Variability in gentamicin use in neonates in England

Following a large number of patient safety incidents relating to the use of intravenous gentamicin in neonates, a national telephone surgery was conducted on the use of gentamicin in neonatal units in England for the treatment of early or late onset infection, as part of the National Patient Safety Agency project. Prescribing regimes and gentamicin monitoring practices were surveyed.

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Key points

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1. Gentamicin administration was responsible for 15% of all neonatal medication incidents reported to the National Patient Safety Agency from April 2008 to March 2009.
2. Gentamicin prescribing and serum drug concentration monitoring regimes were found to vary considerably in neonatal units throughout England.
3. More studies are needed to develop national guidance on appropriate gentamicin dose and interval regimes for very preterm infants.

Gentamicin is the aminoglycoside of choice in the UK[1] and is widely used in the treatment of neonatal infection. From 1 April 2008 to 31 March 2009, the National Patient Safety Agency (NPSA) captured 507 patient safety incidents relating to the use of IV gentamicin – 15% of all reported neonatal medication incidents. In February 2010 the NPSA released a Patient Safety Alert on 'The Safer Use of Intravenous Gentamicin for Neonates' which applies to all National Health Service organisations that provide neonatal services[2]. A telephone survey on the use of gentamicin in neonatal units in England was undertaken as part of the NPSA project and is reported below.

Methods

All hospitals in England with neonatal units were contacted via telephone by a specialist registrar and clinical educator over one week in 2008. A standardised questionnaire (**FIGURE 1**) was used to establish the first line antibiotics used for early and late onset sepsis, and, if gentamicin was used, the procedures for and the dosing of gentamicin were examined. The respondents were either the neonatal registrar or neonatal nurse in charge on the unit.

Results

All 180 units contacted responded to the survey (100% response rate). One hundred and sixty units (89%) used gentamicin whereas 20 units (11%) did not use gentamicin at all. Of the 160 units, 139 units (87%) used gentamicin (with another antibiotic) in early onset sepsis and 127 units (79%) used gentamicin (with another antibiotic) in late onset sepsis.

Of the 160 units that used gentamicin, 50 units (31%) had a single regime with the same dose and interval for all gestations and ages of babies, 98 units (61%) had two regimes (different dose or interval) and three units had multiple regimes (two with six and one with eight). The extended interval dose regime (EIDR) was more commonly used than a multiple daily dose regime (MDDR). The dose and frequency varied greatly as illustrated in **TABLE 1**.

There was also variation in practice in undertaking trough and/or peak serum drug concentration (SDC) monitoring and in assigning responsibility for obtaining the results from the laboratory. Of the 160

Gestation	4mg/kg/ dose	5mg/kg/ dose	Other doses	36 hourly	24 hourly	Other intervals
<28 weeks	97 (61%)	40 (25%)	23 (14%)	78 (49%)	71 (44%)	11 (7%)
28-31 weeks	86 (54%)	40 (25%)	34 (21%)	66 (41%)	53 (33%)	41 (26%)
32-36 weeks	82 (51%)	46 (29%)	32 (20%)	11 (7%)	139 (87%)	10 (6%)
≥37 weeks	87 (54%)	51 (32%)	22 (14%)	4 (2%)	147 (92%)	9 (6%)

TABLE 1 Number of neonatal units in England (% of total 160 units) showing gentamicin dose and interval variations used. Other doses = 2.5, 3.0, 3.5 and 4.5mg/kg/dose. Other intervals = 12, 18 and 48 hourly.

Gentamicin questionnaire

Name of the unit _____

Name and grade of the respondent _____

1) What is/are your first line antibiotic(s) for early onset sepsis (<48 hours old)

Benzyl penicillin	Gentamicin	Cefotaxime	Ampicillin	Flucloxacillin
Amikacin				

2) What is/are your first line antibiotic(s) for late onset sepsis (>48 hours old)

Benzyl penicillin	Gentamicin	Cefotaxime	Ampicillin	Flucloxacillin
Teicoplanin	Tazocin	Augmentin	Piperacillin	Meropenem
Vancomycin	Amikacin			

3) If the answers for questions 1 and 2 do not include gentamicin, do you use gentamicin on your unit? **YES/NO**

If the answer to question 3 is NO the questionnaire is complete, otherwise continue with the questionnaire

4) What gentamicin dose do you use? Does it vary due to gestation and age?

Category a) GA/age mg/kg Category b) GA/age mg/kg
Category c) GA/age mg/kg Category d) GA/age mg/kg
Category e) GA/age mg/kg Category f) GA/age mg/kg

5) What gentamicin interval do you use? Does it vary based on gestation and age?

Category a) 24hr 36hr 48hr __hr Category b) 24hr 36hr 48hr __hr
Category c) 24hr 36hr 48hr __hr Category d) 24hr 36hr 48hr __hr
Category e) 24hr 36hr 48hr __hr Category f) 24hr 36hr 48hr __hr

6) Do you have a special programme to prescribe gentamicin? (Such as a dose calculator software or electronic prescribing) **YES/NO**

If **YES** – describe the special programme

7) When are gentamicin levels measured?

Pre second dose Post second dose Pre third dose Post third dose

8) Who is responsible for chasing gentamicin levels?

Doctors / Nurses / Lab

9) Do you have a pharmacist visiting your unit to check prescriptions? **YES/NO**

10) Do you have a competency assessment in place for junior doctors during the induction period before they undertake drug prescription? **YES/NO**

FIGURE 1

	Gestation weeks	Dose	Frequency
Extended interval dose regime (EIDR)	<32	4-5 mg/kg	36 hourly
	≥32	4-5 mg/kg	24 hourly
Multiple daily dose regime (MDDR)	<29	2.5 mg/kg	24 hourly
	29-35	2.5 mg/kg	18 hourly
	>35	2.5 mg/kg	12 hourly

TABLE 2 Five dosing regimes for gentamicin recommended by the BNFC.

units using gentamicin, 112 units (70%) only do trough SDC, 38 units (24%) do trough and peak SDC and 10 units (6%) only do peak SDC. One hundred units (62%) do SDC after the third dose and 49 units (31%) do SDC with the second dose.

Almost all units (147 units – 92%) had a visiting paediatric pharmacist to check the prescribing chart. Only 38 units (24%) had formal arrangements to check a doctor's competency in drug prescribing.

Discussion

The survey highlighted significant variations in prescribing regimes, undertaking SDC monitoring and a doctor's competency assessment in drug prescribing. These issues were borne out by data from the NPSA's National Reporting and Learning System. The NPSA Alert provides a national care bundle approach to the prescription, administration and monitoring of gentamicin and aims to reduce error and improve the safety associated with its use[2]. The care bundle's key elements include using the 24 hour clock, ensuring no interruption during administration, using a double checking prompt and giving the prescribed dose within one hour of the prescribed time.

The survey did not investigate the link between trough and peak SDC with different dosing regimes. Adverse events associated with IV gentamicin include ototoxicity and nephrotoxicity relating to high trough SDC, reduced efficiency associated with lower peak SDC and ineffectiveness of the drug related to the late administration of doses[3-5]. It is therefore important to use gentamicin effectively and safely within an accurate timing regime with close monitoring of SDC. Hearing loss in neonates may not be detected while they are on the neonatal unit therefore evidence of harm due to gentamicin or any other cause may not be apparent until sometime after discharge. The discovery of 12S rRNA mutations related to aminoglycoside ototoxicity may predict which individuals are at risk, resulting in improvement in the safety of gentamicin and decreasing the incidence of hearing loss [6].

The British National Formulary for Children (BNFC) currently details five dosing regimes for the administration of gentamicin for neonates (two EIDR and three MDDR)[1] as shown in **TABLE 2**. There is insufficient evidence from the currently available RCTs to conclude whether EIDR or MDDR is superior in treating proven neonatal sepsis[7]. However data suggest that the pharmacokinetic properties of EIDR are superior to MDDR in that EIDR achieves higher peak SDC while avoiding toxic trough SDC. A meta-analysis also showed EIDR in neonates is safe and effective, with a reduced risk of SDC outside the therapeutic range[8]. Furthermore EIDR requires less pharmacy preparation time and less administration time and is more cost effective than MDDR[9]. The question remains whether a 24 hourly interval is the most appropriate for all neonates and which dose should be used[10,11]. Evidence is accumulating that EIDR in 36[10-12] to 48[13] hour intervals may be more suitable for very preterm infants less than 32 weeks' gestation.

Conclusions

The results of the survey of 180 neonatal units in England showed that gentamicin prescribing and monitoring regimes varied considerably and not all units complied with the BNFC's recommendations. The reason for this is unclear. The implementation of the NPSA care bundle and details of gentamicin errors should be reviewed within the governance structure of neonatal units. More studies are needed to decide the appropriate dose and interval regimes for very preterm infants. A standardised national guidance on dose regime together with SDC monitoring may improve the safety issue.

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