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Therapeutic drug monitoring of amikacin in preterm and term infants

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ABSTRACT

Introduction: Amikacin is a commonly-prescribed drug used for the empirical treatment of bacterial infections in neonates. A marked change in the pharmacokinetics of amikacin has been reported during neonatal life. Amikacin has a very narrow therapeutic range and can cause very serious side effects such as nephrotoxicity and ototoxicity. The current therapeutic dose of amikacin, i.e. 15 mg/kg of body weight, may increase the risk of toxicity in preterm infants with immature renal functions. We aimed to determine the frequency of amikacin toxicity in preterm as compared to term infants by measuring its serum trough levels following the administration of the current therapeutic dose.

Methods: A comparative study was conducted at the neonatal intensive care unit of the Military Hospital, Rawalpindi, Pakistan. A total of 104 infants (52 term and 52 preterm) receiving amikacin at a dose of 15 mg/kg of their body weight, once daily for bacterial infection, were included. After clinical evaluation, serum creatinine levels were measured at admission and on the third day. Amikacin trough levels were taken after 72 hours of therapy and measured on the TDx Abbot Drug Analyser.

Results: The gestational age range was 37–40 weeks in term and 29–36 weeks in preterm infants. The term and preterm infants had a median weight of 2.8 kg and 2.1 kg, respectively. The preterm infants had significantly higher median (range) 11.33 (1.50–42.60) ug/ml levels of serum amikacin as compared to 8.5 (2.8–33.0) ug/ml in term infants (p-value is less than 0.01). The preterm infants had a high frequency of toxic 32 (62 percent) and subtherapeutic 12 (23 percent) levels, as compared to 11 (21 percent) and 5 (10 percent) in term infants, respectively. Serum amikacin levels revealed a positive correlation with post-dose serum creatinine (r equals 0.48; p-value is less than 0.05).

Conclusion: This study demonstrated that the current practice of amikacin treatment for bacterial infection needs to be adjusted due to unique pharmacokinetic variability in preterm infants. There is a need for regular therapeutic drug monitoring and renal function assessment in all infants receiving amikacin therapy in order to avoid nephrotoxicity.

Keywords: amikacin, bacterial infection, neonatal sepsis, nephrotoxicity, serum trough levels, therapeutic drug monitoring

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INTRODUCTION

One of the greatest dilemmas in today's paediatric practices is the emerging threat of neonatal sepsis. The incidence of morbidity and mortality as a result of sepsis is very high in Pakistan.[1] The majority of the cultured isolates of these neonates were found to be susceptible to amikacin,[2] which is a bactericidal antibiotic belonging to the aminoglycoside group with a narrow therapeutic range.[3] Therapeutic drug monitoring (TDM) of amikacin is not being carried out routinely among newborns. Various dosing regimens have been used in children, but their safety and efficacy has still not been established in infants. Newborns with bacterial infection and sepsis have been treated with 15 mg/kg of their body weight in a single dose. The risk of amikacin toxicity is likely to increase at this dosage, especially in preterm infants.[4] TDM enables a healthcare provider to ensure that the drug level remains within an effective range.[5]

Amikacin should be used with caution in preterm infants because of the renal immaturity of these patients and the resulting prolongation of the serum half-life of this drug.[6] Amikacin is predominantly excreted by glomerular filtration.[3] The pharmacokinetics of amikacin have shown variable drug levels in neonates.[7] The serum drug concentration level should be maintained within the therapeutic range to secure a therapeutic effect and to avoid toxic effects such as nephrotoxicity and ototoxicity.[8] Large unexplained variability in amikacin clearance stresses the need for establishing a target concentration

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Table I. Demographical data: amikacin and creatinine levels.

Parameters	Term infant		Preterm infant	
	Mean ± SD	Median (range)	Mean ± SD	Median (range)
Gestational age (weeks)	38.7 ± 1.1	39 (37–40)	32.2 ± 2.1	31 (29–36)*
Post-natal age (days)	2.1 ± 1.1	2 (1–5)	1.4 ± 0.8	1 (1–3)*
Length (cm)	50.2 ± 4.0	50 (39–60)	44.1 ± 4.5	45 (33-54)*
Weight (kg)	2.7 ± 0.4	2.8 (1.96–380)	1.9 ± 0.48	1.80 (90–3.4)*
Amikacin trough level (ug/ml)	9.97 ± 5.67	8.5 (2.81–31.0)	14.4 ± 9.28	11.33 (1.50–42.6)*
Serum creatinine (µmol/L)				
Baseline	56.4 ± 17.1	54.5 (28–99)	59.2 ± 18.6	55 (24–95)
After 72 hours	61.4 ± 22.8	57 (36–140)	76.0 ± 28.9	71 (25–145)*

* $p < 0.01$

level with dose adjustment.[3] However, there is a scarcity of scientific data that could help distinguish between safe and toxic levels of amikacin, especially in preterm infants particularly in this part of the world. This is the first study in Pakistan to compare the serum trough levels of amikacin between preterm and term infants following a therapeutic dose of 15 mg/kg of body weight. In addition, the frequency of subtherapeutic toxic levels of amikacin and its nephrotoxicity in the infants were determined.

METHODS

A comparative study was conducted at the Department of Chemical Pathology in collaboration with the neonatal intensive care unit at the Military Hospital, Rawalpindi, Pakistan, from March 2007 to April 2008 after obtaining approval from the institutional review committee. A total of 104 neonates, consisting of equal numbers of term and preterm infants receiving amikacin for bacterial infections, were included by a convenient sampling technique. Four infants died in the hospital. However, the data of all the infants was included in the study. Informed parental consent for each child was obtained. The history of illness, findings of the physical examination, demographical data including weight, length, gestational and postnatal age of the infants were recorded. Gestational age was assessed by the expected date of delivery, last menstrual period and ultrasonography. The full term infants had a gestational age ≥ 37 weeks while preterm infants had a gestational age < 37 weeks. Neonates with congenital anomalies, multiple drug therapy and deranged renal functions were excluded from the study.

All the subjects were residents of Pakistan and were treated in the neonatal intensive care unit of the Military Hospital, Rawalpindi. Blood samples were collected by venous puncture for blood culture, and serum was separated by centrifugation at the same time. Amikacin and cefotaxime were used for the treatment of neonates with suspected or proven Gram-negative bacterial infection as the standard protocol. *Escherichia coli*, *Klebsiella pneumoniae* and *Enterobacter* spp. were isolated from the blood culture. Biosensitivity testing revealed that the bacterial isolates were sensitive to amikacin. Both groups were treated with Amikin injection (Bristol-Myers Squibb, New York, USA) 15 mg/kg of body weight once daily,[9] through infusion over 30 minutes for 7–10 days. All the infants were followed up and renal function was monitored till discharge from the hospital. Serum creatinine levels were measured before administering the first dose and on the third day. Trough levels of amikacin were measured from a sample collected after 72 hours, 30 minutes prior to the fourth dose of amikacin infusion by Fluorescence Polarization Immunoassay (Abbott Laboratories, Diagnostic Division, Abbott Park, USA).[10] The coefficient of the variation of the amikacin assay was 4.3%. Statistical analysis of all the data was entered in the Statistical Package for Social Sciences version 15.0 (SPSS Inc, Chicago, IL, USA) for analysis. Mean, median, standard deviation (SD) and range were calculated for length, weight, gestational age, postnatal age, creatinine and amikacin trough levels of both preterm and term infants. We compared the quantitative variable including the serum amikacin trough level in both groups by using the Mann-Whitney U test. Chi-square test was applied for the frequencies of subtherapeutic, therapeutic and toxic amikacin between the two groups. Spearman correlation (r) was calculated between the 72-hour serum creatinine and amikacin levels. A p-value of ≤ 0.05 for the two-tail test was considered to be significant.

RESULTS

The newborns, comprising of an equal number of preterm and term infants, with a female to male gender distribution of 25:27 and 30:22, respectively, participated in the study. Gestational age, postnatal age, length and weight are shown in Table I. The preterm infants had significantly higher serum creatinine levels as compared to the term

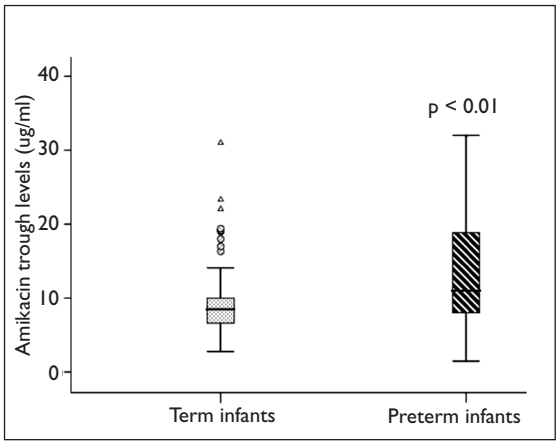

Fig. 1 Box plot shows the amikacin trough levels among term and preterm infants.

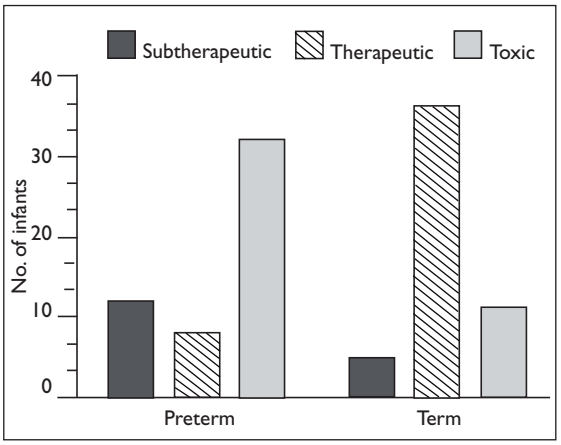

Fig. 2 Bar chart shows the frequency of subtherapeutic and toxic levels in preterm and term infants (n = 104).

infants (Table I). Serum amikacin levels revealed a positive correlation with post-dose serum creatinine levels ($r = 0.48$; $p < 0.05$). The preterm infants had significantly higher median (range) 11.33 (1.50–42.60) levels of serum amikacin as compared to 8.5 (2.81–31.0) in the term infants ($p < 0.01$). The box plot of serum amikacin reveals significantly wide variation in amikacin trough levels in preterm as compared to term infants (Fig. 1).

The serum trough levels of amikacin in most of the term infants were within the therapeutic range. The frequency of toxic levels in preterm infants was found to be significantly higher as compared to that of term infants (Fig. 2). The preterm infants had a high frequency of toxic, 32 (62%), and subtherapeutic, 12 (23%), levels as compared to 11 (21%) and 5 (10%) in term infants, respectively. Serum amikacin levels revealed a positive correlation with post-dose serum creatinine levels ($r = 0.48$; $p < 0.05$). After 72 hours, the serum creatinine levels for the term infants group were significantly lower ($p = 0.002$), with a mean (SD) of 61.4 ± 22.8 µmol/L, than those of the preterm infants group, with a mean (SD) of 76.0 ± 28.9 µmol/L. Serum amikacin levels revealed a positive correlation with post-dose serum creatinine levels ($r = 0.48$; $p < 0.05$).

DISCUSSION

There are concerns regarding the safety and efficacy of the dose recommendations of amikacin in neonates, especially in preterm infants. This TDM of amikacin was the first study carried out on aminoglycosides in Pakistan. The aim was to highlight the importance of a revision of the dosage regimen of amikacin according to gestational age and the monitoring of drug levels by TDM. The dosage in neonates has historically been subject to TDM for two reasons: clinical effect and toxicity.[5] The preterm infants in our medical setup had significantly higher levels of serum amikacin as compared to the term infants ($p < 0.01$). Preterm infants pose specific problems in terms of striking a balance between toxic and therapeutic levels of amikacin.[11] Amikacin elimination and the volume of distribution are dependent upon gestational age.[12] Clearance of amikacin can vary in preterm and term infants, probably because of renal immaturity.[4,13] Other authors have shown size and postnatal age to be the major markers of amikacin clearance variability in preterm infants.[3,4,12] Serum trough and peak levels are used to assess the efficacy and to avoid toxicity of the drug.[14] However, we used only the trough level in this study.

In our study, 32 (62%) preterm infants receiving amikacin in a once daily dosage regimen had toxic trough levels, whereas the level of toxicity of amikacin in term infants was found to be comparatively low at 11 (21%). Our results are compatible with a study conducted by Kenyon et al.[15] The researchers found that current doses of amikacin produce toxicity in 70% of preterm and low birth weight babies, consistent with the results of our study.[16,17] Rusconi et al (1983) also showed the influence of gestational age on high trough levels of amikacin.[12]

Tréluyer et al reported that there was no significant relation between gestational age and toxic drug levels of amikacin. In this study, only 49 neonates were included out of 155 paediatric cases. Data regarding their gestational age was also not mentioned and the drug levels were monitored with a once-daily dosage only. However, postnatal age and birth weight had significant associations with the development of drug toxicity.[11] Similarly, Berger et al showed that 88% of preterm infants have achieved therapeutic blood levels with current dosing protocols,[4] a result that is in contrast to the findings of our study. However, this study was non-comparative, was done only in the first week of life, and the study population was

small. The authors did not determine the safe levels in the extremely low birth weight and extremely premature infants.

In our study, 12 (23%) preterm and 5 (10%) term infants had subtherapeutic levels. This was probably because of interindividual variability, which has also been shown by Tréluyer et al in their study.[11] Interindividual variability in the pharmacokinetics of amikacin has been found to be very high in preterm infants in studies carried out by Want et al,[18] and by Howard and McCracken.[19] This factor makes it even more difficult to achieve a safe effective treatment in these infants by avoiding the toxicity of the drug. The risk of amikacin toxicity is likely to increase with immature renal functions, especially in preterm infants.[6] This has been shown in our study as well with a significantly high correlation (r = 0.48) between amikacin with third day serum creatinine levels in preterm infants. Giapros et al indicated that the effect of aminoglycosides on tubular function is dependent upon kidney maturity,[20] thus further supporting our results. Newborn infants have longer serum half-lives than older infants, presumably because of a less effective renal function in the early newborn period.[13] The kinetic parameters of amikacin differ among neonates, and the gestational age is an important factor determining variability. Monitoring amikacin serum concentration levels is important in neonates, particularly in premature infants.[21]

The limitation of our study was that we did not monitor peak levels because of the agreement not to obtain a second blood sample from our neonates. The study emphasised the need to monitor the drug in order to reduce the chances of toxicity in our newborns. The use of TDM services encourages doctors to adjust the dose in light of the observed serum amikacin concentration levels.[22] This study has demonstrated that the present dose protocol of amikacin causes toxic drug levels in preterm infants, thus underlining a need for TDM in infants and keeping a check on drug levels and renal functions, especially in preterms who are at an increased risk of kinetic variability due to renal prematurity and who are receiving aminoglycosides treatment to avoid nephrotoxicity. The dosing protocol should be individualised, especially for preterm infants, on the basis of body weight. We propose a safe and yet effective dose of amikacin to be 7.5 mg/kg/day for neonates who weigh < 1,200 g, and 10 mg/kg/day for those who weigh 1,000–2,000 g. It should be monitored with serum creatinine levels where a TDM facility is not available. We recommend further studies to establish a standard dosing regimen of amikacin in preterm infants.

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