

Simplified Dosing of Gentamicin for Treatment of Sepsis in Bangladeshi Neonates

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ABSTRACT

Extended-interval dosing of gentamicin has several advantages over conventional multiple-daily dosing for the treatment of sepsis. The study was conducted to evaluate the pharmacokinetics of gentamicin for the treatment of neonatal sepsis in predetermined doses at 24- or 48-hour intervals, according to weight category, and to develop a simplified protocol for use in peripheral healthcare settings in developing countries. This prospective observational study was conducted among 59 neonates admitted to the Special Care Nursery at Dhaka Shishu Hospital, Bangladesh, with suspected sepsis and treated with antibiotics, including gentamicin. Intravenous dosing of gentamicin according to weight category was: 10 mg every 48 hours if the infant weighed <2,000 g (n=23), 10 mg every 24 hours if the infant weighed 2,000-2,249 g (n=12), or 13.5 mg every 24 hours if the infant weighed 2,500-3,000 g (n=24). Peak and trough concentrations of gentamicin and the presence of signs of nephrotoxicity and ototoxicity were determined. The mean±standard deviation peak concentration of gentamicin was 12.3±3.7 µg/mL in infants weighing <2,000 g, 9.6±3.1 µg/mL in infants 2,000-2,249 g, and 10.0±3.4 µg/mL in infants 2,500-3,000 g. Initial peak concentration of gentamicin was >12 µg/mL in 28.8% and initial trough concentration was >2 µg/mL in 6.8% of the subjects. No signs of nephrotoxicity or ototoxicity were detected. Favourable pharmacokinetic parameters found with the simplified dosing regimen suggest that it is safe for the treatment of neonatal sepsis.

Key words: Aminoglycoside; Antibiotics; Gentamicin; Infection; Newborns; Observational studies; Pharmacokinetics; Prospective studies; Sepsis; Bangladesh

INTRODUCTION

An estimated 20% of all children born in developing countries acquire an infection during the neonatal period, and infectious diseases account for ap-

proximately one-third of all neonatal deaths (1,2). Many neonatal deaths can be averted if the signs of infection could be recognized early by caregivers and first-line health workers and the disease is treated promptly (3-8).

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Gentamicin is a potent aminoglycoside antibiotic with bactericidal activity against Gram-negative bacteria. Among the causative agents of neonatal sepsis, Gram-negative pathogens play a crucial role, and gentamicin is the drug of choice for first-line management. On the basis of the large volumes of distribution and slow renal clearance of aminoglycosides in neonates, larger doses based on body-weight, administered at longer intervals, are advantageous (9-12). To treat neonatal sepsis more effectively in low-resource settings, it is necessary to develop a strategy for extended-interval dosing of

gentamicin, i.e. 24 hours or more in between doses since more frequent contact with a health worker is often not feasible.

Based on the evidence that extended-interval dosing of gentamicin has many advantages over more frequent-interval dosing regimens, we aimed at evaluating extended-interval dosing regimens for gentamicin, which were developed based on issues of pharmacokinetics, safety, frequency of dosing, body-weight of the patient, and acceptability as described previously (13,14). Here, we report pharmacokinetic and safety evaluation results from the Bangladesh site of a two-site study reported elsewhere (13).

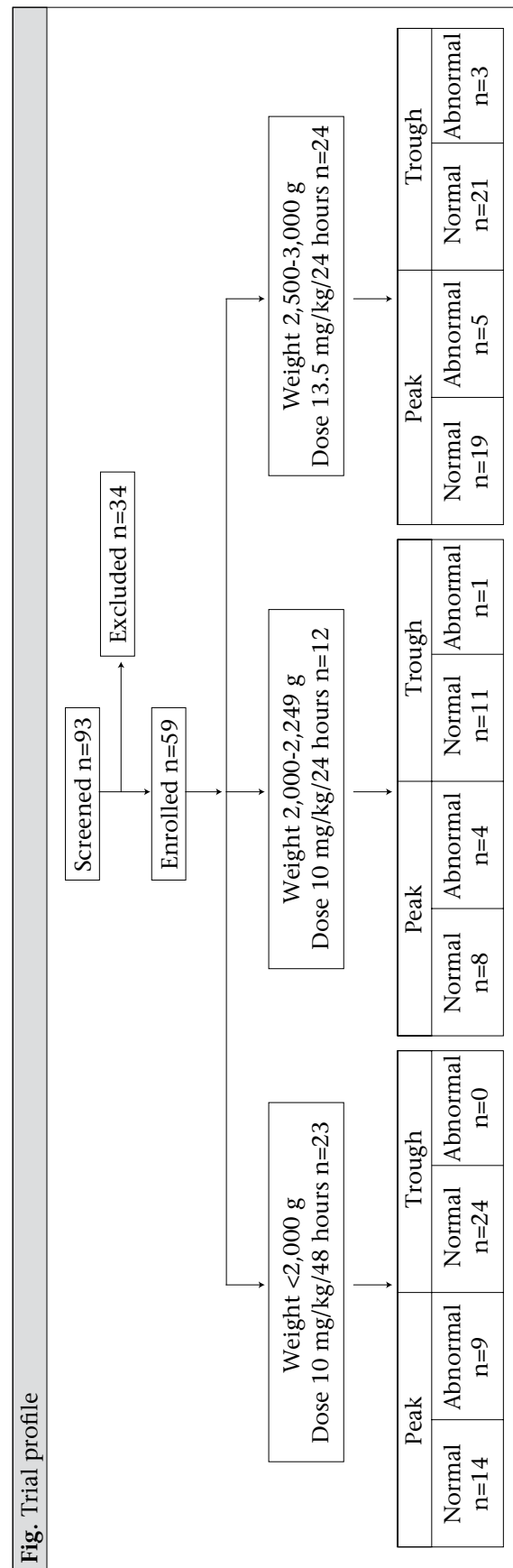
MATERIALS AND METHODS

Patients

The study was conducted in Dhaka Shishu (Children's) Hospital, a major medical centre for children in South Asia, in the Neonatal Special Care Nursery where out-born neonates are admitted. We initially aimed at enrolling 20 patients weighing <2,000 g, 10 patients weighing 2,000-2,240 g, and 20 patients weighing 2,500-3,000 g with guidance on total enrollment from the study's Data Safety Monitoring Board, which regularly reviewed progress of the trial, with an aim to ensure safety of patients. Neonates up to 28 days of age, who were admitted from 15 February to 15 June 2003 for the treatment of suspected or culture-proven neonatal sepsis, were included in the study (Fig.). Neonates with major congenital anomalies, haemodynamic instability, or compromised renal function were excluded. Once a potential participant was identified, a parent was counselled in the presence of a senior staff nurse, and informed written consent was obtained. The Ethical Review Committee at the Bangladesh Institute of Child Health, the Committee on Human Research at the Johns Hopkins Bloomberg School of Public Health, and the PATH Human Subjects Protection Committee approved the protocol. All unexpected adverse events were reported to the appropriate authorities within 24 hours. The study was registered at clinicaltrials.gov (#H.22.02.08.30.B1).

Gentamicin-dosing and monitoring

All patients received standard clinical management of sepsis, which included use of additional antibiotics in combination with gentamicin to provide broad-spectrum coverage as indicated based on available clinical and laboratory data. Neonates were enrolled into different weight categories and



received a fixed dose and frequency of administration of gentamicin specific for each weight category (Fig. and Table). The rationale for selection of these dosing-interval regimens has been reported previously (13,14). Patients weighing 2,250-2,499 g were not included in the study because extended-interval dosing regimens of gentamicin, which reliably produce favourable pharmacokinetics, are already available, and further testing was, thus, not warranted.

The dose was pushed intravenously over a 30-second period, followed by a flush with 0.5 mL of normal saline. For monitoring trough concentrations of gentamicin, blood was obtained 30 minutes prior to the administration of the third dose, and the peak level was monitored in serum separated from blood collected one hour after the administration of the third dose. Since renal excretion of gentamicin is slower in low-birthweight (LBW) babies, the safety of administration in patients with very LBW, weighing <2,000 g was further ensured by giving the doses only at 48-hour intervals. The monitoring strategy for these babies was modified so that the serum level of drug was available as early as possible. Thus, serum levels were obtained 2 and 24 hours after the first dose of gentamicin rather than the trough and peak levels around the third dose as for patients weighing $\geq 2,000$ g. Serum levels of gentamicin were measured by chemiluminescent assay with Immulite 2000 (Diagnostic Products Corporation, Los Angeles, CA). Pharmacokinetic indices, including peak and trough levels of gentamicin, were determined as described previously (13).

For infants weighing $\geq 2,000$ g, whenever abnormal gentamicin trough levels were detected, i.e. >2 $\mu\text{g/mL}$, the dosing-interval was extended from 24 to 48 hours. If the peak concentration was >12 $\mu\text{g/mL}$, the dose was decreased by 10-15%, and if the peak was <4 $\mu\text{g/mL}$, the dose was increased by

10-15%. Whenever dose modifications were made, repeat gentamicin levels were determined 48 hours later.

Blood samples were collected from 23, 12, and 24 patients in the three weight categories: <2,000 g, 2,000-2,249 g, and 2,500-3,000 g respectively. Haemoglobin concentration, serum electrolytes, plasma creatinine, and urine output were monitored during the study period. All the enrolled patients were followed up once for hearing assessment between 6 and 12 weeks of age. Hearing assessment was done by Brainstem Auditory Evoked Response (BAER) testing.

RESULTS

Of the 59 patients, 30 (51%) were preterm (<37 completed weeks of gestation), 46 (78%) were male, and 29 (49%) were aged one day. Duration of hospital stay was 2-22 days (mean \pm standard deviation 8.6 \pm 4.2 days). Culture-positive septicaemia was identified in 10.1% (6/59) of the cases. The isolated organisms were *Escherichia coli* (n=2), *Klebsiella pneumoniae* (n=1), *Staphylococcus aureus* (n=1), *Salmonella* spp. (n=1), and *Haemophilus influenzae* (n=1). Total doses of gentamicin given to patients across the three weight categories ranged from 1 to 10, and the duration of treatment was 2-10 days (Table).

Initial peak concentrations of gentamicin were >12 $\mu\text{g/mL}$ and <4 $\mu\text{g/mL}$ in 28.8% and 1.7% of the patients respectively (Table). Initial trough concentration was ≥ 2.0 $\mu\text{g/mL}$ in 6.8% of the cases. Nineteen (32.2%) neonates required adjustment of gentamicin dose; nine were in the category of <2,000 g and five each were in the categories of 2,000-2,249 g and 2,500-3,000 g. Nine patients each weighing <2,000 g had a high peak level; none had a high trough level. In the category of 2,000-2,249 g, adjustment of dose was needed for three patients for high peak, one for high trough, and one for low

Table. Pharmacokinetics of gentamicin by neonatal weight category

Pharmacokinetic parameter	Weight category		
	<2,000 g (n=23)	2,000-2,249 g (n=12)	2,500-3,000 g (n=24)
Dosage of gentamicin (mg)	10	10	13.5
Interval of dose (hours)	48	24	24
Number of doses	1-6	3-10	2-10
Days of treatment	2-10	3-10	2-10
Peak concentration (mean \pm SD, $\mu\text{g/mL}$)	12.1 \pm 3.6	9.6 \pm 3.1	9.7 \pm 2.9
Trough concentration (mean \pm SD, $\mu\text{g/mL}$)	0.4 \pm 0.4	1.6 \pm 1.3	1.4 \pm 1.2
SD=Standard deviation			

peak. Five (24.0%) patients in the group of 2,500-3,000 g needed correction; two for both high peak and trough serum concentrations, and three for high peak concentration only.

On enrollment, plasma creatinine level was normal (<120 $\mu\text{mol/L}$) in 91.4% (53/58) of the patients. At the time of discharge, all the patients, except one (serum creatinine level 169 $\mu\text{mol/L}$), including the cases with elevated serum gentamicin peak and/or trough levels, had normal plasma creatinine levels. The frequency of urine output was also normal in 98.3% (57/58) of the cases.

Seven patients died, none of whom had an abnormal serum level of gentamicin. Causes of death included prematurity with septicaemia (n=2), birth asphyxia with septicaemia (n=2), and birth asphyxia (n=3). Three patients left against medical advice, and two of them had an abnormal level of gentamicin. Two patients (5%; 2/40) were labelled as impaired for hearing on assessment at 6-12 weeks of age. However, gentamicin levels of all these cases were normal (peak 8.9 $\mu\text{g/mL}$ to 9.7 $\mu\text{g/mL}$, trough 0.1 $\mu\text{g/mL}$ to 2.0 $\mu\text{g/mL}$).

DISCUSSION

This study evaluated the dosing of gentamicin at an interval of 24-48 hours in different weight groups, considering pharmacokinetics and safety. Studies have shown that pharmacokinetics of gentamicin are essentially equivalent following intravenous and intramuscular injections (15). The results of this study, which involved intravenous administration, can be extrapolated to intramuscular injections, the suitable mode to use in the community, including peripheral health facilities, where intravenous access is not available.

Pharmacokinetic data of gentamicin indicate that half-lives are longer in neonates compared to older children (16-18). These data lend support to the recommendation to increase the dosing-interval from 12 to 18 hours up to 24 hours or more. There has been recent interest in extended (e.g. daily or less frequent) dosing of aminoglycosides because higher doses given at longer intervals are likely to improve efficacy and reduce the toxic effects (9,12,14). In a developing country like Bangladesh, once-daily dosing of gentamicin can be used as an important treatment option in neonatal sepsis whereas more frequent dosing is not feasible for use in the community and peripheral health-facility settings (14,19).

In our study, the mean peak concentrations around

the third dose in patients weighing 2,000-2,249 g and 2,500-2,999 g were consistent with other studies of once-daily dosing of gentamicin (9,11,12,20-22). Skopnik compared two groups of neonates who received once- and twice-daily doses of gentamicin and found that the once-daily group did better regarding efficacy and toxicity (21). High peak concentration of aminoglycoside is the major determinant of bacterial killing rather than the minimum inhibitory concentration of the antibiotic (23,24). The target peak concentration of gentamicin is 4-12 $\mu\text{g/mL}$ (25) but 29% (17/59) of the cases in this study had higher peak values (range 12.1-20.6 $\mu\text{g/mL}$). Nonetheless, all the cases had normal renal function as measured by plasma creatinine level. Further, hearing assessment of 12 of the cases at 6-12 weeks of age did not reveal any sign of ototoxicity attributable to antibiotic exposure. This is in accordance with previous findings about the safety of higher peak levels of gentamicin (25).

Pharmacokinetic data of gentamicin administration in neonates with very low birthweight indicate that the elimination half-life is longer in preterm compared to full-term neonates (26). Thus, we fixed the initial dose for preterm babies with very low birthweight as 10 mg given every 48 hours. In this weight category, we found a high peak concentration (>12 $\mu\text{g/mL}$) in more than one-third (39.1%) of the babies, although their trough concentrations were uniformly normal. Evidence would suggest that the dose used in this weight category will be efficacious (14), and since trough levels were normal, this dose is acceptable.

A low trough concentration of <2 $\mu\text{g/mL}$ is a desirable goal because aminoglycosides exhibit a marked post-antibiotic effect (persistent suppression of microbial growth after antimicrobial drug exposure ceases), and longer duration of low levels helps prevent the rapid development of microbial resistance (adaptive resistance) and minimizes nephrotoxicity and ototoxicity (27). In the present study, the mean trough concentrations of gentamicin in all the three weight categories were acceptable. The distributions of trough levels were the same as reported in previous studies where gentamicin was given once or twice daily at doses of 4-5 mg/kg of body-weight per day (9-12,14,21). Our findings are consistent with those of Hayani *et al.* who showed that trough concentration is not increased if a larger dose is given at a prolonged interval (9). Nephrotoxicity is one of the recognized complications of aminoglycoside therapy. Clinical studies have shown that renal toxicity is less frequent in newborns (28,29); this is due, in part, to the lower rate of renal accumulation of gentamicin

in neonates (28). In the present study, we had only one neonate with raised plasma creatinine; however, the infant had normal peak (11.2 µg/mL) and trough (0.1 µg/mL) levels of gentamicin. Mulhall *et al.* showed that the incidence of nephrotoxicity is reduced when the dosing interval is >18 hours in neonates (25). Ototoxicity is another potential complication of gentamicin therapy. Hearing assessment at 6-12 weeks revealed only two infants with hearing impairments. However, this did not appear to be attributable to gentamicin therapy as none of the cases had any abnormality in peak and trough levels of gentamicin.

In conclusion, this study of extended-interval dosing of gentamicin, stratified for different weight categories of neonates, indicates that this dosing scheme is simple, adequate, safe, and feasible for the treatment of neonatal sepsis in communities and peripheral health facilities. Such dosages are now being manufactured in pre-filled Uniject™ (Becton Dickinson) devices and used for the evaluation of safety and acceptability for the treatment of neonatal sepsis at the community level.

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