J Med Sci 2018;38(6):275-279
DOI: 10.4103/jmedsci.jmedsci_103_18

ORIGINAL ARTICLE

A Retrospective Study to Estimate Serum Vancomycin Trough Concentrations in Pediatric Patients with Current Recommended Dosing Regimen

Chia-Ning Chang[1], Wen-Tsung Lo[1,2], Ming-Chin Chan[3], Chih-Chien Wang[1]

Departments of [1]Pediatrics and [3]Infection Control Office, Tri-Service General Hospital, National Defense Medical Center, Taipei, [2]Department of Pediatrics, St. Joseph Hospital, Kaohsiung, Taiwan

Wen-Tsung Lo and Chia-Ning Chang contributed equally to this work

Background: Vancomycin is widely prescribed to treat infections caused by methicillin-resistant *Staphylococcus aureus* (MRSA). According to the Infectious Disease Society of America 2011 MRSA guidelines for adults, trough concentrations of 15–20 μg/ml were recommended with vancomycin 15–20 mg/kg/dose every 8–12 h not to exceed 2 g per dose in patients with normal renal function. As the data for dosage and monitoring of vancomycin in children are still controversial, physicians often follow the guidelines established for adults. To evaluate serum vancomycin trough concentrations in pediatric patients with currently recommended dosing regimen, we evaluated clinical data. **Methods:** This retrospective observational study collected pediatric patients aged <18 years for whom vancomycin was administered at a single medical center between 2009 and 2015. **Results:** Fifty pediatric patients were analyzed. Two groups were identified according to the vancomycin dosage. Fourteen (28%) patients underwent vancomycin at 60 mg/kg/day (high dose) and 36 (72%) patients at 40 mg/kg/day (low dose). The average serum vancomycin trough concentrations of the two groups were 13.12 μg/ml (high-dose group) and 9.02 μg/ml (low dose group), respectively. In addition, 71% (high-dose group) and 91% (low-dose group) of patients could not reach the target trough concentrations 15–20 μg/ml, set by the Infectious Disease Society of America. **Conclusion:** This investigation revealed that the current recommended vancomycin dosing regimens in children (40–60 mg/kg/day) mostly brought out trough concentrations <10 μg/ml in this research population.

Key words: Methicillin-resistant *Staphylococcus aureus*, pediatric dose, trough concentration, vancomycin

INTRODUCTION

Staphylococcus aureus (*S. aureus*) is a Gram-positive coccus that induces serious diseases, including pneumonia, endocarditis, necrotizing fasciitis, and others. During the 1950s, methicillin was invented and used against *S. aureus*. However, methicillin-resistant *S. aureus* (MRSA) was reported in the United Kingdom in 1961. Fortunately, vancomycin, a glycopeptide antimicrobial agent that inhibits bacterial cell wall synthesis, was discovered. Vancomycin was active against infections caused by Gram-positive bacteria such as streptococci, enterococci, and *Staphylococcus* species including MRSA. Thereafter, vancomycin became the mainstay of treatment for the most severe MRSA infections based on the guidelines recommended by the Infectious Diseases Society of America in pediatric and adult patients.[1]

Gradual elevation of glycopeptide minimum inhibitory concentrations (MICs) for *S. aureus* strains, a phenomenon recognized as vancomycin MIC creep, has become a concern in recent years. Many researchers have reported that vancomycin MIC creep for MRSA isolates constitutes a substantial risk of treatment failure. In our hospital, we found vancomycin MIC creep in MRSA isolates from both adults

Received: July 14, 2018; Revised: July 23, 2018; Accepted: July 27, 2018
Corresponding Author: Dr. Chih-Chien Wang, Department of Pediatrics, Tri-Service General Hospital, National Defense Medical Center, No. 325, Section 2, Cheng-Kung Road, Neihu 114, Taipei, Taiwan. Tel: 886-2-87927025; Fax: 886-2-87927293. E-mail: ndmcccw@yahoo.com.tw

How to cite this article: Chang CN, Lo WT, Chan MC, Wang CC. A retrospective study to estimate serum vancomycin trough concentrations in pediatric patients with current recommended dosing regimen. J Med Sci 2018;38:275-9.

and children.[2] According to the 2011 Infectious Disease Society of America MRSA guidelines, measuring serum vancomycin trough concentrations are the most accurate way to guide vancomycin dosing in adults. For severe infections such as osteomyelitis, meningitis, bacteremia, pneumonia, serious skin and soft tissue infections (e.g., necrotizing fasciitis), and infective endocarditis caused by MRSA, vancomycin trough concentrations of 15–20 μg/ml are required for adults.[1] Nevertheless, data are lacking to guide vancomycin dosing in children. The effectiveness and safety of target trough concentrations of 15–20 μg/ml require further study in children. Current dosing advice for pediatric use of vancomycin is 15 mg/kg/dose every 6 h for the treatment of children with severe or invasive diseases, and the target trough concentration of 15–20 μg/ml for adults is applied.[1] However, several studies have shown that such target trough levels are rarely achieved in pediatric patients.[3,4]

There are few studies of vancomycin dosing in children in Taiwan. Hwang *et al*.[5] found that 15 mg/kg/dose every 6 h compared to a 10 mg/kg/dose every 6 h is more likely to reach the target trough concentrations of 15–20 μg/ml. The purpose of this study was to assess the vancomycin trough concentrations in pediatric patients with current dosing guidelines.

METHODS

Study design and enrolment criteria

This retrospective observational study was conducted from 2009 to 2015 at the Tri-Service General Hospital (TSGH), a 1400-bed tertiary medical center in northern Taiwan. The Ethics Review Committee of TSGH approved this study (2-104-05-028). All patients aged <18 years of age who received intravenous vancomycin for more than three doses and had one or more appropriately analyzed trough concentrations were enrolled. Vancomycin was dosed according to Nelson's Pediatric Antimicrobial Therapy, 20th edition.[6]

Data collection and analysis

The medical records of pediatric patients with trough vancomycin concentrations were reviewed. Each patient's age, sex, body weight, serum creatinine, vancomycin dosage, and trough concentrations were gathered. The vancomycin trough concentrations were further categorized into <10 μg/ml, 10–14 μg/ml, 15–20 μg/ml, and >20 μg/ml. Because the standard dose of vancomycin recommended for children is 40–60 mg/kg/day, two groups were identified based on the vancomycin dosage (60 mg/kg/day [high dose] vs. 40 mg/kg/day [low dose]).

Statistical analysis

Descriptive analyses were performed to characterize demographic and clinical data using the Statistical Package for the Social Sciences (SPSS), version 18.0 (Inc., Chicago, IL, USA). Data were offered as numbers, percentages, mean (with or without standard deviation), and median while declared.

RESULTS

There were 101 intravenous vancomycin orders during the study. After exclusion criteria were applied, 50 pediatric patients and 50 trough vancomycin concentrations were enrolled in this study. All of the children had a normal renal function during vancomycin treatment. The main reasons for exclusion were patients' age younger than 1 month ($n = 15$) due to immature renal function and repeated checks of vancomycin trough concentrations during the same hospitalization ($n = 36$). Demographic data and vancomycin parameters are listed in Table 1.

To evaluate the relationship between serum vancomycin trough concentrations and pediatric dosing, two groups were identified according to the vancomycin dosage. Fourteen (28%) patients underwent vancomycin at 60 mg/kg/day (high dose) and 36 (72%) patients at 40 mg/kg/day (low dose). The high dose was prescribed for patients with life-threatening infections such as infective endocarditis, meningitis, and ongoing bacteremia, whereas low dose was administered for patients with nonsevere diseases such as skin and soft-tissue infections. The mean applied dose in high-dose group was 59.5 ± 0.78 mg/kg/day (median: 60 mg/kg/day) and in low-dose group was 39.53 ± 1.40 mg/kg/day (median: 40 mg/kg/day). The average serum vancomycin trough concentrations of the two groups were 13.12 μg/ml (high-dose group) and 9.02 μg/ml (low-dose group), respectively. In addition, 71% (high-dose group) and 91% (low-dose group) of patients could not reach the target trough concentrations 15–20 μg/ml [Table 2 and Figure 1].

Table 1: Demographic data and vancomycin parameters

	Median (range)	Mean±SD
Weight (kg)	17 (1.6-56.8)	23±18.6
Age (year)	5.05 (0.1-17)	9±4.8
Vancomycin dose (mg/kg/day)	40 (30-60)	44.5±9.3
Vancomycin trough levels (μg/ml)		
High-dose group (60 mg/kg/day)	8.8 (4.56-45.67)	13.12±7.59
Low-dose group (40 mg/kg/day)	7.93 (1.16-45.06)	9.02±4.54
Total	8.1 (1.16-45.67)	9.99±5.47

SD=Standard deviation

DISCUSSION

Vancomycin serum trough levels are routinely measured to optimize dosing and monitor renal toxicity. Adults' researches revealed that the area-under-the-concentration-time-curve (AUC) for 24 h divided by the MIC (AUC24/MIC) >400 is the finest predictor of therapeutic outcome while treating severe MRSA infections.[7-9] According to the 2009 consensus recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists, the value of the AUC divided by the MIC being >400 is a proper target to achieve a successful clinical outcome while treating MRSA, but the studies were designed for adults.[7,8] Moreover, the recommendation from Nelson's Pediatric Antimicrobial Therapy suggested that vancomycin dosing of 30–40 mg/kg/day divided into three or four doses is advised in children with noninvasive infections.[6] For children with life-threatening MRSA infections, vancomycin dosing of 60–70 mg/kg/day is recommended to yield an AUC of serum concentrations versus time over 24 h to an MIC ratio of 400 at the lowest.[6] However, measuring the AUC is not routinely done in clinical practice.

Changes in vancomycin MIC are clinically significant because a higher vancomycin MIC could induce an unfavorable response to the medication and lead in a more serious condition.[9] Elevated vancomycin MICs are usually associated with deteriorated clinical outcomes and the phenomenon called "MIC creep."[10,11] A high dose of vancomycin (60 mg/kg/day) is recommended for pediatric patients infected with MRSA in the setting of vancomycin MIC creep.[7] Frymoyer *et al.*[12] performed detailed analyses for doses of 15 mg/kg every 6 h, 15 mg/kg every 8 h, and 20 mg/kg every 8 h. When an MIC of 1.0 was assumed with dosing of 15 mg/kg every 6 h, 90% patients achieved an AUC/MIC >400 with trough levels of 7–10 μg/ml. At dosing of 15 mg/kg every 8 h, trough levels of 8–10 μg/ml were necessary to achieve the target AUC/MIC; with dosing at 20 mg/kg every 8 h, trough levels of 6–8 μg/ml were predictive of AUC/MIC >400. Assuming an MIC of 0.5 mg/l, all cases reached an AUC/MIC >400, with trough levels >5 μg/ml with dosing of 15 mg/kg every 6 h. However, for MICs of 2.0 mg/l, few patients achieved AUC/MIC >400 with dosing of 15 mg/kg every 6 h, even though their trough levels reached 15–20 μg/ml. They concluded that if the MIC for the organism being treated was 1.0 mg/l or less, targeting higher trough concentrations are not essential.[12]

In the current study, only 4% (2/50) of the total vancomycin trough concentrations reached the traditional target concentration of 15–20 μg/ml with empiric dosing regimens, which is within the reported range.[4,13-17] Le *et al.*[15] computed that the AUC/MIC >400 was about equivalent to a trough level of 8–9 μg/ml in their study of 1660 samples from 702 patients. In addition, Glover *et al.*[16] found that the pediatric patients with normal renal function required an average dose of 60 mg/kg/day to reach a mean trough concentration of 7.8 μg/ml. Arfa *et al.*[17] also revealed that about 69% of their patients' vancomycin trough levels were <10 μg/ml with 60 mg/kg/day dosing. Vancomycin is an age-dependent pharmacokinetic antibiotic agent because its renal clearance in children is 2–3 times higher

Table 2: The distribution of the corresponding vancomycin trough levels with the current empiric dosing regimen

Vancomycin dose (mg/kg/day)	Trough levels (μg/ml)				
	<10 (%)	10-14 (%)	15-20 (%)	>20 (%)	Total (%)
High (60 mg/kg/day)	9 (64)	1 (7)	1 (7)	3 (22)	14 (100)
Low (40 mg/kg/day)	26 (72)	7 (19)	1 (3)	2 (6)	36 (100)
Total	35 (70)	8 (16)	2 (4)	5 (10)	50 (100)

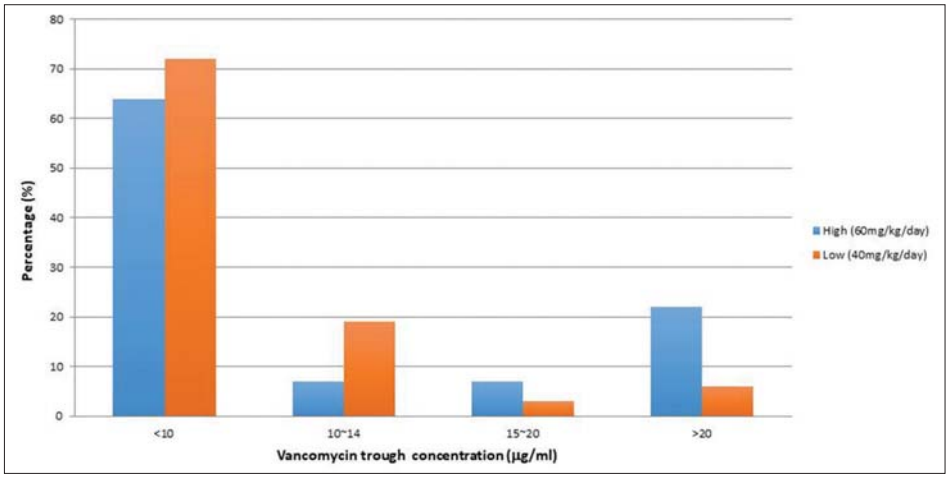

Figure 1: The distributive percentages of vancomycin trough concentrations in two groups (n = 14 in the high-dose group and n = 36 in the low-dose group)

than that of adults.[18,19] As a result, it was difficult to gain the adult target extent in most children with the current dosage of 40–60 mg/kg/day.[20] Some experts even suggested that the daily dose of vancomycin should be added to 70–85 mg/kg/day in pediatric patients.[21]

The trough concentrations could be classified into four types: <10 μg/ml (subtherapeutic scale), 10–14 μg/ml (therapeutic scale for low-dose vancomycin), 15–20 μg/ml (therapeutic scale for high-dose vancomycin), and more than 20 μg/ml (over-therapeutic scale).[1,7,21] Among our pediatric patients, most (70%) of their vancomycin trough concentrations were <10 μg/ml (subtherapeutic scale) both in high-dose (64%) and low-dose (72%) groups. However, only one patient died, and the others survived without any complication. Therefore, even if the vancomycin trough levels lie in subtherapeutic scale, the corresponding outcomes are not necessarily unfavorable in our pediatric patients.

Our data are subject to certain limitations, and the leading one is its retrospective design. Second, it was performed with relatively small numbers in a single medical center, restricting its generalizability. Third, a few patients lacked data for creatinine changes, which could have revealed nephrotoxicity induced by vancomycin.[21] Finally, the inclusion of young infants in the study might have impacted some proportion of patients with low trough levels.[22]

CONCLUSION

We found that the currently recommended vancomycin dosing regimens in children (40–60 mg/kg/day) mostly brought out trough concentrations <10 μg/ml in our research population. Multiple pharmacokinetic modeling studies can provide discussion about vancomycin dosage.[5,10,23-25] To conform to the trough goals of the Infectious Diseases Society of America and the American Society of Health-System Pharmacists, further grand-scale, and prospective studies are required to identify adequate vancomycin dosing strategies in children.

Acknowledgment

We would like to thank Yu-Lung Chiu for help with the statistical analyses.

Financial support and sponsorship

This work was financially supported by a grant from the Tri-Service General Hospital (TSGH-C105-024).

Conflicts of interest

There are no conflicts of interest.

REFERENCES

1. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, *et al.* Clinical practice guidelines by the infectious diseases society of America for the treatment of methicillin-resistant *Staphylococcus aureus* infections in adults and children. Clin Infect Dis 2011;52:e18-55.
2. Chang CN, Lo WT, Chan MC, Yu CM, Wang CC. An investigation of vancomycin minimum inhibitory concentration creep among methicillin-resistant *Staphylococcus aureus* strains isolated from pediatric patients and healthy children in Northern Taiwan. J Microbiol Immunol Infect 2017;50:362-9.
3. Ringenberg T, Robinson C, Meyers R, Degnan L, Shah P, Siu A, *et al.* Achievement of therapeutic vancomycin trough serum concentrations with empiric dosing in neonatal intensive care unit patients. Pediatr Infect Dis J 2015;34:742-7.
4. Seixas GT, Araujo OR, Silva DC, Arduini RG, Petrilli AS. Vancomycin therapeutic targets and nephrotoxicity in critically ill children with cancer. J Pediatr Hematol Oncol 2016;38:e56-62.
5. Hwang D, Chiu NC, Chang L, Peng CC, Huang DT, Huang FY, *et al.* Vancomycin dosing and target attainment in children. J Microbiol Immunol Infect 2017;50:494-9.
6. Bradley JS, Nelson JD, Kimberlin DW, Leake JA, Palumbo PE, Sanchez PJ, *et al*. Alphabetic listing of antimicrobials. In: Nelson's Pediatric Antimicrobial Therapy. 20th ed. San Diego: American Academy of Pediatrics; 2014. p. 157.
7. Rybak M, Lomaestro B, Rotschafer JC, Moellering R Jr., Craig W, Billeter M, *et al.* Therapeutic monitoring of vancomycin in adult patients: A consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 2009;66:82-98.
8. Rybak MJ, Lomaestro BM, Rotschafer JC, Moellering RC, Craig WA, Billeter M, *et al.* Vancomycin therapeutic guidelines: A summary of consensus recommendations from the Infectious Diseases Society of America, the American Society of Health-System Pharmacists, and the Society of Infectious Diseases Pharmacists. Clin Infect Dis 2009;49:325-7.
9. Miller CE, Batra R, Cooper BS, Patel AK, Klein J, Otter JA, *et al.* An association between bacterial genotype combined with a high-vancomycin minimum inhibitory concentration and risk of endocarditis in methicillin-resistant *Staphylococcus aureus* bloodstream infection. Clin Infect Dis 2012;54:591-600.

10. McNeil JC, Kok EY, Forbes AR, Lamberth L, Hulten KG, Vallejo JG, *et al.* Healthcare-associated *Staphylococcus aureus* bacteremia in children: Evidence for reverse vancomycin creep and impact of vancomycin trough values on outcome. Pediatr Infect Dis J 2016;35:263-8.
11. Dhand A, Sakoulas G. Reduced vancomycin susceptibility among clinical *Staphylococcus aureus* isolates ('the MIC creep'): Implications for therapy. F1000 Med Rep 2012;4:4.
12. Frymoyer A, Guglielmo BJ, Hersh AL. Desired vancomycin trough serum concentration for treating invasive methicillin-resistant staphylococcal infections. Pediatr Infect Dis J 2013;32:1077-9.
13. Mehrotra N, Tang L, Phelps SJ, Meibohm B. Evaluation of vancomycin dosing regimens in preterm and term neonates using Monte Carlo simulations. Pharmacotherapy 2012;32:408-19.
14. Gordon CL, Thompson C, Carapetis JR, Turnidge J, Kilburn C, Currie BJ, *et al.* Trough concentrations of vancomycin: Adult therapeutic targets are not appropriate for children. Pediatr Infect Dis J 2012;31:1269-71.
15. Le J, Bradley JS, Murray W, Romanowski GL, Tran TT, Nguyen N, *et al.* Improved vancomycin dosing in children using area under the curve exposure. Pediatr Infect Dis J 2013;32:e155-63.
16. Glover ML, Cole E, Wolfsdorf J. Vancomycin dosage requirements among pediatric intensive care unit patients with normal renal function. J Crit Care 2000;15:1-4.
17. Arfa P, Karimi A, Rafiei Tabatabaei S, Fahimzad A, Armin S, Sistanizad M, *et al.* A prospective study to assess vancomycin serum concentrations in pediatric patients with current dosing guidelines. Iran J Pharm Res 2016;15:341-6.
18. Song KH, Kim ES, Sin HY, Park KH, Jung SI, Yoon N, *et al.* Characteristics of invasive *Staphylococcus aureus* infections in three regions of Korea, 2009-2011: A multi-center cohort study. BMC Infect Dis 2013;13:581.
19. van Hal SJ, Lodise TP, Paterson DL. The clinical significance of vancomycin minimum inhibitory concentration in *Staphylococcus aureus* infections: A systematic review and meta-analysis. Clin Infect Dis 2012;54:755-71.
20. Yoo RN, Kim SH, Lee J. Impact of initial vancomycin trough concentration on clinical and microbiological outcomes of methicillin-resistant *Staphylococcus aureus* bacteremia in children. J Korean Med Sci 2017;32:22-8.
21. Eiland LS, English TM, Eiland EH 3rd. Assessment of vancomycin dosing and subsequent serum concentrations in pediatric patients. Ann Pharmacother 2011;45:582-9.
22. Garazzino S, Aprato A, Baietto L, D'Avolio A, Maiello A, De Rosa FG, *et al.* Glycopeptide bone penetration in patients with septic pseudoarthrosis of the tibia. Clin Pharmacokinet 2008;47:793-805.
23. Cole TS, Riordan A. Vancomycin dosing in children: What is the question? Arch Dis Child 2013;98:994-7.
24. Frymoyer A, Hersh AL, Benet LZ, Guglielmo BJ. Current recommended dosing of vancomycin for children with invasive methicillin-resistant *Staphylococcus aureus* infections is inadequate. Pediatr Infect Dis J 2009;28:398-402.
25. Miloslavsky M, Galler MF, Moawad I, Actis J, Cummings BM, El Saleeby CM, *et al.* The impact of pediatric-specific vancomycin dosing guidelines: A quality improvement initiative. Pediatrics 2017;139. pii: e20162423.