Bayesian Pharmacokinetic Analysis of a Gentamicin Nomogram in Neonates: A Retrospective Study

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ABSTRACT

Background: Although gentamicin is used extensively within the first week of life for suspected sepsis in neonates, little is known about the performance of gentamicin dosing nomograms in this population.

Objective: The goal of our study was to retrospectively assess the performance of a gentamicin dosing nomogram in neonates given gentamicin during the first week after birth.

Methods: In this retrospective study, gentamicin therapeutic drug monitoring data were collected during routine clinical care for all neonates who were born in St. Boniface General Hospital (Winnipeg, Manitoba, Canada) between January 1999 and April 2001 and given gentamicin during the first week after birth. We used Bayesian pharmacokinetic analysis to retrospectively assess the performance of our gentamicin dosing nomogram in neonates born at gestation ages <32 weeks, between 32 and 34 weeks, and >34 weeks. Bayesian pharmacokinetic values for parameters within groups were compared and used to explore predicted peak and trough serum gentamicin concentrations based on the institutional dosing nomogram.

Results: In a total of 58 neonates, those neonates 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 ($P < 0.001$), as identified by Bayesian analysis. Weight-normalized gentamicin clearance was 22% lower in the youngest age category ($P < 0.01$). Only 33% of predicted peak serum gentamicin concentrations were >6 mg/L for neonates born at ≤34 weeks'

Presented as a poster at the 103rd Annual Meeting of the American Society of Clinical Pharmacology and Therapeutics, Atlanta, Georgia, March 2, 2002.

Accepted for publication January 6, 2003.

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doi:10.1016/S0011-393X(03)00022-5
0011-393X/03/\$19.00

gestation, whereas 90% were therapeutic in neonates born at >34 weeks' gestation ($P < 0.001$). With the present nomogram, the likelihood of an indication for adjustment of the dosing regimen was 12.4-fold higher (95% CI, 3.5–43.7) for those neonates born at ≤ 34 weeks' gestation.

Conclusions: These results have important clinical implications with regard to the advisability of determining peak serum gentamicin concentrations in neonates born at ≤ 34 weeks' gestation. Sampling of peak serum concentrations is indicated in this population to avoid underdosing and potential loss of therapeutic efficacy. (*Curr Ther Res Clin Exp.* 2003;64:178–188) Copyright © 2003 Excerpta Medica, Inc.

Key words: neonatal sepsis, gentamicin, nomograms, Bayesian pharmacokinetics.

INTRODUCTION

Gentamicin, a frequently used aminoglycoside antibiotic for the management of gram-negative sepsis, is associated with nephrotoxicity and otovestibular toxicity in adults.¹ Evidence of gentamicin nephrotoxicity in neonates, derived from a study that indicated that one of the markers of proximal renal tubular injury (*N*-acetyl-beta-glucosaminidase), was 1.6-fold higher in those exposed to the drug compared with controls.² However, firm clinical evidence of neonatal aminoglycoside nephrotoxicity is lacking. Also, little evidence shows auditory or vestibular toxicity in neonates exposed to aminoglycosides.^{3,4}

In our neonatal unit, we were concerned about the appropriateness of determining only trough gentamicin concentrations in neonates, as well as the usefulness of these concentrations in guiding further dosing with this drug. In all neonates given gentamicin, the practice was to obtain trough serum gentamicin concentrations between the third and fifth doses and to maintain this concentration between 0.5 and 2.0 mg/L.

The goal of our study was to use Bayesian pharmacokinetic analysis to retrospectively assess the performance of our gentamicin dosing nomogram in neonates given this drug during the first week after birth, using data collected during routine clinical care. Bayesian pharmacokinetics often is used to identify individual pharmacokinetic parameters in patient care settings in which little serum concentration–time data may be available.^{5–7}

PATIENTS AND METHODS

The Health Research Ethics Board of the University of Manitoba (Winnipeg, Manitoba, Canada) approved the protocol. Gentamicin therapeutic drug monitoring (TDM) data were retrospectively collected for neonates who were born between January 1999 and April 2001 at the St. Boniface General Hospital (Winnipeg, Manitoba, Canada) and received gentamicin within the first week of life.

The dosing history (including doses, timing of the doses, timing of blood samples, and the measured gentamicin concentration[s]) of each neonate was examined. All serum gentamicin concentrations had been analyzed in the Department of Biochemistry, St. Boniface General Hospital, using an automated clinical chemistry analyzer (CEDIA Gentamicin II, Roche Diagnostics, Indianapolis, Indiana). The limit of sensitivity of this assay was 0.2 mg/L.

The decision to initiate gentamicin therapy for suspected sepsis was made by the neonatologist, as was the selection of dose and serum sampling schedule. The drug was given by IV infusion over 10 minutes. Dosing of all neonates within the first week of life was guided by our institutional nomogram stating neonates born at gestational age (GA) <30 weeks should receive gentamicin 2.5 mg/kg once a day; GA 30 to 34 weeks, 3 mg/kg once a day; and GA >34 weeks, 2.5 mg/kg every 12 hours.⁸ This nomogram is based on data from a number of clinical pharmacokinetic studies.⁹⁻¹² These regimens were designed to achieve steady-state serum gentamicin concentrations with peaks ≥ 6 mg/L¹³ and troughs between 0.5 and 2.0 mg/L.¹⁴ Troughs usually were drawn between the third and fifth doses. For our initial pharmacokinetic analysis, the infants were selected and stratified according to the earlier mentioned GA categories.

Pharmacokinetic Data Analyses

Data on gentamicin doses and serum concentrations from all neonates included in the study were entered into PASTRX version 10.6 of the USC*PACK collection of personal computer programs from the University of Southern California (Los Angeles, California). The overall assay error pattern for gentamicin concentrations was determined by fitting a second-order polynomial to the plot of the assay SD versus the measured serum gentamicin concentration (C), producing the formula:

$$SD = 0.18 - 0.0083 \times C + 0.0049 \times C^2$$

Bayesian fitting weighted the individual concentrations in the serum by the reciprocal of the earlier mentioned assay error variance model. The modeling procedure used 1 or 2 trough serum samples per neonate in a 1-compartment open model with zero-order infusion to identify the following parameters: apparent volume of distribution (V_d), elimination rate constant (k_e), half-life ($t_{1/2}$), and serum clearance rate (Cl_s). A priori values for Bayesian fitting for infants born at GA ≤ 34 weeks were obtained from published data¹⁵ using nonparametric expectation maximization analysis. For neonates born at GA <32 weeks, a priori mean (SD) V_d was 0.75 (0.35) L/kg and mean (SD) k_e was 0.062 (0.021) h^{-1} .¹⁵ For neonates born between GA 32 and 34 weeks, V_d was 0.65 (0.25) L/kg and k_e was 0.080 (0.038) h^{-1} .¹⁵ For neonates born at GA >34 weeks, V_d was 0.45 (0.18) L/kg and k_e was 0.173 (0.070) h^{-1} .¹⁶ A priori estimates for drug clearance were the product of k_e and V_d . Bayesian values for parameters within GA groups were compared with a priori values, and Bayesian pharmacokinetic values were compared between GA groups. The Bayesian-derived parameter

estimates then were used to explore predicted steady-state peak and trough values for the GA groups based on the institutional gentamicin dosing nomogram.

Comparisons of the values of the pharmacokinetic parameters were analyzed by the Tukey-Kramer test for multiple comparisons for differences between GA groups. For parametric data, statistical analysis was performed using a 2-sided Student *t* test. Frequencies were compared using the Fisher exact test, where appropriate. For all analyses, alpha was set at <0.05 for statistical significance.

RESULTS

The records of 58 neonates (38 males, 20 females; mean [SD] GA for males, 35 [4] weeks; mean [SD] GA for females, 37 [3] weeks) were studied. The comparative demographic characteristics of these infants are shown in Table I. The group born at GA $\leq$ 34 weeks (group 1) comprised 27 patients; the group born at GA >34 weeks (group 2), 31 patients. All patients appeared to have appropriate demographic characteristics for their GA; however, group 1 included more male neonates than did group 2, as evidenced by the higher sex ratio (2.9:1 vs 1.4:1, respectively).

Sixty-three serum gentamicin concentrations were obtained from the data of the 58 neonates. Because Bayesian parameter values were no different for the infants born at GA <32 weeks than for those born between GA 32 and 34 weeks, the pharmacokinetic data for these 2 groups were combined (Table II). Although a priori values from the literature for the GA of individual infants were used

Table I. Gestational age (GA)-related demographic characteristics of study patients (N = 58).

Characteristic	Group 1* (n = 27)	Group 2† (n = 31)
Sex, no. (%)		
Male	20 (74)	18 (58)
Female	7 (26)	13 (42)
Male:female ratio	2.9:1	1.4:1
Birth weight, mean (SD), g	2015 (742)	3328 (660)
Apgar score, mean (SD)		
1 min	6 (2)	6 (2)
5 min	7 (2)	8 (2)
Head circumference, mean (SD), cm	30 (3)	34 (2)
Body length, mean (SD), cm	45 (5)	52 (4)
Length of hospital stay, mean (SD), d	29 (25)	8 (6)

*Born at GA $\leq$ 34 weeks.

†Born at GA >34 weeks.

Table II. Comparison of Bayesian-derived pharmacokinetic parameters (mean [SD]) with published a priori values as a function of gestational age (GA).*

Pharmacokinetic Parameter	Group 1 [†] (n = 27)	Group 2 [‡] (n = 31)
V_d , L/kg		
A priori	0.70 (0.30)	0.45 (0.18)
Bayesian	0.64 (0.04)	0.41 (0.03) [§]
k_e , h ⁻¹		
A priori	0.071 (0.030)	0.173 (0.070)
Bayesian	0.070 (0.014)	0.140 (0.025) [§]
$t_{1/2}$, h		
A priori	9.8	4.0
Bayesian	10.5	5.0
Cl_s , L/kg/h		
A priori	0.050 (0.021)	0.078 (0.023)
Bayesian	0.045 (0.015)	0.058 (0.016)

V_d = volume of distribution; k_e = elimination rate constant; $t_{1/2}$ = half-life; Cl_s = serum clearance.

*All a priori values except half-life are found in references 15 (infants born at GA ≤ 34 weeks) and 16 (infants born at GA > 34 weeks).

[†]Born at GA ≤ 34 weeks.

[‡]Born at GA > 34 weeks.

[§] $P < 0.001$ versus infants at GA ≤ 34 weeks.

^{||} $P < 0.01$ versus infants at GA ≤ 34 weeks.

for fitting, the reported a priori values for neonates born at GA ≤ 34 weeks in Table II are means of the combined values for those GAs.

Considering only the Bayesian results, group 1 had a mean weight-normalized V_d 1.6-fold higher than that of group 2 ($P < 0.001$). The mean k_e also was different between groups ($P < 0.001$), resulting in a $t_{1/2}$ in group 1 that was 2-fold that in group 2. Overall weight-normalized gentamicin Cl_s was 22% lower in the youngest age group ($P < 0.01$).

The a priori linear plots in relation to the uniquely identified values for the pharmacokinetic parameters of k_e and V_d are shown in Figures 1 and 2, respectively. Although the mean Bayesian values were not found to be significantly different, the spread in individual values within Figures 1 and 2 suggests significant heterogeneity.

The predicted steady-state peak serum gentamicin concentrations for the nomogram-derived regimens are shown in Figure 3. Our nomogram resulted in predicted peak serum concentrations for group 1 that were on average 24% lower than that of group 2 ($P < 0.001$). No significant difference was found between GA and the mean trough serum concentrations predicted using the nomogram (Figure 4).

Examining the overall performance of the institutional nomogram by GA, only 33% of predicted peak serum gentamicin concentrations were > 6 mg/L in group 1, whereas 90% were therapeutic in group 2 ($P < 0.001$). With respect to

Figure 1. Bayesian-derived parameter estimates for gentamicin elimination rate constant (k_e) in relation to gestational age (GA) at birth. The dashed line represents the a priori pharmacokinetic values from the literature that were incorporated in the Bayesian estimation.^{15,16}

numbers of patients with recommended trough serum concentrations in the range of 0.5 to 2.0 mg/L, the nomogram demonstrated similar performance (85% vs 74% in group 1 vs 2, respectively). Only 12 of the 58 neonates (21%) had predicted trough serum gentamicin concentrations >2 mg/L. Dosing adjustments were considered necessary for peak concentrations <6 mg/L and trough concentrations outside the desired range of 0.5 to 2.0 mg/L. Overall, dose adjustments were indicated for 70% ($n = 19$) of patients in group 1, whereas it was

Figure 2. Bayesian-derived parameter estimates for volume of distribution (V_d) of gentamicin in relation to gestational age (GA) at birth. The dashed line represents the a priori pharmacokinetic values from the literature that were incorporated in the Bayesian estimation.^{15,16}

Figure 3. Performance of the institutional dosing nomogram with respect to predicted steady-state peak serum gentamicin concentrations (peak) and gestational age (GA) at birth. The symbols represent individual values from Bayesian pharmacokinetic analysis. Average concentration data are presented as mean (95% CI). * $P < 0.001$ versus the group born at GA >34 weeks.

indicated in only 19% ($n = 6$) of patients in group 2 (odds ratio, 12.4; 95% CI, 3.5–43.7; $P < 0.001$).

DISCUSSION

This study demonstrated from routine clinical data that weight-normalized V_d of gentamicin in neonates is significantly higher in infants born at GA <34 weeks. These findings were consistent with the findings of a number of other

Figure 4. Performance of the institutional dosing nomogram with respect to predicted steady-state trough serum gentamicin concentrations (trough) relative to gestational age (GA). The symbols represent individual values from Bayesian pharmacokinetic analysis. Average concentration data are presented as mean (95% CI).

studies.^{12,14,15,17} The physiochemical properties of gentamicin suggest that it is strongly affected by total body water because it is a highly polar compound.^{17,18} Therefore, it is understandable that in premature neonates with an expanded extracellular fluid volume, gentamicin distribution space also would be expanded relative to older neonates.

Our finding of a lower k_e in neonates born at a younger GA, with its subsequent increase in $t_{1/2}$, is due to both a reduction in weight-normalized Cl_s and an expanded weight-normalized drug distribution space. The clinical implication of the expanded V_d with prematurity is that for the same dosing interval, a larger weight-based dose would be required to maintain the same therapeutic peak serum concentrations.

A desire to simplify gentamicin TDM and minimize the frequency of blood sampling in this patient population led our clinicians and others to sample only trough serum concentrations. The importance of a trough serum gentamicin concentration >2 mg/L is its association with the subsequent development of nephrotoxicity, a finding in adults.¹⁹ Therefore, trough concentrations provide information about drug accumulation and the potential for nephrotoxicity. However, without data about peak serum concentrations, little information is available to assess the adequacy of therapy for the treatment of serious gram-negative infections.^{13,20} The original work of Moore and colleagues²⁰ demonstrated that the maximal clinical response to therapy occurred with peak concentration to minimum inhibitory concentration (MIC) ratios $\geq 12:1$. Most gentamicin-susceptible gram-negative organisms have average MICs of ~ 0.5 mg/L; therefore, achieving peak concentrations ≥ 6 mg/L is a desirable goal of TDM.

In 1 literature review,²¹ up to 33% of trough serum gentamicin concentrations were >2 mg/L in neonates dosed using traditional methods. Our nomogram performed relatively well, with only 21% of trough serum gentamicin concentrations >2 mg/L. In addition, Glover et al²² found that 42% of traditionally dosed neonatal patients required some form of adjustment in dosing because the range of the serum concentrations was inappropriate. This observation is similar to our finding of 41% of neonates requiring some form of adjustment in gentamicin dosing. Our identification of only 33% of peak serum concentrations being within the target range in the neonates born at GA ≤ 34 weeks suggests that a larger dose may be necessary in this population and can be explained by our finding of a relatively expanded drug distribution space with prematurity.

Some investigators²³ have suggested that early TDM is unnecessary in the neonatal population within the first week after birth, based on their own derived nomogram. Although they found that the performance of TDM did not improve the predictive performance related to trough serum concentrations, they did not examine the role of TDM on adequately identifying peak concentrations.

The advent of technologies such as population modeling has allowed the identification of parameters and their covariates from just a few serum samples per patient accompanied by well-researched a priori parameter values taken

from the literature.⁵ Bayesian estimation uses prior parameter probability distributions, together with the patient's measured serum concentration(s), to arrive at values for the pharmacokinetic parameters that are most likely to represent the patient's true values when data are sparse. The information gained then can assist in analyzing the performance of any drug dosing nomogram, allowing us to identify patient populations that require intensive TDM.

The drawback of analyzing only trough serum concentrations, however, is that D-optimal sampling theory suggests that little information about the V_d is obtained from such samples.²⁴ Although gentamicin concentrations sampled $1.44 t_{1/2s}$ after dosing are most informative of k_e , in clinical practice, trough serum samples usually are taken $2.4 t_{1/2s}$ after the last dose. Obviously, these deficiencies have some influence on the uncertainties within our parameter estimates. Nonetheless, the advantage of Bayesian modeling is that the presence of the a priori population estimates restricts the newly estimated parameter values so that they are less likely to give odd combinations that simply happen to fit the data. The attractiveness of Bayesian modeling when assessing a patient's therapy is that we are not constrained by the assumption of steady state or the need to have samples drawn exactly within the recommended time window before or after dosing.

Bayesian analysis is a useful tool for an information-sparse environment such as the neonatal intensive care unit. Our results have important clinical implications for the use of gentamicin in neonates born at GA ≤ 34 weeks. Sampling of peak serum gentamicin concentrations is indicated in these very young, critically ill infants, to avoid underdosing and potential loss of therapeutic efficacy. Assessment of peak serum concentration ensures individualization of regimens to a higher peak to MIC ratio, which is critical for a patient with serious gram-negative sepsis.^{25,26}

CONCLUSION

These results have important clinical implications with regard to the advisability of determining peak serum gentamicin concentrations in neonates born at ≤ 34 weeks' gestation. Sampling of peak serum concentrations is indicated in this population to avoid underdosing and potential loss of therapeutic efficacy.

ACKNOWLEDGMENTS

The authors wish to acknowledge Carol Green, ART, FCSMLS, and John Krahn, PhD, Department of Biochemistry, St. Boniface General Hospital, Winnipeg, Manitoba, Canada, for their assistance with this project.

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