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Gentamicin Pharmacokinetics in Neonates Undergoing Therapeutic Hypothermia

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Abstract

Objective—To identify whether therapeutic hypothermia in newborns with hypoxic ischemic encephalopathy affects gentamicin pharmacokinetics.

Study Design—Retrospective case–control study consisting of 16 neonates who underwent therapeutic hypothermia and received gentamicin with interpretable peak and trough serum levels obtained during the period of cooling and at steady state; comparator group consisting of 7 neonates met the criteria but did not undergo therapeutic hypothermia.

Results—Significant differences in gentamicin pharmacokinetics were noted between the therapeutic hypothermia group and the comparator group in elimination rate constant (0.08/h versus 0.11/h; $P < 0.01$), elimination half-life (9.16 hours versus 6.56 hours; $P < 0.01$), and clearance (0.04 L/kg.h^{−1} versus 0.05 L/kg.h^{−1}; $P < 0.01$), respectively. Higher gentamicin trough serum concentrations were seen with the therapeutic hypothermia group (1.68 mcg/mL versus 0.77 mcg/mL; $P < 0.01$).

Conclusions—Therapeutic hypothermia is associated with alterations in gentamicin pharmacokinetics, reducing gentamicin clearance by 25.5% in neonates with hypoxic ischemic encephalopathy, which may result in increased trough serum concentrations.

Keywords

hypoxic ischemic encephalopathy; cooling; aminoglycoside

INTRODUCTION

Hypoxic ischemic encephalopathy (HIE) is a syndrome of disturbed neurologic function that occurs secondary to decreased blood oxygenation or diminished brain perfusion as a result of an asphyxial event in the perinatal period. The incidence of HIE is estimated to be 1.5 per 1000 live births.¹ Neuronal death occurs in 2 phases following a hypoxic–ischemic event: a primary phase consisting of immediate neuronal death, related to cellular hypoxia and exhaustion of cellular energy supply, and a secondary phase that begins after a 6-hour period of latency. The delayed phase is associated with encephalopathy and increased seizure activity; thus, an opportunity to modify disease progression exists between the time of resuscitation of the asphyxiated newborn and the second phase of neuronal injury.²

Therapeutic hypothermia is the current standard intervention for neonates with HIE. This therapy reduces mortality without increasing the major disability in newborns with HIE by decreasing the extent of anoxic brain damage. Two methods of therapeutic hypothermia exist: head cooling and whole-body cooling. The standard of care at our institution is whole-body cooling, which must be initiated within 6 hours of life. Hypothermia is administered for a period of 72 hours and is followed by a rewarming period of 6 hours. The goal rectal temperature per our institutional hypothermia protocol is 33.5°C.

Hypothermia has been associated with decreased glomerular filtration rate in a number of animal studies, and it may, therefore, impair the elimination of renally excreted drugs in humans.³ Potential mechanisms of decreased renal clearance include reduced tubular secretion or reabsorption, decreased cardiac output, increased blood viscosity, cold-induced vasoconstriction, blood redistribution, and increased renal renin secretion.⁴

Gentamicin is often a component of antimicrobial regimens for the empiric treatment of presumptive infections in neonates with HIE. Because gentamicin is excreted unchanged by the kidney, it is hypothesized that a decreased glomerular filtration rate could lead to increased gentamicin serum levels and, consequently, toxicity. To our knowledge, one study, thus far, has evaluated gentamicin serum concentrations in neonatal human subjects. This retrospective study by Liu et al⁵ evaluated the effect of therapeutic hypothermia on gentamicin trough serum levels in 55 infants with HIE and included both head and whole-body cooling. The authors found no difference in trough concentrations resulting from intravenous administration of 4–5 mg/kg of gentamicin once daily between the hypothermic study group, in which the infants were cooled to 34°C, and the normothermic control group (2.19 mcg/mL $\pm$ 1.7 versus 2.30 $\pm$ 2.0). Neither pharmacokinetic parameters nor peak serum concentrations were reported.⁵

This study aims to identify whether therapeutic hypothermia affects gentamicin pharmacokinetics and related peak and trough serum concentrations in neonates with HIE.

MATERIALS AND METHODS

Study Design

A retrospective chart review was performed in all neonates admitted to the Neuro-Intensive Care Nursery (NICN) from January 1, 2007, to July 31, 2010, who underwent therapeutic hypothermia and received concomitant intravenous gentamicin therapy. Patients included in this study were those who had gentamicin peak and trough serum concentrations available for characterizing pharmacokinetic parameters. These gentamicin serum levels must have been drawn during the period of cooling and around the third or subsequent consecutive dose (at steady state). Gentamicin was infused over 30 minutes.

Our institutional criteria for therapeutic hypothermia are described in Table 1. Based on the gestational age (GSA) criterion of ≥ 36 weeks, all patients received intravenous gentamicin 4 mg/kg every 24 hours, which is the specified age-appropriate dosing regimen in Neofax.⁶

The neonates in the study group were compared with a historical control group, as therapeutic hypothermia became the standard of care at our institution on October 1, 2006. This comparator group must have met the inclusion criteria for therapeutic hypothermia as specified in the hypothermia protocol (Table 1). This study was approved by the Johns Hopkins Medicine Institutional Review Board.

Objectives

The primary objective was to determine gentamicin pharmacokinetic parameters, that is, elimination rate constant (k_e), elimination half-life ($t_{1/2}$), volume of distribution (V_d), and clearance (CL) and to describe peak and trough serum concentrations of gentamicin in all neonates undergoing therapeutic hypothermia. Secondly, we sought to compare the values obtained from the aforementioned neonates who underwent therapeutic hypothermia with those obtained from neonates who were not cooled.

Data Collection

Patient Identification—Patients with HIE who underwent therapeutic hypothermia were identified through a patient database maintained by the NICN. Patient records were then evaluated for the treatment with gentamicin and therapeutic drug monitoring during the period of cooling.

The control group, neonates with HIE who were eligible for but did not receive therapeutic hypothermia, was identified via a query of the case mix billing database using an *International Classification of Diseases, Ninth Revision (ICD-9)* code specific to HIE before October 1, 2006. Therapeutic hypothermia was introduced as standard HIE therapy at our institution on this date. *ICD-9* codes were verified by identifying all patients in the study group who were assigned *ICD-9* code 7687 for HIE. Approximately 80% of the study group was assigned this *ICD-9* code; thus, the risk of ascertainment bias in control group selection was minimized. Neonates were not included in the control group if they did not meet inclusion criteria, as specified in the hypothermia protocol (Table 1).

Patient Demographics—Patient information was collected using electronic patient records and computerized provider order entry and pharmacy computer systems. Recorded baseline characteristics were demographic information, characteristics related to therapeutic hypothermia, and those related to renal function. Data collected included gentamicin dose and frequency, gentamicin peak and trough serum concentrations (in micrograms/ milliliter), intravenous gentamicin administration times and related laboratory draws for therapeutic drug monitoring, dose adjustment, urine output (in milliliters/kilogram per hour), sex, GSA (weeks), birth weight (in kilograms), blood urea nitrogen (in milligrams/deciliter), serum creatinine (in milligrams/deciliter), Apgar scores at 1, 5, and 10 minutes of life, arterial pH, and cord pH. Administration of concomitant nephrotoxic medications and vasopressors was also recorded. Nephrotoxic agents for which data were collected include amphotericin B, acyclovir, angiotensin-converting enzyme inhibitors, ibuprofen, indomethacin, and intravenous vancomycin. Vasopressors included epinephrine, dobutamine, dopamine, and phenylephrine.

Gentamicin serum concentrations were assayed by a commercial recombinant DNA immune assay (CEDIA Gentamicin II; Roche Diagnostics, Indianapolis, IN). The calibration curve ranged from 0.24 to 12 mcg/mL, and precision during the assay validation was <4.13% at 2.6, 4.9, and 8.8 mcg/mL.⁷ Gentamicin pharmacokinetic parameters were calculated by the standard first-order pharmacokinetic model.⁸ Peak and trough serum concentrations reflect time points of half hour from the end of dose infusion and immediately before the start of dose administration, respectively. These adjustments were necessary for routine clinical interpretation of serum concentrations.

Statistical Analysis

Continuous, ordinal, and nominal data were analyzed using the *t* test, Fisher exact test, and Wilcoxon rank sum test, respectively. The Mann–Whitney *U* test was used to compare the pharmacokinetic parameters. Statistical computation was performed by Minitab version 16 (State College, PA).

RESULTS

Of the 57 neonates who underwent therapeutic hypothermia from January 1, 2007, to July 31, 2010, 41 did not meet inclusion criteria. The most frequent reasons for not meeting criteria were receipt of 2 gentamicin doses (*n* = 20, 49%) and gentamicin serum sampling before administration of the third gentamicin dose (*n* = 13, 32%). In total, 16 patients met criteria for inclusion.

One hundred fifty-eight patients with HIE who did not receive therapeutic hypothermia were identified via ICD-9 code search from September 1, 1997, through September 30, 2006; 151 of these patients did not meet inclusion criteria. Reasons for not meeting criteria were receipt of 2 gentamicin doses (*n* = 71, 47%), not meeting cooling criteria (*n* = 40, 26%), and serum sampling around the first or second gentamicin dose (*n* = 17, 12%). In total, 7 patients were included in the final comparator group. Baseline characteristics were similar between the 2 groups, with only the 1-minute Apgar score being significantly lower in the group that underwent therapeutic hypothermia (Table 2).

Significant differences in gentamicin pharmacokinetic parameters were noted between the therapeutic hypothermia group and the control group in k_e ($0.08 \pm 0.02/\text{h}$ versus $0.11 \pm 0.03/\text{h}$; $P < 0.01$), $t_{1/2}$ (9.16 ± 2.08 hours versus 6.56 ± 1.81 hours; $P < 0.01$), and CL ($0.04 \pm 0.01 \text{ L/kg.h}^{-1}$ versus $0.05 \pm 0.01 \text{ L/kg.h}^{-1}$; $P < 0.01$). No difference in V_d was found between the groups. Figures 1 through 4 depict individual data points for each parameter.

A significant difference was found between the 2 groups in time-corrected trough concentrations, where the group that underwent therapeutic hypothermia had a mean trough level 2.2 times higher than the group that did not undergo therapeutic hypothermia ($1.68 \pm 0.69 \text{ mcg/mL}$ versus $0.77 \pm 0.53 \text{ mcg/mL}$; $P < 0.01$). Figure 5 depicts individual data points for gentamicin trough serum concentrations. The resultant mean trough concentrations in the cooled group were supratherapeutic based on goal trough serum concentrations of $<1 \text{ mcg/mL}$. No difference was found in the time-corrected peak concentrations between the groups ($9.54 \pm 1.30 \text{ mcg/L}$ versus $8.71 \pm 1.43 \text{ mcg/mL}$; $P > 0.05$) (Fig. 6).

DISCUSSION

This study formally characterizes gentamicin pharmacokinetic parameters in neonates undergoing therapeutic hypothermia. We found that therapeutic hypothermia resulted in a 28% decrease in k_e , 40% lengthened $t_{1/2}$, and 25.5% decrease in CL of gentamicin. Based on these alterations, gentamicin trough serum concentrations significantly increased in the cooled group. Eighty-eight percent, or 14 of 16 patients, of the therapeutic hypothermia group required lengthening of the dosage interval to every 36 hours as a result of supratherapeutic trough serum concentrations ($>1 \text{ mcg/mL}$). At our institution, goal gentamicin serum troughs are $<1 \text{ mcg/mL}$. Seven of the 16 neonates (44%) in the therapeutic hypothermia groups had time-corrected troughs $>2 \text{ mcg/mL}$.

These results are consistent with the findings in a recent population pharmacokinetic study, in which investigators found a 33% reduction in gentamicin CL in neonates with HIE undergoing therapeutic hypothermia.⁹

In addition to this population pharmacokinetic study, our results were also consistent with the findings from a study in pigs that assessed gentamicin pharmacokinetic parameters and serum concentrations in normothermic condition and when cooled to 29°C . The investigators noted consistently higher serum concentrations during hypothermia when compared with normothermia. Additionally, the half-life ($t_{1/2}$) of gentamicin was significantly prolonged by 39% in the hypothermic group, whereas the k_e , V_d , and CL were significantly reduced by 27%, 32%, and 51%, respectively.¹⁰ This difference in CL is attributed to changes in $t_{1/2}$ and is consistent with the proposed physiologic effect of hypothermia on renal drug clearance. Animal studies in less severe hypothermia have not shown the same pharmacokinetic alterations. One study in which investigators induced hypoxic ischemia in newborn pigs and cooled them to 35°C to evaluate the effect of mild whole-body hypothermia on gentamicin pharmacokinetics. No difference in pharmacokinetic parameters was found between the hypothermic study group and the normothermic control group.¹¹

In comparison with the previous study in neonates by Liu et al,⁵ a potential rationale for discrepancy in results is the type of therapeutic hypothermia used in each study. Liu et al⁵ used both head and whole-body cooling, whereas our study used solely whole-body cooling. Additionally, gentamicin dosing regimens varied in the previous study, with 64% of neonates receiving 5 mg/kg intravenous gentamicin every 24 hours and 36% receiving the dosing used in this study of 4 mg/kg intravenous gentamicin every 24 hours. Resultant trough serum concentrations in this earlier study were >2 mcg/mL in both the therapeutic hypothermia and control groups, for which we would dose adjust at our institution. Lack of a notable difference in gentamicin serum trough concentrations between the groups in this previous study may be confounded by the varied dosing regimen and may have blunted the investigators' ability to identify a difference between cooled and noncooled groups.

The significant difference in baseline characteristics related to the Apgar score at 1 minute was the result of 1 outlier who met criteria for therapeutic hypothermia on the basis of his initial pH and need for ventilation. Differences in Apgar scores at 5 and 10 minutes were not significant between the 2 groups.

A large portion of the screened populations were not included due to receipt of 2 gentamicin doses. Reasons for this short duration of therapy included receipt of gentamicin as component of a 48-hour antibiotic course for sepsis rule out and exchanging gentamicin for an alternative antimicrobial agent. Additionally, an equally large portion of the screened populations were not included secondary to the sampling of gentamicin serum levels before the third gentamicin dose, which was before steady state. Although this is clinically appropriate to ensure therapeutic efficacy and appropriate clearance of a nephrotoxic and ototoxic agent in a newborn, these data were excluded on the basis of inability to accurately calculate gentamicin pharmacokinetic parameters.

Recognizing the clinical appropriateness of drawing gentamicin levels around the second dose, the poststudy NICN experience was evaluated from August 1, 2010, through December 31, 2011. This analysis included all neonates with HIE undergoing therapeutic hypothermia and receiving intravenous gentamicin and aimed to document our current clinical practice; thus, pharmacokinetic parameters were calculated and doses were adjusted based on pre-steady state levels. Thirty-six neonates were cooled during the poststudy time. Nine of 36 neonates (25%) were excluded due to the lack of gentamicin levels or inability to ascertain timing of the first dose when administered at an outside institution. The remaining 27 patients were analyzed for gentamicin dose adjustments.

Ten of these 27 patients (27%) did not require a dose adjustment, with time-corrected troughs <1 mcg/mL. Seventeen patients (63%) required dose adjustment of gentamicin, evidenced by time-corrected troughs $\geq$ 1 mcg/mL. Of these 17 patients, 10 (37%) had their dose adjusted as follows: 60% (6 of 10) had the dosage interval increased to every 36 hours, 20% (2 of 10) required dosing of gentamicin by levels, 10% (1 of 10) had the dosage interval increased to every 48 hours, and 10% (1 of 10) had an intravenous gentamicin dose reduction to 3.5 mg/kg while maintaining the every 24 hours dosing interval. The remaining 7 patients either warranted dose adjustment (trough $\geq$ 1 mcg/mL), but gentamicin was discontinued or was already being dosed at an interval of every 36 hours.

To assess the clinical safety and efficacy of empirically initiating intravenous gentamicin at 4 mg/kg every 36 hours in neonates undergoing therapeutic hypothermia, we calculated the time-corrected trough and peak values for neonates whose gentamicin trough and peak concentrations were within the therapeutic range on a 4 mg/kg intravenously every 24 hours regimen using the patients' individual pharmacokinetic parameters. Resultant corrected trough and peak serum concentrations were 0.15 ± 0.06 mcg/mL and 8.22 ± 1.31 mcg/mL, respectively. These levels continued to meet therapeutic goal troughs of <1 mcg/mL and peaks of 8–10 mcg/mL. Thus, we conclude that we would risk minimal harm of under dosing these neonates with an empiric dosing interval of every 36 hours. Of note, this dosing strategy is also being adopted by other institutions based on the results of population pharmacokinetic studies (Frymoyer AR, personal communication via e-mail, 11/12/12).

There were several limitations to this study, including its retrospective design and limited sample size; however, post hoc power analysis yielded 86% power with regard to the 25.5% reduction in clearance in the therapeutic hypothermia group with our given sample size. Use of a historic control group is suboptimal, as changes to standards of care have the potential to confound results. Additionally, use of *ICD-9* codes to capture control group data could lead to ascertainment bias by excluding patients whose HIE *ICD-9* code may not have been entered into the billing system due to character limitations. Of note, analysis of the study group indicated an *ICD-9* code capture rate of approximately 80%; as such, risk of ascertainment bias was minimized.

Although we did find a difference in clearance and serum trough concentrations between the study groups, we did not assess the impact of these differences on antimicrobial effect or clinical outcome of the subjects, which was outside of the scope of this observational study. Additionally, given our strict hypothermia protocol, the results of this observational study may not be generalizable to populations with more liberal cooling criteria. A final limitation involves the assumption that gentamicin pharmacokinetics in both HIE and non-HIE patients behave in accordance with the first-order pharmacokinetic model. Determination of the true pharmacokinetic model is unachievable with the 2-point serum sample scheme used in clinical practice.

With the results and limitations in mind, the Johns Hopkins Hospital NICN now recommends the initiation of gentamicin at a dose of 4 mg/kg intravenously every 36 hours for all neonates undergoing therapeutic hypothermia. Serum concentration monitoring should occur around the fourth intravenous gentamicin dose, at a postcooling steady state level so as to facilitate accurate dose adjustment.

CONCLUSIONS

Therapeutic hypothermia reduces gentamicin clearance in neonates with HIE, which may result in increased trough serum concentrations. Given the frequent use of gentamicin in this population, providers should be aware of pharmacokinetic variation and consider the initiation of gentamicin at a dose of 4 mg/kg intravenously every 36 hours.

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FIGURE 1.
Individual data points for elimination rate constant (k_e).

FIGURE 2.
Individual data points for half life ($t_{1/2}$).

FIGURE 3.
Individual data points for clearance (CL).

FIGURE 4.
Individual data points for volume of distribution (V_d)

FIGURE 5.
Individual data points for trough serum gentamicin concentrations.

FIGURE 6.
Individual data points for peak serum gentamicin concentrations.

TABLE 1

Indications for Use of Hypothermia

Inclusion criteria	<p>Newborn infants <6 hours of age and 36 weeks gestation and 1800 g with HIE are eligible for whole-body hypothermia if</p> <p>Cord pH or infant pH 7.0 (ABG, CBG, VBG) or base deficit 16 mmol/L at <1 hour of life AND moderate to severe encephalopathy</p> <p>OR</p> <p>Cord pH or infant pH is between 7.01 and 7.15 or base deficit is between 10 and 15.9 mmol/L at <1 hour of life or no cord</p> <p>pH or infant pH available, then infant must have evidence of an acute perinatal event (such as late or variable decelerations, cord rupture, uterine rupture, maternal trauma, hemorrhage, or cardiorespiratory arrest) AND</p> <p>10 minute Apgar score < 5 OR</p> <p>Need for assisted ventilation initiated at birth with continuation for at least 10 minutes AND</p> <p>Moderate to severe encephalopathy</p> <p>Definition: Moderate to severe encephalopathy</p> <p>Lethargy</p> <p>Stupor or coma</p> <p>Decreased or no activity</p> <p>Distal flexion, complete extension</p> <p>Decerebrate posture</p> <p>Hypotonia or flaccidity</p> <p>Abnormal primitive reflexes</p> <p>Weak or absent Moro</p> <p>Incomplete or absent Moro</p> <p>Abnormal autonomic nervous system</p> <p>Constricted pupils</p> <p>Deviated, dilated pupils, or pupils that are nonreactive to light</p> <p>Bradycardia</p> <p>Periodic breathing or apnea—need for continued ventilation qualifies</p> <p>Seizures</p>
Exclusion criteria	<p>Greater than 6 hours of life</p> <p>Major congenital anomaly</p> <p>Severe growth restriction (body weight 1800 g)</p> <p>Severe PPHN with anticipated need to ECMO</p> <p>Coagulopathy with active bleeding</p> <p>Severe hemodynamic compromise requiring large doses of vasopressors</p> <p>GSA 36 weeks</p>

ABG, arterial blood gas; CBG, capillary blood gas; ECMO, extracorporeal membrane oxygenate; PPHN, persistent pulmonary hypertension of the newborn; VBG, venous blood gas.

TABLE 2

Patient Characteristics

Characteristic	Therapeutic Hypothermia (n = 16)	No Therapeutic Hypothermia (n = 7)	P
Sex	7 males (44%)	4 males (57%)	NS
GSA (weeks)	38.4 ± 1.4	39.3 ± 1.7	NS
Birth weight (kg)	2.93 ± 0.60	3.27 ± 0.53	NS
BUN (mg/dL)	10.5 ± 3.9	11.4 ± 5.0	NS
SCr (mg/dL)	0.8 ± 0.2	0.8 ± 0.2	NS
UOP (mL/kg. h ⁻¹)	2.89 ± 1.64	2.59 ± 1.20	NS
Apgar, 1 min	1.4 ± 1.5	3.6 ± 2.9	<0.05
Apgar, 5 min	3.9 ± 1.7	5.4 ± 3.2	NS
Apgar, 10 min	5.0 ± 1.9	6.8 ± 0.9	NS
Arterial pH	7.11 ± 0.14	7.24 ± 0.06	NS
Cord pH	7.00 ± 0.17	7.06 ± 0.11	NS
Concurrent nephrotoxins	10 (63%)	4 (57%)	NS

All values expressed as mean ± standard deviation.

BUN, blood urea nitrogen; NS, not significant; SCr, serum creatinine; UOP, urine output