MedCrave
Step into the World of Research

Pharmacy & Pharmacology International Journal

Research Article

Open Access

CrossMark

Evaluation of the effects of two vancomycin dosing frequencies on the incidence of acute kidney injury in a community hospital: A retrospective pilot study

Abstract

Objective: Practice guidelines recommend an initial vancomycin dose of 15 to 20 mg/kg of actual body weight (ABW) given intravenously (IV) every 8 to 12 hours in patients with normal renal function.[1] Currently at our institution, there is a concern among providers that empiric vancomycin intravenous dosing intervals of eight hours may be associated with an increased rate of nephrotoxicity compared to longer intervals of 12 hours or more. The objective of this study is to evaluate the effects of two vancomycin dosing intervals (eight hours and 12 hours) on renal function.

Methods and results: A retrospective chart review was conducted for patients who empirically received vancomycin at a dosing interval of eight hours and 12 hours from 2015 to 2018. Patients at least 18 years old who received vancomycin due to a suspected or proven gram-positive infection and had at least one trough drawn at steady state were included. Patients were excluded if they were pregnant, had renal insufficiency, or if trough levels were not drawn appropriately. The eligible patients were divided into two groups according to the vancomycin dosing intervals (eight hours versus 12 hours), then evaluated for nephrotoxicity. The primary endpoint of this study was the incidence of acute kidney injury (AKI) as defined by Kidney Disease Improving Global Outcomes criteria among the two groups.

Seventy patients met the inclusion criteria in the study including 35 patients in the eight-hour dosing interval group and 35 patients in the 12-hour dosing interval group. Patients (mean age 52.8) were primarily male (60%), Caucasian (70%), and majority of them received concomitant nephrotoxic agents (60%). Most common vancomycin indication among both groups was skin and soft tissue infection. AKI was observed in two patients (5.7%) in the eight-hour group versus one patient (2.9%) in the 12-hour group, however, the difference was not statistically significant (p=0.552). All three of these patients who developed AKI were also on concurrent nephrotoxic agents, such as intravenous contrast dye and piperacillin/tazobactam. Among the secondary endpoints even though a higher percentage of patients achieved a goal trough level in the eight-hour group compared to patients in the 12-hour group (74% vs. 63% respectively), the results were not statistically significant (p=0.445).

Conclusion: No statistically significant difference in rates of AKI was observed among the two dosing interval groups in this study. Patients who experienced AKI were on concomitant nephrotoxic agents and given the small sample size of this feasibility study, the true incidence of AKI due to vancomycin dosing intervals cannot be established. A larger scale study is needed to determine the optimal vancomycin dosing interval.

Keywords: vancomycin, dosing interval, vancomycin trough, vancomycin level, acute kidney injury, nephrotoxicity

Volume 10 Issue 1 - 2022

Irandokht Khaki Najafabadi,[1] Hua Ling,[2] Essie Samuel[3]

[1]Assistant professor of pharmacy practice, Philadelphia College of Osteopathic Medicine Georgia School of Pharmacy Suwanee Georgia, USA

[2]Associate professor of pharmacy practice, Philadelphia College of Osteopathic Medicine Georgia School of Pharmacy Suwanee Georgia, USA

[3]Assistant professor of pharmacy practice, clinical infectious disease specialist pharmacist, Philadelphia College of Osteopathic Medicine Georgia School of Pharmacy Suwanee Georgia, USA

Correspondence: Essie Samuel, Pharm.D., BCPS, Assistant professor of pharmacy practice, Clinical infectious Disease specialist pharmacist, Philadelphia College of Osteopathic Medicine Georgia School of Pharmacy Suwanee, Georgia, USA, Tel 678-407-7367, Email essiesa@pcom.edu

Received: December 08, 2022 | **Published:** January 31, 2022

Introduction

Vancomycin is a glycopeptide antibiotic prescribed for infections caused by suspected or confirmed gram-positive organisms. It is frequently used for skin and soft tissue infections caused by methicillin-resistant *Staphylococcus Aureus* (MRSA) in hospitalized patients.

Per the 2009 consensus recommendations on vancomycin dosing from the Infectious Diseases Society of America (IDSA), the American Society of Health-System Pharmacists (ASHP), and the Society of Infectious Diseases Pharmacists (SIDP), an initial vancomycin dose of 15 to 20 mg/kg of actual body weight (ABW) given intravenously (IV) every 8 to 12 hour is recommended for patients with normal renal function.[1] An area under the serum drug concentration-versus-time curve (AUC) to minimum inhibitory concentration (MIC) ratio of ≥400 correlates best with vancomycin efficacy based on data from animal models.[2] However, obtaining AUC values from blood levels is not practical in most settings, and therefore trough blood levels are used as a surrogate marker by most institutions.[1] Data suggest that trough blood levels of vancomycin <10 mcg/mL can potentially increase the risk for treatment failures and development of resistant organisms.[3] Therefore, IDSA, ASHP, and SIDP provided a joint recommendation that trough blood levels of vancomycin be always maintained above 10 mcg/mL in the 2009 vancomycin dosing guidelines.[1] In addition, higher trough levels of 15 to 20 mcg/mL are recommended for certain infections including bloodstream infections, endocarditis, osteomyelitis, meningitis, and pneumonia. Since the adoption of the higher trough levels for some infections, increased nephrotoxicity cases associated with vancomycin have been reported.[4,5] Even though targeting trough levels greater than

10 mcg/mL may be essential to ensure efficacy, there is limited data to support its safety. There was a concern among providers that shorter interval duration of eight hours may be associated with an increased rate of nephrotoxicity compared to longer intervals of 12 or more hours. A retrospective study by Brumer and colleagues showed that vancomycin dosed at eight-hour intervals resulted in higher incidence of troughs greater than 20 mcg/mL.[6] The objective of this pilot study is to evaluate the effects of two vancomycin dosing intervals: every eight hours (Q8H) and every 12 hours (Q12H) on kidney function by evaluating the incidence of acute kidney injury (AKI). Per Kidney Disease Improving Global Outcomes criteria, AKI is defined by an increase in SCr by ≥0.3 mg/dl within 48 hours; or an increase in SCr to 1.5 times its baseline value.[7]

Methods

This was a small pilot study done at a 200-bed community hospital in Georgia, United States. The study consisted of a retrospective chart review of patients who empirically received vancomycin at dosing intervals of Q8H and Q12H from 2015 to 2018. This retrospective chart review received an Institutional Review Board exception.

Inclusion criteria consisted of patients 18 years old who received vancomycin during the study period, had at least one trough level drawn at steady state, and had serum creatinine (SCr) recorded. Patients who were pregnant, had acute renal insufficiency, had trough levels that were not drawn appropriately (eg, not drawn at steady state, drawn during infusion, drawn after the dose was administered, etc). Two hundred patients were evaluated for inclusion into the study. Of them, 130 patients were excluded because they did not have a steady state trough level recorded or had a trough level drawn inappropriately. Data was collected on 70 patients (35 patients in each group) and analyzed. Patients who met the criteria were stratified into two groups according to the dosing interval: Q8H group and Q12H group. Patient data such as age, gender, height, weight, SCr, comorbidities, location during hospital stay (eg, intensive care unit vs medical floor), concomitant nephrotoxic agents (eg. aminoglycoside, piperacillin/tazobactam, contrast dye), vancomycin dose in mg/kg, dosing interval, indication, vancomycin trough levels, time of trough collections, and dose administration times were collected. The secondary endpoints included percent of patients that fell within goal trough range (10-15 mcg/mL or 15-20 mcg/mL depending on the indication) as well as percent of patients with sub-therapeutic (less than 10 or 15 mcg/mL depending on the indication) or supra-therapeutic trough levels (greater than 20 mcg/mL) in each group. Statistical Package for Social Sciences (IBM Corp. Released 2019. IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp) was used for statistical analysis, Fisher's exact test was conducted to compare the rate of AKI between the two groups, and Chi-square test was used to determine the percent of patients within goal trough range in each group. Descriptive statistics were also used as appropriate.

Results

Baseline demographic and clinical characteristics are summarized in Table 1. Patients (mean age 52.8) were primarily male (60%) and Caucasian (70%), and received at least one concomitant nephrotoxic agent (60%). The most common indication for vancomycin use was abscess/cellulitis observed in 23 of the 70 patients where eight of them had confirmed MRSA as well. Overall, patients who were initially started on Q8H dosing interval were younger than patients who received Q12H dosing interval with a median age of 42 years compared to 53 years respectively. No major difference in weight or SCr was observed between the two groups based on descriptive statistics. The mean duration of treatment in the Q8H group was three days compared to four days in the Q12H group.

Table 1 Baseline patient demographics and clinical characteristics

Demographics	12 hr Interval Group(n=35)	8 hr Interval Group(n=35)
Age <30, n	5	9
Age 30-40,n	8	8
Age>=50, n	22	18
Male gender, n	20	26
White	26	23
African American	6	6
Hispanic	1	2
Non-Hispanic	2	4
Concomitant disease states, n (%)		
• Hypertension		
• Hyperlipidemia	9	7
• Diabetes	3	5
• Hypothyroidism	700	1
• Malignancy	0	3
• COPD		0
Mean ABW, kg	43.03	50.7
BMI, kg/m2 ≥30, n (%)	7	8
Clinical characteristics		
Estimated CrCL,>100 mL/min, n (%)	21	23
Age <50 years and CrCL>=80 mL/min, n(%)	14	21
Intensive care unit stay while on vancomycin, n (%)	7	3
Concomitant nephrotoxic agents, n (%)		8
· IV contrast dye	10	0
· Acyclovir	1	0
· Diuretics	1	0
· Aminoglycosides	1	7
· NSAIDS	1	2
· ACEI	7	0
· Tacrolimus	3	0
Concomitant vasopressors, n (%)	0	0
Site of infection, n (%)		
· Respiratory	8	7
· Bloodstream	3	1
· Skin and soft tissue	11	12
· Central nervous system	2	1
· Bone	3	1
· Urinary tract	1	1
Microbiological data		
Positive cultures, n (%)		
• MRSA	4	6
• MSSA	4	2
• Streptococcus	3	1
Treatment Course		
Mean duration of therapy, days	4.2	3.2

Abbreviations: ABW, actual body weight; BMI, body mass index; CrCL, creatinine clearance; NSAID, nonsteroidal anti-inflammatory drug; ACEI, angiotensinogen converting enzyme inhibitor; MRSA, methicillin-resistant *Staphylococcus aureus*; MSSA, methicillin-sensitive *Staphylococcus aureus*

AKI was observed in 5.7% (two of 35) patients in the Q8H group vs 2.9% (one of 35) patients in the Q12H group, p= 0.552. Median

time to development of AKI was two days in the Q8H and seven days in the Q12H group.

Patient characteristics of the nephrotoxicity cases are summarized in Table 2. All three patients had received concomitant nephrotoxic agents and none of them required renal replacement therapy. SCr returned to normal range in one of these patients within four days while data was unavailable for the other two patients as they got discharged with outpatient follow-up. Vancomycin was discontinued in one of the three patients who developed AKI while the other two patients were switched to intermittent vancomycin dosing (level based dosing).

Table 2 Nephrotoxicity cases

Patient	days to nephrotoxicity	Age, years	Max trough level, mg/l	Days to max trough	Concomitants nephrotoxins	Dose (mg/kg) at the time of nephrotoxicity
1	2	47	24	2 days	Piperacillin/tazobactam x6 doses	14.9 1750 mg IV Q8 H with ID of 2 g
2	2	41	10.1	5 days	IV contrast x1 dose and piperacillin/ tazobactam x15 doses	18.75 1500 mg IV Q8H with ID of 2 g
3	7	24	25	7	Piperacillin/ tazobactam x21 doses, contrast and ketorolac IV X1 dose	14.01 1500 mg IV Q12H with LD of 2 g

Abbreviations: IV, intravenous; Q8H, every eight hours; Q12H, every 12 hours

Secondary endpoints were evaluated and of 35 patients in each group, 25 patients (74.2%) had trough levels within goal range in the Q8H group while 22 patients (62.8%) had trough levels within goal trough range in the Q12H group, p=0.445. Supra-therapeutic trough levels were observed in five of the 35 patients (14.4%) in the Q8H group and six of the 35 patients (17.1%) in the Q12H group. Sub-therapeutic trough levels were observed in two patients (5.7%) in the Q8H group versus six patients (17.1) in the Q12H group.

Discussion

The purpose of this study was to decide whether Q8H dosing interval of vancomycin is associated with higher rates of nephrotoxicity and should therefore be avoided empirically in the patient population at our institution. Even though the incidence of AKI was higher in the Q8H group, a statistically meaningful conclusion cannot be drawn due to the small sample size of the study. The difference in the percentage of patients with trough levels within goal range in the Q8H and the Q12H groups was not statistically significant which is also most likely due to the small sample size.

A meta-analysis on vancomycin-induced nephrotoxicity by Van Hal et al reported a nephrotoxicity rate between 5% and 43%. They also concluded that a higher nephrotoxicity rate was observed in critically ill patients and was associated with a vancomycin trough >15 mcg/mL.[8] Compared with the meta-analysis, our study results showed an overall lower rate of nephrotoxicity of 4.2% (three of 70 patients), which may be attributed to trough levels being frequently monitored and doses being adjusted accordingly.

There were a number of limitations to this study including retrospective study with a small sample size from a single center. We acknowledge that the nature of this study is a pilot study conducted for quality assurance purposes. Therefore, it is expected that the study may be insufficiently powered. However, the trends shown in our study are consistent with the previous studies.[6] Another limitation is that all three patients who developed AKI were on concomitant nephrotoxic agents and therefore a definitive cause of AKI cannot be established. In addition, patients in this study were younger with excellent renal function (62% with CrCL>100 mL/min) at baseline which may limit the generalizability of the study. Lastly, some providers at our institution are unaccustomed to dosing vancomycin IV at shorter intervals of Q8H as a standard of practice in hospitalized adult patients with normal renal function in order to achieve therapeutic trough levels.

Conclusion

This study provides a single-center evaluation of the rate of AKI with dosing vancomycin IV at Q8H and Q12H intervals. This study observed a higher but non-significantly different rate of AKI in the Q8H group compared to patients in the Q12H group. However, all patients that experienced AKI were on concomitant nephrotoxic agents and given the small sample size of this feasibility study, the true incidence of AKI due to vancomycin dosing intervals cannot be established. Further evaluation of vancomycin therapy is needed to determine optimal initial dosing interval for adult patients.

Acknowledgments

None.

Conflicts of interest

Dr. Ling served on the advisory board for Alnylam Pharmaceuticals.

References

1. Rybak M, Ben L, 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(1):82–98.
2. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. *Clin Infect Dis*. 2006;42 Suppl 1:S35–S39.
3. Sakoulas G, Gold HS, Cohen RA, et al., Effects of prolonged vancomycin administration on methicillin-resistant Staphylococcus aureus (MRSA) in a patient with recurrent bacteraemia. *J Antimicrob Chemother*. 2006;57(4):699–704.
4. Wong-Beringer A, Joo J, Tse E, et al. Vancomycin-associated nephrotoxicity: a critical appraisal of risk with high-dose therapy. *Int J Antimicrob Agents*. 2011;37(2):95–101.
5. Sinha Ray A, Haikal A, Hammoud KA, et al. Vancomycin and the Risk of AKI: A Systematic Review and Meta-Analysis. *Clin J Am Soc Nephrol*. 2016;11(12):2132–2140.
6. Brumer E, Dubrovskaya Y, Scipione MR, et al. Evaluation of Treatment Courses When Vancomycin Is Given Every 8 Hours in Adult Patients. *J Pharm Pract*. 2015;28(6):511–517.
7. Stevens PE, Levin A. Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Guideline Development Work Group, Evaluation and management of chronic kidney disease: synopsis of

the kidney disease: improving global outcomes 2012 clinical practice guideline. *Ann Intern Med*. 2013;158(11):825–830.

8. van Hal SJ, Paterson DL, Lodise TP. Systematic review and meta-analysis of vancomycin-induced nephrotoxicity associated with dosing schedules that maintain troughs between 15 and 20 milligrams per liter. *Antimicrob Agents Chemother*. 2013;57(2):734–744.

Citation: Najafabadi IK, Ling H, Samuel E. Evaluation of the effects of two vancomycin dosing frequencies on the incidence of acute kidney injury in a community hospital: A retrospective pilot study. *Pharm Pharmacol Int J*. 2022;10(1):1–4. DOI: 10.15406/ppij.2022.10.00356