Clinical Investigation

Extended-Interval Gentamicin Dosing in Achieving Therapeutic Concentrations in Malaysian Neonates

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OBJECTIVE: To evaluate the usefulness of extended-interval gentamicin dosing practiced in neonatal intensive care unit (NICU) and special care nursery (SCN) of a Malaysian hospital.

METHODS: Cross-sectional observational study with pharmacokinetic analysis of all patients aged ≤28 days who received gentamicin treatment in NICU/SCN. Subjects received dosing according to a regimen modified from an Australian-based pediatric guideline. During a study period of 3 months, subjects were evaluated for gestational age, body weight, serum creatinine concentration, gentamicin dose/interval, serum peak and trough concentrations, and pharmacokinetic parameters. Descriptive percentages were used to determine the overall dosing accuracy, while analysis of variance (ANOVA) was conducted to compare the accuracy rates among different gestational ages. Pharmacokinetic profile among different gestational age and body weight groups were compared by using ANOVA.

RESULTS: Of the 113 subjects included, 82.3% (n = 93) achieved therapeutic concentrations at the first drug-monitoring assessment. There was no significant difference found between the percentage of term neonates who achieved therapeutic concentrations and the premature group (87.1% vs. 74.4%), p = 0.085. A total of 112 subjects (99.1%) achieved desired therapeutic trough concentration of <2 mg/L. Mean gentamicin peak concentration was 8.52 mg/L (95% confidence interval [CI], 8.13-8.90 mg/L) and trough concentration was 0.54 mg/L (95% CI, 0.48-0.60 mg/L). Mean volume of distribution, half-life, and elimination rate were 0.65 L/kg (95% CI, 0.62-0.68 L/kg), 6.96 hours (95% CI, 6.52-7.40 hours), and 0.11 hour^{-1} (95% CI, 0.10-0.11 hour^{-1}), respectively.

CONCLUSION: The larger percentage of subjects attaining therapeutic range with extended-interval gentamicin dosing suggests that this regimen is appropriate and can be safely used among Malaysian neonates.

INDEX TERMS: aminoglycosides, extended-interval, gentamicin, neonate, pharmacokinetics

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INTRODUCTION

Gentamicin is one of the most commonly prescribed drugs used for empirical treatment of suspected or proven neonatal bacterial infection worldwide.[1,2] It is highly effective against early neonatal pathogens and is one of the inexpensive antibiotics that can be easily procured. Gentamicin, like other aminoglycoside antibiotics, has narrow therapeutic index with potential nephrotoxicity and ototoxicity that sometimes restrict its clinical use.[3] Close monitoring of serum drug concentration is required to secure its clinical efficacy and avoid toxicity.[3,4] With its concentration-dependent bacterial-killing property, higher peak concentrations will result in more effective bacterial killing and better clinical response. Meanwhile, it is crucial to maintain the desirable trough concentration, as uptake of gentamicin into site of toxicity (renal and auditory cell) is mainly associated with its persistently high trough concentrations.[4]

Variable gentamicin dosing regimens, from the conventional multiple-dose daily regimen to the recently used extended-interval dosing (EID), have been extensively discussed in pediatric literature without arriving at a consensus protocol. The suggested dosing varies widely, from 2.5 mg to 5 mg/kg given every 12 hours in traditional multiple-dose daily regimens to every 36 to 48 hours in extended-interval regimens.[5,6] Generally, most regimens target a therapeutic

peak of 5 to 10 mg/L and a trough concentration of less than 2 mg/L to maximize efficacy and to prevent toxicity.[6–8]

The pharmacokinetics of a drug in neonates is more erratic and complicated because of their immature renal function, low plasma protein, and a high body water to body weight ratio, compared to adults.[4,6] Several factors such as gestational age (GA), birth weight, and postnatal age affect the serum gentamicin concentration (SGC) and need to be taken into account when deciding the dosing protocol.[3,6] Extended-interval gentamicin dosing, which uses a larger dose at longer intervals, has better accuracy in achieving optimum peak and safe trough concentrations than traditional multiple daily dose regimens. It provides a higher peak concentration and allows sufficient time for drug clearance before the next dose.[4–7]

Because of individualized variation of gentamicin pharmacokinetics observed in neonates, a customized gentamicin dosing regimen based on pharmacokinetic monitoring may be ideal to optimize its therapeutic concentrations.[4] However, this often involves multiple repeated blood sampling at various time points to ascertain that the desired drug concentrations are achieved. This drug monitoring process is not only time-consuming, costly, and manpower intensive, it also causes patients considerable pain and may lead to significant blood loss especially in premature neonates.[4,5] Furthermore, adjustment of the dosage involves frequent rewriting of medication orders, which increases potential risk of prescribing error.[4,9]

A dosing regimen that provides early attainment of its target therapeutic concentrations would likely result in better clinical outcomes and reduce the necessity of serum concentration monitoring. This is important in resource-limited centers where drug concentration monitoring may not be feasible. Moreover, most of the time, gentamicin therapy in the neonatal ward is intended for short-term use while awaiting blood culture results, and therapy is only prolonged if infection is confirmed. Therefore, a dosing protocol with high accuracy in achieving target concentration may be safely used for short duration without drug monitoring. This would also significantly reduce the hospital cost associated with gentamicin therapy.[4,5,9]

Extended-interval dosing of gentamicin and its accuracy in achieving target concentrations have been widely discussed in numerous published studies. Most of these studies were undertaken in developed countries and among the Caucasian population.[4–8] Several of the current gentamicin regimens used in developing countries have been adapted from the protocols of countries at the forefront of pediatric care, such as the United Kingdom, United States, and Australia.[9,10]

Table 1. Empirical Gentamicin Dosing Regimen

Age	Recommended Dose*
Premature	
<1200 g	5 mg/kg every 48 hr
1200–2500 g	5 mg/kg every 36 hr
>2500 g	5 mg/kg every 24 hr
Term, 1-28 days	5 mg/kg every 24 hr

*Modified from Shann[11]

In Malaysian hospitals, the pocket-sized *Drug Doses* by Frank Shann[11] remains one of the primary references in pediatric medicine. Hence, its recommendation for gentamicin EID has been widely followed locally. However, the appropriateness of this regimen among local neonates has yet to be evaluated. So far, there is no published evidence to support the use of this dosing guideline in our setting. The aim of this study is to evaluate the usefulness of an extended-interval gentamicin dosing in achieving target therapeutic range in Malaysian neonates and thus to assess the necessity of gentamicin serum monitoring.

METHODS

This was a cross-sectional observational study that was conducted during a 3-month period from March 2012 to May 2012. Universal sampling method was used to include subjects. All neonates younger than 28 days who received gentamicin treatment in the neonatal intensive care unit or special care nursery of Sultanah Fatimah Specialist Hospital were included in the study.

Gentamicin sulphate (Garasent, CCM Duopharma Bio Tech, Klang, Malaysia) injection was given as a 30-minute intravenous infusion in the ward, and the dose was prescribed according to the dosing guideline described in Table 1. Serum gentamicin concentration monitoring was done at the second dose. Trough sample was taken within 30 minutes before the next dose and the

Table 2. Patient Demographics

	Gestational Age				Total (%)
	Premature			Term	
	≤28 wk n = 3	29–34 wk n = 27	35-36 wk n = 13	≥37 wk n = 70	n = 113
Sex, n					
Male	3	11	13	47	74 (65.5%)
Female	0	16	0	23	39 (34.5%)
Race, n					
Malay	2	19	11	49	81(71.7%)
Chinese	1	4	2	18	25 (22.1%)
Indian	0	1	0	1	2 (1.8%)
Others	0	3	0	2	5 (4.4%)
Gestational age, wk*	27.67 ± 0.58	32.48 ± 1.28	35.62 ± 0.51	37.74 ± 0.79	35.97 ± 2.75
Weight, kg*	1.07 ± 0.19	1.91 ± 0.40	2.59 ± 0.68	3.31 ± 0.56	2.83 ± 0.85
Serum creatinine, mg/dL*	0.87 ± 0.35	0.81 ± 0.15	0.87 ± 0.22	0.73 ± 0.24	0.77 ± 0.23
Gentamicin					
5 mg/kg every 48 hr, n	3	0	0	0	3 (2.7%)
5 mg/kg every 36 hr, n	0	24	6	0	30 (26.5%)
5 mg/kg every 24 hr, n	0	3	7	70	80 (70.8%)

*Mean ± SD

peak sample, at 30 minutes after completion of gentamicin infusion. Trained personnel carried out blood sampling via venipuncture or from an arterial line; the minimal blood volume required was 1.5 mL. All samples were processed within 2 hours by using fluorescence polarization immunoassay (Abbott Axsym, Abbott Laboratories, Irving, TX). Every assay was run according to machine specification.

Subjects were excluded if gentamicin was discontinued before the second dose was given, if the dose prescribed was outside the predefined dosing guidelines (5% difference from the recommended dose), if blood samples were drawn at inappropriate time, and if only 1 sample was sent.

Target peak and trough concentrations were defined as 5 to 10 mg/L and <2 mg/L, respectively, within the study. Dosing accuracy was defined as the achievement of both target peak and trough concentrations within the first pharmacokinetic evaluation. The following data were collected: GA, body weight (BW), prescribed dose/dosing interval, serum creatinine concentration, and concurrent use of indomethacin/ibuprofen during gentamicin therapy. Serum creatinine concentration was measured after 24 hours of life and monitored throughout gentamicin therapy. The latest creatinine concentration obtained during the course of therapy was used for analysis.

All data collected were statistically analysed by using SPSS (Statistical Package for the Social Sciences, Released 2006 SPSS for Windows, SPSS Inc., Chicago IL) version 15. Descriptive percentage was used to determine the overall dosing accuracy and a one-way between groups analysis of variance (ANOVA) was conducted to compare the accuracy among different GA groups. Subjects were divided into 4 groups according to their GA (group 1: GA ≤ 28 weeks; group 2: GA 29-34 weeks; group 3: GA 35-36 weeks; group 4: GA ≥ 37 weeks) and into 3 groups by their BW (group 1: <1200 g; group 2: 1200-2500 g; group 3: >2500 g).

RESULTS

A total of 113 of 137 subjects were included in the study, 6 were excluded owing to discontinuation of gentamicin therapy before the second dose, while 18 were excluded because of sampling time error. Patients' demographic profiles are listed in Table 2. Approximately 38% were premature babies and 62% were term babies with GA of at least 37 weeks. None of the subjects were

Table 3. Percentage of Subjects Achieving Therapeutic Concentrations With Empirical Gentamicin Dosage Regimen Among Premature and Term Neonates

Gestational Age	No. of Patients Within Therapeutic Range* n (%)	Inaccuracy			p Value
		Peak Out of Range		Trough Out of Range	
		Subtherapeutic, <5 mg/L	Supratherapeutic, >10 mg/L	>2 mg/L	
Overall (n = 113)	93 (82.3%)	0	19	1	
Term (n = 70)	61 (87.1%)	0	9	0	0.085†
Premature (n = 43)	32 (74.4%)	0	10	1	
35-36 wk (n = 13)	10 (76.9%)	0	3	0	
29-34 wk (n = 27)	20 (74.1%)	0	6	1	
≤28 wk (n = 3)	2 (66.7)	0	1	0	

* Attainment of therapeutic range is defined as subjects obtaining both the predefined peak and trough concentrations
† Therapeutic concentrations among premature and term neonates

concurrently treated with indomethacin/ibuprofen during gentamicin therapy in the study. The mean serum creatinine concentration was 0.77 ± 0.23 mg/dL.

Overall, there was an 82.3% (93/113) accuracy with the EID guideline followed in the study. There was no significant difference between the accuracy rates of term (87.1%) and premature neonates (74.4%), p = 0.085 (Table 3). Of 113 neonates, 99.1% achieved target trough SGC (<2 mg/L), while a total of 16.8% subjects failed to attain therapeutic peak SGC. All term neonates achieved a desired therapeutic trough SGC of <2 mg/L.

When further analysis was carried out among the group of subjects who did not achieve the therapeutic range, it was found that most (95%, n = 19) of the subjects had supratherapeutic peak (>10 mg/L), while none of the neonates had subtherapeutic peak (<5 mg/L). There was only 1 subject who had a trough SGC of more than 2 mg/L (Table 3).

Table 4 shows the pharmacokinetic profile of gentamicin in neonates classified according to GA. There was a statistically significant difference found in gentamicin half-life and elimination rate across the 4 GA groups when using ANOVA. Gentamicin's elimination rate increases with increasing GA. However, there was no significant difference in gentamicin peak concentration (p = 0.273), trough concentration (p = 0.272), and volume of distribution (Vd, p = 0.358) across the 4 GA groups.

Table 5 shows the pharmacokinetic profile of gentamicin in neonates classified according to BW. There was a significant difference in the elimination rate (p < 0.001) and half-life (p < 0.001) of gentamicin for the 3 BW groups. However, as with the different GA groups, there was no significant difference found between the Vd (p = 0.144) and the peak (p = 0.155) and trough concentrations (p = 0.951) of gentamicin among the various BW groups.

Generally, the study population demonstrated a mean peak concentration of 8.52 mg/L (95% confidence interval [CI], 8.13-8.90 mg/L) and trough concentration of 0.54 mg/L (95% CI, 0.48-0.60 mg/L). The mean gentamicin Vd was 0.65 L/kg (95% CI, 0.62-0.68 L/kg), while the mean half-life and elimination rate were 6.96 hours (95% CI, 6.52-7.40 hours) and 0.11 hour^{-1} (95% CI, 0.10-0.11 hour^{-1}), respectively.

DISCUSSION

The EID regimen (Table 1) used in this study achieved target concentrations in 82.3% of the subjects. This accuracy rate was observed to be higher than that of several EID regimens reported in other articles.[6,10,12–15] Although it was believed that drug handling in premature neonates may be more unpredictable than in term neonates, owing to their differences in body composition and prematurity of renal function,[16] this study shows that there was no significant differences in the accuracy rates of both groups.

As the current regimen has taken into consideration the subjects' BW and GA, it is within the researchers' expectations that there would be no statistical difference in mean peak and trough concentrations across all GA and BW groups in this study. As the peak SGC is dependent upon

Table 4. Patient Pharmacokinetic Profile Among Different Gestational Age Groups*

	Gestational Age				Total (n = 113)	p Value
	≤28 wk (n = 3)	29-34 wk (n = 27)	35-36 wk (n = 13)	≥37 wk (n = 70)		
Trough SGC, mg/L	0.64 ± 0.35	0.57 ± 0.41	0.69 ± 0.38	0.50 ± 0.29	0.54 ± 0.34	0.272
Peak SGC, mg/L	10.47 ± 2.82	8.47 ± 1.88	9.01 ± 2.01	8.36 ± 2.08	8.52 ± 2.05	0.273
Volume of distribution, L/kg	0.50 ± 0.20	0.65 ± 0.15	0.63 ± 0.14	0.66 ± 0.16	0.65 ± 0.16	0.358
Elimination rate, hr^{-1}	0.06 ± 0.01	0.08 ± 0.02	0.09 ± 0.02	0.12 ± 0.02	0.11 ± 0.03	<0.001
Half-life, hr	11.89 ± 2.61	8.89 ± 2.77	7.66 ± 1.80	5.87 ± 1.16	6.96 ± 2.33	<0.001

SGC, serum gentamicin concentration
* All data presented as mean ± SD

the dose and Vd, a standard dose of 5 mg/kg is expected to produce similar peak concentrations among the neonates regardless of GA and BW. On the other hand, the adjustment of the dosage interval according to GA and BW allows sufficient time for drug clearance.

One of the major drawbacks of gentamicin use is its association with nephrotoxicity, which is nearly always reversible, and ototoxicity, which is generally irreversible.[17] All but 1 neonate in the premature group attained a desired therapeutic trough SGC of less than 2 mg/L at the first pharmacokinetic evaluation. This finding is particularly important, as nephrotoxicity is mainly associated with persistently high trough concentrations of gentamicin.[18–21] On the other hand, there is insufficient evidence addressing the determinants of ototoxicity. Although several risk factors, such as duration of treatment, total dose, AUC, and impaired renal function, have been identified, the mechanism of ototoxicity remains undetermined.[19,22,23] Despite the unresolved controversy mentioned above, the results in this study suggest that the current dosing regimen could be safely applied in neonates even without trough SGC monitoring.

Gentamicin is primarily eliminated unchanged by the kidney; any change in renal function will influence its elimination rate. Gestational age and BW remain as two of the most significant factors affecting the elimination rate within the study, which is consistent with previously published results.[5,24–26] Maturation of kidney structure and function is directly proportional to GA. Therefore, the preterm infant with fewer glomeruli will possess reduced glomerular filtration rate and diminished kidney function, resulting in longer gentamicin half-life.[27]

When taking into account these dynamic principles, our findings support the use of this EID regimen in local neonates, especially in premature neonates whose renal function is immature. In addition, studies have also shown that longer dosing interval and lower trough concentrations may prevent adaptive microbial resistance.[7,28] A cost-effectiveness analysis carried out by Thureen et al[29] also proved that once-daily administration of gentamicin in neonates older than 34 weeks is safe, efficacious, and less costly than a twice-daily regimen.

Gentamicin is an antibiotic with a concentration-dependent bacterial-killing effect, and based on studies *in vitro* and with patients, it has been suggested that it is important to achieve a ratio of peak plasma concentration to minimum inhibitory concentration (C_{peak}/MIC) greater than 8 to 10.[30] Some studies targeted a higher peak SGC of more than 8 mg/L for a better bactericidal effect.[13,25,31] However, the impact of higher peak SGC compared to conventional peak SGC (5-10 mg/L) in clinical outcome was not measured in those studies. Routine measurement of MIC of infecting pathogen is not viable in our setting, which leads to inability to determine the optimum peak SGC. Hence, based on the currently available data it is reasonable to suggest a target peak SGC of 5 to 10 mg/L for gentamicin-susceptible pathogens.[4,8]

Supratherapeutic (>10 mg/L) gentamicin concentration was the most common cause of dosing inaccuracy within the study. Of 113 subjects, 9.73% had a peak SGC between 10 and 12 mg/L and 7.08% of the subjects achieved peak SGC ranging between 12.01 and 16.05 mg/L. Hossain et al,[12] who designed a simplified dosing regimen for treatment of sepsis in Bangladeshi neonates, reported that 29% (17/59) of the subjects recruited in their study had a supratherapeutic

Table 5. Pharmacokinetic Profile Among Different Weight Groups*

	Body Weight			Total (n = 113)	p Value
	<1200 g (n = 4)	1200-2500 g (n = 35)	>2500 g (n = 74)		
Trough SGC, mg/L	0.58 ± 0.31	0.53 ± 0.39	0.54 ± 0.32	0.54 ± 0.34	0.951
Peak SGC, mg/L	10.38 ± 2.31	8.29 ± 1.77	8.52 ± 2.14	8.52 ± 2.05	0.155
Volume of distribution, L/kg	0.50 ± 0.16	0.66 ± 0.14	0.65 ± 0.16	0.65 ± 0.16	0.144
Elimination rate, hr^{-1}	0.07 ± 0.02	0.09 ± 0.03	0.12 ± 0.03	0.11 ± 0.03	<0.001
Half-life, hr	10.83 ± 3.01	8.50 ± 2.77	6.02 ± 1.23	6.96 ± 2.33	<0.001

SGC, serum gentamicin concentration
* All data presented as mean ± SD

peak SGC (12.1–20.6 mg/L), but hearing assessment done at 6 to 12 weeks of age did not reveal any sign of ototoxicity. According to Darmstadt et al,[15] a peak SGC greater than 25 mg/L did not result in increased toxicity. Although Bauer[32] described that there was an increased risk of ototoxicity with peak SGC exceeding 12 to 14 mg/L, some studies have suggested that gentamicin exposure time rather than peak SGC alone is the main determinant of gentamicin ototoxicity.[9,18,19] Hearing loss was suggested as a rare complication in infants with prior exposure to aminoglycosides.[7,33–35] Other contributing factors should be taken into consideration and audiometry is believed to be more beneficial for monitoring and early detection of ototoxicity.[36] Adequate clinical experience of EID use in adults suggests discontinuation of routine peak monitoring.[15] Nevertheless, it is still recommended for neonates today until more conclusive evidence indicates otherwise.

None of the subjects showed subtherapeutic peak SGC in this study. As peak SGC is substantially correlated to its clinical efficacy, our result indicates that the dosing regimen of 5 mg/kg/dose used in our setting can achieve therapeutic peak concentration and thus ensure pharmacologic efficacy of gentamicin in the subjects.

Peak SGC is related to its Vd as gentamicin distributes into the extracellular fluid in the body. In the study, the mean Vd (0.65 ± 0.16 L/kg) was slightly larger than most of the mean Vd values reported in others studies, which range from 0.4 to 0.6 L/kg. [5,10,13,14,24,25] This may possibly be due to variation in population pharmacokinetics. The slightly larger Vd observed is believed to be a true representation of the neonates in our study population, based on continuity of the data collected. However, the lack of published evidence pertaining to local pharmacokinetic parameters hinders the confirmation of this finding. Further studies with larger sample size may be warranted to verify this observation.

Most of the neonates were empirically treated with gentamicin for suspected bacterial infection that often warranted a short-course therapy. Increasing evidence in attainment of optimum peak and trough SGC with EID use in neonates has led some authors to propose that routine therapeutic drug monitoring is not necessary in such circumstances.[3,9,31,34,37,38] According to the study findings, the current empiric dosing guideline used is able to achieve therapeutic peak and trough SGC at the first pharmacokinetic evaluation. Thus, it is suggested that SGC monitoring for short-term course (<72 hours) of gentamicin be reduced. This will effectively translate into a decrease in the cost associated with gentamicin therapy and avoid blood loss resulting from serum drug monitoring. Sampling in the neonates is often complicated by difficulty in blood taking and stringent gentamicin sampling times. Moreover, more blood has to be harvested to obtain similar volumes of plasma owing to higher hematocrit level in infants. With a blood volume of 80 mL/kg, a preterm infant weighing 2 kg has only 160 mL of blood. Repeated blood sampling, not just for therapeutic drug monitoring but also for other laboratory investigations, has also been implicated in neonatal anemia.[27]

Although our study has overall high accuracy, the decision to reduce gentamicin's monitoring as a standard national guideline would warrant further studies with a larger sample size. Future studies that aim to provide evidence for the clinical safety of gentamicin in neonates may include long-term follow-up on the subjects' auditory function. In addition, the findings for

the subgroup of neonates ≤ 28 weeks should be interpreted with caution, as only 3 subjects were recruited. Another limitation is that the extent to which patients' underlying diseases could influence their pharmacokinetic outcome was not measured in this study.

CONCLUSION

The extended-interval gentamicin regimen used in this study showed high accuracy in achieving target therapeutic concentrations. Study findings showed that this regimen is appropriate and effective in achieving therapeutic peak and trough concentrations in our population while avoiding toxicity in short-term gentamicin course. Although the results do not provide sufficient evidence to suggest the discontinuation of gentamicin monitoring in all neonates at the moment, it implies that therapeutic drug monitoring can be reduced in infants who receive short-term gentamicin treatment (≤72 hours). When gentamicin treatment may need to be extended, therapeutic drug monitoring may still be warranted to ensure the attainment of target ranges.

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Abbreviations ANOVA, analysis of variance; AUC, area under the plasma drug concentration versus time curve; BW, body weight; CI, confidence interval; C_{peak}, peak plasma concentration; EID, extended-interval dosing; GA, gestational age; MIC, minimum inhibitory concentration; NICU, neonatal intensive care unit; SCN, special care nursery; SGC, serum gentamicin concentration; Vd, volume of distribution

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