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Original article

Pharmacokinetics of Once-Daily Intravenous Gentamicin in Term Neonates: Comparison of 4 mg/kg and 5 mg/kg Dosing in Tanzania

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Abstract
Gentamicin, a bactericidal aminoglycoside, is used with penicillins to treat neonatal infections. It has a narrow therapeutic index and can cause nephrotoxicity and/or ototoxicity even at therapeutic doses, making serum monitoring essential. In Tanzania, neonates often receive once-daily intravenous gentamicin at a dose of 5mg/kg without monitoring, raising safety concerns since toxicity relates to high, dose-dependent troughs. Although recommended neonatal doses are 4–5mg/kg, reports show 5mg/kg produces high trough concentrations. This study compared the pharmacokinetics of 5mg/kg with 4mg/kg to determine whether the lower dose is safer. Two hundred fifty term neonates with sepsis received intravenous gentamicin once-daily 5mg/kg (n=125) or 4mg/kg (n=125) based on routine clinical practice. Sparse sampling estimated clearance and volume of distribution. In addition, blood samples for peak (30 minutes post-dose) and trough (5 minutes pre-dose) were taken from each patient at steady state (after the fourth dose). Pharmacokinetic parameters were estimated using Python (version 3.12.3), and groups were compared with independent-samples t-tests. Mean steady-state peak gentamicin concentrations were higher with 5 mg/kg (18.80 ± 0.83 µg/mL) than with 4 mg/kg (7.82 ± 0.90 µg/mL), with trough concentrations also elevated (2.52 ± 0.93 vs 1.46 ± 0.36 µg/mL). Clearance was lower with 5mg/kg (0.361 vs 0.575 $mL \cdot min^{-1} \cdot kg^{-1}$), as was the volume of distribution (0.248 vs 0.494 $L \cdot kg^{-1}$). Once-daily intravenous gentamicin at 5mg/kg results in higher peak and trough concentrations with reduced clearance and distribution. In contrast, 4mg/kg achieves levels within therapeutic ranges. These findings support 4mg/kg as the safer regimen for neonates in Tanzania and similar settings.
Keywords. Gentamicin, Once-Daily Dosing, Term Neonates, Peak Concentration, Population Pharmacokinetics, Trough Concentration.

Introduction

Gentamicin, a bactericidal aminoglycoside, is recommended by the World Health Organisation (WHO) in combination with β-lactam antibiotics as first-line therapy for neonatal sepsis [1]. Following intravenous administration, gentamicin is not metabolised and is eliminated unchanged via glomerular filtration, with clearance strongly dependent on renal maturation in neonates [1]. Although highly active against resistant Gram-negative organisms, its clinical utility is constrained by a narrow therapeutic index, where suboptimal exposure risks treatment failure and sustained elevation of trough concentrations increase the likelihood of nephrotoxicity and ototoxicity [2,3]. Accordingly, therapeutic drug monitoring (TDM) is recommended to optimise peak concentrations for efficacy while limiting trough exposure associated with toxicity [4-6]. However, TDM is rarely available in many low-resource settings, including Tanzania [1], where gentamicin remains a cornerstone of neonatal sepsis management. In Tanzania, national treatment guidelines recommend gentamicin in combination with ampicillin–cloxacillin, with dosing typically ranging from 4–5 mg/kg administered intravenously at extended intervals adjusted for gestational age and body weight [7]. In routine clinical practice, however, a once-daily regimen of 5 mg/kg is frequently employed for suspected neonatal sepsis. This strategy is intended to maximise bactericidal peak concentrations while maintaining low trough levels to minimise toxicity risk [8]. Nevertheless, pharmacokinetic studies in term neonates have demonstrated that once-daily 5 mg/kg dosing may be associated with elevated trough concentrations and reduced clearance [9-11], thereby increasing the risk of gentamicin-related toxicity, particularly where TDM is unavailable. Historically, lower doses such as 4 mg/kg were considered safer due to reduced systemic exposure; however, concerns regarding inadequate peak concentrations in severe infections have contributed to a shift toward higher dosing strategies in many clinical settings. In contrast, emerging evidence suggests that once-daily 4 mg/kg dosing can achieve pharmacokinetic targets within accepted therapeutic ranges [12-15]. Despite these findings, uncertainty persists regarding the optimal gentamicin dosing strategy for term neonates in Tanzania, driven by limited local pharmacokinetic data and the absence of routine TDM. This study therefore aimed to characterize and compare the pharmacokinetics of once-daily intravenous gentamicin at 5 mg/kg versus 4 mg/kg in term neonates in Tanzania, to inform safer and more evidence-based dosing strategies for this population.

Methods

Study Design and Setting

This pharmacokinetic analysis was conducted as a sub-study within a larger prospective observational cohort study evaluating the pharmacokinetics and safety of once-daily intravenous gentamicin in term neonates receiving either 4 mg/kg or 5 mg/kg as part of routine clinical care. The parent study enrolled 375 neonates, comprising 250 neonates who received

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gentamicin (125 receiving 4 mg/kg and 125 receiving 5 mg/kg) and 125 neonates who received alternative antibiotics (ceftriaxone or cefotaxime).

No experimental intervention or investigator-driven assignment of treatment was performed. All treatment decisions were made by the attending clinicians in accordance with standard hospital protocols. Pharmacokinetic sampling was performed exclusively in neonates receiving gentamicin in the two dosing groups. A sparse sampling technique was used to estimate population pharmacokinetic parameters, including clearance (CL) and volume of distribution (Vd). Peak and trough serum gentamicin concentrations were measured in all neonates receiving gentamicin. The study was conducted in the neonatal unit of Mwananyamala Regional Referral Hospital (MRRH) in Dar es Salaam, Tanzania, between January and March 2025. MRRH admits approximately 400 neonates per month and is staffed with trained medical personnel and supported by a laboratory capable of performing essential biochemical analyses.

Study Population and Sample Size Estimation

The study population comprised term neonates (gestational age ≥37 weeks) admitted with a clinical diagnosis of neonatal sepsis during the study period. Inclusion criteria were: age 1–28 days, indication for treatment with gentamicin anticipated to exceed 48 hours, and provision of written informed consent by the mother or legal guardian. Exclusion criteria were: severe illness requiring resuscitation; severe congenital malformations; prior exposure to nephrotoxic or ototoxic medications (for example, vancomycin, furosemide, acyclovir, amphotericin B, and ibuprofen) or drugs with potential pharmacokinetic interactions with gentamicin (such as phenobarbital, erythromycin, and phenytoin) within 72 hours before admission; serum creatinine above the upper limit of the laboratory reference range (>132.63 µmol/L); evidence of hearing loss at baseline; and prior gentamicin therapy within the 72 hours preceding study enrollment. The sample size for the parent study was calculated using the Fisher and Leslie formula. After adjusting for a 10% attrition rate, the required sample size was 125 neonates per study group. The parent study enrolled three groups: neonates receiving gentamicin 4 mg/kg once daily (n=125), gentamicin 5 mg/kg once daily (n=125), and an alternative antibiotic regimen (n=125), giving a total sample size of 375 neonates. For this sub-study, all 250 neonates who received gentamicin were included, comprising 125 neonates receiving 4 mg/kg and 125 receiving 5 mg/kg. The 125 neonates who received alternative antibiotics were not included in the present pharmacokinetic analysis.

Recruitment and Drug Administration

Eligible neonates were consecutively enrolled upon admission and categorised according to the antibiotic regimen they were to receive as part of routine clinical care. Treatment decisions were made solely by the attending clinicians. Each participant was assigned a unique study identification number. Gentamicin (5 mg/kg or 4 mg/kg) was administered once daily as an intravenous bolus injection.

Blood Sampling and Quantification of Serum Gentamicin Concentrations

For population pharmacokinetic (PopPK) analysis, 0.5 mL blood samples were collected via heel prick from each participant at different scheduled sampling times within 24 hours following the fourth gentamicin dose. Sampling times were set at 0.25, 0.5, 1, 2, 3, 5, 6, 8, 10, 12, 14, 16, 18, 20, 23, and 24 hours post-dose. Each participant contributed two samples at different time points to cover the full 24-hour concentration–time profile. Therefore, a total of 250 serum samples (125 participants × 2 samples) were collected for each gentamicin dosing group (5 mg/kg and 4 mg/kg), and concentrations at each time point were averaged and used to generate serum concentration–time profiles, which were fitted using Python version 3.12.3, assuming a one-compartment model, enabling estimation of population PK parameters, specifically clearance (CL) and volume of distribution (Vd). Steady-state peak serum gentamicin concentrations were assessed with a 0.5 mL blood sample drawn 30 minutes after the fourth dose, while trough concentrations were determined from a 0.5 mL sample collected five minutes before the fourth dose. All blood samples for PopPK and peak/trough determination were collected in red-topped serum separator tubes containing granules. Samples were immediately stored at –20°C at Mwananyamala Regional Referral Hospital and transported in a temperature-controlled cool box (2–8°C) to the Central Pathology Laboratory (CPL) at Muhimbili National Hospital within one hour of collection. At CPL, serum was transferred to another tube, centrifuged at 3,000 × g for 10 minutes, and stored at –80°C before analysis for gentamicin concentration using chemiluminescent microparticle immunoassay technology (Abbott Architect ci4100 analyzer®, Abbott Diagnostics in Illinois, United States), at the end of the study. The chemiluminescent microparticle immunoassay used for serum gentamicin quantification was validated according to standard procedures, demonstrating acceptable accuracy, precision, and linearity across the therapeutic range using a commercially available clinical CMIA platform (ARCHITECT iGentamicin assay) with performance characteristics established in regulatory documentation [16].

Data Analysis

Serum gentamicin concentration–time profiles were fitted to generate characteristic serum concentration–time curves following intravenous drug administration using Python (version 3.12.3). Population pharmacokinetic (PopPK) parameters, including elimination rate constant (k_e), elimination half-life ($t_{½}$), area under the curve (AUC), clearance (CL), and volume of distribution (Vd), were estimated from these profiles. Clearance (CL) and volume of distribution (Vd) were calculated using standard one-compartment pharmacokinetic formulas [17]. Data were analysed using IBM SPSS Statistics version 26.0 (IBM Corp., Armonk, NY, USA). Continuous variables were assessed for normality using the Shapiro–Wilk and

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Kolmogorov–Smirnov tests. Normally distributed variables were summarised as mean ± standard deviation (SD), while non-normally distributed variables were summarised as median and interquartile range (IQR). Categorical variables were summarised as frequencies and percentages. Gentamicin peak and trough concentrations were normally distributed and were compared between the 4 mg/kg and 5 mg/kg dosing groups using independent-samples t-tests. Categorical outcomes were expressed as frequencies and percentages and compared using the Chi-square or Fisher's exact test, as appropriate. Statistical significance was set at $p < 0.05$.

Ethical Considerations

Ethical approval was obtained from the University of Dodoma Institutional Research Review Ethics Committee (IRREC) (MA.84/261/74/38), and permission to conduct the study was granted by Mwananyamala Regional Referral Hospital. Written informed consent was obtained from mothers or legal guardians before enrolment of neonates. The study was conducted in accordance with the principles of the Declaration of Helsinki.

Results

During the study period, 493 neonates were screened for eligibility. Of these, 118 (23.9%) were excluded, with the majority (84; 71.2%) having received gentamicin before admission at Mwananyamala Regional Referral Hospital (MRRH). A total of 375 neonates (76.1%) met the eligibility criteria and were enrolled. Among these, 250 received gentamicin and were categorised into the 5 mg/kg group (n=125) and the 4 mg/kg group (n=125). These 250 neonates were included in the present analysis to characterise and compare the pharmacokinetics of once-daily intravenous gentamicin at 5 mg/kg versus 4 mg/kg in term neonates (Figure 1). No participants withdrew consent, died, or were lost to follow-up.

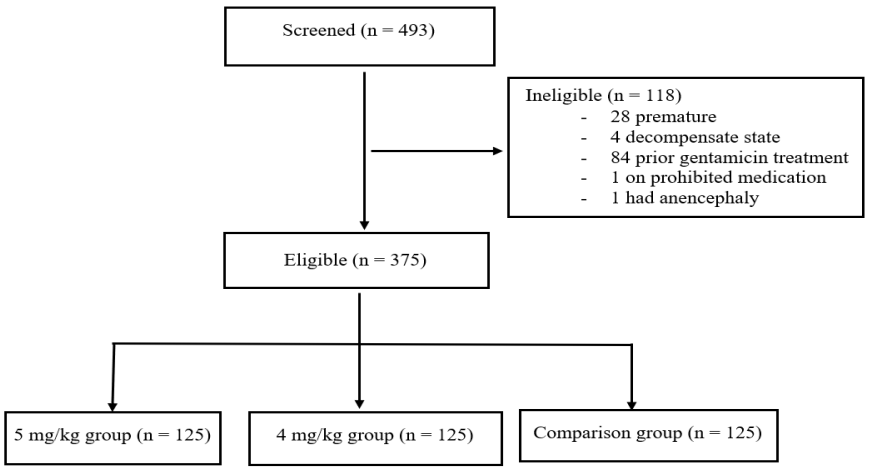

Figure 1. Participants' screening, eligibility and recruitment

Sociodemographic Data and Clinical Records by Gentamicin Dosing Group

Most participants had normal birth weight and normal weight at enrolment, with no significant differences between the 4 mg/kg and 5 mg/kg groups. Age distribution and APGAR scores were also comparable between the groups. However, diarrhoea was significantly more common among participants receiving 5 mg/kg than among those receiving 4 mg/kg, whereas the prevalence of vomiting did not differ significantly between the groups. The majority of neonates in both groups were able to suck, with no significant difference in the proportion unable to suck. Overall, baseline characteristics were comparable between the two dosing groups, including renal function profiles, and no participants had pre-existing hearing impairment, consistent with the study eligibility criteria (Table 1).

Table 1. Baseline characteristics of the study participants

Variable	Study group			
	5mg/kg (n = 125)	4mg/kg (n = 125)	Comparison group	p–value
Median age (IQR) (days)	8 (6, 11)	8 (6, 11)	8 (6, 9)	0.378
Sex, n (%)				
Male	78 (62.4)	72 (57.6)	54 (43.2)	0.007
Female	47 (37.6)	53 (42.4)	71 (56.8)	
Median gestational age (weeks) (IQR)	38 (37, 38)	38 (37, 38)	38 (37, 38)	0.962
Median birth weight in Kg (IQR)	3.0 (2.8, 3.5)	3.0 (2.6, 3.4)	3.0 (2.6, 3.4)	0.427
Median weight at enrolment in Kg (IQR)	3.10 (2.4, 3.2)	3.04 (2.4, 3.6)	3.07 (2.3, 3.8)	0.49
Weight at enrolment category, n (%)				
Normal (≥ 2.5 kg)	100 (80.0)	96 (76.8)	101 (80.8)	0.712

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Low (< 2.5 kg)	25 (20.0)	29 (23.2)	24 (19.2)	
Median height in cm (IQR)	50.0 (48.5, 52.0)	50.0 (48.0, 52.3)	50.0 (48.0, 52.8)	0.696
Median Apgar score (IQR)	8.0 (7.0, 9.0)	8.0 (7.0, 8.5)	8.0 (7.0, 8.5)	0.222
Diarrhoea, n (%)				
Yes	24 (19.2)	11 (8.8)	7 (5.6)	0.002
No	101 (80.8)	114 (91.2)	118 (94.4)	
Vomiting, n (%)				
Yes	27 (21.6)	24 (19.2)	26 (20.8)	0.892
No	98 (78.4)	101 (80.8)	99 (79.2)	
Unable to suck, n (%)				
Yes	10 (8.0)	14 (11.2)	15 (12.0)	0.548
No	115 (92.0)	111 (88.8)	110 (88.0)	
Median creatinine (µmol/L) (IQR)	79.0 (56.9, 99.1)	80.0 (60.0, 100)	78.5 (62.9, 100)	0.819
Median urinary KIM-1 (ng/mL) (IQR)	0.38 (0.28, 0.51)	0.39 (0.29, 0.50)	0.39 (0.30, 0.45)	0.594
Median AABR threshold (dB) (IQR)	7.0 (5.0, 9.0)	7.0 (4.0, 9.0)	6.0 (4.5, 9.0)	0.389
Median baseline eGFR (IQR)	25.9 (20.2, 34.5)	24.4 (19.9, 33.1)	25.6 (20.7, 33.3)	0.854

Steady State Pharmacokinetics

Steady State Peak Serum Gentamicin Levels

The mean steady-state peak serum gentamicin concentration in the gentamicin 5 mg/kg once-daily group was 18.80 ± 0.83 µg/mL, significantly higher than in the gentamicin 4 mg/kg once-daily group (7.82 ± 0.90 µg/mL; $p < 0.001$, independent samples t-test) (as shown in Table 2). Therapeutic peak levels (5–12 µg/mL) were observed in 124 of 125 neonates (99.2%) in the gentamicin 4 mg/kg once-daily group, whereas all neonates in the gentamicin 5 mg/kg once-daily group had supratherapeutic steady-state peak concentrations, a statistically significant difference ($p < 0.001$, Fisher's exact test). These results indicate that a 5 mg/kg dose produces supratherapeutic peaks, whereas the 4 mg/kg dose resulted in steady-state peak concentrations within recommended therapeutic levels.

Steady State Trough Serum Gentamicin Levels

The mean steady-state trough serum gentamicin concentration was higher in the gentamicin 5 mg/kg once-daily group (2.52 ± 0.93 µg/mL) compared to the gentamicin 4 mg/kg once-daily group (1.46 ± 0.36 µg/mL; $p < 0.001$, independent samples t-test) (as shown in Table 2). Sixty-five of 125 neonates (52.0%) in the gentamicin 5 mg/kg once-daily group had steady-state trough concentration above the safety threshold level (< 2 µg/mL), compared to only 3 of 125 neonates (2.4%) in the gentamicin 4 mg/kg once-daily group ($p < 0.001$, Chi-square test). These findings demonstrate that neonates receiving 5 mg/kg gentamicin are at substantially higher risk of drug accumulation compared to those receiving 4 mg/kg.

Table 2. Steady-state peak and trough serum gentamicin concentrations

Variable	**Study group**		**p-value**
	5 mg/kg (n=125)	4 mg/kg (n=125)	
Mean steady-state peak serum gentamicin (µg/mL)	18.80 ± 0.83	7.82 ± 0.90	<0.001
Proportion of neonates with peak above therapeutic range (%) (5–12 µg/mL)	100	0.8	<0.001
Mean steady-state trough serum gentamicin (µg/mL)	2.52 ± 0.93	1.46 ± 0.36	<0.001
Proportion of neonates with trough >2 µg/mL (%)	52.0	2.4	<0.001

Population pharmacokinetics (Clearance and Volume of distribution)

A population serum concentration-time, single-compartment model revealed concentration-time curves consistent with intravenous administration for both (5mg/kg and 4mg/kg) doses (as shown in Figure 2). From these fitted curves, key population pharmacokinetic parameters were directly estimated for each study group. In the gentamicin 5 mg/kg once-daily group, the elimination rate constant (k_e) was 0.0873 hr^{-1}, corresponding to an elimination half-life ($t_{½}$) of 7.94 hours. The area under the concentration–time curve (AUC) was 231.1 $\mu g \cdot mL^{-1} \cdot h^{-1}$, with an estimated clearance (CL) of 0.361 $mL \cdot min^{-1} \cdot kg^{-1}$ and volume of distribution (Vd) of 0.248 $L \cdot kg^{-1}$. In the gentamicin 4 mg/kg once-daily group, k_e was 0.0699 hr^{-1}, with a half-life of 9.92 hours. The AUC was 115.9 $\mu g \cdot mL^{-1} \cdot h^{-1}$, clearance was 0.575 $mL \cdot min^{-1} \cdot kg^{-1}$, and volume of distribution was 0.494 $L \cdot kg^{-1}$. Comparing these parameters with established reference ranges for term neonates (CL: 0.50–1.71 $mL \cdot min^{-1} \cdot kg^{-1}$; Vd: 0.40–0.70 $L \cdot kg^{-1}$), our data showed that the 5mg/kg dose resulted in lower-than-expected clearance and volume of distribution, suggesting reduced drug elimination and distribution. This aligns with the observed supratherapeutic peak and elevated trough concentrations and indicates a higher risk of prolonged systemic exposure and potential toxicity. By contrast, the gentamicin 4 mg/kg once-daily group displayed clearance and volume of distribution within physiological ranges, consistent with therapeutic peak and safe trough concentrations. These findings indicate that

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the 4 mg/kg once daily gentamicin regimen achieves therapeutic and safe gentamicin exposure in term neonates, whereas the 5 mg/kg dose may predispose to drug accumulation and toxicity.

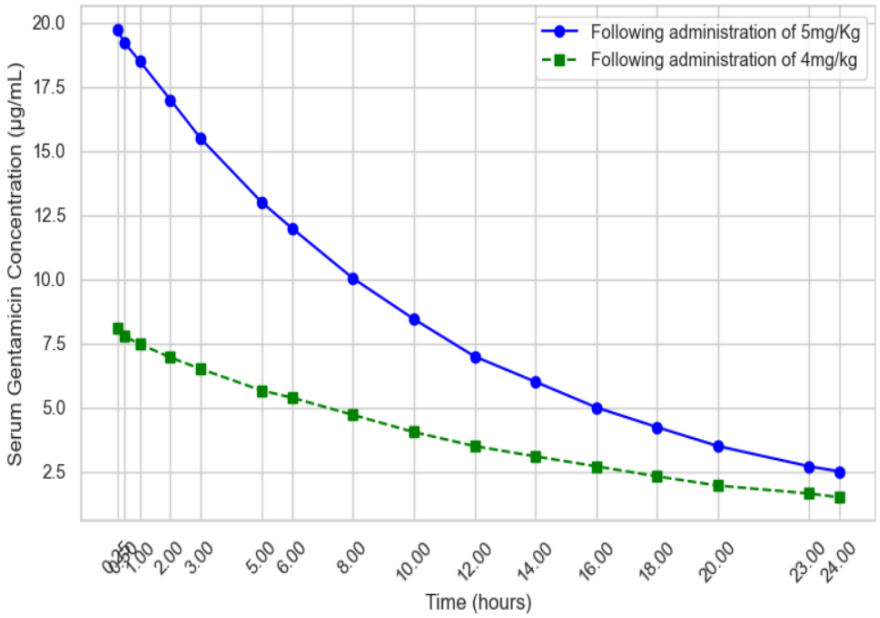

Figure 2. Serum gentamicin concentration (µg/mL) versus Time (hours) profile following administration of intravenous 5 mg/kg and 4 mg/kg doses of gentamicin

Discussion

This study evaluated the steady-state peak and trough serum gentamicin concentrations in term neonates receiving once-daily intravenous (IV) gentamicin at either 5 mg/kg or 4 mg/kg. The results revealed a clear dose-dependent relationship, with a significantly higher proportion of neonates in the 5 mg/kg group exceeding established therapeutic thresholds compared to those in the 4 mg/kg group. In the gentamicin 5 mg/kg once-daily group, the mean peak gentamicin concentration (18.80 ± 0.83 µg/mL) significantly surpassed the recommended upper therapeutic limit of 12µg/mL for term neonates. Notably, all neonates in this group had peak levels above the safe threshold. These findings align closely with our previous finding [9], where we observed peak levels exceeding 16 µg/mL in term neonates treated with 5 mg/kg once daily. Similar observations were made by Hayani et al. [10] and Hollander et al. [11], who documented peak values above the upper therapeutic limit of 12 µg/mL, providing further evidence of the risk of supratherapeutic exposure at this dose. Although the 5 mg/kg regimen is recommended in numerous studies for its ability to achieve higher peak concentrations and enhance bactericidal activity, particularly against gram-negative organisms [18], our findings indicate that this advantage comes with a substantial risk of supratherapeutic exposure, in contrast to the 4 mg/kg dose that appears to achieve concentrations within accepted therapeutic ranges, suggesting a comparatively lower risk of gentamicin toxicity, while therapeutic drug monitoring remains essential to ensure patient safety. By contrast, neonates who received 4 mg/kg once daily achieved significantly lower peak concentrations (but within the recommended therapeutic range), with a mean of 7.82 ± 0.90 µg/mL. Only one neonate (0.8%) exceeded the 12 µg/mL threshold, supporting the safety and pharmacokinetic suitability of this regimen. These results are consistent with those reported by Hollander et al. [11], Krishnan and George [12], Shabuj et al. [13], Serane et al. [14], Saad [15], and Lundergan et al. [19], all of whom reported safe and effective peak gentamicin levels ranging between 5 and 9 µg/mL with 4 mg/kg dosing. While the 4 mg/kg regimen demonstrated an overall favourable pharmacokinetic profile, it remains essential that therapeutic drug monitoring (TDM) and renal function assessments be performed routinely. This is vital for identifying inter-individual variability in drug clearance, and for preventing potential accumulation and toxicity. Trough concentrations followed a similar pattern. In the 5 mg/kg group, a substantial proportion of neonates (52%) had trough levels exceeding the recommended safety limit, indicating a higher potential for gentamicin toxicity at this dose. These findings echo those of James et al. [9] and Hayani et al. [10], and are consistent with observations from Hollander et al. [11], who reported increased trough levels in neonates receiving a 5 mg/kg dose of gentamicin. Elevated trough concentrations are clinically significant, as they have been strongly associated with higher risks of nephrotoxicity and/or ototoxicity in neonates [8]. Conversely, neonates on the 4mg/kg dose had considerably lower trough concentrations, with only 2.4% of samples exceeding 2 µg/mL. The mean trough concentration was 1.46 ± 0.36 µg/mL, which is well within the accepted safety range. These results highlight the pharmacokinetic advantage of the 4 mg/kg dosing regimen in reducing the risk of gentamicin accumulation while maintaining therapeutic efficacy. This observation is consistent with previous studies by Hollander et al. [11], Krishnan and George [12], Shabuj et al. [13], Serane et al. [14], Saad [15], and Lundergan et al. [19], which demonstrated trough levels consistently below toxic thresholds in neonates treated with 4 mg/kg once-daily gentamicin. Nonetheless, it is important to recognise that even within our cohort, a small subset of neonates receiving the 4 mg/kg dose exhibited elevated trough

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concentrations above 2 µg/mL. This variability reflects individual differences in gentamicin clearance and echoes findings reported in other investigations. For example, a study by Mustafa et al. [20] similarly documented sporadic cases of high trough levels in neonates treated with the 4 mg/kg regimen, underscoring the argument that while the lower dose generally confers a safer profile, therapeutic drug monitoring remains essential to identify neonates at risk of accumulation and potential toxicity. Taken together, these findings strongly support the use of the 4 mg/kg once-daily gentamicin regimen as a safer option for term neonates, effectively achieving therapeutic serum levels with a substantially reduced risk of exceeding toxicity thresholds. Although 5 mg/kg dosing may provide enhanced bactericidal activity in specific clinical scenarios requiring higher peaks, its use necessitates rigorous monitoring of renal function and drug levels. These results underscore the critical importance of dose optimisation, individualised therapy, and adherence to evidence-based monitoring protocols in minimising aminoglycoside-related toxicity in neonatal care. The population pharmacokinetic (PopPK) evaluation of gentamicin in this study revealed distinct pharmacokinetic profiles associated with the two dosing regimens in term neonates, providing insight into drug disposition and reinforcing the rationale for dose optimisation.
In the 5mg/kg group, pharmacokinetic modelling indicated higher overall gentamicin exposure, with clearance and volume of distribution lower than reported reference ranges for term neonates (CL: 0.50–1.71 mL/min/kg; Vd: 0.4–0.7 L/kg). This pattern suggests reduced renal elimination and limited tissue distribution, likely reflecting physiological immaturity of neonatal renal function, including low glomerular filtration rate and limited tubular handling capacity, which may partly explain the increased likelihood of drug accumulation and supratherapeutic exposure observed with this dosing regimen. These kinetic properties likely contributed to the elevated peak and trough concentrations observed in this group, as gentamicin is eliminated almost exclusively by glomerular filtration and undergoes saturable uptake in proximal tubular cells, predisposing to intracellular accumulation and prolonged elimination. These findings are in agreement with those of James et al. [9], who reported comparable CL and Vd values in Tanzanian neonates receiving 5 mg/kg gentamicin. Previous reports by Hayani et al. [10], Hollander et al. [11], and Murphy et al. [21] similarly documented reduced clearance (< 0.5 mL/min/kg) and low Vd (< 0.4 L/kg) at this dosing level, supporting the observed pattern of limited elimination and higher accumulation risk, which may be amplified at higher doses when renal handling capacity is exceeded, despite the underlying mechanisms remaining consistent across dosing levels. In the 4 mg/kg group of the study, clearance was higher at 0.575 $mL \cdot min^{-1} \cdot kg^{-1}$ and the apparent volume of distribution was larger at 0.494 $L \cdot kg^{-1}$, resulting in a modestly longer t½ of 9.92 hours and an AUC of 115.9 $\mu g \cdot mL^{-1} \cdot h^{-1}$. Although the half-life was slightly longer than that observed in the 5 mg/kg group, it remained well within the physiological range expected for term neonates (5–10 hours). The relatively prolonged half-life in this group reflects a more extensive distribution phase rather than impaired elimination. The higher clearance combined with the larger Vd indicates more efficient drug elimination and broader tissue penetration, resulting in lower systemic exposure and reduced risk of accumulation. These pharmacokinetic parameters are consistent with prior findings by Hollander et al. [11], Krishnan and George [12], Shabuj et al. [13], Serane et al. [14], Saad [15], and Lundergan et al. [19], which similarly demonstrated that 4 mg/kg once-daily dosing in term neonates results in peak and trough concentrations within generally accepted therapeutic ranges. Taken together, these findings indicate that the 4 mg/kg dosing regimen results in pharmacokinetic parameters within generally accepted ranges in term neonates. Higher clearance and larger Vd reduce systemic peak and trough concentrations, minimising the risk of nephrotoxicity and ototoxicity, despite the slightly longer half-life. In contrast, the 5 mg/kg regimen provides higher systemic exposure and a shorter half-life, which may enhance bactericidal activity but substantially increases the risk of supratherapeutic levels. These results emphasise the importance of individualised dosing and routine therapeutic drug monitoring in neonates, particularly since renal function is not fully developed and inter-individual variability in drug clearance is significant.

Study Strengths and Limitations

A major strength of this study lies in its prospective observational cohort design and relatively large sample size, which together enhance internal validity and reduce the risk of selection bias. The prospective nature of data collection ensured temporal accuracy in exposure and outcome measurement, while the inclusion of a substantial number of neonates improves the precision of pharmacokinetic parameter estimates. These design features are comparable to, and in some cases exceed, those reported in similar neonatal gentamicin pharmacokinetic studies, thereby strengthening the applicability of the findings to resource-limited clinical settings. The study further contributes to the existing literature by generating population pharmacokinetic (PK) estimates in term neonates, a population for which high-quality PK data remain limited. The adopted modelling approach, population pharmacokinetic analysis with sparse sampling, was well suited to neonatal research, where intensive sampling is neither ethical nor feasible. Although sparse sampling limits the construction of individual concentration–time profiles and may reduce precision compared with intensive sampling, previous studies [22] have demonstrated that as few as two samples per participant can yield reliable estimates of key PK parameters, including clearance (CL) and volume of distribution (Vd), when analysed using population-based modelling techniques [22]. In this context, the use of sparse sampling represents a methodological compromise that balances scientific rigour with participant safety, rather than a replacement for intensive sampling. The robustness of the PK analysis was further supported by the use of established population modelling techniques that are widely accepted for neonatal pharmacokinetic studies and have been successfully applied in similar investigations. This approach allowed for the characterisation of gentamicin disposition at the population level while accounting for inter-individual variability, thereby maximising the utility of the available data. Several limitations should also be acknowledged. The use of a chemiluminescent microparticle immunoassay (CMIA) for gentamicin quantification may be subject to interference from

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β-lactam antibiotics, potentially leading to underestimation of gentamicin concentrations, particularly if samples are not adequately refrigerated. This limitation is relevant given that neonates with sepsis at MRRH commonly receive gentamicin in combination with ampicillin and cloxacillin. To mitigate this risk, blood samples were promptly frozen when analysis was anticipated to be delayed beyond eight hours, preserving sample integrity. While minor assay interference cannot be entirely excluded, any residual bias would likely be non-differential across study groups and therefore unlikely to substantially affect comparative conclusions. Furthermore, although the findings are likely generalizable to term neonates in similar resource-limited settings where routine therapeutic drug monitoring is unavailable, it is important to note residual limitations. Inter-individual variability in drug clearance may differ in neonates outside the study site, and preterm neonates were excluded from the analysis, limiting the applicability of these results to this population. Overall, despite inherent limitations associated with sparse sampling, assay methodology, and population specificity, the study's strong design, appropriate analytical modelling, and alignment with existing literature support the validity, clinical relevance, and cautious generalizability of the findings.

Conclusion

In term neonates with sepsis, once-daily intravenous gentamicin at 4 mg/kg achieves therapeutic peak concentrations while maintaining trough levels well within the recommended safety range, thereby providing an optimal balance between efficacy and safety. In contrast, the 5 mg/kg regimen results in supratherapeutic peak and elevated trough concentrations, reflecting reduced clearance and limited distribution, which may predispose neonates to drug accumulation and toxicity. These findings highlight the pharmacokinetic advantage of the 4 mg/kg dose and support its prioritisation as the preferred empiric regimen in neonatal populations, particularly in settings where pharmacokinetic data are scarce. These results are likely generalizable to term neonates in similar resource-limited settings where routine therapeutic drug monitoring is unavailable, providing evidence to guide empiric gentamicin dosing safely. Nevertheless, careful dose optimisation, baseline and ongoing renal function assessment, and, where feasible, serum gentamicin monitoring remain essential to minimise aminoglycoside-associated adverse effects and to ensure safe and effective therapy.

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Competing interests

The authors declare that they have no competing interests.

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Author contributions

MEJ, PS, AL, and DB contributed to the conception and design of the study. MEJ was responsible for data collection, data analysis, and drafting of the manuscript. PS, AL, and DB supervised the study and critically reviewed the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.

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