

Once-Daily-Dosing Intramuscular Gentamicin in Neonates

Dear Editor,

Aminoglycosides with beta-lactam antibiotics remain the first-line therapy in neonatal septicaemia, effective against aerobic, gram-negative organisms, with synergy against some gram-positive organisms. Aminoglycosides exhibit a concentration-dependant killing rate and a long post-antibiotic effect. An antibacterial peak concentration ([peak]) of >4 mcg/mL is ideal, with potential nephrotoxicity and ototoxicity, especially when the trough level ([trough]) exceeds 2 mcg/mL.^{1,2}

Traditionally, multi-dosing gentamicin has been administered. Subsequent animal studies demonstrated reduced toxicity with single-bolus dosing. Review revealed 40% of departmental infants on the original multi-dosing regime had high gentamicin [trough]. The authors therefore prospectively evaluated a once-daily-dosing (ODD) intramuscular (IM) gentamicin protocol targeting adequate serum gentamicin levels with reduction of frequency/severity of toxicity.

All neonates requiring gentamicin (November 1997 to April 2000) admitted to our Department were enrolled, with Phase A before and Phase B after February 1999. Gestational age (GA) scoring was routinely carried out by Ballard and Dubowitz scores. Daily weights were recorded unless unfit. ODD IM gentamicin dose at commencement was calculated based on the latest weight taken.

Doses were prescribed accordingly:

- Group I (GA <30 weeks) — 2.5 mg/kg/dose;
- Group II (GA 30 to 37 weeks) — 3.5 mg/kg/dose;
- Group III (GA ≥ 37 weeks) A — 5 mg/kg/dose and B — 4.5 mg/kg/dose (after Phase A review).

Serial serum creatinine (SeCr) and urine output were monitored. The [trough] and [peak] gentamicin ranging 0 to 2.0 mg/L and 5 to 12 mg/L respectively were taken before and 1 hour after the third dose. Adjustments for high levels were made accordingly, with levels repeated at the third amended dose. Gentamicin may be discontinued with a negative initial blood culture where the baby was clinically well, when repeat SeCr remained >144 mmol/L or with reduced urine output <1 mL/kg/h. Hypotension was considered significant when the volume and inotropes support were required. Babies without the third dose [trough] or had wrong dosing were excluded. Universal newborn

hearing screen became available in November 1998.

The study was approved by the hospital ethics committee, with a waiver of consent due to it being a change in departmental dosing protocol. Data were analysed using SPSS, Version 10.5, Chicago, IL, USA.

There were 255 patients enrolled—Group I: 68, Group II: 99; Group IIIA: 51 and Group IIIB: 54. Thirteen were excluded: 17 with no [trough] done; 7 for inappropriate dosing for GA; leaving 248 babies for analysis (Table 1).

The distribution of serum gentamicin levels is demonstrated in Figure 1. In Group I, 5 had high [trough]: 2 each of 24- and 29-weeks postmenstrual age (PMA) and one of 25-weeks PMA at commencement. One 29-weeks PMA baby had a chromosomal anomaly, with patent ductus arteriosus (PDA), opto-septic dysplasia, agenesis corpus callosum and tethered cord. Four had PDA requiring Indomethacin and were simultaneously significantly hypotensive, with 1 having an abnormally high Day 3 SeCr. The only baby without a PDA or hypotension (25-weeks PMA) also had a high Day 3 SeCr.

In Group II, 4 babies (three 30-weeks and one 32-weeks PMA) had high [trough] but normal Day 3 SeCr; all were hypotensive, with 2 on inotropes. Three of them also had PDA requiring Indomethacin. One 36-weeks PMA baby with high [peak] had no obvious risk.

In Group IIIA, of 2 babies with high [trough], 1 had an intra-abdominal cyst, with associated right hydronephrosis and hydronephrosis. The other baby had hypoxic ischaemic encephalopathy, with a raised Day 3 SeCr and significant hypotension. Of 11 babies with high [peak], 9 had no obvious risk factors, with normal SeCr; the other 2 were the ones with high [trough]. In Group IIIB ($n = 52$), the single baby with abnormal levels had a low [peak] of 4.9 mg/L. All babies in this group had normal SeCr.

With regard to ototoxicity, 142 babies had data on hearing screening. Three were eventually diagnosed with moderate-to-severe hearing impairment (HI): 1 Group II baby (28-weeks PMA) with hypoxia and neonatal seizures; 2 Group I babies (29-weeks PMA baby with chromosomal anomaly and 25-weeks PMA baby on prolonged ventilation also had retinopathy of prematurity). Only this last baby had high [trough].

ODD gentamicin regimes, effective even in severe

Table 1. Dosing Data for All Groups

Group	n	GA (weeks)	PMA (weeks)*	DOL*	n	[Trough] mg/L [†]	n with High Level	n with Low Level
		BW (g)	Weight (g)*			[Peak] mg/L [‡]		
All [§] (125M 122F)	248	34 (24, 42)	34 (24, 42)	1 (1, 34)	248	1.0 (0.1, 3.9)	11 (4.4%)	NA [†]
					202	1.0 (0.1, 3.9)	9 (3.6%)	NA [†]
		2195 (470, 4630)	2200 (470, 4630)		244 [§]	8.0 (1.3, 16.5)	12 (4.8%)	17 (7.0%)
					196	7.4 (1.3, 14.3)	1 (0.5%)	17 (8.6%)
I	56	28 (24, 29)	28 (24, 29)	1 (1, 27)	56	1.3 (0.5, 3.9)	5 (8.9%)	NA [†]
		938 (470, 1405)	938 (470, 1405)			5.6 (2.9, 8.8)	0	12 (22.0%)
II	94	33 (29, 36)	33 (30, 36)	1 (1, 34)	94 [§]	1.1 (0.1, 3.1)	4 (4.3%)	NA [†]
		1817 (985, 4040)	1790 (1025, 4040)		90	7.7 (1.3, 14.3)	1 (1.1%)	4 (4.3%)
IIIA	46	39 (37, 41)	39 (37, 41)	1 (1, 10)	46	1.0 (0.4, 3.5)	2 (4.3%)	NA [†]
		3065 (2155, 4260)	3065 (2155, 4260)			10.9 (5.0, 16.5)	11 (23.9%)	0
IIIB	52	39 (37, 42)	39 (37, 42)	1 (1, 7)	52	0.7 (0.2, 1.5)	0	NA [†]
		3095 (1890, 4360)	3095 (1890, 4030)			8.7 (4.9, 11.6)	0	1 (1.9%)

All values are expressed as median (range).

GA: gestational age; 82% were appropriate for gestational age.

BW: birth weight; PMA: postmenstrual age; DOL: day of life

*at commencement

[†]Target Trough 0 – 2 mg/L; there were no babies with undetected trough.

[‡]Target Peak 5 – 12 mg/L

[§]four patients in Group II did not have peaks done

^{||}excluding Group IIIA

[¶]132 Chinese, 84 Malays, 23 Indians and 8 others

Median Day 3 serum creatinine was 60 (30 to 218) μ mol/L. Mean duration of therapy was 7 \pm 1 days.

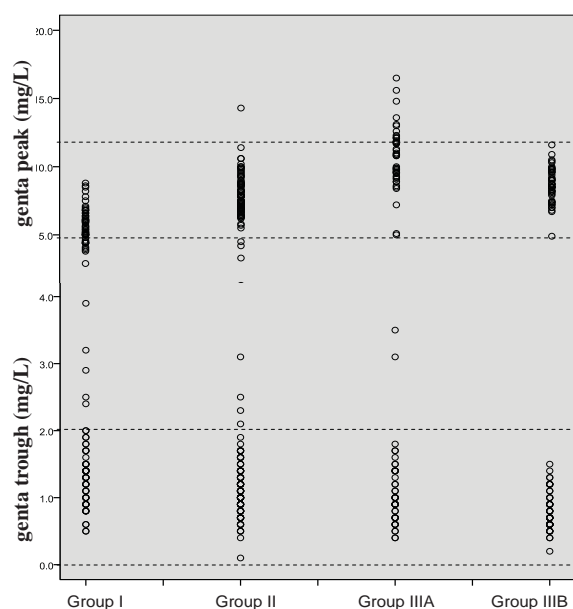


Fig. 1. Distribution of Serum Gentamicin Trough and Peak Levels Accordingly to Groups.

Lines denote the target range for serum gentamicin trough (0 to 2 mg/L) and peak levels (5 to 12 mg/L).

infections, have resulted in high, infrequent and short-lived [peak], with less renal cortical uptake, and reduced nephrotoxicity, particularly with a single short-term compared to continuous infusion. In neonates with slower renal clearance, high [trough] and high [peak] levels can occur independently.^{2,3} Given its convenience and lower costs, ODD was recommended as the preferred regime.

With neonatal ODD gentamicin regimens, most authors evaluated only term or near-term babies (weight \geq 1500 grams), with 4.0 to 5.0 mg/kg and 3.5 to 4 mg/kg/d reportedly safe respectively, without increased renal or ototoxicity.⁴⁻⁶ Amongst very-low-birth-weight infants, a loading dose, followed by ODD was found safe albeit significantly higher mean [trough]. In 2003, Hansen et al⁷ reported using a once-daily gentamicin regime of 3 mg/kg in those $<$ 35 (75% therapeutic [peak]; 100% non-toxic [trough]) weeks and 4 mg/kg in those \geq 35 weeks (93% therapeutic [peak]).⁷ A 2006 Cochrane review, examining 11 ODD-gentamicin studies, demonstrated superior ODD pharmacokinetics.⁸ Our study achieving consistent clinical outcomes though it was done prior to the Cochrane review, supersedes Hansen's study⁷ as the largest study published to date. We have fine-tuned the ODD regime implementation, with differentiated dose/kg for different GA groups and advocate it for all infants.

Most authors also restricted gentamicin usage to the IV route. However, without significant pharmacokinetic differences between IM and IV routes,⁹ the former conveys several advantages to these small babies, with reduced pokes, nosocomial infection, extravasation and cellulitis. Our first-line antibiotic unit protocol, in the absence of significant thrombocytopenia or coagulopathy, has consistently practiced IM ODD aminoglycoside administration.

PDA on indocid therapy, high SeCr and hypotension were seen in preterms with high [trough]. In Phase IIIA, the 2 babies with high [trough] had either a renal malformation or hypotension associated with a raised SeCr. These factors clearly impact gentamicin clearance and must be considered when using aminoglycosides.

This remains, to date, the largest reported study on neonatal (IM) gentamicin administration. This once-a-day PMA-based IM regime is safe with good serum levels, convenient in the absence of thrombocytopenia/coagulopathy, with dose adjustment recommended with concurrent high SeCr, indomethacin therapy or significant hypotension.

Wee Bin Lian,¹ *MMed (Paeds), MRCP (UK), FAMS*, Cheo Lian Yeo,¹ *MBBS, MMed (Paeds), FAMS*, Lai Yun Ho,¹ *MBBS, MMed (Paediatrics), FAMS*

¹Department of Neonatal and Developmental Medicine, Singapore General Hospital

Address for Correspondence: Dr Wee Bin Lian, Department of Neonatal and Developmental Medicine, Singapore General Hospital, Outram Road, Singapore 169608.

Email: lian.wee.bin@sgh.com.sg

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