

Gentamicin dosage intervals in neonates: Longer dosage interval—less toxicity

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Objectives: The aim of this study was to determine the incidence of toxic trough serum gentamicin levels in neonates in the first week of life, with different dosage intervals.

Methods: This was a retrospective study of neonates born between 01.07.95 and 31.12.95, who received gentamicin. Data were collected on birth weight, gestation, gentamicin dose, the trough level of gentamicin, serum creatinine and urine output. A trough serum gentamicin level of ≥ 1.5 mg/L was considered toxic.

Results: One hundred and seventy infants met the study criteria. All 21 infants in group one (24–29 weeks) received gentamicin with a dosage interval of 24 h. Sixteen (76%) infants had toxic trough serum gentamicin levels. In group two (30–34 weeks) 8 infants had gentamicin q12hly and all (100%) had toxic trough serum gentamicin levels. Fourteen infants had gentamicin every 18 h and 13 (93%) had toxic trough serum gentamicin levels. Sixty-one infants had gentamicin q24hly and 25 (41%) had toxic trough serum gentamicin levels. The differences in proportions with toxic levels were statistically significant. In group three (≥ 35 weeks) 29 infants had gentamicin q12hly and 25 (86%) had toxic trough serum gentamicin levels. Six infants had gentamicin every 18 h and 2 (33%) had toxic trough serum gentamicin levels. Thirty-one infants had gentamicin q24hly and 4 (13%) had toxic trough serum gentamicin levels. The differences in proportions comparing infants having gentamicin q12hly with those having it q24hly were statistically significant.

Conclusions: A starting gentamicin dosage interval of 12 h in infants of any gestational age, or a starting dosage interval of 24 h for infants of less than 30 weeks gestational age, leads to most having toxic trough serum gentamicin levels. In infants of 30 weeks gestational age or greater, most have safe non-toxic trough serum gentamicin levels if started on a dosage interval of 24 h.

Key words: drug administration schedule; drug monitoring; drug toxicity; gentamicins; infant, newborn.

Gentamicin is one of the most common antibiotics used in neonatal units. It is used in the first line treatment for sepsis in the neonate. Serum gentamicin levels are monitored routinely, particularly to check predose trough levels to avoid toxic accumulation.

The starting dose and dosage interval of gentamicin are usually based on the infant's weight and gestation.¹⁻³ Over the last decade, there has been a shift from giving the drug every 12 h, in the term infant, to giving a larger dose every 24 h (q24hly).^{1,4,5} This has resulted from studies done in adults and children.⁶⁻¹⁰ Conflicting advice on gentamicin dosing regimens from commonly used paediatric and neonatal drug dosage booklets in Australia over the last few years^{1,4,5} has led to the situation where neonatal house staff have been commencing neonates on varying doses and dosage intervals of gentamicin. It was our impression that infants who received gentamicin every 12 h (q12hly) had higher trough levels, requiring lengthening of the dosage interval, than infants who received the drug q24hly.

The aim of this study is to determine the incidence of inappropriately high trough gentamicin levels in neonates in the

first week of life and to determine if the incidence differed with dosage interval.

METHODS

This was a retrospective study of all infants born between 01.07.95 and 31.12.95 admitted to our neonatal unit who received gentamicin intravenously. Data were collected (pertaining to the first course of gentamicin commenced in the first week of life) on the infant's birth weight, gestation, dose and dosage interval of gentamicin, the trough level of gentamicin before the third dose, serum creatinine on the day of the gentamicin level and the urine output in the 24 h prior to the gentamicin level.

Infants were excluded from the analysis if: (1) no gentamicin level was carried out; (2) the dosage interval was not clearly known; (3) the dose or dosage interval of gentamicin were altered before the serum gentamicin level was carried out; and (4) renal function was impaired—defined as having a serum creatinine greater than 0.09 mmol/L or a poor urine output (less than 1 mL/kg/h if measured, or less than four wet nappies in the 24 h preceding the gentamicin level). Infants were also excluded from the analysis if there was any documented birth asphyxia or renal tract disease.

In our unit a level of ≥ 1.5 mg/L was considered to indicate a significant risk of toxic drug accumulation and the dosage interval of gentamicin was increased.

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RESULTS

One hundred and seventy infants met the study criteria. The infants were divided into three groups for analysis. Group one, infants from 24 to 29 completed weeks gestation ($n=21$). Group two, infants from 30 to 34 completed weeks gestation ($n=83$). Group three, infants of ≥ 35 weeks gestation ($n=66$). Birthweights, gestational ages and gentamicin doses are summarised in Table 1.

All 21 infants in group one received gentamicin q24hly. Sixteen (76%) infants had toxic trough serum gentamicin levels.

In group two, 8 infants had gentamicin q12hly and all (100%) had toxic trough serum gentamicin levels. These infants were significantly larger and more mature than the infants receiving gentamicin q24hly. Fourteen infants had gentamicin every 18 h (q18hly) and 13 (93%) had toxic trough serum gentamicin levels. These infants were significantly larger than the infants receiving gentamicin q24hly. Sixty-one infants had gentamicin q24hly and 25 (41%) had toxic trough serum gentamicin levels. The differences in proportions with toxic levels were statistically significant (Table 2). That is gentamicin given every 12 or 18 h was more likely to lead to toxic trough serum gentamicin levels compared with gentamicin given q24hly.

In group three, 29 infants had gentamicin q12hly and 25 (86%) had toxic trough serum gentamicin levels. These infants were significantly larger than the infants receiving gentamicin q24hly. Six infants had gentamicin q18hly and 2 (33%) had toxic trough serum gentamicin levels. Thirty-one infants had gentamicin q24hly and 4 (13%) had toxic trough serum gentamicin levels. The differences in proportions comparing infants having gentamicin q12hly with those having it q24hly were statistically significant (Table 2). That is gentamicin given q12hly was more likely to lead to toxic trough serum gentamicin levels than was gentamicin given q24hly.

DISCUSSION

In our unit, in 1995, infants were commenced on different dosing regimens of gentamicin. This gave us an opportunity to ascertain how many of our infants had toxic trough serum gentamicin levels and to see if the incidence of toxicity varied with the dosage interval. Any evidence of renal impairment would normally influence the prescribed dosage interval and gentamicin clearance, so we excluded these infants from our analysis. Our results confirm our impression that the shorter

the dosage interval of gentamicin the greater the likelihood of high trough levels.

Non-toxic or safe trough gentamicin levels are set arbitrarily and there is no good evidence that any particular trough level to aim for is correct—threshold levels between 0.5 and 2.0 mg/L have been recommended.¹¹ The threshold level we use for trough gentamicin levels is 1.5 mg/L. Our gentamicin assays are carried out at the Department of Microbiology, Royal Brisbane Hospital. They recommend that gentamicin dosage intervals be increased if levels are ≥ 1.5 mg/L. This level was initially introduced years ago before the use of TDX technology with its speed of turnaround time of 1–2 h. The recommended level has been retained “because it has an inbuilt sense of ‘safety’ in case of delays in action by clinical staff or if there is a loss of test sensitivity/reproducibility, and because staff are familiar with and understand what it means”. (Faogali J, personal communication, 1997).

Toxicity of aminoglycosides is related to accumulation of the drug if it is given too often. Harmful effects on the kidney and middle ear can lead to renal failure and deafness.^{12,13} Renal toxicity results from accumulation of gentamicin in lysosomes of cells in the proximal tubule. This leads to disordered reabsorption and decreased glomerular filtration rate.¹⁴ Auditory brain stem evoked responses in neonates demonstrate a clear effect from gentamicin (even in the absence of any trough gentamicin levels of ≥ 2.0 mg/L) and animal studies demonstrate anatomical damage to the cochlea with electron microscopy.¹⁵ However, sensorineural hearing loss is common in graduates of neonatal intensive care¹⁶ and the contribution of gentamicin is largely unknown.^{16,17}

Once the decision has been made to start a baby on gentamicin the clinician must then decide how much of the drug to give (the dose) and how often to give it (the dosage interval). For term neonates, the recommended dosage regimen up until the early 1990s has been 2.5 mg/kg/dose given q12hly.¹⁴ Neonates have a longer half life for gentamicin than adults¹⁸ and in the very preterm infant it may be prolonged to 14 h.¹⁹ Therefore neonates require a longer dosage interval compared with older children and adults, and preterm neonates require even longer dosage intervals. Preterm neonates also have a larger volume of distribution for gentamicin than more mature infants and may require larger doses of gentamicin to achieve adequate peak gentamicin levels.^{20–23}

There are many compelling reasons for giving gentamicin less often, apart from the decreased incidence of high trough levels found in this study. These include savings related to drug

Table 1 Birthweight, gestation and gentamicin dose data for the three gestational age groups

Gestation	24–29 ⁺ 6 weeks	30–34 ⁺ 6 weeks	≥ 35 weeks
Number	21	83	66
Birthweight (kg)			
-median (IQR)	1.10 (0.90–1.26)	1.84 (1.57–2.20)	3.19 (2.85–3.51)
Gestation (weeks)			
-median (IQR)	28.1 (26.1–29.6)	32.6 (31.3–33.6)	38.6 (37.2–39.6)
Dose of gentamicin			
-median (range)			
mg	2.20 (1.5–4.0)	4.00 (1.0–8.0)	7.00 (4.0–15.0)
mg/kg/dose	2.00 (1.91–2.62)	2.03 (1.89–3.60)	2.04 (1.79–4.53)
mg/kg/day	2.00 (1.91–2.62)	2.36 (1.92–5.13)	3.00 (1.79–5.06)

IQR—interquartile range.

Table 2 Birthweight, gestation and gentamicin dose data by dosage interval

	Dosage Interval		
	12 h	18 h	24 h
24–29⁺6 week gestation infants			
Number	0	0	21
sGent < 1.5 mg/L – n (%)			5 (24)
sGent ≥ 1.5 mg/L – n (%)			16 (76)
30–34⁺6 week gestation infants			
Number	8	14	61
sGent < 1.5 mg/L – n (%)	0 (0) *	1 (7)†	36 (59)
sGent ≥ 1.5 mg/L – n (%)	8 (100)	13 (93)	25 (41)
Birthweight (kg)			
-median (IQR)*	2.24 (1.82–2.59)‡	2.06 (1.78–2.35)§	1.73 (1.42–2.13)
Gestation (weeks)			
median (IQR)	34.1 (32.9–34.8)§	32.9 (31.8–33.9)	32.6 (31.1–33.4)
Dose of gentamicin			
-median (IQR)	2.24 (2.03–2.55)	2.02 (1.95–2.39)	2.02 (1.98–2.47)
≥ 35 week gestation infants			
Number	29	6	31
sGent < 1.5 mg/L – n (%)	4 (14)†	4 (67)	27 (87)
sGent ≥ 1.5 mg/L – n (%)	25 (86)	2 (33)	4 (13)
Birthweight (kg)			
-median (IQR)*	3.40 (3.11–3.75)§	3.04 (2.15–3.36)	3.06 (2.74–3.36)
Gestation (weeks)			
-median (IQR)	38.7 (37.6–40.0)	38.6 (37.4–39.7)	39.4 (36.0–39.6)
Dose of gentamicin			
-median (IQR)	2.03 (1.99–2.37)	2.02 (1.98–2.03)	2.28 (2.01–2.55)

IQR: interquartile range, sGent: trough serum gentamicin level, ns: not significant.

*: $P < 0.01$ (Fisher's exact test comparing proportions with 24 h dosage interval group).

†: $P < 0.001$ (Fisher's exact test comparing proportions with 24 h dosage interval group).

‡: $P < 0.01$ (Mann Whitney test for difference in medians with 24 h dosage interval group).

§: $P < 0.05$ (Mann Whitney test for difference in medians with 24 h dosage interval group).

costs and nursing time, the postantibiotic effect and decreased postexposure resistance. The postantibiotic effect is that time after administration of an antibiotic when bacterial regrowth does not occur despite the concentration of antibiotic being below the minimum inhibitory concentration.^{6,7,9,10,13,24} It is probably due to disrupted and/or delayed bacterial protein synthesis. The length of the postantibiotic effect is variable and the factors that determine it are unknown. Post-exposure resistance is a phenomenon in which organisms are more likely to develop resistance to an antibiotic if they are continuously exposed to it.²⁴ The effect has been demonstrated in vitro for many antibiotics including aminoglycosides. It can lead to a progressive decrease in antibiotic efficacy and may result in resistant organisms. Once daily dosing minimises contact time with the organism decreasing the incidence of postexposure resistance.

In the light of our results, we cannot continue to use a gentamicin dosage regimen which produces such a high incidence of toxic drug accumulation. Primum non nocere. The use of longer dosage intervals in neonates would be safer with regard to toxic accumulation of the drug. Adoption of longer dosage intervals must be accompanied by monitoring to confirm decreased toxic trough serum gentamicin levels and continued efficacy of gentamicin.

CONCLUSION

A starting gentamicin dosage interval of 12 h in infants of any gestational age leads to most having toxic trough serum gentamicin levels. The same can be said for infants of less than 30 weeks gestational age with a starting dosage interval of 24 h. In infants of 30 weeks gestational age or greater, most have safe non-toxic trough serum gentamicin levels if started on a dosage interval of 24 h.

In our unit, as a result of the above data, we recommend that gentamicin is commenced at a dose of 2.5 mg/kg at a dosage interval of 36 h for infants less than 30 weeks gestation and a dosage interval of 24 h for infants of 30 weeks or more.

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