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

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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 ($t_{1/2}$) 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 (≤7days) (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.[7,8]

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.

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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 (<7days 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 system protocol and specified the exact time and date for peak and trough collection to ensure that samples were obtained between the third and fourth doses, assumed to be steady state concentrations. Variability in sampling time was minimal. The initial doses for each patient were based on the simplified dosing nomogram. Exact dosing regimens and collection times were noted for the analysis. Table 1 is a description of the distribution of the frequency sampling by dosing regimen. Estimated postdistribution peak concentrations were calculated from two drug concentrations (peak and trough) using a single compartment model and first order Sawchuk-Zaske pharmacokinetic equations by the pharmacist.[18] The gentamicin dose, interval, peak (Cpmax) and trough (Cpmin) concentrations for each patient at assumed steady state were used to calculate clearance of the drug (Cl), volume of distribution (Vd) and the elimination rate constant (kel^{-1}). Therapeutic range of Cpmax and Cpmin concentrations were defined as 6–10 mcg/mL and <1 mcg/mL, respectively.[19] Dose adjustments post levels were required for gentamicin peak levels >10 mcg/mL or gentamicin trough levels >1.2 mcg/mL.

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

Dose (mg/kg/dose)	Frequency
2.5 q12	34
2.5 q24	10
3 q24	61
3 q36	32
3.5 q24	49
3.5 q36	30
4 q24	19
4.5 q24	1
Total	236

Gentamicin serum samples were analyzed using turbidometric inhibition immunoassay technique (Siemens Healthcare Diagnostics). Medical and pharmacy records, and laboratory results were reviewed to obtain neonatal demographic and clinical data. Gestational age was recorded from the medical records from the history and physical and is typically the best obstetric estimate, if available, or a postnatal estimate using Ballard scoring, if unavailable. Infants were classified as AGA (10th–90th gender-specific centile) or SGA (<10th gender-specific centile) using the Olsen growth curves.[20] Postmenstrual age was calculated, as is the convention, as the sum of gestational age (weeks) at birth and the postnatal age (weeks). Assumed steady state gentamicin Cpmax and Cpmin (mcg/ml) were used to calculate half-life ($t_{1/2}$) in hours, elimination rate constant (kel^{-1}) in $hour^{-1}$, volume of distribution (Vd) in L/kg 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. Comparisons of categorical variables between groups were performed using chi-square test. Significance was taken as a *P*-value <.05.

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 dosing was required in 54 (23%) infants, based on initial 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 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 the time of TDM [1,265 (610–1,865) g vs. 1572.5 (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^{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

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

Median (IQR)	SGA (n = 29)	AGA (n = 135)	*P*-value by Mann–Whitney *U*-test
Gestational age (weeks)	30 (27–38)	32 (27–38)	.694
Birth weight (g)	770 (545–2,312)	1,850 (1,030–2,980)	.0001
Gentamicin dose (mg/kg/dose)	3.1 (3.0–3.4)	3.3 (2.9–3.5)	.082
Age at TDM (days)	4 (3.5–4)	4 (3–5)	.317
Weight at TDM (g)	860 (535–2,300)	1,780 (920–2,940)	.001
Kel ($hour^{-1}$)	0.069 (0.050–0.081)	0.081 (0.064–0.106)	.017
$T_{1/2}$ (hours)	10 (8.5–14.1)	8.6 (6.9–10.8)	.008
Clearance (mL/kg/min)	0.58 (0.41–0.84)	0.68 (0.57–0.90)	.036
Vd (L/kg)	0.5 (0.41–0.67)	0.5 (0.42–0.62)	.969
Cpmax (mcg/mL)	7.7 (5.5–8.5)	7.6 (6.2–8.6)	.645
Cpmin (mcg/mL)	1.2 (1.1–1.6)	1.1 (0.8–1.6)	.278
Serum creatinine (mg/dL)	0.8 (0.5–1.1)	0.8 (0.6–0.9)	.524

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

Median (IQR) or n (%)	SGA (n = 19)	AGA (n = 53)	*P*-value
Gestational age (weeks)	28 (25–31)	27 (26–30)	0.847
Birth weight (g)	750 (545–879)	1,030 (750–1,380)	.004
Gentamicin dose (mg/kg/dose)	3.1 (2.8–3.3)	3.1 (2.9–3.5)	.599
Age at TDM (days)	44 (21–75)	22 (13–42)	.021
Weight at TDM (g)	1,420 (1,020–1,745)	1,280 (980–1,703)	.848
<10th centile PMA at TDM	18 (95%)	21 (40%)	.001
Kel ($hour^{-1}$)	0.107 (0.086–0.124)	0.095 (0.081–0.111)	.195
$T_{1/2}$ (hours)	6.5 (5.6–8.1)	7.3 (6.25–8.6)	.138
Clearance (mL/kg/min)	0.90 (0.77–1.05)	0.80 (0.67–0.95)	.197
Vd (L/kg)	0.5 (0.4–0.6)	0.5 (0.4–0.6)	.919
Cpmax (mcg/mL)	7 (5.5–8.4)	6.9 (5.4–8.05)	.964
Cpmin (mcg/mL)	0.5 (0.3–0.6)	0.7 (0.5–0.9)	.013
Serum creatinine (mg/dL)	0.3 (0.3–0.5)	0.5 (0.35–0.60)	.04

P-value by Mann–Whitney *U*-test.

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.[1] 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.[1,22] 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, Pacifici 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.[1] The author emphasized the need for individualized therapy, especially for premature infants for this reason.[1] Due to the accelerated maturation of renal tubules, there is an increased clearance of aminoglycosides with increasing gestational ages.[23–25] Ariano et al. used

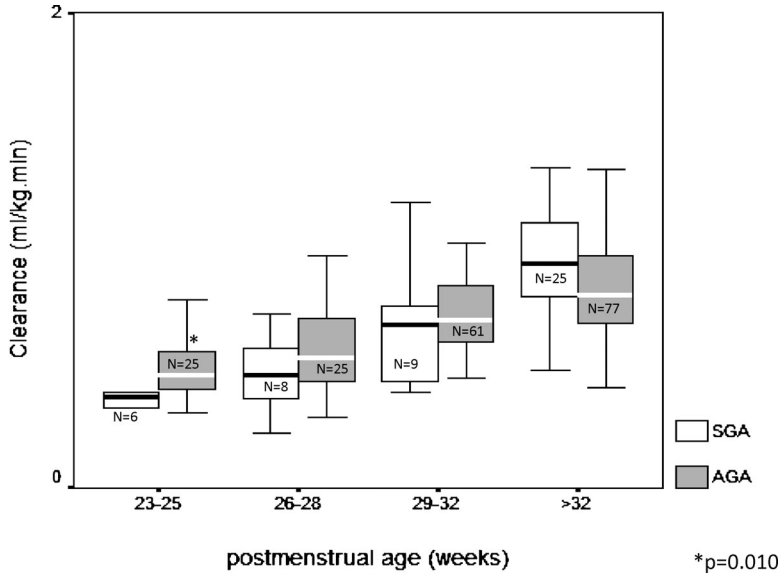

Figure 1. Box plot showing median (IQR) clearance (mL/kg/min) by postmenstrual age of infants born AGA and SGA.

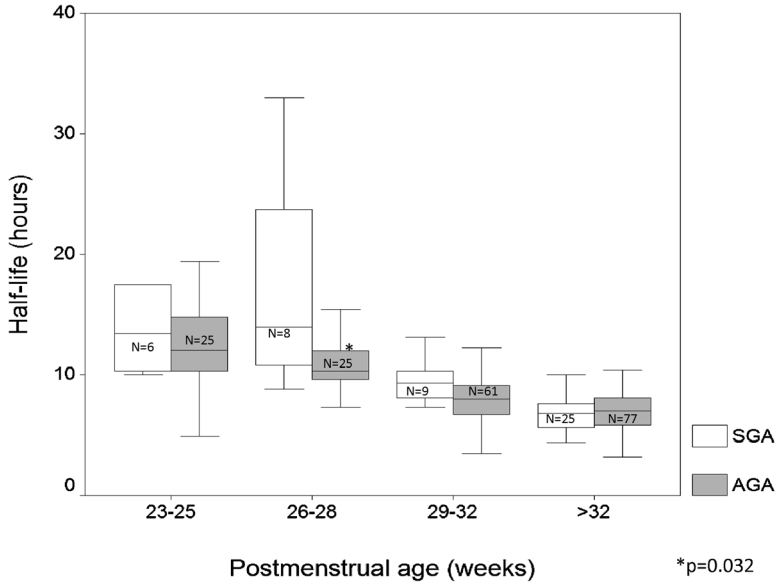

Figure 2. Box plot showing median (IQR) half-life (hours) by postmenstrual age of infants born AGA and SGA.

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.[26] Young and Mangum[27] 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

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

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

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 preterm 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-oxygenase 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 comorbidities 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 extremely preterm (43% $\leq$28 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 extrapolated from adult or pediatric studies, often result in variable serum concentrations. In addition, intra and extra-uterine 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 nephrotoxicity, which is related to the renal cortical aminoglycoside concentration. Further pharmacokinetic modeling is required to elucidate the extent of the effect of SGA on gentamicin pharmacokinetics.

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