162

Vancomycin Loading Dose in Pediatric Patients Receiving Intermittent Vancomycin Dosing

Allison H. Bartlett, MD, MS; Danielle Brown-Alm, PharmD, BCPS; Emily Landon, MD; Benjamin D. Brielmaier, PharmD, BCPS; Palak H. Bhagat, PharmD, BCPS

University of Chicago Medicine

Contact information: 5841 S. Maryland Ave MC 6054, Chicago, IL 60637 | Ph: 773-834-1189 | Fax: 773-702-1196 | Email: abartlett@peds.bsd.uchicago.edu

Background

- Vancomycin (VAN) is a glycopeptide antibiotic that inhibits peptidoglycan synthesis, thereby inhibiting bacterial cell wall synthesis.
- VAN was first developed over 50 years ago, and dosing recommendations were based mostly on *in vitro* and animal studies.
- The best predictor of treatment efficacy is an area under the curve (AUC) to minimum inhibitory concentration (MIC) (AUC/MIC) ≥400.
- Because AUC/MIC is complicated to determine in a clinical setting, most institutions instead use VAN trough levels to assist with dose-adjustment.
- Consensus guidelines recommend total trough serum VAN concentrations of 15–20 mg/L for serious infections as this trough should achieve an AUC/MIC of ≥400 in most adult patients if the VAN MIC is ≤1 [Rybak et al 2009].
- Clinical practice guidelines for the treatment of methicillin-resistant *S. aureus* in adults and children acknowledge that the safety and efficacy of targeting VAN trough concentrations of 15-20 mg/L in children requires additional study [Liu 2011].
- Furthermore, multiples studies have demonstrated the inability of a variety of dosing schemes to obtain trough levels in the targeted range [Frymoyer 2011, Miller 2011, Gordon 2012].
- In adults, a loading dose of VAN has been shown to be safe and effective in improving the likelihood of attaining a desirable initial trough level (10-20 mg/L) [Truong 2012].
- A recent randomized controlled trial in pediatric patients ages 2-18 years did not show any benefit of a VAN loading dose on reaching an initial (8hr) vancomycin trough concentration of 10-15 mg/L [Demirjian 2013].
- Despite many years of experience, the appropriate PK/PD parameter to predict efficacy of VAN dosing in children is uncertain.
- We examined VAN dosing and subsequent troughs in a pediatric population to evaluate the effect of a loading dose.

Methods

- Single-center, retrospective chart review of all patients > 3 months old with a least 1 recorded steady-state VAN trough concentration obtained between 12/15/2012 – 8/31/2013 was performed.
- Only the first course of VAN for each patient was included in the analysis.
- Patients on VAN therapy prior to admission or with renal dysfunction were excluded.
- Patients were included in the loading dose group if they received a VAN loading dose.
- Patients were included in the standard dose group if they did not receive a loading dose.
- Data collected included patient age, weight, baseline serum creatinine, VAN loading dose and maintenance dose, duration of VAN therapy prior to trough level, initial VAN steady-state trough level, time VAN trough level was obtained in relation to the dose, and evidence of toxicity.
- VAN trough concentrations drawn prior to the 4th dose were considered to be steady-state trough levels.
- VAN trough concentrations between 10-20 mcg/mL were considered therapeutic.

Statistical Analysis

- Descriptive statistics are presented as median [range].
- Data was analyzed using Stata 10.0, College Station, Texas.

Results

- A total of 54 patients were identified for inclusion in the study.
- Table 1 shows the dosing strategy and initial trough level for each patient that received a loading dose.
- Initial VAN troughs were obtained before the 4th dose in 60% (27/45) patients, and as late as before the 9th dose.
- For patients who received a loading dose of 18-27 mg/kg (n=11):
  - Median initial trough was 10.5 mg/L (range 6.7-13.9); 0/10 initial troughs were supratherapeutic (> 20 mg/L).
- For those who did not receive a loading dose (n=39):
  - Median initial trough was 9.8 mg/L (range <5-22.6); 8/39 (20.5%) initial troughs were undetectable (<5 mg/L); 2/39 (5.1%) initial troughs were supratherapeutic.
- Four patients had VAN dose increased prior to obtaining a level. All of these patients were started on VAN overnight, when pharmacist coverage is limited. Median doses were increased from 10 mg/kg to 17.5 mg/kg once pharmacist review of the order occurred.

Table 1: Patients with Vancomycin Loading Dose and Levels

Patient	Age	Loading Dose (mg/kg)	# Loading Doses Given	Maintenance Dose (mg/kg)	Dosing Interval	Initial VAN Trough	Trough Drawn Before Dose #
1	6 mo	25	1	15	Q 6h	11.2	4
2	4 yr	25	1	15	Q 6h	13.9	4
3	5 mo	25	1	15	Q 6h	9.5	4
4	19 mo	25	1	15	Q 6h	8.3	4
5	25 yr	27	1	13.5	Q 8h	11.3	4
6	17 yr	18	1	13.6	Q 6h	12.5	6
7	8 mo	20	1	14.6	Q 6h	9.1	5
8	13 mo	20	1	15	Q 6h	10.5	5
9	2 yr	25	1	14.7	Q 6h	10.2	4
10	23 mo	20	1	15	Q 6h	6.7	4
11	3.5 mo	22.5	1	18	Q 6h	11.6	5

Table 2: Comparison of Initial Vancomycin Serum Trough Concentrations

VAN Dosing Strategy (n)	Median (Range) Initial Serum Trough Concentration (mg/L)	# (%) Troughs <5 mg/L (undetectable)	# (%) Troughs 5 – 10 mg/L	# (%) Troughs 10 – 20 mg/L	# (%) Troughs >20 mg/L
Loading Dose (n= 11)	10.5 (6.7-13.9)	0	4 (36.4%)	7 (63.6%)	0
All controls (n=43)	9.0 (<5-22.6)				
Standard Dose (n=39)	9.8 (<5-22.6)	8 (20.5%)	16 (41%)	13 (33.3%)	2 (5.1%)
Low Dose (n=4)	8.5 (5-10.8)	0	3 (75%)	1 (25%)	0

Nephrotoxicity

- Overall rate of nephrotoxicity for patients receiving VAN therapy was 10% (5/50 patients).
- 0/11 (0%) patients who received a VAN loading dose experienced nephrotoxicity compared to 5/39 (12.5%) who received standard dose.
- Rate of nephrotoxicity in patients with an initial VAN trough >15 mg/L was 16.7% (1/6 patients).
- Nephrotoxicty was observed 2 days into VAN therapy (2 patients), 4 days into therapy (1 patient), 10 days into therapy (1 patient) and 25 days into therapy (1 patient).
- Median time required for serum creatinine to return to baseline was approximately 9 days (range: 7 – 28 days).
- Median dose at time the toxicity occurred was 63.6 mg/kg/day (range: 30 – 88.3 mg/kg/day).

Conclusions

- Loading doses of VAN result in higher initial VAN troughs in pediatric patients.
- Conventional pediatric dosing strategies (no loading dose) resulted in initial VAN trough <10 mg/L in 61.5% (24/39) patients.
- Overall rate of nephrotoxicty was 10% (5/50 patients) with 0/11 patients in the loading dose group experiencing nephrotoxicity.
- Serum creatinine returned to baseline in all patients experiencing nephrotoxicity at a median of 9 days (range: 7 – 28 days).
- Use of a loading dose was safe and resulted in higher initial troughs in this study population and suggests that more aggressive and standardized dosing strategies may benefit pediatric patients on VAN therapy.

Limitations

- Small sample size of patients receiving a VAN loading dose.
- Lack of standardization in timing of VAN level attainment.
- Possible discrepancy between documented versus actual time of VAN dose administration and serum trough concentration attainment.

References

1. Rybak M, Lomaestro B, Rotschafer JC, 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.
2. Liu D, Bayer A, Cosgrove SE, 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: Executive Summary. *Clin Infect Dis* 2011;52:285-92.
3. Frymoyer A, Guglielmo BJ, Wilson SD, et al. Impact of a Hospital-wide Increase in Empiric Pediatric Vancomycin Dosing on Initial Trough Concentrations. *Pharmacotherapy* 2011;31:781-6.
4. Miller M, Miller JL, Hagemann TM, et al. Vancomycin Dosage in Overweight and Obese Children. *Am J Health Syst Pharm* 2011;68:2062-8.
5. Gordon CL, Thompson C, Carapetis JR, et al. Trough Concentrations of Vancomycin: Adult Therapeutic Targets are Not Appropriate for Children. *Pediatr Infect Dis J* 2012;31:1269-71.
6. Truong J, Levkovich BJ, Padiglione AA. Simple approach to improving vancomycin dosing in intensive care: a standardized loading dose results in earlier therapeutic levels. *Internal Med J* 2012:42;23-29.
7. Demirjian A, Finkelstein Y, Nava-Ocampo A, et al. A Randomized Controlled Trial of a Vancomycin Loading Dose in Children. *Pediatr Infect Dis J* 2013 Jun 28. [Epub ahead of print].

Disclosure

The authors of this presentation have no financial or personal relationships with commercial entities that may have a direct or indirect interest in the subject matter of this presentation.