Dose regimen for vancomycin not needing serum peak levels?

W-H Tan, N Brown, A W Kelsall, R J McClure

Aim: To determine the safety, efficacy, and need to measure peak serum vancomycin concentrations in a neonatal population using a standard vancomycin dosage regimen.

Method: A total of 101 infants who were admitted to a regional neonatal intensive care unit and received vancomycin (15 mg/kg every 12 or 18 hours depending on postnatal age) were studied retrospectively. Infants who had been started on vancomycin before they were transferred to the unit were excluded. The proportion of infants that were measured whose serum vancomycin concentrations were within a conservative therapeutic range of trough 5–10 mg/l, peak 20–40 mg/l, and a less conservative, but still safe, range of trough 5–12 mg/l, peak 15–60 mg/l.

Results: Trough concentrations of 5–10 mg/l were achieved by 46.5% of infants, and 5–12 mg/l by 55.4%. Peak concentrations of 20–40 mg/l were found in 83.2% of infants, and 15–60 mg/l in 99.0%. Highest peak concentration was 47.2 mg/l. Some 89.4% of infants with trough concentrations of 5–10 mg/l had a peak concentration of 20–40 mg/l.

Conclusions: The vancomycin dosage regimen used in this study produces acceptable therapeutic serum vancomycin concentrations. Peak serum vancomycin concentrations do not need to be measured in neonates using this dosage regimen.

Methods

All infants who were admitted to the neonatal intensive care unit, The Rosie Hospital, Cambridge, and received vancomycin from 1 January 1998 to 31 March 2000 were considered for inclusion in the study. Infants admitted from other hospitals who had received vancomycin using different dosage regimens were excluded. Ethical approval for the study was given by the relevant local hospital ethics committee.

The vancomycin dosage regimen used was 15 mg/kg every 18 hours for infants up to 1 week of age, and 15 mg/kg every 12 hours for infants more than 1 week old irrespective of postnatal age.

In addition, serum vancomycin concentrations were taken around the third dose. Blood samples for assay of serum vancomycin concentrations were taken around the third dose. Trough samples were taken just before vancomycin was given, and peak samples were taken one hour after the end of the infusion. Serum vancomycin concentrations were measured by fluorescent polarisation immunoassay (TDx, Abbott Laboratories, Abbott Park, Illinois, USA), and the results were recorded on the microbiology laboratory computer system (MediTech HCIS, Boston, Massachusetts, USA). Data for this study were obtained from this database retrospectively. The following parameters were also recorded: date of birth, date of...
specimen, gestational age, and serum creatinine concentrations in the preceding two days before serum vancomycin concentrations were measured.

To assess the effect of PCA on serum vancomycin concentration, infants were divided into three subgroups according to PCA: less than 28 weeks, 28–34 weeks inclusive, and greater than 34 weeks. To assess the importance of renal function, mean serum creatinine concentrations for infants with high (> 12 mg/l) trough vancomycin concentrations were compared with those with therapeutic or low trough vancomycin concentrations.

The proportion of infants whose trough and peak serum vancomycin concentrations were both within the therapeutic ranges in the different subgroups was compared using the χ² test. Mean serum creatinine concentrations were compared using Student’s t test.

RESULTS

A total of 101 patients were recruited. The median gestational age was 28 weeks (range 23–41), median postnatal age was 10 days (range 4–99), and median PCA was 30 weeks (range 23–45). Thirty two patients had a PCA of less than 28 weeks, 48 patients were 28–34 weeks, and 21 patients were more than 34 weeks. Fifty eight patients received vancomycin at 12 hourly intervals, and 43 received vancomycin at 18 hourly intervals.

Figure 1 shows the paired values for trough and peak serum vancomycin concentrations for each infant. The median trough serum concentration was 7.1 mg/l (range 0.6–23.4), and the median peak serum concentration was 25.5 mg/l (range 9.0–47.2). The maximum peak concentration was 47.2 mg/l in an infant of PCA 31 weeks. This infant also had the highest trough concentration of 23.4 mg/l. About 42% of the infants had both trough and peak concentrations within therapeutic range A. Of the 47 infants with trough concentrations of 5–10 mg/l, only four had peak concentrations less than 20 mg/l, and only one had a peak concentration greater than 40 mg/l (range of peak concentration 17.6–40.2 mg/l). Some 83% of infants had a peak concentration within range A.

Table 1 Proportion of infants in each postconceptional age (PCA) subgroup with both trough and peak concentrations within the respective therapeutic ranges

<table>
<thead>
<tr>
<th>PCA &lt;28 weeks</th>
<th>PCA 28–34 weeks</th>
<th>PCA &gt;34 weeks</th>
</tr>
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<tbody>
<tr>
<td>Range A</td>
<td>9/32 (28)</td>
<td>23/48 (48)</td>
</tr>
<tr>
<td>Range B</td>
<td>17/32 (53)</td>
<td>29/48 (60)</td>
</tr>
</tbody>
</table>

The first value is the number of infants with both trough and peak vancomycin concentration in the respective intended range. The second value is the total number of infants in each PCA subgroup. Values in parentheses are percentages.

DISCUSSION

The serum concentrations of vancomycin compare favourably with those measured in studies using different dosage regimens in premature infants. Koren and James² four found that 75% of their 32 premature infants (mean (SD) PCA 34.2 (3.5) weeks) achieved their target trough concentration of less than 10 mg/l, and 67% achieved peak concentrations of 25–40 mg/l (compared with 73% and 83% respectively in this study). McDougall et al.²⁵ in their study of 44 infants with a PCA of 27–44 weeks found that 25% of the infants achieved the targeted trough concentration of 5–10 mg/l (compared with 47% in this study), and 64% achieved a peak concentration of 25–35 mg/l. Neither study analysed the proportion of infants whose trough and peak concentrations were both within the therapeutic ranges.

The greatest concern about the use of vancomycin is the potential for ototoxicity and nephrotoxicity. The incidence of these side effects and the vancomycin concentrations at which they occur remain controversial.¹ Although there have been a few reports of ototoxicity in the adult population, most of the patients had received other drugs known to be ototoxic, and irreversible deafness occurred only with serum vancomycin concentrations above 80 µg/ml.²³⁻²⁵ There have been no reported cases of ototoxicity caused by vancomycin in neonates. Nephrotoxicity is thought to occur in 5% of adult patients treated with vancomycin, and in most of these cases the nephrotoxicity was reversible.²⁶⁻²⁸ In the newborn, vancomycin induced nephrotoxicity is relatively rare. None of the 69 infants (PCA 26–54 weeks) in the study of Bhatt-Mehta et al.²⁷ developed nephrotoxicity even with trough vancomycin concentrations up to 39.4 mg/l and peak vancomycin concentrations reaching 49.7 mg/l.

The minimal inhibitory concentration of vancomycin against Staphylococcus epidermidis and Staphylococcus aureus is generally in the range 0.5–2 µg/ml.²² As vancomycin is 50% protein bound, it has been suggested that serum vancomycin concentrations should be kept above 2–4 µg/ml.²² The key determinant of bactericidal activity rests on the length of time during which serum vancomycin concentration remains above the minimal inhibitory concentration.¹ There is little evidence that the rate of bacterial killing increases at concentrations above the minimal inhibitory concentration,²¹ and peak concentrations do not affect clinical efficacy or toxicity.²⁹ Thus the routine measurement of peak serum vancomycin concentration is of dubious clinical value as it gives little, if any, useful information about possible toxicity or bactericidal efficacy.
With our dosage regimen, no infant had a peak serum vancomycin concentration above the conservative range A if they had a trough concentration within the therapeutic range A or B. All infants had peak serum vancomycin concentrations well below 60 mg/l (maximum concentration 47.2 mg/l). Only one patient had an inappropriately low peak vancomycin concentration at less than 15 mg/l, and that was associated with the lowest trough concentration of 0.8 mg/l. Trough concentrations below 5 mg/l were never associated with peak concentrations above 40 mg/l, and trough concentrations above 10 mg/l were never associated with peak concentrations below 20 mg/l. These data suggest that vancomycin dosages in premature or term infants can be safely and routinely adjusted up or down on the basis of trough concentration monitoring alone. The one exception to this may be in infants with established renal failure, as we have shown that potentially toxic trough concentrations are associated with significantly higher creatinine concentrations.

In conclusion, the dosage regimen used in this study results in acceptable therapeutic serum vancomycin concentrations in premature infants. Trough serum vancomycin concentrations, however, appears to be unnecessary. Currently in the United Kingdom, the incremental cost of each vancomycin assay is about £10. Abandoning the measurement of peak serum vancomycin concentrations, and to ensure that adequate dosing is achieved. Routine measurement of peak serum vancomycin concentrations, however, appears to be unnecessary. Currently in the United Kingdom, the incremental cost of each vancomycin assay is about £10. Abandoning the measurement of peak serum vancomycin concentrations should result in significant financial savings as well as of laboratory and sampling manpower time. It will also reduce unnecessary trauma to infants.

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