Variation in gentamicin and vancomycin dosage and monitoring in UK neonatal units

S. Kadambari1*, P. T. Heath1, M. Sharland1, S. Lewis2, A. Nichols3 and M. A. Turner4

1Paediatric Infectious Disease Unit, St George’s University of London, Cranmer Terrace, London SW17 0RE, UK; 2National Perinatal Epidemiology Unit (NPEU), Oxford OX3 7LF, UK; 3Croydon University Hospital, 530 London Road, Thornton Heath, Surrey CR7 7YE, UK; 4Liverpool Women’s Hospital, Crown Street, Liverpool, Merseyside L8 7SS, UK

*Corresponding author. Tel: +44-(0)208-725-5382; Fax: +44-(0)208-725-0716; E-mail: skadamba@sgul.ac.uk

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Background: Gentamicin and vancomycin are commonly used in neonatal units for the treatment of life-threatening infections. This study aimed to describe the dosage regimen and the approach to therapeutic drug monitoring (TDM) for both antibiotics in units that participate in a UK neonatal network.

Methods: Questionnaires were sent to all units across the Extended Neonatal Network, requesting details of each unit’s dosing regimen and TDM practice.

Results: A total of 43 (of 114) units replied to the gentamicin questionnaire and 29 to the vancomycin questionnaire. Ten different gentamicin dosing regimens were used, depending on gestational age and weight. Most units (79%) followed British National Formulary for Children dosing guidance regarding vancomycin, but there were nine variations in TDM practice.

Conclusions: There is significant variation in gentamicin and vancomycin dosing regimens and TDM guidance across a UK network of neonatal units. The development of standardized, evidence-based protocols should be prioritized.

Keywords: antibiotic policy, antibiotics, aminoglycosides, drug monitoring, neonatal infections

Introduction

Previous work has shown that there is considerable variation between UK neonatal units with regard to antibiotic choice.1 We speculated that there is also variation in the dosage regimen and therapeutic drug monitoring (TDM) between neonatal units. We selected two medications commonly used in neonates as case studies; gentamicin and vancomycin.

Gentamicin

Recent studies conducted by the National Patient Safety Agency (NPSA) and the Medicines for Children Research Network (MCRN) have shown that gentamicin is the most widely used antibiotic for treating life-threatening bacterial infections in neonates in the UK (Review of Patient Safety for Children and Young People, June 2009).2

Gentamicin has a narrow therapeutic range, which necessitates tight TDM to minimize adverse effects. There is a significant body of research regarding the pharmacokinetics of gentamicin in neonates.3 The British National Formulary for Children (BNFc) provides national guidance on medicines for children.4 It offers two different dosing regimens for gentamicin in neonates.

Vancomycin

Vancomycin is the first-choice antibiotic for the treatment of coagulase-negative staphylococci, which account for over half of all nosocomial infections on UK neonatal units.5

There is an extensive body of research regarding the pharmacokinetics of vancomycin and TDM in neonates.6 Various studies have shown that a vancomycin AUC0–24/MIC index best predicts treatment outcomes for invasive methicillin-resistant Staphylococcus aureus (MRSA) infection in adults.7,8 Some have suggested that a continuous infusion may be preferable to intermittent infusion. In adults, an American consensus statement concluded that there was no advantage to continuous infusion.9 There are no comparative trials in neonates. Appropriate TDM is essential in order to maximize clinical response, but the national guidance (the BNFc) makes no specific recommendations regarding TDM in neonates receiving vancomycin.

Methods

A standardized questionnaire was designed, piloted and sent by e-mail to named representatives of the 114 participating units in the Extended Neonatal Network (ENN).
The gentamicin questionnaire (sent in August 2009) asked the following questions:

(i) What is your current gentamicin dosing regimen for terms and pre-terms?
(ii) Is the dose adjusted by post-natal age?
(iii) At what point during the treatment course do you take levels?

The vancomycin questionnaire (sent in May 2010) asked the following questions:

(i) What is your current vancomycin dosing regimen for terms and pre-terms?
(ii) Does your unit use continuous or intermittent infusion, or both?
(iii) At what point during the treatment course do you take levels?

Results

Gentamicin

Forty-three units across the ENN responded to the gentamicin questionnaire, revealing 24 different combinations of dose, timing of dose and timing of monitoring. Figure 1 demonstrates significant discrepancies in dosing, with one unit even using a 2.5 mg/kg regimen across all gestational ages. The dosing interval also varied markedly, e.g. at 28 weeks of gestation, 27 units (63%) used a 36 hourly regimen, 12 units (28%) used a 24 hourly regimen and the remaining units used 12 hourly, 18 hourly or 48 hourly regimens.

Ten units (23%) obtained blood levels before the second dose, 17 (40%) before the third dose, 4 (9%) before the second or third dose and 12 units had no written monitoring guidance. Three units took a trough level after the second dose if the baby was born before 32 weeks of gestation and after the third dose if the baby was born at 32 weeks or later. Twenty-two units gave information about their target trough concentrations for gentamicin. Six units aimed for $1 \text{ mg/L}$ and 16 units aimed for $2 \text{ mg/L}$. Fifteen units used dosage intervals of $\geq 24 \text{ h}$, with a trough range of $< 2 \text{ mg/L}$. Nine units took peak levels; one of these did not take trough levels. Target peak levels were 5–10 mg/L in two units and 5–8 mg/L in another; the remainder did not report their target peak levels.

Vancomycin

Twenty-nine units across the ENN responded to the vancomycin questionnaire, revealing 17 different combinations of dose, timing of dose and timing of monitoring.

One unit used continuous infusion. Twenty-three units (79%) followed the BNFc regimen. There was significant variation in regimen amongst other units. For instance, one unit used a 10 mg/kg three times daily regimen for term neonates, while another unit employed a 15 mg/kg three times daily course.

TDM was even more inconsistent. Twenty-one units (72%) took trough samples only, 7 units (24%) took both trough and peak samples, and 1 unit took only peak samples. Samples were also taken at different points during treatment. Eighteen units (62%) took trough levels before the third dose. The remaining 11 units monitored levels before and after the third dose, before and after the fourth dose, before the second or the fourth dose, or just after the third dose.

Discussion

Our surveys demonstrate considerable variation amongst gentamicin and vancomycin dosage regimens and monitoring protocols among neonatal units in the UK, with no clear justification. Clearly, not all units can be using the appropriate regimen or TDM. This implies that either toxic or subtherapeutic treatment courses may be a common problem.

A review of neonatal medication incidents, reported to the Reporting and Learning System of the NPSA between April 2008 and April 2009, found that patient safety incidents relating to the use of intravenous gentamicin accounted for 15% of all reported neonatal medication incidents. Neonatal trainees frequently rotate through different hospitals during training and
have to reacquaint themselves accordingly with individual units’ antibiotic guidelines. The BNFc currently offers two different dosing regimens and our survey shows that current clinical practice is even more variable. Risk management may be particularly difficult in the absence of uniform guidelines for gentamicin use.

The NPSA report (Review of Patient Safety for Children and Young People, June 2009) concluded that a standardized dosing regimen and TMD would help minimize medication errors. A recent prospective pharmacokinetic study in Sweden has suggested extending the gentamicin dosing interval for pre-term infants and using higher loading doses. The most informative approach to gentamicin TDM is to use concentrations from the decay part of the time-concentration curve. However, neither approach has been adopted into UK clinical practice and both may be worthy of further consideration.

Studies have shown that extending the dosing interval to 48 h and increasing the dose of gentamicin to 5 mg/kg causes an increase in the peak concentration and a decrease in the trough concentration compared with a dose of 2.5 mg/kg every 12 h. Gestational age is an important factor in determining dosing, as the glomerular filtration rate is lower in the premature neonate than in the full-term neonate. No large randomized control trials have yet been performed to assess the efficacy and safety of an extended gentamicin regimen in premature neonates.

In 2007, the BNFc changed its recommendation about trough vancomycin levels from 5–10 mg/L to 10–15 mg/L. However, dosing guidance varied on the MCRN. Follow BNFc guidance may now underdose neonates. This concern is particularly acute given that coagulase-negative staphylococci have higher MIC values than MRSA.

Adult data have shown that continuous vancomycin infusions ensure target concentrations are reached more quickly, the levels achieved are more frequently above the MICs and there is less interindividual variability. Continuous infusions may not be applicable to neonates, because of their relatively low clearance of vancomycin, its post-antibiotic effect and the practical difficulties with ensuring dedicated vascular access.

The lack of well-designed randomized control trials focusing on therapeutic monitoring in neonates results in variable clinical practice amongst neonatal units. Plan et al. have shown that a continuous vancomycin infusion based on body weight and serum creatinine results in 75% of serum levels being within the therapeutic range. Efficacy rates were reported, but are difficult to assess in the absence of any comparator data. Others have examined the feasibility of the continuous infusion of vancomycin in neonates. There are, however, scant pharmacokinetic data for vancomycin regimens, especially comparing intermittent dosing with continuous infusions. Further studies are required with larger cohorts to assess whether post-natal age is also an important covariate in achieving efficacy. When using intermittent infusions, the trough concentration is a good predictor of efficacy if taken at steady-state. The variation in the timing of these measurements in our study suggests varied understanding of the relevant principles of pharmacokinetics.

Our surveys may not be representative of gentamicin and vancomycin practice across the UK, as we asked only those units that participated in a neonatal network (representing 55% of all UK neonatal units) and had responses from <50% of the surveyed units. We cannot, therefore, claim to make a universal statement about neonatal antibiotic prescribing in the UK. Even so, the response is large enough to show significant variation in the dosing and monitoring of gentamicin and vancomycin across neonatal units. The two separately conducted surveys highlighted similar issues in relation to these two commonly prescribed antibiotics with different modes of action.

This variation could stem from a lack of translation of a known best approach to dosing or a lack of information about the best approach to dosing. Part of the problem is with a lack of translation, e.g., there were several discrepancies between the BNFc recommendation and clinical practice. An updated systematic review of dosing and TMD is required for each drug.

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Transparency declarations
None to declare.

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