Impact of Small-for-Gestational Age (SGA) Status on Gentamicin Pharmacokinetics in Neonates

Mirjana Lulic-Botica, BSc, RPh, BCPS1,2, Terri Sheer, PharmD1, David Edwards, BScPhm, PharmD, MPH2, Ronald L. Thomas, PhD3, and Girija Natarajan, MD4

Abstract
We compared gentamicin pharmacokinetics among neonates born small-for-gestational age (SGA) and appropriate for gestational age (AGA). We further compared gentamicin pharmacokinetics in subgroups of AGA and SGA neonates born preterm and term and treated within and after the initial week of age. Steady state peak and trough serum gentamicin concentrations were used to calculate clearance (Cl), elimination constant (Kel), volume of distribution (Vd), and half-life (t1/2) in infants (n = 236) who received ≥48 hours therapy. Statistical analyses (SPSS 17.0) included chi-square and the non-parametric Mann–Whitney U-test. SGA infants treated early (<7 days) (n = 29) and at postmenstrual ages ≤32 weeks (n = 23) had significantly lower median Kel (0.069/h vs. 0.081/h and 0.067/h vs. 0.075/h) and clearance (0.58 mL/kg/min vs. 0.68 mL/kg/min and 0.46 mL/kg/min vs. 0.65 mL/kg/min), compared to those born AGA. There were no significant differences in pharmacokinetic profiles with later therapy or at more mature ages. The prolonged half-life of gentamicin may need to be considered in dosing regimens for preterm SGA infants in the initial week of life.

Keywords
aminoglycoside, gentamicin, pharmacokinetics, small-for-gestation

Gentamicin is a commonly used aminoglycoside in neonates, both in empiric and treatment regimens for bacterial pathogens isolated in the Neonatal Intensive Care Unit (NICU). Gentamicin is eliminated unchanged in the urine, almost exclusively by glomerular filtration and has low (<30%) protein binding.1–3 Gentamicin dosing regimens have included traditional lower doses at more frequent intervals or extended-interval higher dose regimens.1–5 The weight-based gentamicin extended-interval dosing regimens aim to achieve adequate peak concentrations to ensure pathogen killing while avoiding elevated trough concentrations, which may be associated with toxicity.4,6 In preterm infants, weight-based dosing regimens are adjusted further for developmental stages or postmenstrual age to account for maturational changes in renal excretion.5,8

The effect of small-for-gestational age (SGA) status in neonates on gentamicin pharmacokinetic parameters of clearance and elimination has not been previously examined. SGA status, which may be a result of intrauterine growth restriction (IUGR), may be associated with a decrease in nephron number and renal organ mass, altered tubular function, and impaired glomerular filtration.8–11 In limited studies with other medications, the impact of intrauterine growth restriction appears to vary with postnatal and postmenstrual age.7,12–13 This may be, in part, due to lower creatinine clearance in the initial 5–10 days of life, specifically in those born preterm.14 Further, gestational age, postnatal age, other clinical factors such as hypoxemia have all been shown to affect drug clearance in neonates, with postmenstrual age having the greatest effect on drug clearance.15–17 Therefore, the specific aims of this study were to compare gentamicin pharmacokinetic parameters in infants born SGA and those born AGA; and, in subgroups of AGA and SGA infants who were administered the drug early (<1 week of age) and late (>1 week) and, finally, in subgroups of AGA and SGA infants whose postmenstrual age at the time of gentamicin administration was ≤32 weeks and >32 weeks.

1Department of Pharmacy, Hutzel Women’s Hospital, Detroit, MI, USA
2Department of Pharmacy Practice, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, MI, USA
3Division of Biostatistics, Children’s Hospital of Michigan, Detroit, MI, USA
4Division of Neonatology, Children’s Hospital of Michigan, Wayne State University, Detroit, MI, USA

Submitted for publication 22 March 2013; accepted 17 September 2013.

Corresponding Author: Girija Natarajan, MD, Division of Neonatal-Perinatal Medicine, Children’s Hospital of Michigan, 3901 Beaumbien Blvd, Detroit, MI, USA
Email: gnatara@med.wayne.edu
Material and Methods

This was a retrospective chart review of consecutive infants who received gentamicin for ≥48 hours in the NICU at Hutzel Women’s Hospital over a 7-year period between 2004 and 2010 and had at least one gentamicin serum concentration measured. The 7-year study period was selected because of availability of electronic searchable pharmacy database; a simplified extended-interval dosing nomogram was initiated early in the study period and was used for most of the infants. Infants were identified from the electronic database using “gentamicin” and “antibiotics” as search words. The patient list was validated using the pharmacy database. The dosing regimen for early (<7 days of age) onset sepsis was 3 mg/kg IV q 36 hours for infants <1,200 g, 3 mg/kg IV q 24 hours for infants 1,200–2,000 g and 3.5 mg/kg IV q 24 hours for infants >2 kg at birth. For gentamicin use beyond 7 days, doses of 3–4 mg/kg q 24 hours were administered for infants <1,200 g, 4 mg/kg q 24 hours for infants who weighed 1,200–2,000 g and 4–5 mg/kg q 24 hours for those who weighed >2 kg. Gentamicin doses were infused over a 0.5-hour-period. Permission to access the medical records and electronic databases with waiver of parental consent were obtained from the Wayne State University Investigational Review Board and Detroit Medical Center Research Review.

In our institution, gentamicin concentrations were measured in all infants who were administered the drug for ≥48 hours. Peak (Cpmax) and trough (Cpmin) concentrations of gentamicin were timed with Cpmin being obtained 0.5 hour prior to a dose and Cpmax 0.5 hour following the end of infusion of the dose to allow for distribution of the drug. Clinical pharmacists entered orders for gentamicin levels according to a dosing regimen and collection times were noted for the study period and underwent therapeutic drug monitoring (TDM). All gentamicin concentrations were obtained after the 3rd dose, which were assumed to be steady state concentrations. A second set of peak and trough concentrations were calculated as the sum of gestational age (weeks) at birth and the postnatal age (weeks). Assumed steady state gentamicin concentrations were used to calculate half-life (t1/2), distribution (Vd) and clearance (ml/kg/min). Statistical analysis was performed using SPSS version 17 (SPSS, Inc., Chicago, IL, USA). Descriptive statistics included number (%), mean (SD) and median (range) values as appropriate. The Shapiro–Wilk test of normality of data revealed a non-normal distribution of pharmacokinetic parameters; therefore all further comparisons of continuous data were performed using the non-parametric Mann–Whitney U-test. Significance was taken as a P-value < .05.

Table 1. Distribution of Frequency of Sampling (n = 236)

<table>
<thead>
<tr>
<th>Dose (mg/kg/dose)</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.5 q12</td>
<td>34</td>
</tr>
<tr>
<td>2.5 q24</td>
<td>10</td>
</tr>
<tr>
<td>3 q24</td>
<td>61</td>
</tr>
<tr>
<td>3 q36</td>
<td>32</td>
</tr>
<tr>
<td>3.5 q24</td>
<td>49</td>
</tr>
<tr>
<td>3.5 q36</td>
<td>30</td>
</tr>
<tr>
<td>4 q24</td>
<td>19</td>
</tr>
<tr>
<td>4.5 q24</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>236</td>
</tr>
</tbody>
</table>

Results

A total of 236 infants were treated with gentamicin during the study period and underwent therapeutic drug monitoring (TDM). All gentamicin concentrations were obtained after the 3rd dose, which were assumed to be steady state concentrations. A second set of peak and trough Cpmax and Cpmin measurements were obtained in 23 (9.7%) infants and 1 infant had a 3rd gentamicin peak and trough concentration obtained.
Clinical Profile
The mean (SD) gestational age at birth was 30.8 (5.4) weeks and mean (SD) birth weight was 1,641 (1,012) g. The vast majority [194 (82%)] of our cohort was born preterm (<37 weeks gestational age). Males comprised 54.7% of the cohort. Forty-eight (20%) infants in the study cohort were SGA at birth. The mean (SD) postnatal age at which gentamicin TDM was performed was 13 (19) days. At the time of TDM, serum creatinine levels were 0.5 mg/dL or less in 75 (32%) infants, between 0.6 and 1 mg/dL in 133 (56%) infants, between 1.1 and 1.5 in 21 (9%) and above 1.5 mg/dL in 2 (0.8%) infants; measurements were unavailable in 5 (2.2%) infants. Mean (SD) serum creatinine was 0.7 (0.3) mg/dL. An adjustment in gentamicin serum concentrations. Bacteria were isolated from the blood in 21 (8.9%) infants; they comprised gram negative bacilli, (12) gram positive cocci (8) and gram positive bacilli. (1) Respiratory endotracheal cultures were performed in 89 (38%) infants and were positive in 41 (17.4%) infants for gram negative bacilli, (28) gram positive cocci (5) and multiple organisms. (8) Spinal fluid cultures were performed in 89 (38%) infants and were negative in all cases. Concomitant vancomycin was administered in 9 and indomethacin in 2 infants.

Effect of SGA Status on Gentamicin TDM
When infants born SGA (n = 48) were compared with those born AGA (n = 188), the median (IQR) birth weights [752.5 (546–1,746) g] vs. 1,400 (880–2,635) g, P = .0001 and weight at TDM [1,265 (610–1,865) g] vs. 1,572.5 (930–2,599) g, P = .005 were significantly different between groups. The median (IQR) durations of therapy in SGA and AGA infants were identical at 7–10 days. All TDM parameters were comparable between groups.

Effect of SGA Status on TDM Parameters With Early and Late Gentamicin Therapy
We then separately analyzed the effects of SGA status on gentamicin TDM performed within the initial week (≤7 days) of life. When infants born SGA (n = 29) were compared with those born AGA (n = 135), the median birth weights and weights at the time of TDM were significantly different (Table 2). In addition, clearance was significantly lower in those born SGA, whereas T_{1/2} was significantly longer (P < .05).

Among infants who underwent gentamicin TDM after 7 days of age, there were significant differences between those born SGA (n = 19) and those born AGA (n = 53) in median birth weights, age at TDM, Cpmin, and serum creatinine (Table 3). At the time of TDM, 39 infants were below the 10th centile for gender-specific postmenstrual age. Of the 19 infants who were SGA at birth, 18 remained below the 10th centile for gender-specific postmenstrual age. The median (IQR) durations of therapy in both groups were 10 (7–14) days.

Effect of SGA Status on TDM Parameters in Preterm Infants With Postmenstrual Age ≤32 Weeks and Those >32 Weeks
Figures 1 and 2 depict mean (SE) clearance and half-lives by postmenstrual age in subgroups of infants born AGA and SGA. Among infants with postmenstrual age ≤32 weeks, those born SGA (n = 23) had significantly lower median clearance and prolonged T_{1/2}, compared to those born AGA (n = 111) (Table 4). Among infants with postmenstrual age >32 weeks, SGA and AGA infants had comparable pharmacokinetic parameters. The median gestational ages, birth weights, age at TDM and weight at TDM remained significantly different between SGA and AGA subgroups administered gentamicin at ≥32 weeks postmenstrual age.

Discussion
Among neonates administered a weight-based extended-interval dosing of gentamicin in the initial week of life and at postmenstrual ages at or below 32 weeks, gentamicin clearance was decreased and half-life was prolonged in

<p>| Table 2. Comparison of Median (IQR) Baseline and TDM Parameters Between Groups of SGA (n = 29) and AGA (n = 135) Infants Who Underwent Gentamicin TDM at ≤7 Days of Life |
|-----------------------------------|-----------------|-----------------|-----------------|</p>
<table>
<thead>
<tr>
<th>Median (IQR)</th>
<th>SGA (n = 29)</th>
<th>AGA (n = 135)</th>
<th>P-value by Mann-Whitney U-test</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>30 (27–38)</td>
<td>32 (27–38)</td>
<td>0.694</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>770 (545–2,312)</td>
<td>1,850 (1,030–2,980)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Gentamicin dose (mg/kg/dose)</td>
<td>3.1 (3.0–3.4)</td>
<td>3.3 (2.9–3.5)</td>
<td>0.082</td>
</tr>
<tr>
<td>Age at TDM (days)</td>
<td>4 (3.5–4)</td>
<td>4 (3–5)</td>
<td>0.317</td>
</tr>
<tr>
<td>Weight at TDM (g)</td>
<td>860 (535–2,300)</td>
<td>1,780 (920–2,940)</td>
<td>0.001</td>
</tr>
<tr>
<td>Kel (hour⁻¹)</td>
<td>0.069 (0.050–0.081)</td>
<td>0.081 (0.064–0.106)</td>
<td>0.017</td>
</tr>
<tr>
<td>T_{1/2} (hours)</td>
<td>10 (8.5–14.1)</td>
<td>8.6 (6.9–10.8)</td>
<td>0.008</td>
</tr>
<tr>
<td>Clearance (mL/kg/min)</td>
<td>0.58 (0.41–0.84)</td>
<td>0.68 (0.57–0.90)</td>
<td>0.036</td>
</tr>
<tr>
<td>Vd (L/kg)</td>
<td>0.5 (0.41–0.67)</td>
<td>0.5 (0.42–0.62)</td>
<td>0.969</td>
</tr>
<tr>
<td>Cpmax (mg/mL)</td>
<td>7.7 (5.5–8.5)</td>
<td>7.6 (6.2–8.6)</td>
<td>0.645</td>
</tr>
<tr>
<td>Cpmin (mg/mL)</td>
<td>1.2 (1.1–1.6)</td>
<td>1.1 (0.8–1.6)</td>
<td>0.278</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.8 (0.5–1.1)</td>
<td>0.8 (0.6–0.9)</td>
<td>0.524</td>
</tr>
</tbody>
</table>
those born SGA, compared to their AGA counterparts. Beyond a week of age and beyond 32 weeks postmenstrual ages, these differences were no longer apparent. Infants born SGA and administered gentamicin after 1 week of age did have significantly lower trough concentrations. This was probably related to older age and lower serum creatinine in this group, compared to those born AGA.

Clinical pharmacokinetics of aminoglycosides in neonates vary substantially compared to adults due to ongoing developmental changes in drug absorption, distribution, metabolism, and excretion. The higher total body water and fraction of extracellular water, compared to adults, resulted in higher volume of drug distribution in neonates, with reported values of 0.5–0.7 L/kg in premature infants, 0.2–0.5 L/kg in children and 0.2–0.3 L/kg in adults respectively. The half-life of gentamicin rapidly changes with postnatal renal maturation, with reported values of 3–11.5 hours in the term neonate <1 week of age, 3–5 hours in the older infant and 1.5–3 hours in the adult, respectively. In a recent review of pharmacokinetics in neonates, Pacifi noted variability, with half-lives ranging from 4.9 to 14.6 hours, clearance from 0.53 to 1.72 mL/kg/min and volume of distribution ranging from 0.45 to 0.75 L/kg. The author emphasized the need for individualized therapy, especially for premature infants for this reason. Due to the accelerated maturation of renal tubules, there is an increased clearance of aminoglycosides with increasing gestational ages.

### Table 3. Comparison of Median (IQR) Baseline and TDM Parameters Between Groups of SGA (n = 19) and AGA (n = 53) Infants Who Underwent Gentamicin TDM at >7 Days of Life

<table>
<thead>
<tr>
<th>Median (IQR) or n (%)</th>
<th>SGA (n = 19)</th>
<th>AGA (n = 53)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>28 (25–31)</td>
<td>27 (26–30)</td>
<td>0.847</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>750 (545–879)</td>
<td>1,030 (750–1,380)</td>
<td>0.004</td>
</tr>
<tr>
<td>Gentamicin dose (mg/kg/dose)</td>
<td>3.1 (2.8–3.3)</td>
<td>3.1 (2.9–3.5)</td>
<td>0.599</td>
</tr>
<tr>
<td>Age at TDM (days)</td>
<td>44 (21–75)</td>
<td>22 (13–42)</td>
<td>0.021</td>
</tr>
<tr>
<td>Weight at TDM (g)</td>
<td>1,420 (1,020–1,745)</td>
<td>1,280 (980–1,703)</td>
<td>0.848</td>
</tr>
<tr>
<td>&lt;10th centile PMA at TDM</td>
<td>18 (95%)</td>
<td>21 (40%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Kel (hour⁻¹)</td>
<td>0.107 (0.086–0.124)</td>
<td>0.095 (0.081–0.111)</td>
<td>0.195</td>
</tr>
<tr>
<td>T₁/₂ (hours)</td>
<td>6.5 (5.6–8.1)</td>
<td>7.3 (6.25–8.6)</td>
<td>0.138</td>
</tr>
<tr>
<td>Clearance (mL/kg/min)</td>
<td>0.90 (0.77–1.05)</td>
<td>0.80 (0.67–0.95)</td>
<td>0.197</td>
</tr>
<tr>
<td>Vd (L/kg)</td>
<td>0.5 (0.4–0.6)</td>
<td>0.5 (0.4–0.6)</td>
<td>0.919</td>
</tr>
<tr>
<td>Cpmax (mcg/mL)</td>
<td>7 (5.5–8.4)</td>
<td>6.9 (5.4–8.05)</td>
<td>0.964</td>
</tr>
<tr>
<td>Cpmin (mcg/mL)</td>
<td>0.5 (0.3–0.6)</td>
<td>0.7 (0.5–0.9)</td>
<td>0.013</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.3 (0.3–0.5)</td>
<td>0.5 (0.35–0.60)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

P-value by Mann–Whitney U-test.

Figure 1. Box plot showing median (IQR) clearance (mL/kg/min) by postmenstrual age of infants born AGA and SGA.
Bayesian analysis and a dosing nomogram in 58 neonates and found that those born at ≤34 weeks gestation had a weight-normalized apparent volume of gentamicin distribution 1.6 times larger than infants born after 34 weeks’ gestation while weight-normalized clearance was 22% lower. Only 33% of predicted peak serum gentamicin concentrations were >6 mg/L for neonates born at or below 34 weeks’ gestation, whereas 90% were therapeutic in neonates born at older gestations. Young and Mangum27 have previously suggested higher gentamicin doses during the first week of life for infants born at lower gestational ages. In contrast, others have reported that more than gestational age or postnatal age, creatinine clearance, which is related to gestational age, plays an important role in the elimination of gentamicin in premature newborns.2 Our data are broadly consistent with previous reported ranges for pharmacokinetic variables.

The effect of varying weights on gentamicin pharmacokinetics in adults has been evaluated in a few studies. Pai et al.28 examined gentamicin pharmacokinetics in more than 1,500 adults across the extremes of weight using a variety of body mass descriptors and found that the lean body weight, rather than true body weight or ideal body weight, normalized the volume of distribution across all weight categories and was the best parameter for initial dosing. In another study in adults, dosing weight

Figure 2. Box plot showing median (IQR) half-life (hours) by postmenstrual age of infants born AGA and SGA.

Table 4. Comparison of Median (IQR) Baseline and TDM Parameters Between Groups of SGA (n = 23) and AGA (n = 111) Infants Who Underwent Gentamicin TDM at ≤32 Weeks Postmenstrual Age

<table>
<thead>
<tr>
<th>Parameter</th>
<th>SGA (n = 23)</th>
<th>AGA (n = 111)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>27 (25–28)</td>
<td>27 (25–29)</td>
<td>.508</td>
</tr>
<tr>
<td>Birth weight (g)</td>
<td>630 (470–750)</td>
<td>1,030 (740–1,360)</td>
<td>.0001</td>
</tr>
<tr>
<td>Gentamicin dose (mg/kg/dose)</td>
<td>3.1 (2.9–3.3)</td>
<td>3.2 (2.9–3.5)</td>
<td>.176</td>
</tr>
<tr>
<td>Age at TDM (days)</td>
<td>4 (4–8)</td>
<td>5 (4–13)</td>
<td>.286</td>
</tr>
<tr>
<td>Weight at TDM (g)</td>
<td>600 (480–860)</td>
<td>1,050 (750–1,360)</td>
<td>.0001</td>
</tr>
<tr>
<td>Postmenstrual age at TDM (weeks)</td>
<td>28 (25–30)</td>
<td>29 (26–31)</td>
<td>.40</td>
</tr>
<tr>
<td>Kel (hour⁻¹)</td>
<td>0.067 (0.046–0.075)</td>
<td>0.075 (0.060–0.095)</td>
<td>.007</td>
</tr>
<tr>
<td>T₁/₂ (hours)</td>
<td>11.2 (9.3–15.1)</td>
<td>9.6 (7.6–11.7)</td>
<td>.006</td>
</tr>
<tr>
<td>Clearance (mL/kg/min)</td>
<td>0.46 (0.39–0.69)</td>
<td>0.65 (0.53–0.83)</td>
<td>.002</td>
</tr>
<tr>
<td>Vd (L/kg)</td>
<td>0.5 (0.4–0.7)</td>
<td>0.5 (0.4–0.7)</td>
<td>.825</td>
</tr>
<tr>
<td>Cmax (mcg/mL)</td>
<td>8 (5.6–8.5)</td>
<td>7 (5.8–8.2)</td>
<td>.592</td>
</tr>
<tr>
<td>Cmin (mcg/mL)</td>
<td>1.2 (0.65–1.60)</td>
<td>0.9 (0.7–1.4)</td>
<td>.318</td>
</tr>
<tr>
<td>Serum creatinine (mg/dL)</td>
<td>0.9 (0.5–1.1)</td>
<td>0.8 (0.6–1.0)</td>
<td>.243</td>
</tr>
</tbody>
</table>

P-value by Mann–Whitney U-test.
correction factors to give equivalent predicted peak
aminoglycoside concentrations with a 2 mg/kg loading
dose were 1.13 times the total body weight for
underweight patients.\(^{21}\) The effect of SGA status on
drug pharmacokinetics in neonates has been examined in a
few previous studies. Schreuder et al.\(^{16}\) evaluated
amikacin clearance in 161 neonates who received
amikacin within 24 hours of birth. Birth weight z-score
and gestational age were correlated with amikacin
clearance with partial correlation coefficients of 0.159
and 0.396, respectively, after correction of other factors.
Amikacin clearance was significantly lower in the lowest
quartile birth weight z-score group of infants, compared to
the highest quartile z-score (0.56 mL/kg/min vs. 0.64 mL/
kg/min). Frattarelli et al.\(^{12}\) studied the impact of SGA
status on vancomycin pharmacokinetics among 143
infants. Overall Vd, clearance and half-life did not differ
between SGA and AGA infants; specific subgroups of
SGA infants: 3–4 weeks old (0.031 L/h vs. 0.088 L/h) and
with a postconceptional age of 27–29 weeks (0.021 L/h vs.
0.066 L/h) had decreased clearance, compared to infants
born AGA. Allegaert et al.\(^{15}\) investigated the same
research question using population pharmacokinetic
studies on perterm neonates within the first month of
life for vancomycin (648 drug concentration measures)
and amikacin (282 measures). Neonates born small-for-
gestational age (SGA) were found to have a 16.2%
(coefficient of variation, 12.2%) reduction in drug
clearance from birth up to a postnatal age of 4 weeks.
Weight explained 47.3% of drug clearance; postmenstrual
age, 25.2%; co-administration of a nonselective cyclo-
oxxygenase inhibitor, 3.5%; renal function, 7.6%; and
SGA, 1.7%. The results of the current and these previous
studies are all remarkably consistent; clearance of drugs
excreted by kidney is decreased in SGA infants, especially
in the early postnatal and postmenstrual weeks of life. In
previous studies, postmenstrual age has been shown to be
a predictor or major determinant of aminoglycoside
clearance, “presumably because it predicts the time course
of development of glomerular filtration.”\(^{15,29}\)

The mechanism of impaired clearance in SGA infants is
probably related to low glomerular filtration rate. Intrauterine
growth restriction is associated with a reduction in the
normalized weight of the kidney, the number of nephrons,
the glomerular filtration rate and tubular function.\(^{30}\)
A compensatory hypertrophy with hyperfiltration is also
thought to occur in the first months of life.\(^{8,9,11}\) Renal blood
flow normalized to weight, urine output and fractional
excretion of sodium have been shown to be comparable in
SGA and AGA animal models, suggesting functional
compensation. It is plausible, therefore, that the early
reduction in clearance normalizes over time.

Our study has some limitations. Our cohort varied in
their gestational ages, postnatal and postmenstrual ages at
gentamicin administration and may have had comorbid-
ities such as sepsis, and patent ductus arteriosus that may
have affected gentamicin clearance. Infants were classified
as SGA based on birth weight and may or may not have
had IUGR. Our classifications of early and late therapy
and the cut-off for postmenstrual ages, although based on
previous data and our dosing regimen, were arbitrary. The
strengths of our study include the fairly large sample size,
our inclusion of all neonates who had gentamicin
concentrations measured, our inclusion of several ex-
tremely preterm (43% \(\leq28\) weeks) infants, a consistent
dosing regimen and TDM protocol and the SGA
categorization by recent North American Olsen growth
curves.

Several studies have shown that dosing of drugs in
neonates, especially in preterm neonates, when extrapo-
lated from adult or pediatric studies, often result in
variable serum concentrations. In addition, intra and extra-
terine growth restriction, although frequent in preterm
neonates, have not traditionally been accounted for in
neonatal dosing regimens. The current study provides
novel insights into the effect of SGA status on gentamicin
pharmacokinetics. Our results suggest that, while volume
of distribution is unaltered, the prolonged half-life in SGA
infants needs to be considered in dosing regimens,
especially in the initial week of life and at early
postmenstrual ages. We speculate that these alterations
may be particularly important in patients with impaired
renal function, high-dose or prolonged therapy and with
concomitant nephrotoxic medications. Regimens taking
the SGA status into consideration may achieve therapeutic
drug concentrations more rapidly, reduce the need for dose
adjustments and most importantly, may reduce nephro-
toxicity, which is related to the renal cortical aminoglyco-
side concentration. Further pharmacokinetic modeling is
required to elucidate the extent of the effect of SGA on
gentamicin pharmacokinetics.

Funding
None.

References
1. Pacifici GM. Clinical pharmacokinetics of aminoglycosides in the
2. Garcia B, Barcia E, Perez F, Molina IT. Population pharmacokinetics
Extended interval dosing of gentamicin in premature neonates <28
5. Hagen I, Oymar K. Pharmacological differences between once daily
and twice daily gentamicin dosage in newborns with suspected