Prolonged Infusion Of Vancomycin Leads To Toxicity: A Case Series.

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Abstract

Objective

To evaluated the incidence of nephrotoxicity in patients who have received prolonged infusions (PI) of vancomycin.

Methods

Retrospective chart review of adolescents (age 12-18 years) who received PI vancomycin between September 2012 and August 2015 was performed. Patients were included if they had serum concentrations obtained at steady state (after 3 doses). Urine output and serum creatinine (SCr) were evaluated for acute kidney injury (AKI): 50% increase in baseline SCr or urine output less than 1 mg/kg/hr over a two day interval.

Results

Seven patients were included in the study with two patients aged 14, two 16, one 13, and one 18 years. Five patients received 1 gm vancomycin, one received 1.25 gm vancomycin, and one received 1.5 gm vancomycin. Similarly, two patients had a every 6 hours dosing interval, four patients had an 8-hour interval, and one patient had a 12-hour dosing interval. Two patients (28.6%) experienced supratherapeutic vancomycin concentrations: patient 1 had four levels ranging from 28.5 to 30.1 mg/dL while receiving an empirical dose of 1 gm over 90 minutes every 6 hours and patient had a level of 22.9 mg/dL while on 1.25 gm over 120 minutes every 8 hours. Patient 1 experienced AKI (one of seven patients, 14.2%).

Conclusion

Vancomycin PI caused supratherapeutic vancomycin concentrations in two of the seven patients studied and AKI in one patient. Further investigation of PI vancomycin-induced nephrotoxicity is warranted.

Background

- Vancomycin is typically dosed at 15 mg/kg/dose over one hour IV every 6 hours when used to treat infections in pediatric patients.[1,2]
- Due to concerns of Red Man's Syndrome (RMS, infusion-related reaction) in adult patients, a protocol was implemented at our institution for vancomycin doses ≥ 1 gm to be infused ≥ 90 min.[3]
- Extending the infusion time without adjusting the short dosing interval in pediatric patients may lead to supratherapeutic vancomycin serum concentration (VSC, greater than 20 mg/L), accumulation, and potentially nephrotoxicity.[4,5]
- This study's purpose was to identify the incidence of nephrotoxicity in adolescents who receive prolonged infusion (PI) vancomycin.

Methodology

Inclusion Criteria

Adolescent patients (ages 12-18 years) who received an extended infusion of vancomycin (≥ 90 min.), at least 4 doses of vancomycin, and had at least one VSC obtained.

Data Collection

Patient age, weight, height, past medical history, reason for admission, indication, dosing regimen(s), serum creatinine (SCr), VSC, culture data if available, and urine output if documented.

Acute Kidney Injury (AKI): a 50% increase (or 0.5 mg/dL) from baseline SCr or urine output < 1 mL/kg/hr over 48 hours.[5]

Results

- 93 children aged 12 – 18 years received vancomycin IV between September 2012 and August 2015; 38 patients had received PI, 10 patients received 4 or more doses, but only 7 had VSC obtained.

Table 1. Patient Baseline Demographics

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7
Age (yr)	14	16	18	16	14	16	13
Gender	M	M	F	M	M	M	M
Weight (kg)	54.4	101.4	79.8	56.2	59.0	74.5	60.4
BMI (kg/m^2)	20.2	28.7	28.3	19.9	20.4	24.3	23.6
PMH	ADHD, mononucleosis, spinal meningitis	--	MRSA, cardiac arrest, hypertension	Asthma	Ewing's sarcoma	--	Asthma
Hospital stay (days)	10	4	58	11	7	42	6

ADHD = Attention Deficit Hyperactivity Disorder; BMI = Body mass index; F = Female; M = Male; MRSA = Methicillin-resistant *Staphylococus aureas*; PMH = Past medical history

Table 2. Vancomycin Indication & Dosing Regimen(s)

	Pt 1	Pt 2	Pt 3	Pt 4	Pt 5	Pt 6	Pt 7
Indication	Meningitis	Potential skin infection	Pharyngitis	OM, cellulitis	OM	OM	Left otitis media
Micro-organism data	*S. pneumoniae* (MIC 0.38 g/L)	NA	beta *Streptococcus* group A	MRSA (MIC 1 g/L)	*Staphylococcus* and *Streptococcus*	*Staphylococcus*	*Enterococcus* (MIC S)
Dose mg (mg/kg)	1000 (18.4)	1500 (14.8)	1000 (12.5)	1000 (17.8)	1000 (16.9)	1250 (19.4)	1000 (16.6)
Infusion duration (min)	90	120	90	90 [a]	90	120	90
Dosing interval (hr)	**6**	8	8	12	8	8	**6**
Daily dose (mg/kg/day)	**73.6**	44.4	37.5	35.6	50.7	58.2	**66.4**
# of regimen changes	4 [b]	--	--	1[c]	1[d]	--	--
Duration therapy (days)	10	3	2	7	4	8	2

MIC = Minimum inhibitory concentration; MRSA = methicillin resistant *S.* aureus; NA = Not available; OM = Osteomyelitis

[a] RMS occurred with 1st dose of vancomycin; infusion duration increased to 2 hr.
[b] 1st 1500 mg (27.5 mg/kg) q8h, 2nd 1250 mg (22.9 mg/kg) q6h, 3rd 1100 mg (20.2 mg/kg) q8h, 4th 1000 mg (18.4 mg/kg) q12h; all doses infused over 90 min.
[c] 1000 mg (17.8 mg/kg) q8h over 90 minutes
[d] 1250 mg (21.2 mg/kg) q8h over 60 minutes

Results (cont.)

Figure 1. Serum Creatinine Levels Based on Vancomycin Therapy Day

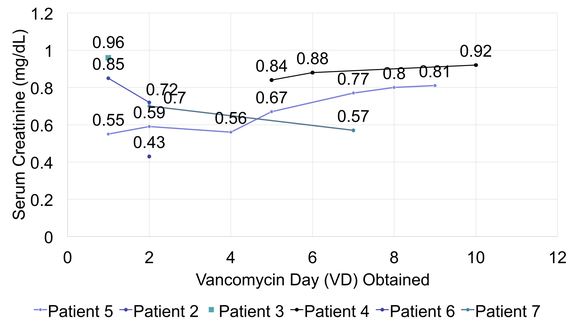


Figure 2. Vancomycin Serum Concentrations in Each Patient

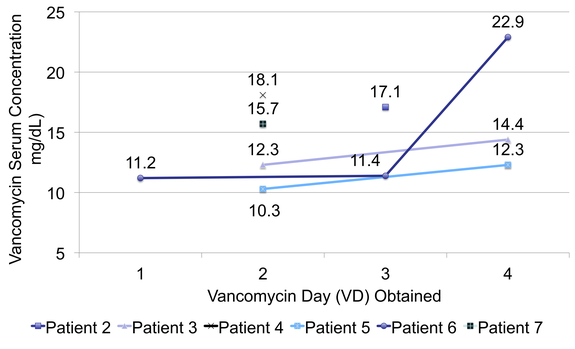
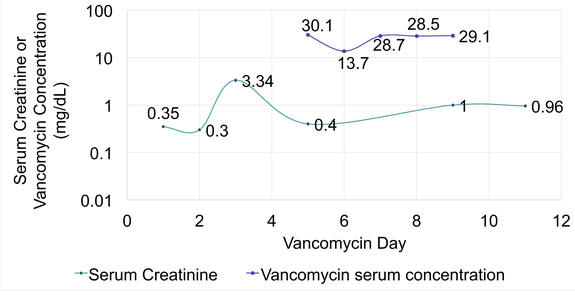


Figure 3. Patient 1 Vancomycin and Creatinine Serum Concentrations



Results (cont.)

- Two patients (Patient 1 and 7) received 1 gm over 90 minutes IV q6h, while the remaining patients had longer dosing intervals of q8h or q12h.
- Two patients (patients 1 and 6) had supratherapeutic VSC (28.5%)
- One patient (patient 1) experienced AKI (14.2%); see Figure 3
- Patient 7 did not have supratherapeutic VSC or AKI; 2 days of therapy with one VSC measured on HD2 (last VD)
- Patient 6 only experienced one supratherapeutic VSC, but did not experience AKI.

Discussion

- During the 3 year study period, 38 patients received PI vancomycin, but only 7 patients received multiple doses and had VSC measured.
- Of the two patients receiving 1 gm PI IV q6h, only one experienced AKI. A potential explanation is patient 1 had a higher weight based dose of 18.4 mg/kg/dose q6h (73.6 mg/kg/day) most likely to aggressively treat the CNS infection compared to patient 7 who received 16.6 mg/kg/dose q6h (66.4 mg/kg/day) for a total of 9 doses with only one VSC measure before the 4th dose. If patient 7's regimen was continued with additional VSC measured, he may have been at risk of AKI.
- Low incidence of RMS in non-oncologic pediatric patients indicates empiric PI of vancomycin is not warranted.[6]
- Based on our results, we recommend if PI vancomycin dosing is used the interval of q6h should be used with great caution and only for severe infections with frequent monitoring of VSC and SCr.
- Empiric PI vancomycin dosing may be optimal with an interval of q8h or q12h if a patient is to receive a PI.

Conclusions

- One patient receiving PI vancomycin experienced AKI potentially due to an aggressive dosing regimen and short dosing interval.
- If PI vancomycin is indicated, the dosing interval should be extended to q8h or q12h to avoid AKI.
- Further investigation in a larger pediatric population is still necessary to evaluate toxicity associated with PI.

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