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Antimicrobial Review

Trough Concentrations of Vancomycin

Adult Therapeutic Targets Are Not Appropriate for Children

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Abstract: Despite the need for effective vancomycin therapy, there are few data guiding vancomycin monitoring in children. We reviewed retrospectively vancomycin use in children 1 month to 12 years of age. Initial and adjusted target trough vancomycin concentrations in serum were infrequently achieved regardless of the dosing schedule. Currently recommended trough concentrations need to be re-examined with more detailed pharmacokinetic study in children.

Key Words: vancomycin, Staphylococcus aureus, therapeutic drug monitoring

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The population of northern Australia experiences a heavy burden of staphylococcal disease, particularly caused by methicillin-resistant Staphylococcus aureus (MRSA), and Aboriginal Australians are disproportionately affected. Approximately 28% of S. aureus blood culture isolates in children are MRSA strains (Daniel Engelman, Royal Darwin Hospital, personal communication).

Vancomycin has for many years been the first-line intravenous antibiotic to treat serious MRSA infections. Local and international guidelines for adults and children have recently increased target trough serum vancomycin concentrations to 12–18 mg/L using 6-hourly or 12-hourly vancomycin dosing [Australian Therapeutic Guidelines: Antibiotic 2010 (ATG)] or 15–20 mg/L using 6-hourly dosing [Infectious Diseases Society of America (IDSA)] for serious MRSA infections to improve target tissue penetration and maintain an area under the curve (AUC) to minimum inhibitory concentration (MIC) ratio (AUC/MIC) >400 mg h/L. This follows the emergence of vancomycin-intermediate S. aureus and the observation that inducible heterogeneous vancomycin-intermediate S. aureus proliferate at vancomycin trough serum concentrations of <10 mg/L, together with evidence from one prospective study suggesting clinical efficacy was optimum when the vancomycin AUC/MIC ratio was at least 345 mg h/L. Furthermore, decreasing efficacy has been observed with higher vancomycin MICs which are still in the susceptible range.

Although increasing trough concentrations may be desirable for reasons of efficacy and resistance selection, the change is not currently supported by clinical trial data in adults or children. Surprisingly, even before the recent emphasis on achieving higher trough vancomycin concentrations, there were only a very small number of pharmacokinetic studies and no pharmacodynamic studies to guide vancomycin dosing and monitoring in children. The AUC/MIC ratio is the best determinant of efficacy and in adults this only modestly correlates with trough concentrations, the current recommended method to monitor vancomycin therapy. However, it is not known in children how well the AUC/MIC correlates with trough vancomycin concentrations, and current guidelines assume that adult target trough concentrations apply equally to children.

After observing a low proportion of vancomycin trough concentrations in either the IDSA target range of 15–20 mg/L or the ATG target range of 12–18 mg/L even with large daily doses of vancomycin administered both 6-hourly and 12-hourly, we performed a 2-year retrospective review of vancomycin use and monitoring in pediatric patients between 1 month and 12 years of age to determine how often the new target vancomycin trough concentrations were actually being achieved.

Materials and Methods

Royal Darwin Hospital (RDH) is the tertiary referral center for the tropical north of the Northern Territory of Australia. All children >1 month corrected age and <12 years, admitted to the pediatric wards at RDH between October 2009 and October 2011 who received vancomycin and had at least one serum trough vancomycin concentration measured, were included. Study participants were identified using the pharmacy dispensing records for vancomycin. Patient demographics, renal function, vancomycin dosage histories, serum vancomycin concentrations and sampling times, and vancomycin side effects were obtained from the patients’ medical file, pharmacy records and pathology results. Trough concentrations were defined as values taken within 1 hour of the next due dose. The hospital guidelines stipulate that the first trough concentration be measured before the fourth dose. For example, the first trough concentration would be 5 hours after the third dose if administered 6-hourly and 11 hours after the third dose if administered 12-hourly. If vancomycin was continued, the next trough concentration was recommended to be taken at least before the eighth dose. If patients received >1 course of vancomycin during their admission, only the first episode was analyzed.

Vancomycin has traditionally been administered in 6-hourly doses in children. However, in March 2010, RDH developed a new vancomycin protocol in accordance with the revised ATG. The recommended dose for children from 1 month to 12 years of age without renal impairment was 30 mg/kg 12-hourly, targeting a trough concentrations of 15 ± 3 mg/L, which was subsequently revised in April 2011 to 15–20 mg/L, aligning with the IDSA trough guidelines. Similar to other Australian hospitals, RDH has
still used vancomycin doses of 10–15 mg/kg 6-hourly for some children, especially for younger ages. Because of the particularly variable plasma clearance of drugs in the pediatric population, children aged 1–11 months were analyzed separately from children 1–12 years of age.

Approval was obtained from Human Research Ethics Committee of the Northern Territory Department of Health and Menzies School of Health Research (QAAR-2011-1662). Proportions were compared using Fisher's exact test, continuous measures using Student's t test or analysis of variance, and rank-sum test for normally distributed and nonparametric data respectively, using STATA, version 11.0 (StataCorp, College Station, TX). A P value of <0.05 was considered significant.

RESULTS

The demographics of 37 children 1–12 years of age who had at least one valid trough serum vancomycin concentration measured are shown in Table (Supplemental Digital Content 1, http://links.lww.com/INF/B343). Seventeen patients were commenced on a 6-hourly vancomycin dosing, 20 were given 12-hourly vancomycin dosing, while 2 patients initially received a loading dose before one started a 6-hourly dosing regime and the other commenced a 12-hourly dosing regime. Patients given 6-hourly vancomycin dosing had a lower initial total vancomycin daily dose (mg/kg) compared with patients receiving 12-hourly vancomycin dosing ($P = 0.002$), reflecting the changeover period between vancomycin dosing protocols (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/B343). Ten children initially received daily vancomycin doses of <45 mg/kg/d in 6-hourly doses, half of which occurred before the change in protocol to 30 mg/kg 12-hourly. Of the 10 children, 9 were <6 years of age. The median duration of vancomycin therapy was 6 days for both 6-hourly [interquartile range (IQR) 3–10 days] and 12-hourly (IQR 2–13 days) dosing groups, suggesting that clinical efficacy was similar in both groups ($P = 0.94$).

Thirteen patients 1–12 years of age had an initial vancomycin trough concentration of <5 mg/L (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/B343). No initial vancomycin trough concentration was in the IDSA target range of 15–20 mg/L, although 2 children aged 6 and 7 years receiving 30 mg/kg 12-hourly were in the ATG target range of 12–18 mg/L. One of these children receiving 30 mg/kg 12-hourly had their initial trough concentration measured beyond the recommended fourth dose, as did another 3 children in the 6-hourly dosing group and 1 child in the 12-hourly dosing group, none of whom had an initial trough concentration of >7.5 mg/L.

One hundred twenty repeat-adjusted vancomycin trough concentrations were obtained on 26 children 1–12 years of age (see Table, Supplemental Digital Content 1, http://links.lww.com/INF/B343). Nearly all patients received vancomycin either 6-hourly or 12-hourly throughout the study; however, 3 patients changed from 12-hourly dosing to 6-hourly dosing and 5 patients changed from 12-hourly dosing to 8-hourly dosing. Seven of 16 (43%) children on 6-hourly dosing achieved the IDSA target trough concentrations of 15–20 mg/L after a median of 8 days (IQR 5–8 days). Four of 15 (27%) children receiving 1-hourly vancomycin recorded at least 1 vancomycin trough concentration in the ATG recommended range of 12–18 mg/L, after a median of 3.5 days (IQR 2.5–4.5 days). Within all dosing groups, patients <6 years of age had significantly lower repeat trough concentrations than older patients ($P \leq 0.001$), despite receiving similar daily doses of vancomycin ($P = 0.51$; Table, Supplemental Digital Content 1, http://links.lww.com/INF/B343).

Eleven patients 1–11 months of age (median age 5.9 months, IQR 4.2–7.6 months) were commenced on vancomycin; 8 on 6-hourly dosing (median daily dose 56 mg/kg, IQR 40.5–60.5 mg/kg) and 3 on 12-hourly dosing (daily doses of 62, 59 and 36 mg/kg), none of which achieved the IDSA target range of 15–20 mg/L, although 3 patients who received 6-hourly vancomycin were in the ATG target range of 12–18 mg/L. Five patients 1–11 months had repeat-adjusted vancomycin trough concentrations performed, of which only 1 receiving 87 mg/kg daily in 6-hourly doses achieved the IDSA target range of 15–20 mg/L, and no children achieved the ATG target range of 12–18 mg/L.

Three patients developed neutropenia after receiving between 28 and 50 days of vancomycin, which resolved after cessation of vancomycin. One patient with glomerulonephritis had temporary worsening of renal function, which was attributed to very high vancomycin trough concentrations (57 mg/L). One patient developed a pruritic skin rash after a vancomycin infusion; however, vancomycin was continued without further reaction.

DISCUSSION

Despite the high burden of MRSA infections in children in northern Australia and in other parts of the world, there are few data to guide the dosing and monitoring of vancomycin in children, the key intravenous antibiotic in treating serious MRSA infections. Reflecting this uncertainty, vancomycin dosing and monitoring practices vary considerably in pediatric hospitals around Australia, including within our own hospital. Although our hospital protocol changed during the study period, a wide variety of vancomycin doses and dosing frequencies was observed, with limited success in achieving currently recommended vancomycin trough concentrations in a timely fashion. Furthermore, younger children had lower repeat trough concentrations than older children, despite receiving similar daily doses of vancomycin, suggesting higher vancomycin clearances occur in younger children.

In recent years, the emphasis of vancomycin monitoring has moved from the prevention of largely reversible toxicity to ensuring optimum pharmacodynamic exposure with the hope of ensuring efficacy in serious infections and to potentially avoid the development of resistance. IDSA recommends 15 mg/kg 6-hourly in children, with target trough concentrations of 15–20 mg/L; however, this has been difficult to achieve in children and doses of up to 85 mg/kg per day have been recommended for serious MRSA infections, based on pharmacokinetic modeling rather than on clinical data. The ATG recommends 30 mg/kg 12-hourly in children with target trough concentrations of 12–18 mg/L, based on the premise that a 12-hourly dosing interval is more convenient for administration than a 6-hourly interval and will have a similar AUC as a 6-hourly dosing interval using the same total daily dose.

A common error in vancomycin monitoring is using trough concentration target ranges without accounting for the dosing frequency. For a particular total daily dose of vancomycin, the same AUC, and presumably the same efficacy, will be achieved whether the total daily dose is given in 6-hourly or 12-hourly dosing intervals. However, trough concentrations will be different for the same total daily dose when different dosing frequencies are used, despite the same total vancomycin exposure and AUC. For example, steady state trough concentrations with 6-hourly dosing will be twice as high as those of 12-hourly dosing with the same daily dose, despite the same AUC. Prescribers need to be aware that different target troughs should be selected for different dosing frequencies.

However, are trough concentrations the correct therapeutic target for monitoring vancomycin therapy in children? There is concern that vancomycin dose adjustment in children may be
overly aggressive to meet the new target trough concentrations, which have been driven by studies in adults using adult pharmacokinetics. AUC\(_{24}\):MIC is the primary predictive pharmacodynamic index for vancomycin efficacy in treating \textit{S. aureus}, and the use of trough vancomycin concentrations to monitor efficacy is based on the assumption made for adults receiving 12-hourly dosing that serum trough vancomycin concentrations are reasonably correlated with AUC\(_{24}\). In our study, children who were younger than 6 years had lower repeat-adjusted serum vancomycin trough concentrations compared with children older than 6 years, independent of total daily dose and dosing frequency, suggesting that the clearance of vancomycin is higher in young children. Because clearance is higher in young children, young children would likely need different trough targets than adults to achieve the target AUC\(_{24}\). In addition, because it is not known what these trough targets should be in the pediatric population, it makes more sense to monitor AUC\(_{24}\) directly. The AUC\(_{24}\):MIC ratio for efficacy targeting 400 mg·h/L may be a more accurate and safe method of therapeutic drug monitoring in children.

Based on our preliminary results, currently recommended trough concentrations need to be re-examined with a more detailed pharmacokinetic study in children which examines the effects of different doses, different schedules, AUC\(_{24}\) and trough concentrations. Furthermore, target trough concentrations, if they continue to be used, should be adjusted for dosing schedule. Based on our preliminary data, for children at our hospital in whom vancomycin is continued as the definitive treatment, we are developing a guideline where the AUC\(_{24}\) is used to direct therapy, aiming for a target of 400 mg·h/L (assuming a vancomycin MIC of 1 mg/L) as an alternative strategy for vancomycin monitoring. Data collection on vancomycin dosing and therapeutic monitoring is continuing to allow assessment of the change of protocol.

REFERENCES


