Paediatric and Perinatal Drug Therapy **Volume 4, Issue 3 2001**

Evaluation of 22 Neonatal Gentamicin Dosage Protocols Using a Bayesian Approach

Roisin Lannigan Medicines Information/Clinical Services Pharmacist
Pharmacy Department, Yorkhill NHS Trust, Dalnair Street, Glasgow G3 8SH, UK, and Department of Pharmaceutical Sciences, University of Strathclyde, 27 Taylor Street, Glasgow G4 0NR, UK. Tel +44 (0) 141 201 0626; Fax +44 (0) 141 201 0835; email druginfo@yorkhill.scot.nhs.uk

Alison Thomson Principal Pharmacist/Honorary Lecturer
Department of Pharmaceutical Sciences, University of Strathclyde, 27 Taylor Street, Glasgow G4 0NR, UK, and Department of Medicine and Therapeutics & Pharmacy Department, Western Infirmary, Glasgow G11 6NT, UK

Abstract

Concerns that concentrations were not optimal led to this study of gentamicin use within a neonatal ICU. Detailed dosage and concentration data were collected prospectively from 100 neonates and analysed using a pharmacokinetic package (OPT®). Individual estimates of gentamicin clearance and volume of distribution were used to predict steady-state peak and trough concentrations using 22 sets of published dosing schedules. The percentages of peaks within 7–12 mg l^{-1}, troughs < 2 mg l^{-1} and peak + trough concentrations within these ranges were then calculated. Eleven of the dosage schedules failed to achieve acceptable peak + trough concentrations in any patient and only four sets of guidelines achieved satisfactory concentrations in more than 50% of patients. The best practical guidelines were 4 mg kg^{-1} every 24–48 hours, depending on gestational age. This regimen was evaluated prospectively in 20 patients and achieved 65% of concentrations within the target ranges.

Key words: Gentamicin – Neonates – Bayesian analysis – Dosage guidelines – Pharmacokinetics

Introduction

Infection is a major cause of morbidity and mortality in the neonatal population. Premature neonates are particularly at risk owing to an immature immune system and frequent exposure to invasive procedures. Aminoglycosides are commonly used for the prophylaxis and treatment of infection in order to ensure cover against Gram-negative bacteria.

Aminoglycoside antibiotics exhibit concentration-dependent efficacy, which means that the rate and extent of bacterial killing depends on the ratio of the peak drug concentration to the minimum inhibitory concentration (MIC) of the infecting organism[1]. Studies *in vitro* have shown that prolonged bacterial exposure to high aminoglycoside concentrations results in downregulation of drug transport into bacterial cells, whereas a drug-free period increases penetration of bacterial cells[1]. Low trough concentrations are also desirable because there is a reduced potential for nephrotoxicity[2]. These pharmacodynamic factors support the use of higher doses of aminoglycosides at longer dosing intervals and have led to the introduction of 'pulsed' doses of 5–7 mg kg^{-1} every 24–48 hours for adults[3].

Compared to adults and children, drug handling in neonates is complicated by immature renal function, a high body water to weight ratio and low plasma protein concentrations[4]. Consequently,

'pulsed' dosing, which would require doses of 10–14 mg kg^{-1} every 48–96 hours to achieve similar concentration–time profiles to those seen in adults, has not yet been applied to neonates. Nevertheless, the trend towards higher doses given less frequently has led to a recognition that traditional neonatal gentamicin dosage guidelines may not even achieve 'conventional' target ranges effectively.

Population pharmacokinetic approaches have been used to study drug handling in neonates because few concentration measurements are required from each patient, and therefore some of the practical and ethical problems associated with conventional pharmacokinetic studies can be avoided[5]. Bayesian programs that combine measured concentrations and information from population studies can then be used to estimate drug clearance and volume of distribution and to design dosage regimens for individual patients. Although originally developed for adults, such programs have been adapted for use in neonates[6].

A number of studies have investigated the clinical characteristics that influence gentamicin handling in neonates. The most frequently cited factors are: gestational age[7–14], postnatal age[7,9,10,12,13,15,16], post-conceptual age[9,13,17,18], serum creatinine concentration[8,10,12,17,19] and birth weight[7–10,13,16–21]. Less common factors include Apgar score at 5 minutes[13,17], patent ductus arteriosus[7,22], mechanical ventilation[17,23], extracorporal membrane oxygenation[7,24], creatinine clearance[16] and indomethacin therapy[7]. These studies have resulted in a range of dosage recommendations, typically 2.5 mg kg^{-1} with dosage intervals of 8–48 hours, depending on various clinical criteria, although more recent studies have investigated higher doses.

Our study was conducted because there was concern that the dosage regimen in use often achieved peak concentrations below the declared target of 7 mg l^{-1} and troughs were sometimes above 2 mg l^{-1}. These problems led to repeated measurement of gentamicin concentrations and frequent dosage alterations. The study was undertaken to audit current practice, determine whether the starting dosage guidelines should be changed and to compare a range of alternative regimens.

Methods

All patients in the neonatal medical intensive care area of Yorkhill NHS Trust (Paediatric Department, Queen Mother's Maternity Hospital) who were prescribed gentamicin during the 12-month study period were eligible for inclusion. Patients were excluded if gentamicin therapy was discontinued before serum concentrations had been measured, if dosing or sampling history were incomplete or if their postnatal age exceeded 35 days. Only the initial course of therapy was included for patients who received two or more courses of gentamicin. Approval for the study was granted by the Trust Ethics Committee.

All data were collected prospectively. Demographic and clinical information were collected from patients' medical and nursing notes, gentamicin dosing data were obtained from drug administration records completed by nursing staff and serum concentration data were obtained from case notes and the hospital information support system.

The usual practice in the paediatric department is to administer gentamicin by bolus intravenous injection. The dosing schedule used in the hospital at the time of the study was 2.5 mg kg^{-1} every 24 hours (≤ 28 weeks' gestation), 18 hours (29–35 weeks' gestation) or 12 hours (≥ 36 weeks' gestation). Term neonates were given 2.5 mg kg^{-1} every 12 hours if < 2 weeks old and 2 mg kg^{-1} every 8 hours if > 2 weeks old[25]. To analyse the adherence of prescribed doses to these recommendations, a range of 2.46 mg kg^{-1} to 2.54 mg kg^{-1} (or 1.96 mg kg^{-1} to 2.04 mg kg^{-1}, as appropriate) were accepted. Steady-state trough concentrations < 2 mg l^{-1} and peak concentrations of 7–12 mg l^{-1} were the target ranges used within the unit.

A computer data file compatible with the Bayesian package OPT®[5] was created for each patient and the relevant dosing and sampling data were entered. Population estimates of clearance and volume of distribution were edited into each file to adapt the program for use in the neonatal population. To investigate the potential for bias arising from the choice of population estimates, a preliminary analysis was conducted that compared four sets of published parameter values[8,9,17,21]. This analysis indicated that individual clearance estimates were essentially identical for three sets of population parameters[8,17,21]. Volume estimates were more variable with a consistent positive bias between population and individual estimates being identified with the parameters of Weber et al.[8] and a small negative bias with parameters identified by Jensen et al.[21]. A smaller bias and better overall precision was found with the parameters described by Thomson et al.[17] and these were chosen for use in the Bayesian analysis.

Individual clearance and volume of distribution estimates were then entered into a Microsoft Excel® spreadsheet together with each patient's weight, serum creatinine concentration, gestational age, postconceptual age and postnatal age. To prevent misinterpretation of results when samples were not taken at steady state or sampling times were not ideal, steady-state peak (one hour post-dose) and trough (end of dosage interval) concentrations were calculated from the individual clearance and volume estimates using the following equation:

$$C_{ss}t = \frac{D}{V}\left(\frac{1}{1-e^{-k\tau}}\right)e^{-kt}$$

where

D = Dose (mg)
V = Volume of distribution (litres)
k = Clearance/volume of distribution (h^{-1})
τ = Dose interval (h)
t = One hour (peak) and τ (trough)

A literature search was undertaken to identify published neonatal gentamicin dosing schedules. Pharmline®, The Cochrane Library on CD-ROM and online PubMed® Medline were searched for relevant references. All manuscripts containing neonatal gentamicin dosing schedules were screened and the bibliography of each paper was searched for relevant references. Several screening criteria were used. The gestational age range had to include premature (> 24 weeks) and term infants. The postnatal age range had to include day 1 of life. Finally, the dosing schedules had to be clearly understood with specific advice on how to calculate the dose and dose interval.

The dosing schedules selected for comparison were entered into the Microsoft Excel® spreadsheet along with relevant patient data and the Bayesian estimates of clearance and volume of distribution. Each dosing schedule was tested by firstly generating doses and dose intervals for each patient using the appropriate patient details. Steady-state peak and trough concentrations for each patient were then calculated as before.

The percentage of predicted peak, trough and combined peak and trough concentrations within the target ranges were determined for the initial dose prescribed for each patient and for each dosing schedule. Ninety-five per cent confidence intervals were calculated for the percentage of patients predicted to achieve peak, trough and combined peak and trough concentrations within target ranges for each dosing schedule, using the following equation:

$$p \pm 1.96 \times \frac{\sqrt{(p(100-p))}}{n}$$

where p is the percentage of patients within the target ranges and n is the number of patients.

The results of this analysis produced recommendations for new gentamicin dosing guidelines and these were introduced into the neonatal unit. Gentamicin dosage histories, measured concentrations and clinical data were collected prospectively for 20 patients following introduction of the new protocol. As samples were typically collected after the first dose, a Bayesian analysis was also performed and steady-state peak and trough concentrations were predicted. The percentages of steady-state concentrations within the target ranges were then calculated.

Results

One hundred neonates, 52 of whom were male, were included in the study. All had received gentamicin for suspected or proven infection or for prophylaxis of infection due to very low birth weight (< 1500 g) or prematurity (< 32 weeks' gestation). Forty-one gentamicin courses prescribed during the study period were excluded from the analysis. In 15 cases, gentamicin was discontinued before serum concentrations were measured, in six cases the patient had already been included in the study, in 17 cases accurate dosing or sampling histories had not been recorded and in three cases the patients were too old.

The clinical and demographic characteristics of the patients at the start of gentamicin therapy are summarised in Table 1. One patient had a serum creatinine concentration of 352 micromol $litre^{-1}$. It was not known that this patient had renal impairment prior to starting gentamicin, although it was found retrospectively that an antenatal scan had shown abnormal kidneys.

Table 1. Clinical and demographic characteristics of the study group at the start of gentamicin therapy

	Median	Range
Postnatal age (days)	1	1–34
Postconceptual age (weeks)	32	25–44
Weight (kg)	1.89	0.59–4.86
Creatinine concentration (µmol/l)	79	25–352

The mean (SD) gentamicin dose was 2.52 (0.10) mg kg^{-1} and individual doses ranged from 2.10 mg kg^{-1} to 2.90 mg kg^{-1}. Examination of the initial dosage regimens revealed that 42% of patients were not prescribed doses according to the hospital formulary[25]. The dose was higher in 22 patients and lower in nine, the interval was shorter in five patients and longer in two and both the dose and the interval were different in four patients.

Figure 1 shows the first set of measured concentrations for each patient. For seven of the patients, the initial dose had been changed by the time the first set of measurements was made. The mean (SD) peak and trough concentrations were 5.7 (1.5) mg l^{-1} and 1.6 (0.7) mg l^{-1}, respectively. Sixteen per cent of patients had gentamicin peaks within the target range and 85% had satisfactory troughs. Only eight patients received doses that achieved both peaks and troughs within the target ranges.

Twenty-seven dosing schedules were obtained from the literature search, of which 18 were accepted for analysis. The reasons for excluding studies were: a narrow gestational age range (n = 6), inadequate details of study methods (n = 1) and inadequate details of the dosing schedule (n = 2). Four additional dosing schedules were included. Two were published in commonly used paediatric formularies[26,27], one was from *Medicines for Children*, a national formulary published by the Royal College of Paediatrics and Child Health[28], and the fourth was the 'in house' formulary[25]. The 22 sets of neonatal gentamicin dosage guidelines that were analysed[7–10,14,15,17,18,25–37] are summarised in Table 2.

All 100 patients were used in the comparison of dosing schedules although four patients were excluded from investigation of the guidelines proposed by Weber et al.[8] and La Reimche et al.[14] because creatinine measurements were not available. In addition, seven patients were not used in the evaluation of the guidelines suggested by Izquierdo et al.[9] because negative values for the dose were obtained.

Although trough concentrations were generally satisfactory, most sets of dosage guidelines produced peaks that were too low. The 95% confidence intervals for the percentage of combined peak and trough concentrations within the target ranges are illustrated in Figure 2. Twelve sets of dosage guidelines, one of which was the hospital formulary[25], did not achieve target concentrations in any patient (0% within ranges); therefore confidence intervals could not be determined. Although no statistically significant differences could be detected among the four best dosing schedules, the guidelines proposed by de Hoog et al.[7] and Weber et al.[8] achieved the highest percentage of both peak and troughs within the target range at 72% and 75%, respectively. The guidelines produced by Weber et al.[8] involved relatively complex calculations, whereas those of de Hoog et al.[7] comprised a dose of 4 mg kg^{-1} every 24, 36 or 48 hours, according to gestational age. Since these recommendations were easier to use, they were introduced into the neonatal unit (Table 3).

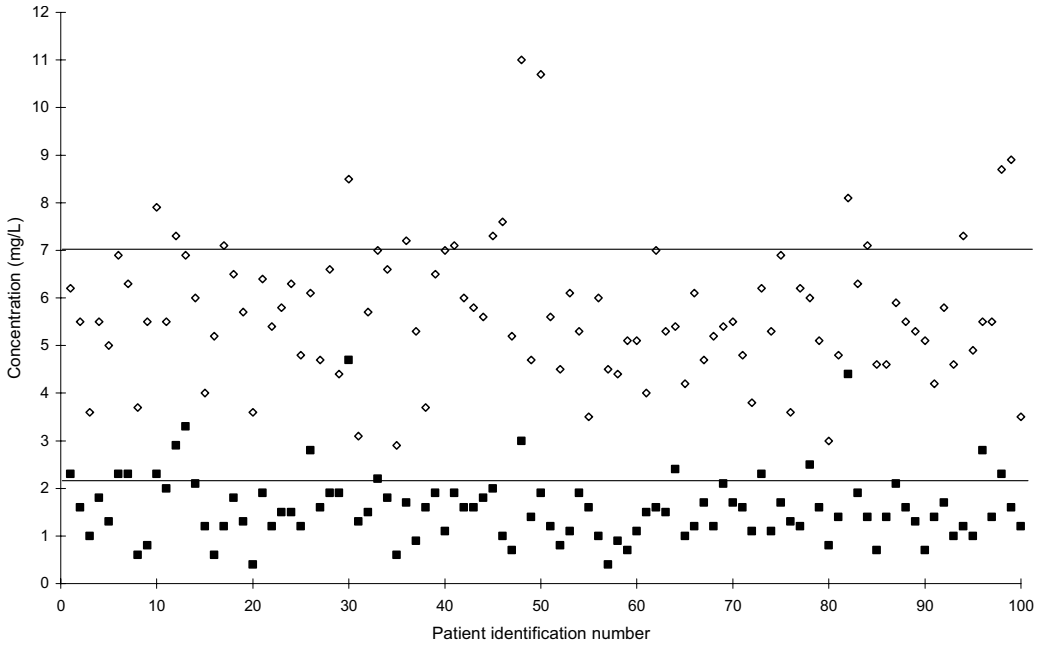

Figure 1. Measured gentamicin peak and trough concentrations in 100 neonates. Peak concentration target is 7 mg l^{-1} and trough concentration target is < 2 mg l^{-1}. Key: ◇ peak, ■ trough

Table 2. Gentamicin dosing schedules examined in the study

Reference	No. of patients	Dose (mg kg^{-1})	Interval (hours)	Dose interval depends on
7	N/A	4	24, 36, 48	Gestational age
17	113	LD then 2.5–3.5	12, 18, 24	Postconceptual age, 5 min APGAR score
8	469	LD = Target conc. × V then LD/(1/(1–$2^{-\tau/t_{½}}$))	18.4 × (36/GAG)$^{1.2}$ × (Creat/96)$^{0.3}$	Equation based on gestational age, creatinine concentration
9	97	Equation based on gestational age, postconceptual age and weight	18, 24	Gestational age
10	165	Table based on gestational age, postnatal age and weight *or* Equation based on postnatal age, and weight	12, 18, 24 0.67 + (GAG × 0.03) + (PNA × 0.03) – (Creat/2) or 0.82 + (PNA × 0.02) + (Wt × 0.3)	Creatinine concentration *or* Equations based on gestational age, postnatal age and creatinine or weight
29	33	5	24	None
14	22	2.5	8, 12, 18, 24, 36, 48	Gestational age, postnatal age, creatinine concentration
15	68	2.5–3	18, 24	Postconceptual age
18	313	2.5	12, 18, 24	Weight, postnatal age
30	86	2.5	12, 16, 24	Postconceptual age
31	46	3.5	24	None
32	28	2.5	12, 18	Gestational age
33	170	2.5	18, 24	Gestational age
34	50	LD 4 then 2.5	12, 18, 24	Gestational age
35	13	LD 4 then 2.5	12, 18	Gestational age
36	18	LD 4 then 2.5	12, 18, 24	Gestational age, weight
37	74	2.5	12, 18, 24	Weight
25	N/A	2–2.5	8, 12, 18, 24	Gestational age, postnatal age
26	N/A	3	12, 18	Weight
27	N/A	2.5–3.5	8, 12, 18, 24, 36	Gestational age, postnatal age
28	N/A	LD 4 (some patients) then 3–4	8, 12, 18, 24, 36	Gestational age, postnatal age

Key: N/A = Not applicable, GAG = Gestational age, LD = Loading dose, PNA = Postnatal age, V = Volume of distribution, τ = Dosage interval, $t_{½}$ = Half-life

Patient demographic, clinical and gentamicin dosing and sampling data were collected for 20 patients (12 male) prescribed gentamicin according to the new dosing schedule. Patient characteristics were similar to those of the initial study, with median values of gestational age of 33 weeks, postnatal age 1 day, weight 2.16 kg and creatinine concentration 83 micromol litre^{-1}. Although all the doses were calculated correctly, an initial dosage interval of 24 hours was incorrectly prescribed for seven patients, who should have had longer intervals. Thirteen patients (65%) achieved the target peak and trough concentrations, two had troughs that were too high and four had peaks that were too low. In one case, the high trough was due to an incorrect dosage interval. The mean peak and trough concentrations were 7.7 mg l^{-1} and 1.2 mg l^{-1} overall and 7.5 mg l^{-1} and 1.1 mg l^{-1} for patients who received the correct dosage regimen.

Table 3. Recommended dosage regimen[7]

	Dosing interval (h)	Gestational age (weeks)
Gentamicin 4 mg/kg	48	< 32
	36	32–37
	24	≥ 37

Discussion

This study was undertaken owing to concerns that target concentrations of the gentamicin were not

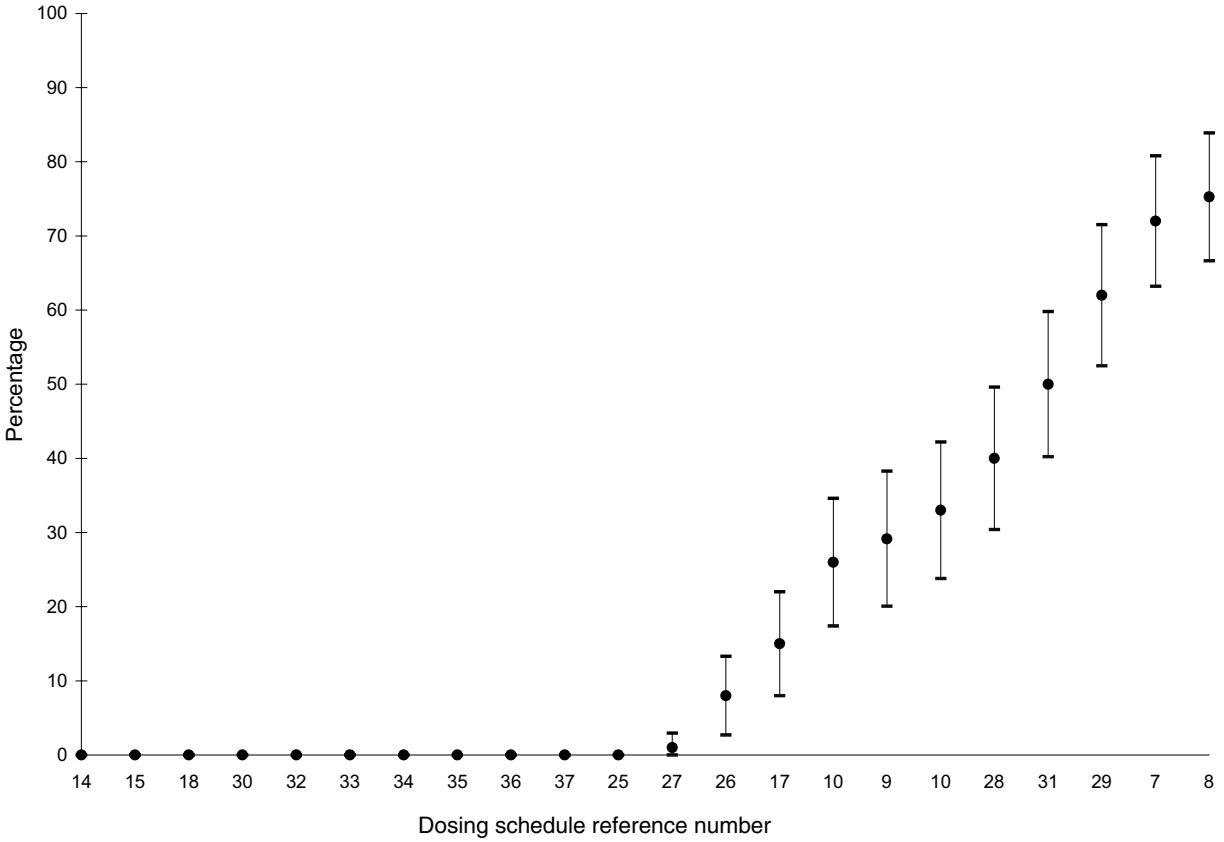

Figure 2. 95% confidence intervals for the percentage of combined peak and trough concentrations within target ranges versus dosing schedule reference number

being achieved efficiently within the neonatal unit. Data collected prospectively from 100 neonates confirmed that current dosage recommendations were inappropriate and were used to evaluate 21 other sets of dosage guidelines.

To allow comparison of dosage regimens and to avoid problems owing to non-steady-state data or suboptimal sampling times, dosage schedules were evaluated and compared using predicted steady-state concentrations. These were calculated using estimates of drug clearance and volume of distribution obtained by Bayesian analysis. To avoid bias due to the population estimates, individual clearance and volume estimates arising from four population parameter sets were compared. Close agreement was found in the individual parameter estimates, which suggested that the population model would not cause bias in the results. As the population estimates of Thomson et al[17]. appeared to have some small advantages over the other estimates, they were used for the main study.

An audit of measured concentrations and predicted steady-state concentrations confirmed that the current dosage guidelines were unsatisfactory. Although 58% of patients received doses that corresponded to the formulary, only 9% of patients would have achieved acceptable steady-state peak and trough concentrations. Had adherence to the formulary been 100%, none of the patients would have had satisfactory concentrations. The mean peak of 5.7 mg l^{-1} and trough of 1.6 mg l^{-1} suggested that the doses were too low and the intervals too short.

Many studies have investigated gentamicin dosing and monitoring in the neonatal population and there is a need for consensus on the most appropriate dosing schedule. However, since a large, randomised trial is not feasible, other methods of comparing dosing schedules must be employed. The present study used individual clearance and volume estimates from 100 neonates to predict the peak and trough concentrations that would be attained using 22 published dosing schedules.

Half the dosing schedules failed to produce satisfactory peak and trough concentrations in any patient. The doses used in these studies were typically 2.5 mg kg^{-1} with intervals adjusted according to gestational age, weight, postconceptual age, postnatal age, or serum creatinine. The main problem was low peaks,

although some high troughs were observed. Since many of these dosage regimens were aiming for peaks of 4–10 mg l^{-1}, it is not surprising that they generally produced peaks below 7 mg l^{-1}. Some authors recommended a loading dose, which would have achieved a higher first peak but no improvement in steady-state concentrations.

Four dosing schedules achieved satisfactory concentrations in 15–33% of patients[10,11,18]. The guidelines produced by Thomson et al.[17] achieved a higher percentage of satisfactory peaks than other regimens, but too many troughs were above 2 mg l^{-1}. The dosing schedule suggested by Izquierdo et al.[9] also performed poorly and was difficult to use. Results were particularly poor for very premature babies and in some cases negative doses with intervals of < 1 hour were generated. This probably occurred because neonates of < 28 weeks' gestation had not been included in the original study.

Faura et al.[10] produced two dosing schedules. One was a table based on serum creatinine and the other was a set of formulae that used gestational age, creatinine and postnatal age to determine the dose and number of doses per day. The creatinine reference ranges were not comprehensive and, for some patients, a subjective decision was required as to which range to use. The formulae for number of doses per day led to impractical intervals that required adjustment. The results produced by the two dosing schedules were similar, with 33% acceptable using the table and 26% using the formulae.

The gentamicin dosing schedules published in three nationally recognised paediatric formularies were also analysed[26–28]. Both the *Alder Hey Book of Children's Doses*[26] and the *Guy's, St Thomas' and Lewisham Paediatric Formulary*[27] performed poorly with only 8% and 1% of patients achieving satisfactory concentrations, respectively. This was partly due to the choice of 8-, 12- and 18-hour intervals[26], which were too short in many cases. *Medicines for Children*[28] is the first national paediatric formulary to be published in Great Britain and recommended two neonatal gentamicin schedules. However, as one is only suitable for neonates of > 32 weeks' gestation, it was not included in the study. The other used doses of 3–4 mg kg^{-1} every 8–36 hours according to weight, gestational, post-natal and post-conceptual age. This resulted in eight combinations of dose and interval and 40% of patients were predicted to have acceptable concentrations.

Four dosing schedules produced satisfactory concentrations in more than 50% of patients and were considered for prospective use. Daily doses of 3.5 mg kg^{-1} were recommended by Capers et al.[31], whereas de Alba Romero et al.[29] suggested 5 mg kg^{-1}. The higher dose produced a better chance of achieving an acceptable peak (87% compared to 63%) but was more likely to produce high troughs. Weber et al.[8] suggested determining a loading dose based on a target peak and an estimate of volume of distribution, then calculating the maintenance dose from the loading dose, half-life and dosage interval. However, each component of the dosing schedule was derived from relatively complex equations. Awkward intervals, such as 15.2 hours, had to be adjusted to the nearest practical interval. Both the loading and maintenance doses were higher than those produced by other dosing schedules, which reflected a high population estimate for volume. Although these guidelines achieved 95% of peak concentrations in the target range, several trough concentrations were high. Nevertheless, this approach produced the best results overall with 75% of patients achieving acceptable concentrations. However, the calculations were difficult to perform and the awkward dosage intervals increased the potential for error in a clinical environment.

A review paper[7] examined the use of aminoglycosides in newborn babies and recommended a dose of 4 mg kg^{-1} at intervals of 24–48 hours according to gestational age (Table 3). It was simple to use and achieved target peaks in 74% of patients, acceptable troughs in 98% and a satisfactory combination in 72%. Although the guidelines were applied to gentamicin in this current study, they were originally developed for tobramycin[38].

Peak gentamicin concentrations of 7 mg l^{-1} [39] and 8 mg l^{-1} [40] have been associated with a better outcome and this led to the decision to use 7 mg l^{-1} at the target peak concentration. The best dosage regimens identified in the present study used higher doses at less frequent intervals. However, although the dosage intervals were 24 hours or more, these regimens achieved peak concentrations towards the top of the 'conventional' target range. Trough concentrations were typically below 2 mg l^{-1} and often below 1 mg l^{-1}. Thus, these neonatal dosage regimens are not equivalent to the 'once daily', or 'pulsed' approach that is being advocated for older children and adults. This approach aims to achieve peaks of around 20 mg l^{-1} and troughs below 0.5 mg l^{-1} for at least four hours[41]. The reason for using high doses every 24–48 hours in neonates, particularly premature neonates, is to account for their poor renal function and relatively high volume of distribution.

A study similar to the present one was undertaken by Murphy et al.[42] who examined 15 dosing schedules, of which six had previously been published. The authors tested doses of 2.1–3.5 mg kg^{-1} with intervals of 16–36 hours, depending on gestational age, postconceptual age, postnatal age and urine output. Their best dose was 2.7 mg kg^{-1} every 24 hours, which resulted in 85% of peak and trough concentrations in the ranges 5–10 mg l^{-1} and < 2 mg l^{-1}, respectively. However, their peak concentrations averaged 6.5 mg l^{-1}, which is lower than the target used in the present study.

Introduction of the new dosage guidelines led to a much higher percentage of patients attaining target peak and trough concentrations. Adherence to the new guidelines was reasonable, although the initial interval was incorrectly set at 24 hours rather than 36 hours or 48 hours for seven patients. This indicated that further education is required about the need to increase the dose interval for very premature neonates. Seventy-five per cent of patients were predicted to have steady-state peak and trough concentrations within target ranges and the measured concentrations, typically sampled after the first dose, achieved acceptable concentrations in 69% of patients.

In conclusion, this study has confirmed that the gentamicin dosage guidelines used within the neonatal unit were unable to achieve the target concentration range. Comparison of a wide range of dosing schedules suggested that 4 mg kg^{-1} with an interval of 24–48 hours, according to gestational age, was easy to use and likely to achieve acceptable steady-state concentrations in 72% of patients. The new guidelines were easier to use and demonstrated an immediate improvement in therapy, although further reinforcement of the need to extend the interval in premature neonates is necessary.

Acknowledgements

The authors would like to thank the staff of the Neonatal Unit, Queen Mother's Hospital, Glasgow for their help with this project and Dr Lilian Murray for statistical advice.

References

1. Rotschafer JC, Zabinski RA, Walker KJ. Pharmacodynamic factors of antibiotic efficacy. Pharmacother 1992;12:64S-70S
2. Barclay ML, Begg EJ. Aminoglycoside toxicity and relation to dose regimen. Adverse Drug React Toxicol Rev 1994;13:207-234
3. Begg EJ, Barclay ML. Aminoglycosides – 50 years on. Br J Clin Pharmacol 1995;39:597-603
4. Speidel B, Fleming P, Henderson J, Leaf A, Marlow N, Russell G, Dunn P (eds). A Neonatal Vade Mecum. Arnold, London, 3rd edn, 1998
5. Tett SE, Holford NHG, McLachlan AJ. Population pharmacokinetics and pharmacodynamics: an underutilized resource. Drug Info J 1998;32:693-710
6. Lui K, Bryson SM, Irwin DB, Costello S. Evaluation of Bayesian forecasting for individualized gentamicin dosage in infants weighing 1000 g or less. Am J Dis Child 1991;145:463-7
7. de Hoog M, Mouton JW, van den Anker JN. The use of aminoglycosides in newborn infants. Paediatr Perinat Drug Ther 1998;2:48-56
8. Weber W, Kewitz G, Rost KL, Looby M, Nitz M, Harnisch L. Population kinetics of gentamicin in neonates. Eur J Clin Pharmacol 1993;44:S23-S25
9. Izquierdo M, Lanao JM, Cervero L, Jimenez NV, Dominguez-Gil A. Population pharmacokinetics of gentamicin in premature infants. Ther Drug Monit 1992;14:177-83
10. Faura CC, Feret MA, Horga JF. Monitoring serum levels of gentamicin to develop a new regimen for gentamicin dosage in newborns. Ther Drug Monit 1991;13:268-76
11. Hindmarsh KW, Nation RL, Williams GL, John E, French JN. Pharmacokinetics of gentamicin in very low birth weight preterm infants. Eur J Clin Pharmacol 1983 24:649-53
12. Mulhall A, De Louvois J, Hurley R. Incidence of potentially toxic concentrations of gentamicin in the neonate. Arch Dis Child 1983;58:897-900
13. Murphy JE, Austin ML, Frye RF. Evaluation of gentamicin pharmacokinetics and dosing protocols in 195 neonates. Am J Health Syst Pharm 1998;55:2280-88
14. Reimche LD, Rooney ME, Hindmarsh KW, Gorecki DKJ, Remillard AJ, Sankaran K. An evaluation of gentamicin dosing according to renal function in neonates with suspected sepsis. Am J Perinatol 1987;4:262-5
15. Lopez-Samblas AM, Torres CL, Wang H, Feuer WJ, Goldberg RN. Effectiveness of a gentamicin dosing protocol based on postconceptual age: comparison to published neonatal guidelines. Ann Pharmacother 1992;26:534-8
16. Rodvold KA, Gentry CA, Plank GS, Kraus DM, Nickel E, Gross JR. Prediction of gentamicin concentrations in neonates and infants using a Bayesian pharmacokinetic model. Dev Pharmacol Ther 1993;20:211-9
17. Thomson AH, Way S, Bryson SM, McGovern EM, Kelman A. Population pharmacokinetics of gentamicin in neonates. Dev Pharmacol Ther 1988;11:173-9
18. Kozyrskyj A, Masih M, Hahn J, Ho C, Wong M, Sirdevan M. New neonatal gentamicin dosing guidelines: results of an evaluation of serum concentrations. Can J Hosp Pharm 1994;47:262-7
19. Keyes PS, Johnson CK, Rawlins TD. Predictors of trough serum gentamicin concentrations in neonates. Am J Dis Child 1989;143:1419-23
20. Kelman AW, Thomson AH, Whiting B et al. Estimation of gentamicin clearance and volume of distribution in neonates and young children. Br J Clin Pharmacol 1984;18:685-92
21. Jensen PD, Edgren BE, Brundage RC. Population pharmacokinetics of gentamicin in neonates using a nonlinear mixed-effects model. Pharmacother 1992;12:178-82
22. Williams BS, Ransom JL, Gal P, Carlos RQ, Smith

M, Schall SA. Gentamicin pharmacokinetics in neonates with patent ductus arteriosus. Crit Care Med 1997;25:273-5
23. Triginer C, Izquierdo I, Fernandez R et al. Changes in gentamicin pharmacokinetic profiles induced by mechanical ventilation. Eur J Clin Pharmacol 1991;40:297-302
24. Cohen P, Collart L, Prober CG, Fischer AF, Blaschke TF. Gentamicin pharmacokinetics in neonates undergoing extracorporal membrane oxygenation. Pediatr Infect Dis J 1990;9:562-6
25. Paediatric and Neonatal Formulary. Royal Hospital for Sick Children, Yorkhill NHS Trust, Glasgow, 1st edn, 1998
26. Alder Hey Book of Children's Doses. Royal Liverpool Children's NHS Trust, Liverpool, 6th edn (with amendments), 1996
27. Guy's, St Thomas' and Lewisham Hospitals Paediatric Formulary. Guy's and St Thomas' Hospitals Trust, London, 5th edn, 1999
28. Medicines for Children. RCPCH Publications, London, 1st edn, 1999
29. de Alba Romero C, Castillo EG, Secades CM, Lopez JR, Lopez LA, Valiente PS. Once daily gentamicin dosing in neonates. Pediatr Infect Dis J 1998;17:1169-71
30. Bloome MR, Warren AJ, Ringer L, Walker PC. Evaluation of an empirical dosing schedule for gentamicin in neonates. Drug Intell Clin Pharm 1988;22:618-22
31. Capers CC, Gregory DF, Herzog CC, Walsh W, Watson B. Optimal gentamicin dosing in neonates. Ann Pharmacother 1995;29:430-31
32. Szefler SJ, Wynn RJ, Clarke DF, Buckwald S, Shen D, Schentag JJ. Relationship of gentamicin serum concentrations to gestational age in preterm and term neonates. J Pediatr 1980;97:312-5
33. Davies MW, Cartwright DW. Gentamicin dosage intervals in neonates: longer dosage interval – less toxicity. J Paediatr Child Health 1998;34:577-80
34. Watterberg KL, Kelly W, Angelus P, Backstrom C. The need for a loading dose of gentamicin in neonates. Ther Drug Monit 1989;11:16-20
35. Semchuk W, Shevchuk YM, Sankaran K, Wallace SM. Prospective, randomized, controlled evaluation of a gentamicin loading dose in neonates. Biol Neonate 1995;67:13-20
36. Isemann BT, Kotagal UR, Mashni SM, Luckhaupt EJ, Johnson CJ. Optimal gentamicin therapy in preterm neonates includes loading doses and early monitoring. Ther Drug Monit 1996;18:549-55
37. Charlton CK, Needelman H, Thomas RW, Kortas K. Gentamicin dosage recommendations for neonates based on half-life predictions from birthweight. Am J Perinatol 1986;3:28-32
38. de Hoog M, Schoemaker RC, Mouton JW, van den Anker JN. Tobramycin population pharmacokinetics in neonates. Clin Pharmacol Ther 1997;62:392-9
39. Moore RD, Smith CR, Lietman PS. Association of aminoglycoside plasma levels with therapeutic outcome in Gram-negative pneumonia. Am J Med 1984;77:657-62
40. Noone P, Parsons TMC, Pattison JR, Slack RCB, Garfield-Davis D, Hughes K. Experience in monitoring gentamicin therapy during treatment of serious Gram-negative sepsis. BMJ 1974;1:477-81
41. Nicolau DP, Freeman CD, Belliveau PB, Nightingale CH, Ross JW, Quintiliani R. Experience with a once-daily aminoglycoside program administered to 2,184 adult patients. Antimicrob Agents Chemother 1995;39:650-55
42. Murphy JE, Austin ML, Frye RF. Evaluation of gentamicin pharmacokinetics and dosing protocols in 195 neonates. Am J Health Syst Pharm 1998;55:2280-8