necessary, an adjusted gentamicin dose regime was recommended.

The SPSS 21.0 (SPSS Inc Chicago, IL) program was used for statistical analysis. Kruskal-Wallis test or Mann Whitney U-test (gestational age, birth weight, serum creatinine), Pearson Chi-square test or Fisher's Exact test (outborn; HIE Stage III at initial assessment; Apgar score <5 at 5-min; gender; umbilical blood gas or first available blood gas with pH<7; need for dosage adjustment) and Mann–Whitney U test (pharmacokinetics parameters) were used for analysis. A p-value< 0.05 was regarded as statistically significant.

## Results

In the initial retrospective evaluation from 2007 to February 2011, a total of 48 infants were identified to have moderate-to-severe HIE during the study period and 14 infants were excluded (1 infant died before 6 h of age; 1 infant underwent extracorporeal membrane oxygenation; 1 infant had congenital anomalies; 11 infants had no gentamicin measurements because antibiotics were discontinued as culture results were negative at 48 h). A total of 15 infants undergoing TN and 19 infants undergoing TH were eligible for this analysis. Of the 15 patients in the TN group, 11 presented symptoms beyond the therapeutic window for cooling and one was from the control arm of ICE study. The other three were born in 2007, after ICE study, but before TH became the standard therapy.

There were no statistically significant differences in gestational age, birth weight, gender, proportion of outborn infants, proportion of infants with Apgar score less than 5 at 5-min of life, serum creatinine at 48–72 h of life and use of inotropes during the first 72-h period between groups (Table 1).

A comparison of pharmacokinetic parameters between these two groups (Tables 1 and 2) showed that there was no statistical difference in 48 to 72 h serum creatinine values but infants undergoing TH had longer gentamicin $t_{1/2}$and lower weight normalized clearance (Cl/kg). Figures 1, 2 and 3 illustrate the measured and calculated pharmacokinetic parameters of each subject in both groups. The calculated serum

**Table 1** Baseline characteristics of the infants

| | Normothermia (n=15) | Hypothermia I (n=19) | Hypothermia II (n=22) |
|---|---|---|---|
| Outborn | 11 (73.3 %) | 14 (73.7 %) | 17 (77.3 %) |
| HIE Stage III at initial assessment | 1 (6.7 %) | 2 (10.5 %) | 3 (13.6 %) |
| [a]Gestational age (wk) | 39 [36, 41] | 39 [38, 40] | 40 [39, 40] |
| [b]Birth weight (g) | 3,356 [2,600, 3,541] | 3,300 [2,960, 3,670] | 3,425 [2,963, 4,169] |
| [b]Apgar score of <5 at 5-min | 5 (33.3 %) | 11 (61.1 %) | 16 (72.7 %) |
| Gender (Male sex) | 11 (73.3 %) | 12 (63.2 %) | 16 (72.7 %) |
| Umbilical blood gas or first available blood gas with pH less than 7 | 5 (33.3 %) | 10 (52.6 %) | 9 (40.9 %) |
| [a]Creatinine, μmol/L | 76 [60, 90] | 77 [58, 89] | 80 [68, 109] |

Hypothermia I refers to the infants undergoing hypothermia between Jan 2007 and Feb 2011; Hypothermia II refers to the infants undergoing hypothermia since Mar 2011, with implementation of closer monitoring of gentamicin levels

[a] Expressed as median [25th, 75th Centiles]

[b] One missing value in hypothermia I

gentamicin concentrations at 12 h post-infusion (*i.e.,* prior to the second dose) were significantly higher in the TH group compared to the TN group. In the TH group, 17/19 subjects needed adjustments in gentamicin dosing because their measured trough levels around the third dose were >2 μg/ml, but only 8/15 subjects in the TN group required dose adjustment.

Using pharmacokinetic parameters obtained from TN and TH groups, theoretical profiles of gentamicin concentrations *vs.* time for different doses were calculated and are illustrated in Fig. 4. For the same dose, infants who were undergoing TH had a longer duration of gentamicin levels above 2 μg/ml compared to the TN group.

**Table 2** Pharmacokinetic properties of gentamicin in both groups of infants

| | Normothermia (n=15) | Hypothermia I (n=19) | p-value |
|---|---|---|---|
| [a]Half-life, median, h | 7.01 [5.29, 7.72] | 9.57 [5.37, 7.66] | 0.007 |
| [a]Ke, median/h | 0.099 [0.090, 0.131] | 0.072 [0.052, 0.100] | 0.007 |
| [a]Cl/kg, median, L/h/kg | 0.051 [0.041, 0.054] | 0.033 [0.025, 0.046] | 0.007 |
| [a]Volume of distribution, median, L/kg | 0.45 [0.40, 0.48] | 0.41 [0.36, 0.48] | NS |
| [a]Calculated $C_{max}$ after one dose, median, μg/ml | 5.31 [5.05, 6.05] | 6.02 [5.12, 6.48] | NS |
| [a]Calculated $C_{min}$ at 12 h post infusion, median, μg/ml | 1.50 [1.24, 1.93] | 2.33 [1.63, 3.14] | 0.009 |
| [a]Measured $C_{max}$ at steady state, median, μg/ml | 7.30 [6.49, 8.49] | 9.26 [7.57, 12.71] | 0.011 |
| [a]Measured $C_{min}$ at steady state, median, μg/ml | 2.10 [1.50, 2.80] | 3.98 [2.29, 5.52] | 0.015 |
| [a]Calculated median AUC per 12 h interval (μg/ml/h) | 55.2 [52.5, 67.1] | 93.8 [58.0, 150.6] | 0.005 |
| [+]Need for dosage adjustment due to elevated trough level ≥2 μg/ml after 1st dose | 8 (53.3 %) | 17 (89.5 %) | 0.025 |
| Number of infants receiving inotropes & gentamicin dosage adjustment | 2 | 6 | |

$C_{max}$: Two side calculated peak gentamicin level after the initial dose

$C_{min}$: calculated trough gentamicin level 12-h at the end of the initial dose

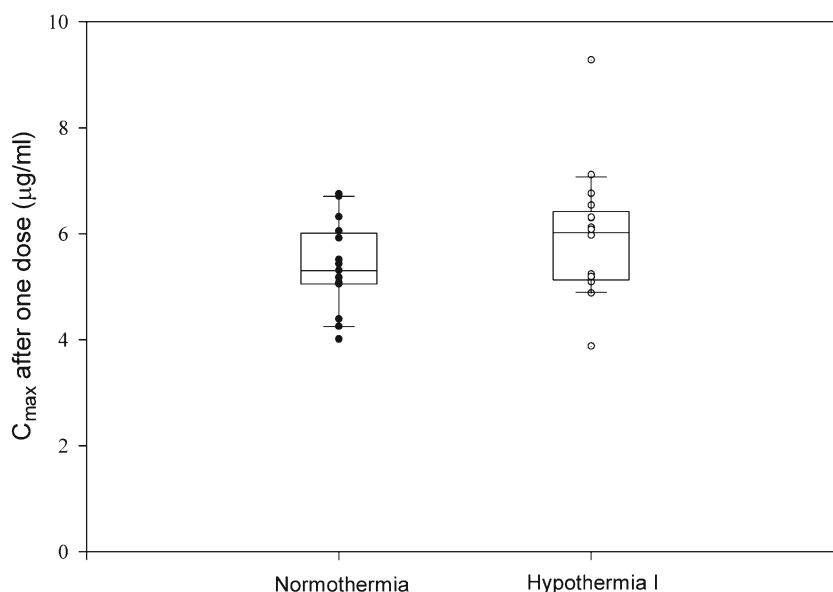By Mann–Whitney U tests except [+] Fisher's Exact Test

[a] Expressed as median [25th Centiles, 75th Centiles]; three babies undergoing hypothermia had missing Vd estimates

**Fig. 1** Half-lives of gentamicin in normothermia and hypothermia I infants. Hypothermia I refers to the infants undergoing hypothermia between Jan 2007 and Feb 2011. There is an outlier in the hypothermia group, with a half-life of 46 h
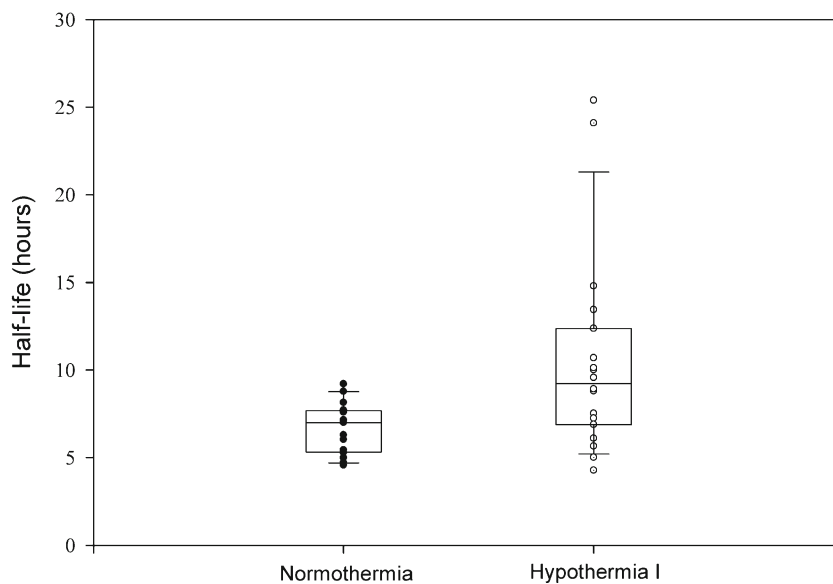


After the initial retrospective evaluation, 22 infants were identified having moderate to severe HIE and underwent TH from Mar 2011 through Feb 2012. There were no statistically significant differences in gestational age, birth weight, gender, proportion of outborn infants, proportion of infants with Apgar score <5 at 5-min of life and highest serum creatinine at 48–72 h of life, as compared to the TN and TH groups in the aforementioned patients (Table 1, Kruskal-Wallis test). The measured median trough gentamicin level 12-h after the first dose was 2.55 µg/ml (2.18, 3.30; 25th & 75th Percentiles respectively) (Fig. 3) and 19/22 (86.4 %) had gentamicin levels above 2 µg/ml, such that their dosage regimes needed to be revised from 2.5 mg/kg/dose q12h to 2.5 mg/kg/dose q18h or up to q36h. Both of these findings were similar to the results in the initial retrospective portion of the study.

## Discussion

Aminoglycosides are widely used in the treatment of suspected early onset sepsis in neonates [5, 22]. It is crucial to use a suitable dosage regimen that will afford optimum serum concentrations. However, dosing with gentamicin in neonates is hampered by the inter- and intra-individual variability in the kinetic behavior of this antibiotic [23]. Aminoglycosides have a low therapeutic index; therefore, increased knowledge of their pharmacokinetics is essential [24]. Gentamicin trough concentrations greater than 2 µg/ml are associated with toxicity, and peak concentrations less than 5 µg/ml are associated with a reduced efficacy [24].

Aminoglycoside nephrotoxicity is associated with necrosis of the cells of the proximal tubule [25]. As a result, there is

**Fig. 2** $C_{max}$ (µg/ml) after one dose in normothermia and hypothermia I infants. Hypothermia I refers to the infants undergoing hypothermia between Jan 2007 and Feb 2011

**Fig. 3** $C_{min}$ (µg/ml) at 12-h after the first dose in normothermia, hypothermia I and hypothermia II infants. Hypothermia I refers to the infants undergoing hypothermia between Jan 2007 and Feb 2011. Hypothermia II refers to the infants undergoing hypothermia from Mar 2011 till Feb 2012
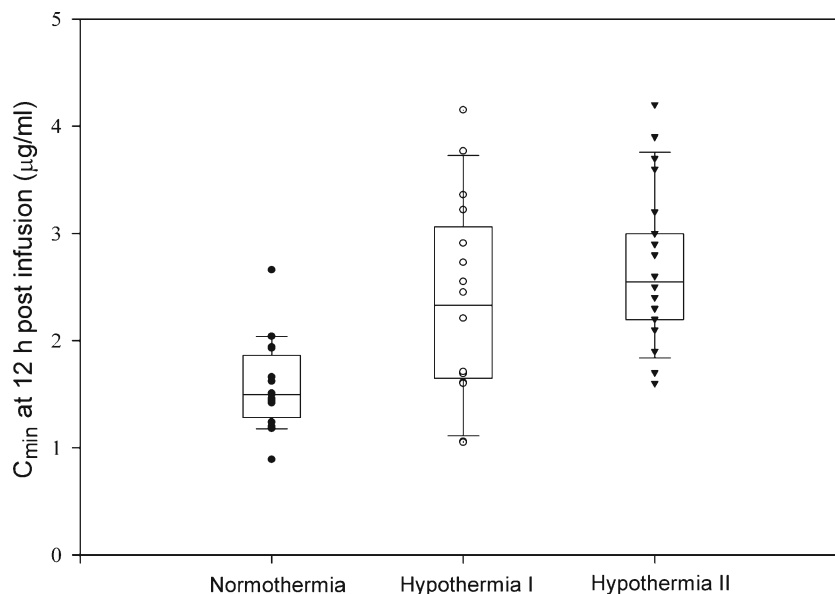


non-oliguric renal impairment and a reduction in glomerular filtration rate (GFR). Pre-existing renal impairment has been proposed to be one of the factors that aggravate clinical aminoglycoside toxicity [25] . Few studies found that genta-micin Cl is significantly reduced in asphyxiated neonates compared to healthy neonates and $t_{1/2}$ is prolonged [19, 20, 26]. Hypothermia is associated with complex physiological changes, including a decrease in cardiac output. Studies in piglets have revealed that cardiac output and renal blood flow decrease with temperature, and renal blood flow decreases more than cardiac output [27]. The authors postulate that hypothermia, in addition to perinatal hypoxia, could lead to a further decrease in renal blood flow, glomerular filtration and consequently, excretion of gentamicin in infants with HIE who undergo TH. As a result, toxic levels of gentamicin in serum are reached, which leads to further nephrotoxicity and possible damage to the cochlea or the vestibular apparatus or both. Animal studies have yielded conflicting results regard-ing the effects of hypothermia after hypoxic-ischemia on the pharmacokinetics of gentamicin. These conflicting results could be related to variations in methodology such as, the degree of hypothermia, the duration of cooling and the choice of animals studied [27, 28].

The index study demonstrated that there were significant alterations in the pharmacokinetics of gentamicin during TH, including a prolonged $t_{1/2}$, a significant reduction in gentamicin Cl, elevated $C_{min}$ at 12 h post 1st dose and an increased $C_{max}$ and $C_{min}$ at steady state. In authors' initial retrospective analy-sis, infants undergoing TH (17/19) were more likely to have their gentamicin doses adjusted due to elevated trough levels. This is consistent with a recently published case–control study by Mark et al. that infants with HIE undergoing TH are asso-ciated with significant alterations in gentamicin pharmacoki-netics [20]. In the population pharmacokinetic study focusing

on full term infants diagnosed with HIE treated with TH, Frymoyer et al. also had similar findings [19]. Of interest, the reported pharmacokinetic parameters during TH by Mark et al.: $t_{1/2}$ of 9.16 h, Ke of 0.08/h, clearance of 0.04 L/h/kg, and Vd of 0.46 L are very similar to present study's findings: $t_{1/2}$ of 9.57 h, Ke of 0.072/h, Cl of 0.033 L/h/kg, and Vd of 0.41 L [20].

Once daily gentamicin dosing regimen of 4–5 mg/kg/dose has been adopted by many institutions. The general therapeu-tic goal of once daily gentamicin dosing is to achieve a peak concentration of 5–12 µg/ml and a trough concentration of <2 µg/ml. As suggested by NeoFax®, for gentamicin trough concentrations ≤1, 1.1 to 2.3 and 2.4 to 3.2 µg/ml, their corresponding suggested intervals are 24, 36 and 48 h [29]. Based on the volume of distribution and elimination half-life observed in this study, a daily dosing regimen of 4–5 mg/kg, theoretical serum gentamicin peak concentrations at steady state would be between 11 and 14 µg/ml and their levels would not reach <2 µg/ml for at least 25 h post infusion in infants receiving TH. Therefore, a reduction of dose or extension of dosing interval is required to minimize the potential for gentamicin-induced ototoxicity and nephrotoxi-city. In fact, 5 mg/kg every 36-h gentamicin dosing in this group of infants has been proposed recently by Frymoyer et al. [30], while Mark et al. found that about 2/3rd of infants receiving 4 mg/kg of gentamicin required to extend their dosing interval from every 24-h to 36 or 48-h [20]. Smit et al. found about 1/3rd of the HIE infants treated with TH and a gentamicin dose of 4 mg/kg every 24-h results in permanent hearing loss and this is likely attributed to reduced gentamicin clearance [9].

Limitations of the present study are: small number of patients, retrospective nature of the study and potential differ-ences in neonates undergoing TN and TH in the initial retro-spective evaluation. Forteen out of 48 patients were not

**Fig. 4** Theoretical plasma concentrations *vs.* time for different doses of gentamicin under hypothermia and normothermia conditions
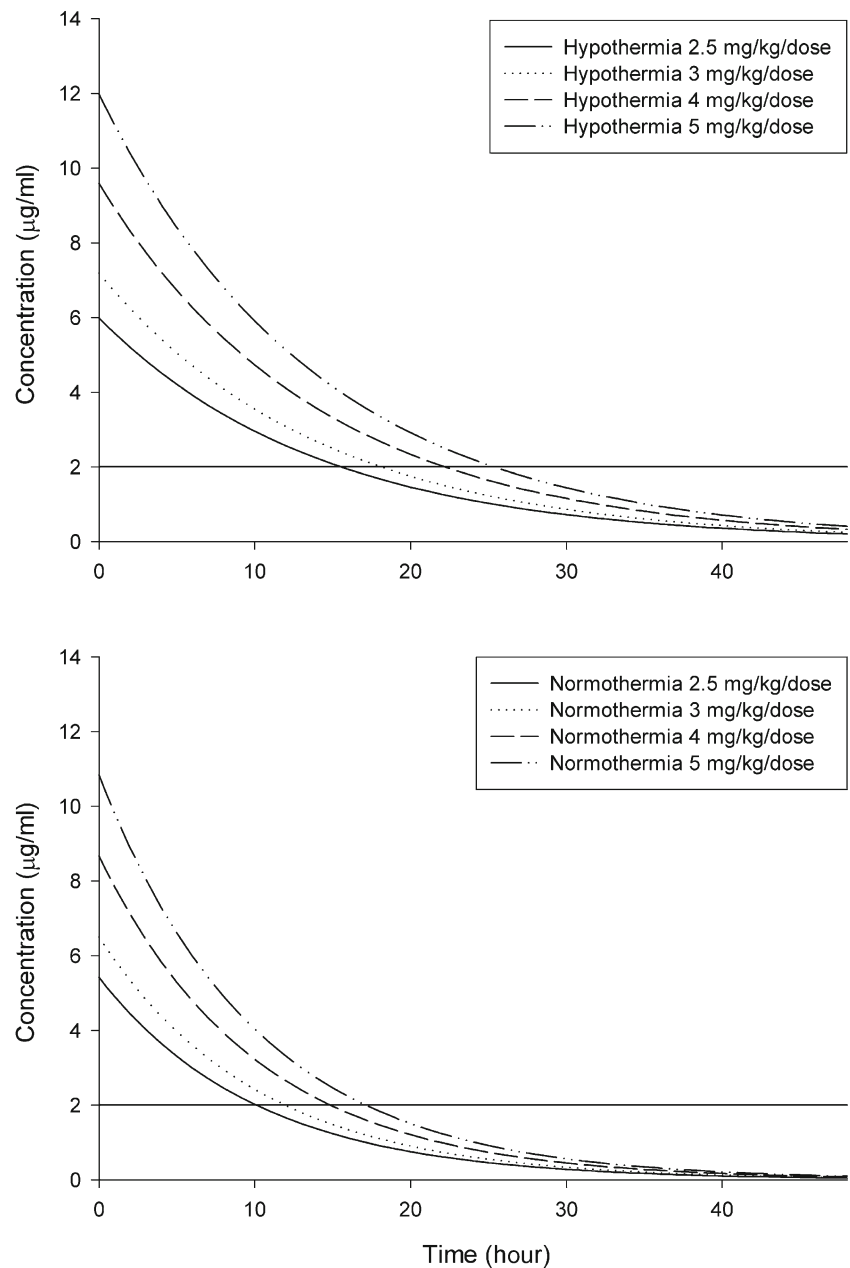


included because gentamicin was discontinued prior to measurement due to a low suspicion of sepsis. Regardless of the limitations, the fact that more than 80 % of infants undergoing TH required dosage regime revision in authors' initial retrospective data could not be overlooked. Previously suggested dosing and monitoring (*i.e., 2.5 mg/kg/dose* and checking trough and peak levels of gentamicin around the third dose in Q12h regime, or 3 to 5 mg/kg/dose and monitor at 24-h in the single dose regime [18]) will result in a significant number of infants being exposed to toxic gentamicin levels >2 µg/ml for an extended period, which has shown to further increase the risk of permanent hearing impairment among the survivors of moderate or severe neonatal encephalopathy [9]. Using pharmacokinetic

parameters obtained in this study, and measuring the gentamicin level at 12-h after the first dose of 2.5 mg/kg/dose can help to optimize the dosing regime in these vulnerable infants and reduce the duration of exposure to toxic gentamicin level.

### Conclusions

Infants with moderate-to-severe HIE who underwent TH may exhibit changes in the pharmacokinetic properties of gentamicin compared to infants who underwent TN. A revision of the current recommended dose of gentamicin should be considered. By close monitoring of gentamicin levels in this

population (measuring the level at 12-h after the first dose of 2.5 mg/kg/dose), appropriate dosing interval could be determined. Cautions should be applied with use of other renal-cleared medications during TH until further information is available.

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