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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 a more detailed pharmacokinetic study in children.

Introduction

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.[1] 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.[2] Local and international guidelines for adults and children have recently increased target trough serum vancomycin concentrations to 12-18mg/L using 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_{24}/MIC) greater than 400 mg*hr/L.[2, 3] This follows the emergence of vancomycin-intermediate *S. aureus* (VISA) and the observation that inducible heterogeneous VISA proliferate at vancomycin trough serum concentrations of less than 10 mg/L,[4] together with evidence from one prospective study suggesting clinical efficacy was optimum when the vancomycin AUC_{24}/MIC ratio was at least 345 mg*m/L.[5] Furthermore, decreasing efficacy has been observed with higher vancomycin MICs which are still in the susceptible range.[6, 7]

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.[3] 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_{24}/MIC ratio is the best determinant of efficacy[3] 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_{24}/MIC correlates with trough vancomycin concentrations and current guidelines assume that adult target trough concentrations apply equally to children.[2, 8]

After observing a low proportion of vancomycin trough concentrations in either the IDSA target range of 15-20mg/L or the ATG target range of 12-18mg/L even with large daily doses of vancomycin administered both 6-hourly and 12-hourly, we performed a two 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 greater than one month corrected age and less than 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 one 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 more than one 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.[2] The recommended dose for children from one month to 12 years of age without renal impairment was 30mg/kg 12-hourly, targeting a trough concentrations of 15+/-3mg/L, which was subsequently revised in April 2011 to 15-20mg/L, aligning with the IDSA trough guidelines.[3] Similar to other Australian hospitals, RDH has still used vancomycin doses of 10-15mg/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 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 non-parametric data respectively, using STATA, version 11.0 (StataCorp, Texas, USA). 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 1. Seventeen patients were commenced on a 6-hourly vancomycin dosing, 20 were given 12-hourly vancomycin dosing, while two

patients initially received a loading dose before one started a 6-hourly dosing regime and the other commenced a12-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, SDC 1). Ten children initially received daily vancomycin doses of less than 45mg/kg/d in 6-hourly doses, half of which occurred before the change in protocol to 30mg/kg 12-hourly. Of the ten children, nine were less than 6 years of age. The median duration of vancomycin therapy was 6 days for both 6-hourly (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, SDC 1). No initial vancomycin trough concentration was in the IDSA target range of 15-20mg/L, although two children aged 6 and 7 years receiving 30mg/kg 12-hourly were in the ATG target range of 12-18mg/L. One of these children receiving 30mg/kg 12-hourly had their initial trough concentration measured beyond the recommended fourth dose, as did another three children in the 6-hourly dosing group and one child in the 12-hourly dosing group, none of whom had an initial trough concentration of more than 7.5mg/L.

One hundred and twenty repeat adjusted vancomycin trough concentrations were obtained on 26 children 1-12 years of age (see Table, SDC 1). Nearly all patients received vancomycin either 6-hourly or 12-hourly throughout the study, however, three patients changed from 12-hourly dosing to 6-hourly dosing and five patients changed from 12-hourly dosing to 8-hourly dosing. Seven out of 16 (43%) children on 6-hourly dosing achieved the IDSA target trough concentrations of 15-20mg/L after a median of 8 days (IQR 5-8 days). Four of fifteen (27%) children receiving 1-hourly vancomycin recorded at least one vancomycin trough concentration

in the ATG recommended range of 12-18mg/L, after a median of 3.5 days (IQR 2.5-4.5 days). Within all dosing groups patients less than 6 years of age had significantly lower repeat trough concentrations than older patients (p=<0.001), despite receiving similar daily doses of vancomycin (p=0.51; Table 1).

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

Three patients developed neutropenia after receiving between 28-50 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 (57mg/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[1] 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 at 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 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 recommends15mg/kg 6-hourly in children, with target trough concentrations of 15 to 20 mg/L[3]; 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.[10] The ATG recommends 30mg/kg 12-hourly in children with target trough concentrations of 12-18mg/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. [11] Prescribers need to be aware that different target troughs should be selected for different dosing frequencies.

But 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 *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 old had lower repeat adjusted serum vancomycin trough concentrations compared with children older than 6 years of age, 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, since 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.hr/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. Further, 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 AUC24 is used to direct therapy, aiming for a

target of 400 mg.hr/L (assuming a vancomycin MIC of 1mg/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.

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Table 1: Patient demographics, initial and repeat vancomycin doses and trough concentrations stratified by frequency of dosing

	6-hourly vancomycin dosing	8-hourly vancomycin dosing	12-hourly vancomycin dosing	p value
Initial vancomycin dosing and monitoring				
No. patients contributing to each group*	17	0	20	
Median age in years (interquartile range [IQR])	3.4 (2.5-5.1)	-	5.8 (2.6-8.2)	0.14
No. males (%)	6 (35%)	-	9 (45%)	0.40
Median weight (IQR), kg	15.0 (13.0-17.3)	-	17.0 (12.9-26.9)	0.18
Median initial vancomycin dose (IQR)*, mg/kg/d	40.5 (39.0-59.5)	-	60.0 (57.0-64.0)	0.002
Median initial vancomycin trough concentration before the fourth dose (IQR)*, mg/L	6.0 (2.5-7.7)	-	8.7 (2.5-14.1)	0.13
Initial vancomycin trough concentration*		-		
< 5 mg/L	6 (38%)	-	7 (37%)	
5-9 mg/L	10 (63%)	-	6 (32%)	
10-14 mg/L	0	-	2 (11%)	
15-19 mg/L	0	-	0	
≥ 20 mg/L	0	-	4^ (21%)	

Initial vancomycin trough concentrations in the target range of 12-18 mg/L*	0	-	2 (11%)	
Repeat adjusted vancomycin dosing and monitoring				
No. patients contributing to each group	16	5	15	
No. of vancomycin trough measurements	61	22	37	
Median adjusted vancomycin daily dose (IQR), mg/kg	72 (60-86)	84 (72-96)	66 (60-80)	
Age < 6 years old	73 (60-87)	96 (96-97)	68 (60-80)	
Age ≥ 6 years old	62 (56-72)	74 (69-88)	66 (59-76)	
Median of adjusted repeat vancomycin trough concentrations (IQR)**, mg/L	13.8 (8.9-17.4)	12.5 (7.7-15.5)	8.8 (5.6-14.7)	
Age <6 years old	11.5 (7.8-15.7)	7.7 (5.9-11.3)	6.9 (2.5-9.4)	
Age ≥ 6 years old	17.5 (14.0-19.2)	13.5 (11.2-16.1)	12.8 (8.5-17.3)	
Adjusted repeat vancomycin trough concentrations				
< 5 mg/L	2 (3%)	1 (5%)	7 (19%)	
5-9 mg/L	17 (28%)	5 (23%)	13 (35%)	
10-14 mg/L	15 (25%)	9 (41%)	8 (22%)	

15-19 mg/L	19 (31%)	4 (18%)	6 (16%)	
≥ 20 mg/L	8 (13%)	3 (14%)	3 (8%)	
Repeat vancomycin trough concentrations in the target range of 12-18 mg/L	25 (41%)	10 (46%)	11 (30%)	

* Two patients had loading doses initially and are not included in the initial vancomycin dosing and concentration calculations.

^ Three patients had renal impairment and were dosed incorrectly.

** trough concentrations taken before 4th dose if vancomycin dose changed.