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CLINICAL INVESTIGATION

# Development of a Gentamicin and Tobramycin Dosing Strategy in the Neonatal Intensive Care Unit

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**OBJECTIVE** To evaluate the ability of a neonatal aminoglycoside dosing nomogram to produce peak serum concentrations greater than 6 mg/L and trough serum concentrations less than 1.5 mg/L.
**METHODS** Neonates admitted to the Intensive Care Unit who received gentamicin or tobramycin were included if they met the following dosing criteria: Patients < 28 weeks postconceptional age (PCA) received 2.5 mg/kg every 24 hours, those 28–34 weeks PCA received 2.5 mg/kg every 16 hours, and neonates ≥ 35 weeks PCA received 2.5 mg/kg every 12 hours. Serum gentamicin or tobramycin concentrations were obtained and mean patient pharmacokinetic values from this group were used to predict concentrations that would have resulted if the following dosing strategy were used: 4 mg/kg every 36 hours in patients < 29 weeks PCA and 3.5 mg/kg every 24 hours in those ≥ 29 weeks. These doses were then prospectively evaluated in a separate group of neonates.
**RESULTS** Two-hundred sixty one peak serum concentrations were obtained in patients receiving the initial dosing strategy and 114 neonates received the revised dosing regimen. There were significantly more peak serum concentrations below 6 mg/L in the initial regimen (43%) compared to the new dosing strategy (7.8%). There was also a difference between the percentage of trough serum concentrations > 1.5 mg/L using the initial strategy (33%) compared to the new one (1.8%).
**CONCLUSION** The new dosing strategy significantly reduced the number of aminoglycoside serum concentrations outside our target reference range; hence, these doses have become the standard of care in our NICU.

**KEYWORDS:** aminoglycoside, gentamicin, intensive care, neonatal, tobramycin

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## INTRODUCTION

Aminoglycosides are one of the most commonly prescribed classes of antibiotics in the neonatal intensive care unit (NICU). The combination of an aminoglycoside and ampicillin is standard therapy for suspected or documented neonatal sepsis.[1] Peak and trough serum concentrations are routinely monitored in order to ensure efficacy and reduce the risk of ototoxicity and nephrotoxicity. In neonates, gentamicin and tobramycin have been traditionally administered at a dose of 2.5 mg/kg every 8–24 hours based on age.[2]

It has been suggested that patients' clinical outcomes are better when peak serum concentrations of at least 6 mg/L are achieved within forty-eight hours of initiating therapy.[3-5] In addition, elevated serum trough concentrations have been associated with an increased risk of nephrotoxicity.[6] Delayed renal physiology development and a larger volume of distribution in the pre- and full-term neonate require an appropriate aminoglycoside dose and interval in order to achieve serum concentrations within the reference range. Over the past decade, several dosing strategies (i.e., large dose and extended interval) have been developed in hopes of increasing the likelihood of efficacy and reduc-

**ABBREVIATIONS:** Ke, elimination rate constant; NICU, Neonatal Intensive Care Unit; $t^1/_2$, half-life; PCA, postconceptional age; Vd, volume of distribution

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ing the risk of toxicity.[7-12]

Many neonates are initially prescribed gentamicin or tobramycin as empiric therapy until the possibility of infection can be eliminated. It was our clinical impression that a fixed 2.5 mg/kg dose with a variable interval based on the postconceptional age (PCA) frequently produced serum gentamicin and tobramycin concentrations outside the desired concentration range, requiring frequent dosage adjustments and repeated serum concentration monitoring. There are many published strategies that use varying patient demographic variables such as age and weight to calculate dosage in order to produce optimal serum drug concentrations.[7-13] The differences in these published dosing regimens made it difficult to choose one that would be optimal for our patient population. Therefore, we decided to study our own patient demographics then devise a dosing strategy based on our institution's specific needs.

The goals of our study were to 1) determine the frequency of peak serum concentrations below 6 mg/L and trough serum concentrations above 1.5 mg/L in our NICU population, 2) calculate the mean pharmacokinetic parameters for these neonates, 3) if necessary, develop a new dosing regimen using the calculated pharmacokinetic values, and 4) prospectively evaluate the ability of the new dosing strategy to produce peak and trough serum drug concentrations within our institution's desired reference range.

## METHODS

### *Retrospective Review*

Fletcher Allen Health Care is a community teaching hospital affiliated with the University of Vermont School of Medicine. It is a 450-bed institution with a 20 bed NICU. Prior to this study a neonate who received an aminoglycoside was dosed based upon weight and PCA (i.e., the sum of gestational age at birth plus the chronological age or postnatal age). Neonates $< 28$ weeks PCA received 2.5 mg/kg every 24 hours, patients between 28–34 weeks PCA received 2.5 mg/kg every 16 hours, and patients $\geq 35$ weeks PCA were given 2.5 mg/kg every 12 hours. Our hospital laboratory reports the reference range for peak and trough serum gentamicin and tobramycin concentrations as 6–10 mg/L and $< 1.5$ mg/L, respectively.

### *Data Collection*

After approval by the University of Vermont Committees on Human Research serving the University of Vermont and Fletcher Allen Health Care, we performed a retrospective analysis using data available from January 1996 through August 2000. Pharmacy monitoring forms containing information collected concurrent with hospitalization were used for this portion of the study. Information included patient identifiers, gestational age, chronological age, serum creatinine, weight, diagnosis, serum aminoglycoside concentrations, and cultures, if available. Administration times were obtained from the patient's nursing administration record and collection times of serum samples were obtained from the laboratory. Medical records were not reviewed. Neonates with PCA $\leq 36$ weeks who had at least one set of peak and trough serum concentrations drawn at steady-state (3 half-lives) were included in the retrospective analysis. If a patient received more than one course of gentamicin or tobramycin at a different PCA, both sets of serum concentrations were use in data analysis. Exclusion criteria included incomplete documentation of administration time or serum sample collection time.

### *Pharmacokinetic Analysis*

Gentamicin and tobramycin peak concentrations were drawn about 30 minutes after the end of a 30 minute infusion and trough concentrations were obtained just prior to the next scheduled dose. Volume of distribution (Vd), half-life ($t^1/_2$), and elimination rate constant (Ke) for each neonate were calculated using a one compartment model described by Sawchuk and Zaske.[14] Serum gentamicin and tobramycin concentrations were measured by our hospital's clinical laboratory using fluorescence polarization immunoassay (AxSYM System, Abbott Laboratories, Abbott Park, IL).

### *Development of the New Dosing Nomogram*

The estimated pharmacokinetic parameters determined in the previous section combined with our neonatal clinical experience led us to believe that a new dosing strategy should be developed using two rather than three PCA groups. The two new groups would be separated at 29 weeks PCA. This age stratification was based on analysis which revealed that the largest difference in Ke and $t^1/_2$ occurred at this age.

**Table 1.** Demographic and Pharmacokinetic Data for Retrospective Patients

| Parameter | | PCA | | |
|---|---|---|---|---|
| | ALL (n = 261) | < 28 weeks (n = 33) | 28–34 weeks (n = 167) | ≥ 35 weeks (n = 61) |
| PCA (wks) (range) | 31.6 ± 3.26 (23–39) | 25.9 ± 1.27 (23–27) | 31.3 ± 2.0 (28–33) | 35.6 ± 0.67 (35–39) |
| Weight (kg) (range) | 1.79 ± 0.76 (0.52–4) | 0.873 ± 0.23 (0.52–1.55) | 1.59 ± 0.51 (0.63–3.29) | 2.57 ± 0.58 (1–4) |
| Gender (male) | 57% | 55% | 57% | 60% |
| Duration of therapy (days) (range) | 6.1 ± 1.9 (2–16) | 6.1 ± 2.5 (2–16) | 6.2 ± 1.8 (2–14) | 6.0 ± 1.9 (3–16) |
| Vd (L/kg) (range) | 0.53 ± 0.12 (0.3–1.3) | 0.56 ± 0.08 (0.43–0.81) | 0.51 ± 0.13 (0.3–1.3) | 0.55 ± 0.09 (0.33–0.92) |
| $t^1/_2$ (hr)* (range) | 7.5 ± 2.1 (3.3–19.7) | 9.5 ± 1.7 (5–14.7) | 7.42 ± 1.96 (3.3–19.7) | 6.58 ± 1.75 (4–12.6) |
| Ke ($hr^{-1}$)* | 0.098 ± 0.027 | 0.075 ± 0.016 | 0.099 ± 0.026 | 0.111 ± 0.024 |
| Peak < 6 mg/L (range) | 43% (3.3–6.0) | 76% (4.3–5.2) | 42% (3.3–6.0) | 9.6% (3.6–5.9) |
| Peak > 10 mg/L (range) | 0.38% (n = 1) | 0 | 0.6% (n = 1) | 0 |
| Trough > 1.5 mg/L (range) | 33% (1.5–3.8) | 33% (1.5–1.5) | 32% (1.5–3.8) | 51% (1.7–3.6) |

*Data reported as mean ± SD.*
*PCA, postconceptional age.*
**P < 0.05.*

Mean pharmacokinetic parameters (Ke, $t^1/_2$, and Vd) for the newly defined age groups were calculated using the retrospective data. The dose and interval that achieved the highest percentage of concentrations within the targeted reference ranges was 3.5 mg/kg every 24 hours for neonates whose PCA was ≥ 29 weeks and 4 mg/kg every 36 hours for patients with a PCA < 29 weeks. The estimated serum peak and trough concentrations that would be achieved using each patient's calculated pharmacokinetic parameters and the appropriate dosing regimen based on PCA were then calculated. Based on results of this analysis we predicted that the new dosing strategy with age stratification at 29 weeks PCA would produce a 50% reduction in peak and trough serum concentrations outside the desired reference range.

### *Statistical Analysis*

Patient demographics and pharmacokinetics were entered into a Microsoft Access® database. These data were used to generate descriptive statistics for each age group. Statistical analysis was performed on the retrospective data using analysis of variance (ANOVA). Multiple comparison testing was performed using Scheffe's test if ANOVA demonstrated a significant difference among groups. A Student's *t*-test was performed on continuous data for the two PCA groups. Comparison of mean peak and trough concentrations for the initial dosing and new dosing strategy were made using a Student's *t*-test. Chi-square analysis was used to compare the frequency of peak and trough serum concentrations in the desired reference range between the two dosing strategies. The *a priori* level of significance for all tests was $P < 0.05$.

### *Implementation of the New Dosing Strategy*

The results of our retrospective analysis and predicted outcomes with the new dosing regimen were presented at the Neonatal Intensive Care Division meeting. This Division consists of the neonatal attending physicians, neonatal nurse practitioners, and neonatal fellows. The group adopted the new dosing strategy as the standard of care in the NICU. The new dosing strategy was implemented with the agreement that a prospective review would be performed and presented to the division on a regular basis. Prior to implementation of the new dosing regimens, educational sessions were held for the medical, nursing, and pharmacy staff.

### *Prospective Evaluation of the New Dosing Strategy*

To assess the efficacy of the new dosing strategy, gentamicin and tobramycin serum concentrations were prospectively evaluated from March 1, 2001, through March 1, 2002. The inclusion and exclusion criteria, data collection methods,

**Table 2.** Demographic and Pharmacokinetic Data for Prospective Patients

| | All (n = 114) | < 29 weeks (n = 17) | ≥ 29 weeks (n = 97) |
|---|---|---|---|
| PCA (wks) (range) | 33.6 ± 4.5 (24–41) | 26 ± 1.3 (24–28) | 34.9 ± 3.4 (29–41) |
| Weight (kg) (range) | 2.25 ± 0.99 (0.63–4.47) | 0.91 ± 0.21 (0.63–1.39) | 2.48 ± 0.88 (0.94–4.47) |
| Gender (male) | 57% | 47% | 58% |
| Duration of therapy (days) (range) | 5.9 ± 2.1 (2–23) | 6.4 ± 1.5 (3–10) | 5.8 ± 2.1(2–23) |
| Vd (L/kg) (range) | 0.5 ± 0.12 (0.22–0.88) | 0.52 ± 0.12 (0.39–0.87) | 0.5 ± 0.11 (0.22–0.43) |
| $t^1/_2$ (hr)* (range) | 7.7 ± 1.8 (4.6–14.2) | 10.1 ± 1.9 (7.1–14.2) | 7.2 ± 1.4 (4.6–12.5) |
| Ke ($hr^{-1}$)* (range) | 0.095 ± 0.02 (0.049–0.149) | 0.071 ± 0.013 (0.049–0.097) | 0.099 ± 0.018 (0.056–0.149) |
| Peak < 6 mg/L | 7.8% | 5.88% | 8.2% |
| Peak > 10 mg/L | 5.2% | 11.8% | 4.1% |
| Trough > 1.5 mg/L | 1.76% | 0 | 2.1% |

*Data reported as mean ± SD.*
*PCA, postconceptional age.*
**There is a significant difference between the two age groups (P < 0.001).*

and pharmacokinetic calculations were identical to those used during the retrospective review. For the first 6 months of the study, serum gentamicin and tobramycin concentrations were measured using a fluorescence polarization immunoassay (AxSYM System, Abbott Laboratories, Abbott Park, IL) with the lower limit of detection being 0.3 mg/L. For the final 6 months serum concentrations were measured with a fluorescence polarization immunoassay (TDX/Flex System, Abbott Laboratories, Abbott Park, IL) with the lower limit of detection at 0.27 mg/L. Target peak serum concentrations ranged between 6–10 mg/L, and target troughs were ≤ 1.5 mg/L.

## RESULTS

### *Retrospective Data*

Two hundred sixty-one sets of serum concentrations were collected from 212 patients who met inclusion criteria. Demographic and pharmacokinetic data are presented in Table 1. The overall age range was 24–36 weeks PCA. The ANOVA demonstrated a significant difference ($P < 0.001$) in the half-life and elimination rate constant among the retrospective patients that comprised the three age groups. Volume of distribution was not significantly different ($P > 0.05$). Multiple comparison testing revealed that all three age groups differed from each other in half-life and elimination rate constant ($P < 0.05$). Results from this group of neonates showed that 43% (111/261) of peaks were below 6 mg/L, 33% (85/261) of troughs were greater than 1.5 mg/L, and 0.33% (1/261) of peaks were greater than 10 mg/L.

### *Prospective Data*

One hundred fourteen sets of serum concentrations from 106 neonates were prospectively reviewed. Ninty-seven (85%) of the patients were in the ≥ 29 week group and 17 were < 29 weeks. Demographics and pharmacokinetic data for the prospective patients, using mean values and standard deviations, are listed in Table 2. Age range was from 24–36 weeks PCA. There was a significant difference ($P < 0.001$) in the $t^1/_2$ and in the ke among the prospective patients that comprised the two groups. Volume of distribution was not significantly different ($P > 0.05$). Two of the trough concentrations (1.8%) were > 1.5 mg/L and 7.8% of peak values were < 6 mg/L. Only 5.2% of the peak concentrations were > 10 mg/L (10.1 mg/L–14.86 mg/L). All of the patients who had peak concentrations > 10 mg/L had trough concentrations < 1.5 mg/L. None of the trough concentrations were below the sensitivity of the assay. No patient had more than one concentration outside the reference range.

Peak concentrations < 6 mg/L were reduced from 43% to 7.8%, while elevated troughs were reduced from 33% to 1.8% ($P < 0.001$) [Table 3]. The mean trough value was significantly lower ($P < 0.001$) using the new dosing regimen (0.83 mg/L) than the previous one (1.4 mg/L). Similarly, the mean peak value of 8.1 mg/L was significantly higher ($P < 0.001$) for the new dosing regimen compared to the previous one (6.1 mg/L).

**Table 3.** Performance Comparison of Previous and New Dosing Strategy

| Concentration (mg/L) | Previous Dosing Regimen (n = 261) | New Dosing Regimen (n = 114) |
|---|---|---|
| Peak* (range) | 6.1 ± 1.15 (3.3–10.5) | 8.1 ± 1.6 (4.7–14.9) |
| Trough* (range) | 1.4 ± 0.6 (0.2–3.8) | 0.8 ± 0.3 (0.3–1.76) |
| Peak < 6* | 43%† | 7.8%† |
| Peak > 10‡ | 0.38%† | 5.3%† |
| Trough > 1.5* | 33%† | 1.76%† |

*Data presented as mean ± SD.*
**P < 0.001.*
*†Percent of levels.*
*‡P < 0.005.*

## DISCUSSION

High-dose, extended-interval aminoglycoside dosing has been shown to be effective and safe in adult patients.[15] Recent investigations with neonates have examined the role of larger aminoglycoside doses at extended intervals.[2,7-13,16-19] Some studies suggest that administration of a loading dose rapidly achieves serum concentrations within the targeted reference range, with a low incidence of elevated trough concentrations.[2,19,20] Currently, optimal guidelines for extended-interval aminoglycoside dosing in the neonatal population have not been established. Because the pharmacokinetic parameters of neonates differ from adults, extrapolations from adult data are difficult to interpret and apply.

The mean pharmacokinetic values for the age groups in the retrospective cohort were consistent with published data.[16-18,21] The mean values for the prospective cohort are comparable to both published data as well as our retrospective population.[22-25] The uneven distribution of patients in each age group in both the retrospective and prospective review accurately reflects the population of neonates in our institution's NICU.

In this investigation, only aminoglycoside serum drug concentrations were quantified. Data were not collected on patient clinical outcomes with respect to resolution of infection or toxicity. Thus, it cannot be demonstrated that the new dosing strategy improves clinical outcomes or reduces toxicity relative to the old one. Nevertheless, there is literature to suggest an association between peak concentrations within the reference range and avoidance of high trough concentrations with improved clinical outcomes and avoidance of toxicity.[19] There is little evidence to support drug-associated toxicity in neonates with elevated peak concentrations.[26] An additional limitation to our study is that the immunoassay that was used to measure the serum drug concentrations was changed during our data collection. Both assays, however, use the same methodology and have a high degree of correlation (r = 0.994, product information, AxSYM System, Abbott Laboratories, Abbott Park, IL). As a result, it is felt that the change in assay did not significantly affect our results.

In conclusion, the implementation of the new aminoglycoside dosing nomogram has significantly reduced the percentage of aminoglycoside serum drug concentrations outside our institution's reference range; hence, this dosing regimen has been adopted as standard of care within our NICU as well as many of our referring hospitals.

This dosing strategy was designed specifically for the patient population at our institution. Clinical judgment is essential for determining when other factors such as disease state or compromised renal function may require dose modifications or random levels to determine the appropriate dose.

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