

New Neonatal Gentamicin Dosing Guidelines: Results of an Evaluation of Serum Concentrations

Anita Kozyrskyj, Mary Masih, Jina Hahn, Cindy Ho, May Wong and Marie Sirdevan

ABSTRACT

Gentamicin is frequently administered in combination with the penicillins for the treatment of suspected or proven neonatal sepsis. Empiric gentamicin dosing regimens based on the neonate's weight, gestational age, postnatal age, post-conceptual age or renal function have been designed to achieve therapeutic serum concentrations. Correlations between gentamicin clearance or half-life and post-conceptual age have been documented. Prior to the study, initial gentamicin dosing guidelines recommended that 2.5 mg/kg be administered every 24 hours for neonates less than 1000 g, every 18 hours for infants between 1000-1500 g and every 12 hours for neonates weighing more than 1500 g. The objective of this study was to prospectively evaluate gentamicin concentrations in neonates administered these doses and determine the frequency of trough concentrations greater than 2 mg/L and peak concentrations greater than 8 mg/L. An additional objective of this study was to evaluate the correlation between gentamicin clearance and weight or post-conceptual age and determine the best factor for calculating the dosing interval in revised gentamicin dosing guidelines.

Three hundred and thirteen neonates with an average post-conceptual age of 33±5 weeks and weight of 2073±1042 g provided 328 peak-trough concentration pairs. Serum gentamicin trough concentrations greater than 2mg/L were observed in 56% of samples. The incidence of elevated trough concentrations was highest in neonates weighing greater than 1000 g. Since the best correlation was observed between gentamicin clearance and weight, the revised dosing guidelines also used neonatal weight to determine dosing interval. The guidelines were revised by extending the interval to 24 hours for weights less than 1500 g and to 18 hours for greater weights. To avoid sub-therapeutic trough concentrations in neonates receiving a second course of gentamicin, dosing guidelines for neonates more than seven days of age remained the same.

Key words: clearance, dose, gentamicin, neonate, serum concentrations

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RÉSUMÉ

La gentamicine est couramment administrée en association avec des pénicillines dans le traitement des septicémies néonatales avérées ou suspectées. Les schémas posologiques empiriques de la gentamicine basés sur le poids, l'âge gestationnel, l'âge post-natal, l'âge post-conceptionnel ou la clairance rénale du nouveau-né ont été établis afin d'atteindre des concentrations plasmatiques thérapeutiques. Des corrélations entre la clairance ou la demi-vie de la gentamicine et l'âge post-conceptionnel du nouveau-né ont été documentées. Nous recommandons l'administration initiale de gentamicine à raison de 2,5 mg/kg toutes les 24 heures pour les nouveau-nés pesant moins de 1 000 g, toutes les 18 heures pour ceux dont le poids varie entre 1 001 g et 1 500 g et toutes les 12 heures pour ceux pesant plus de 1 500 g. Cette étude visait à évaluer de façon prospective les concentrations plasmatiques de gentamicine chez les nouveau-nés et à déterminer les taux de fréquence des creux plasmatiques supérieurs à 2 mg/L et des pics plasmatiques supérieurs à 8 mg/L. Cette étude avait également pour objectif d'analyser la corrélation entre la clairance de la gentamicine et le poids ou l'âge post-conceptionnel du nouveau-né et de déterminer le meilleur facteur pour calculer la fréquence d'administration de la gentamicine, dans un contexte de révision des schémas posologiques.

En tout, 313 nouveau-nés dont l'âge post-conceptionnel moyen était de 33 ± 5 semaines et le poids moyen de 2073 ± 1 042 g, ont permis de créer 328 paires de creux-pics plasmatiques. Les creux plasmatiques de gentamicine supérieurs à 2 mg/L ont été relevés dans 56 % des échantillons recueillis. Les creux plasmatiques élevés étaient plus fréquents chez les nouveau-nés pesant plus de 1 000 g. Étant donné que la corrélation la plus nette a été observée entre la clairance de la gentamicine et le poids, la fréquence d'administration a été déterminée en tenant compte du poids du nouveau-né. Le schéma posologique a été révisé en reportant la fréquence d'administration à toutes les 24 heures pour les nouveau-nés pesant moins de 1 500 g et à toutes les 18 heures pour ceux ayant un poids supérieur à 1 500 g. Afin d'éviter des creux plasmatiques subthérapeutiques chez les nouveau-nés recevant un second traitement à la gentamicine, le schéma posologique chez les nouveau-nés âgés de plus de sept jours est demeuré le même.

Mots clés : clairance, concentrations plasmatiques, gentamicine, nouveau-né, schéma posologique

Anita Kozyrskyj, B.Sc.Pharm., was the Supervisor of the Department of Pharmacy Perinatal Unit Satellite, Mount Sinai Hospital, Toronto. Anita is currently a Masters candidate in the Department of Community Health Sciences, University of Manitoba, Winnipeg, Manitoba.

Mary Masih, B.Sc.Pharm., was a staff pharmacist in the Department of Pharmacy Perinatal Unit Satellite, Mount Sinai Hospital.

Jina Hahn, B.Sc.Pharm., was a staff pharmacist in the Department of Pharmacy Perinatal Unit Satellite, Mount Sinai Hospital, and is currently a staff pharmacist in the Faculty of Pharmacy Drug Information Centre, Ontario College of Pharmacists, Toronto.

Cindy Ho, B.Sc.Pharm., was a staff pharmacist in the Department of Pharmacy Perinatal Unit Satellite, Mount Sinai Hospital.

May Wong, B.Sc.Pharm., was a staff pharmacist in the Department of Pharmacy Perinatal Unit Satellite, Mount Sinai Hospital.

Marie Sirdevan, B.Sc.Pharm., was a staff pharmacist in the Department of Pharmacy Perinatal Unit Satellite, Mount Sinai Hospital.

Address Correspondence to: Ms. Anita Kozyrskyj, Supervisor, Pharmacy Department, Mount Sinai Hospital, 600 University Ave, Toronto, ON, M5G 1X5.

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INTRODUCTION

Gentamicin is frequently administered in combination with the penicillins for the treatment of suspected or proven neonatal sepsis. Gentamicin therapy has traditionally been complicated by the necessity to monitor serum drug concentrations to achieve efficacy and avoid nephro- and oto-toxicity. The extent to which gentamicin is nephrotoxic¹⁻⁸ or ototoxic⁹⁻¹⁴ in the neonate is controversial. Confounding risk factors and renal maturational changes in this population make it difficult to assess the true incidence of these toxicities.

Consequently fixed-doses of gentamicin have been administered empirically in the neonate at various dosing intervals based on weight,¹⁵⁻¹⁷ gestational age,¹⁸⁻²¹ postnatal age,^{22,23} postconceptional age,²⁴⁻²⁶ or a combination of postconceptional age and estimated renal function.²⁷⁻²⁹ Gentamicin dosing regimens based on postconceptional age have been advocated as the most appropriate. This is based on the observation that renal functional development in the neonate is directly related to postconceptional age.³⁰ Correlations between gentamicin half-life or total body clearance and postconceptional age have been documented in the literature.^{31,32}

In the neonatal nurseries at Mount Sinai Hospital, gentamicin (2.5mg/kg) is administered at intervals according to weight: q24h for neonatal weight less than 1000 g, q18h for weight equal to 1001 to 1500 g and q12h for weight greater than 1500 g. An unpublished prospective study conducted in neonates at Mount Sinai Hospital in 1988 showed a 42% incidence of gentamicin serum trough concentrations greater than 2 mg/L, suggesting that these dosing guidelines may be less than optimal.³³

Therefore, a prospective evaluation of serum gentamicin concentrations was undertaken to determine the frequency of trough

concentrations greater than 2 mg/L and peak concentrations greater than 8 mg/L in order to develop new gentamicin dosing guidelines. A secondary objective of this study was to evaluate the correlation between gentamicin clearance and weight or postconceptional age and determine the best factor for calculating the dosing interval in the revised gentamicin dosing guidelines.

METHOD

Prospective Study

A prospective review of serum gentamicin concentrations in preterm and term neonates initiated on gentamicin therapy for suspected or documented sepsis was conducted at Mount Sinai Hospital from May to December 1991. Gentamicin therapy was initiated following the previously established guidelines. A dose of 2.5 mg/kg was administered by IM or IV bolus injection every 24 hours for neonates less than 1000 g, every 18 hours for neonates weighing between 1001 and 1500 g and every 12 hours for weights greater than 1500 g. All neonates were assumed to be at steady-state by the third dose. Serum gentamicin trough (C^{ss} min) were obtained by heel prick 15 minutes before the third dose. Samples were drawn for peak concentrations (C^{ss} max) 30 and 60 minutes following the third IV or IM, respectively. Serum gentamicin concentrations were measured by a fluorescence polarization immunoassay (TDx[®] System, Abbott Laboratories, IL, USA) with a coefficient of variation averaging 5.22% for concentrations between 1-8 mg/L and a lower limit of detection of 0.27 mg/L. The target concentration range was defined *a priori* as serum gentamicin trough concentrations between 0.5 and 2 mg/L and peak concentrations between 4 and 8 mg/L.

All infants initiated on gentamicin therapy were monitored by pharmacists in the Perinatal Unit. For

each neonate the pharmacist documented the following information: patient name, identification number, current weight, postconceptional age (gestational age plus postnatal age), urine output at start of therapy, presence of birth asphyxia, gentamicin dosage and the time interval between the stat and maintenance doses. Blood sampling times were recorded by nursing staff. Serum gentamicin concentrations were documented upon receipt of assay reports from the Microbiology Department.

Neonates were excluded from study if gentamicin concentrations were not drawn (death/transfer of the neonate, discontinuation of therapy), if paired trough and peak concentrations were not available or if baseline data were incomplete. All data were entered into a DBASE IV computer program to determine the frequency of serum gentamicin trough concentrations greater than 2 mg/L and peak concentrations greater than 8 mg/L in various subgroups of neonates.

Revised Guideline Development

The total body clearance and the elimination rate constant were calculated for each gentamicin trough and peak pair where the blood sampling times were recorded. First order elimination kinetics and a one compartment model were assumed for these calculations. It was also assumed that 30 and 60 minutes after the IV and IM doses, respectively, that distribution was complete. Volumes of distribution were corrected for the time between pre-/post-dose sampling and administration of the dose. Neonates were stratified according to the number of courses of gentamicin therapy received. Mean pharmacokinetic parameters were calculated per course of therapy.

Linear regression analysis was carried out to determine the correlation between gentamicin clearance and weight or postconceptional age using the Excel[®] and Lotus[®] 123

computer programs. The factor (postconceptional age vs. weight) which demonstrated the strongest correlation with gentamicin clearance was then used to determine the dosing interval in new dosing guidelines.

Two dosing guidelines were developed. In Guideline I, the dosing interval was adjusted on the frequency of gentamicin serum trough concentrations greater than 2 mg/L in specific weight or postconceptional age groups. In Guideline II, dosing intervals were estimated from regression analysis equations relating the elimination rate constant (k) to weight or postconceptional age. The dosing interval was calculated based on desired peaks of 6 mg/L and troughs of 1 mg/L. Again, correction was made for the time between pre-/post-dose sampling and administration of the dose.

Revised Guideline Evaluation

To test the performance of these two new guidelines, individual study cases were reviewed to evaluate if a different dosing interval would have been recommended. If the new guidelines resulted in a new dosing interval recommendation, predicted steady-state trough and peak concentrations were calculated.

The incidence of predicted trough concentrations greater than 2 mg/L in Guidelines I and II were then compared to that observed in the study. The Student t, Fisher Exact and McNemar tests were used in the analysis of data. A p value of less than 0.05 was used for statistical significance.

RESULTS

Gentamicin therapy was initiated in 340 preterm and term infants born at Mount Sinai Hospital from May to December 1991. Twenty-seven neonates were removed from further study according to the exclusion criteria. Subsequently, 328 serum trough and peak concentrations were available for analysis in 313 neonates

of 33±5 weeks (range: 23-42 weeks) postconceptional age and weight 2073 ± 1042 g (range: 600-4900 g). Eleven neonates were treated with a second course of gentamicin (postnatal age: 12 ± 7 days) and two neonates with a third course (postnatal age: 49 ± 28 days). Serum gentamicin sampling times were not appropriately recorded 32% of the time.

Of the 328 paired peak-trough samples, serum gentamicin trough concentrations greater than 2 mg/L were observed in 56% of concentrations. The frequency in

individual neonatal weight groups ranged from 10 to 85% (Figure 1). The highest incidence of trough concentrations greater than 2 mg/L was noted in neonates weighing between 1500-2500 g who were dosed with gentamicin 2.5 mg/kg every 12 hours. A significantly higher incidence of trough concentrations greater than 2 mg/L was not observed in oliguric neonates (urine output less than 0.5 mL/kg/hr), asphyxiated neonates or in neonates dosed every 12 hours in which the stat dose had been given less than 10 hours before the next dose (Table I). Serum

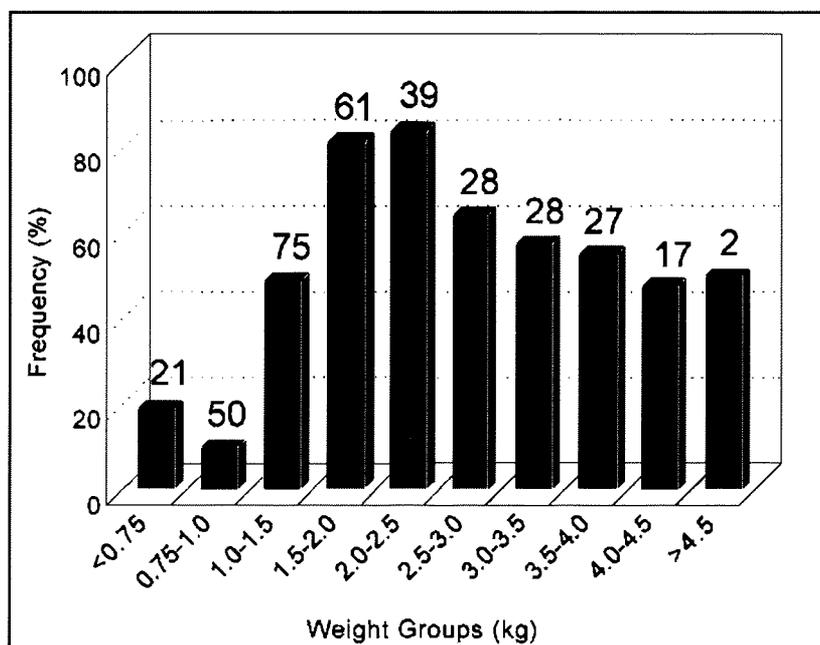


Figure 1. Frequency (percent of 328 samples) of serum gentamicin concentrations greater than 2 mg/L, stratified by weight. Neonates less than 1000 g received gentamicin every 24 hours, infants between 1000 and 1500 grams were dosed every 18 hours and in those weighing more than 1500 g gentamicin was administered every 24 hours. The number of neonates in each weight class is shown above each bar.

Table I. Frequency of trough concentrations greater than 2 mg/L.

	Number of Patients	Frequency (%)	Significance
Asphyxiated	9	67	NS ¹
Nonasphyxiated	319	56	
Oliguric ²	102	63	NS ¹
Nonoliguric	226	53	
Time from Stat dose to First Dose in q12h Patients			
Less than 10 hours	9	78	NS ¹
Greater than 10 hours	202	68	

1. NS indicates no significant difference.
 2. Less than 0.5 mL/kg/hr.

gentamicin peak concentrations greater than 8 mg/L were observed in 37% of concentrations.

Revised Guideline Development

Specific blood sampling times for trough and peak gentamicin concentrations were noted in 233 neonates. Mean pharmacokinetic parameters stratified by the number of courses of gentamicin therapy are summarized in Table II. The gentamicin elimination rate constant and clearance increased significantly with each subsequent course in patients requiring a second and third course of therapy (Table II). A significant correlation between gentamicin clearance and weight ($r^2 = 0.87$, see Figure 2) and gentamicin clearance or postconceptional age ($r^2 = 0.79$) was observed. Based on the higher degree of correlation between gentamicin clearance and weight, weight was retained as the factor used for determining the dosing interval in the revised guidelines. Since neonates greater than 1000 g were observed to have a high proportion of troughs greater than 2 mg/L, the dosing interval for neonates of 1000-1500 g was extended from 18 hours to 24 hours. The dosing interval for neonates greater than 1500 g was also extended from 12 to 18 hours.

In Guideline II, dosing intervals were calculated from the relationship between the elimination rate and weight determined by linear regression. However, as there was a significant increase in the elimination rate with subsequent courses, two different regressions equations were developed to avoid subtherapeutic trough concentrations in neonates receiving a second course of gentamicin (Table II),

Revised Guideline Evaluation

A comparison of the proportion of predicted trough concentrations greater than 2 mg/L among the two revised dosing guidelines compared to those observed in the prospective

study demonstrated a significant reduction in the frequency of troughs greater than 2 mg/L. (Table III). However, the incidence of predicted

trough concentrations less than 0.5 mg/L was significantly greater with Guideline I, in neonates who received second courses of therapy.

Table II. Gentamicin pharmacokinetic parameters

Number of Courses	Number of Patients	PCA ¹ (wk)	Weight (g)	Elimination Rate Constant (K- 1/hr ⁻¹)	Volume of Distribution (L/kg)	Clearance (L/kg/hr)
1	233	33±5	2041±1008	0.096±0.029 ³	0.438±0.158	0.040±0.012
1 ²	11	28±4	1064±572	0.075±0.016 ^P	0.390±0.0525	0.030±0.010 ^P
2	11	30±3	1092±497	0.100±0.040 ^{4,P}	0.447±0.083	0.044±0.018 ^P
3	2	33±2	1435±315	0.174±0.002 ^P	0.409±0.009	0.071±0.001 ^P

1. Post Conceptional Age

2. First course parameters for neonates that subsequently received a second course.

3. Correlation of elimination rate constant observed after the first dose and weight yields the equation: $K = 0.06087 + 0.00002 \times \text{weight (g)}$, $r^2 = 0.37$.

4. Correlation of elimination rate constant observed after the second dose and weight yields the equation: $K = 0.02783 + 0.00007 \times \text{weight(g)}$, $r^2 = 0.67$.

p. Elimination rate constant and clearance increase significantly ($p < 0.05$) with each subsequent course when the same infants are followed.

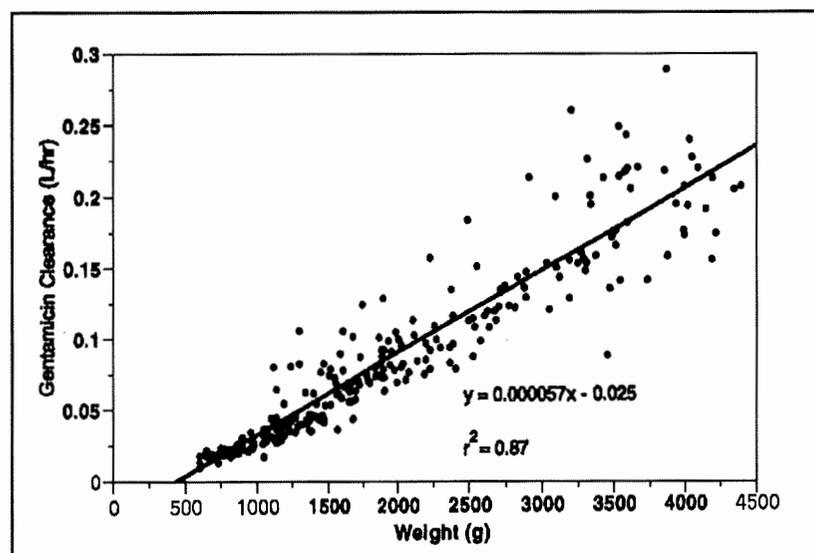


Figure 2. Correlation of gentamicin clearance and neonatal weight based on 233 peak-trough pairs. The correlation indicates that 87% of the variability in neonatal gentamicin clearance can be explained by a change in neonatal weight.

Table III. Comparison of trough target concentration performance

Number of Courses	Observed ¹ (%)	Guideline I ² (predicted) (%)	Guideline II ² (predicted) (%)
Frequency of Concentrations greater than 2 mg/L			
1 Course	58	2	10
2 Courses	0	0	0
Frequency of Concentrations less than 0.5 mg/L			
1 Course	0	5	0
2 Courses	0	27	0

1. Observed in the prospective study with 233 first course neonates and 11 second course neonates.

2. Predicted trough concentrations based on pharmacokinetic simulation using observed elimination rates and volumes.

DISCUSSION

Several attempts have been made to design appropriate empiric neonatal gentamicin dosing regimens with the goal of achieving therapeutic serum concentrations. Many of these report unacceptably high incidences of elevated trough and peak gentamicin concentrations, especially in premature neonates.^{4,15-18,20-24,27}

Our study reports a 56% incidence of trough concentrations greater than 2 mg/L in 313 preterm and term neonates. This is comparable, albeit slightly higher, than the 42% incidence observed in our earlier study. Although our dosing practices had not changed since that time, a higher incidence could be attributed to a smaller proportion of neonates receiving second courses of gentamicin (and hence fewer neonates with greater renal maturation) than in the 1988 study.

In our study, gentamicin clearance and elimination rate constant values were comparable to those reported in the literature and increased in neonates receiving subsequent courses of gentamicin therapy.^{16,25,31,32} This is in agreement with the increase in creatinine clearance shown in neonates with advancing post-conceptual age.³⁰ Previous studies have documented a good correlation between gentamicin half-life or clearance and postconceptional age^{31,32} and either good¹⁶ or poor^{19,28} correlations between clearance and weight. Our findings show a slightly better correlation between clearance and weight than clearance and post-conceptional age. Most of our neonates received gentamicin therapy at birth, when postconceptional age and gestational age are equal, and it is known that a good correlation between weight and gestational age exists.^{16,19} As a result, we felt confident to continue to base the dosing interval on the neonate's weight, especially as the weight is required for calculation of the dose (mg/kg). Our studies and

Table IV. Comparison of original and revised dosing guidelines

Postnatal age	Weight (g)	Original Guideline	Revised Guideline
0-7 days	up to 1000g	2.5 mg/kg q24h	2.5 mg/kg q24h
	1001-1500g	2.5 mg/kg q18h	2.5 mg/kg q24h
	more than 1500g	2.5 mg/kg q12h	2.5 mg/kg q18h
more than 7 days ¹	up to 1000g	2.5 mg/kg q24h	2.5 mg/kg q24h
	1001-1500g	2.5 mg/kg q18h	2.5 mg/kg q18h
	more than 1500g	2.5 mg/kg q12h	2.5 mg/kg q12h

1. Originally there was no specific guideline, for neonates more than 7 days. All infants were dosed using the same guideline.

others with similar dosing guidelines,¹⁷ have identified the 1000-1500 g and the 1500 g groups as those with the highest incidence of trough concentrations greater than 2 mg/L. Therefore, we extended the dosing interval to 24 hours and 18 hours, respectively, in Guideline I for these two weight groups.

We were unable to identify any other risks factors to predict high gentamicin concentrations. Although renal function is reduced in asphyxiated neonates, a significant difference in the frequency of high serum trough concentrations was not found between asphyxiated and non-asphyxiated neonates, similar to other study results²². This lack of difference could be attributed to the small sample size of asphyxiated neonates. Similarly, no significant differences were noted between oliguric and non-oliguric neonates, although this finding may be difficult to interpret as urine outputs recorded at the start of therapy increased with advancing age. Some authors recommend the use of renal indices such as serum creatinine as a guide to gentamicin dosing.²⁶⁻²⁸ Ideally blood sampling should be performed in these neonates after the first dose and the dosing interval based on the neonate's individual gentamicin clearance.³⁴

Guideline I has been accepted at Mount Sinai Hospital as the new gentamicin dosing guideline. However, to address the concern of potential subtherapeutic trough concentrations in neonates receiving subsequent courses of gentamicin it was decided that the former dosing

guidelines be used for neonates more than seven days of age. The original and new gentamicin dosing guidelines used at Mount Sinai Hospital are summarized in Table IV.

Although there was an interest in utilizing the regression analysis equations (Guideline II) to determine the dosing interval, staff neonatologists felt that this was impractical. As more data on once daily gentamicin dosing become available,³⁵ our gentamicin dosing guidelines will once again be revisited. We will also be increasing our education efforts to improve compliance with documentation of the sampling time on the assay requisition forms. ☐

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