RESEARCH ARTICLE

Correlation between serum vancomycin trough level and therapeutic response in septic patients during augmented renal clearance phase

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Background: Vancomycin is a glycopeptide antibiotic that was extensively used for treatment of gram positive infections. Therapeutic drug monitoring (TDM) is recommended to optimize efficacy and safety of vancomycin. Data regarding TDM of vancomycin are scant in septic patients especially during augmented renal clearance (ARC) phase.

Methods: In this observational study, 39 patients with diagnosis of sepsis that were in ARC phase were evaluated. The breakpoint for serum trough level of vancomycin was considered as 15 mg/l. The patients were stratified in two groups based on the measured serum trough levels (< 15 mg/l versus ≥15 mg/l).

Results: Clinical response and microbiological clearance were compared between the groups. In terms of clinical response, there was no significant difference between the groups (P = 0.677). Also, the microbiological clearance was not different between the groups (P= 1.00).

Conclusion: Septic patients during ARC phase had comparable clinical and microbial responses regardless of serum trough levels of vancomycin.

Keywords: Vancomycin, Clinical response, Microbiological clearance, Sepsis

Vancomycin is a glycopeptide antibiotic that is widely used for treatment of resistant gram-positive organisms [1-4]. Augmented Renal Clearance (ARC) is a complex issue for antibiotics' dose adjustment [1-3]. This phenomenon is defined as a creatinine clearance (CrCl) more than 130 ml/min [2, 4]. This phenomenon is common in early phase of sepsis [2, 4]. According to the sepsis guideline, vancomycin is recommended to cover gram-positive organisms [5]. Serum vancomycin trough levels between 10-15 mg/l and 15-20 mg/l are recommended for mild to moderate and severe infections respectively [6].

There are some evidences that even in serum vancomycin trough levels less than 15 mcg/l patients had acceptable clinical response renal safety [7-9]. Serum vancomycin trough level is a surrogate marker of targeted AUC/MIC (area under the curve/minimum inhibitory concentration) index [6]. In recent study, both patients with serum vancomycin trough levels≥ 15 mg/l and <15 mg/l reached the targeted AUC/MIC [10].

In this study clinical response and microbiological clearance were compared in septic patients in ARC phase with serum vancomycin trough levels≥ 15 mg/l and< 15 mg/l.

Methods

In this observational study, the information of 39 septic patients in ARC phase from ICU wards of Imam Khomeini Hospital Complex were recorded. Vancomycin had been administered with a loading dose of 25 mg/kg initially and then with maintenance doses of 15 mg/kg every 8 hours. Vancomycin trough concentration had been measured before the fourth dose of vancomycin, and dose adjustment had been done if necessary. After that, another trough concentration was measured at day of four. The breakpoint for trough concentration was considered 15 mg/l. Patients were stratified by serum trough concentration of vancomycin in fourth day into two groups (less than 15mg/l versus equal or more than 15mg/l). Because the treatment response to vancomycin is delayed, the trough concentration in fourth day was considered for data analysis. Clinical response and microbiological clearance were considered as main outcomes of the study. Clinical response was defined as reversal of Systemic Inflammatory Response Syndrome (SIRS) parameters. If positive cultures became negative after 72 h of vancomycin therapy it was considered as microbiological clearance.

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Data were analysed with SPSS version 21. Distribution of data was assessed with Kolmogorov-Smirnov normality test. Categorical data was reported as a number and percentage. Continuous data was reported as mean ± SD. In statistical analysis, p value less than 0.05 was considered as statistical significant.

Results

During this study, 39 patients were included. Twenty-two and 17 patients had serum vancomycin trough levels <15 mg/l and ≥15 mg/l respectively. Most of the patients received meropenem as a concomitant antibiotic with vancomycin. The patients did not significantly differ in terms of demographic and baseline characteristics (Table 1). The vancomycin pharmacokinetic parameters are summarized in (Table 2).

Clinical response and microbiological clearance were assessed at day 4 of treatment. From 22 patients with serum vancomycin trough concentration <15 mg/l, 19 patients had clinical response. From 17 patients with trough concentration ≥15 mg/l, 13 patients had clinical response. The clinical response was not different between the groups (p= 0.677). Only 16 patients in this study had positive blood cultures and microbiological clearance was similar between the groups (p= 1.00). Clinical response and microbiological clearance data are shown in (Table 3).

Table 1- Demographic and baseline characteristics of patients

Variable (Mean ± SD) or number (%)	Patients with serum vancomycin levels< 15 mg/l (n=22)	Patients with serum vancomycin levels≥ 15 mg/l (n=17)	P value
Gender (%)			0.307a
Male	12 (54.5%)	12 (70.60%)	
Female	10 (45.5%)	5 (29.40%)	
Age (years)	42.18 ± 13.84	48.09 ± 19.54	0.262b
Weight (kg)	80.40 ± 13.06	73.33 ± 10.52	0.063b
Comorbidity (%)			
Cardiovascular disease (CVD)	7 (31.80%)	5 (29.40%)	0.872a
Malignancy	4 (18.20%)	5 (29.4%)	0.465c
Diabetes	3 (13.60%)	1 (5.90%)	0.618c
HIV or another viral disease	2 (9.10%)	0 (0.00%)	0.495c
Serum creatinine (mg/dl)	0.82 ± 0.18	0.86 ± 0.17	0.466b
GFR (ml/min/1.73 m2)	138.63 ± 7.78	134.91 ± 4.11	0.121b
Concomitant drugs (%)			
PPI (Pantoprazole, omeprazole)	18 (81.80%)	14 (82.40%)	1c
Heparin			
Carbapenem	17 (77.30%)	13 (76.50%)	1c
Sedation & analgesic (Fentanyl + midazolam)	17 (77.3%)	12 (70.60%)	0.721c
Furosmide	18 (36.40%)	11 (64.70%)	0.079a
Corticosteroid			
Vasopressor (norepinephrine)	7 (31.80%)	6 (35.30%)	0.819a
Enoxaparine	10 (45.50%)	3 (17.60%)	0.068a
Piperacillin-tazobactam	2 (9.10%)	6 (35.30%)	0.059c
Aminoglycosides (amikacin, gentamycin)	4 (18.30%)	3 (17.60%)	1c
Oral anticoagulants	1 (4.50%)	2 (11.80%)	0.570c
NSAIDs	0 (0.00%)	3 (17.60%)	0.074c
Amphotericin			
	1 (4.50%)	1 (5.90%)	1c
	4 (18.20%)	1 (5.90%)	0.363c
	1 (4.50%)	0 (0.00%)	1c

Table 1- Demographic and baseline characteristics of patients (Continued)

Variable (Mean ± SD) or number (%)	Patients with serum vancomycin levels< 15 mg/l (n=22)	Patients with serum vancomycin levels≥ 15 mg/l (n=17)	P value
Nutrition:			0.492a
Enteral	15 (68.20%)	14 (82.40%)	
Enteral + parenteral	6 (27.30%)	2 (11.80%)	
Parenteral	1 (4.50%)	1 (5.90%)	
Total intake (ml)	1900.00 ± 414.04	1942.86 ± 485.99	0.832b
Total output (ml)	1580.00 ± 348.87	1657.14 ± 492.8	0.676b
Cause of admission (%)			
Surgical	13 (59.10%)	12 (70.60%)	0.458a
Medical	9 (40.90%)	5 (29.40%)	
APACHE II score	14.36 ± 6.24	15.43 ± 7.89	0.625b
SOFA score	5.09 ± 2.02	6.33 ± 2.09	0.079b
Source of sepsis (%)			0.864a
CNSd	7 (31.80%)	6 (35.30%)	
Pulmonary	6 (27.30%)	5 (29.40%)	
Bone or Join	4 (18.20%)	1 (5.90%)	
Abdominal	2 (9.10%)	3 (17.60%)	
Soft tissue	1 (4.50%)	1 (5.90%)	
Others	2 (9.10%)	1 (5.90%)	

Chi-square.
Independent sample t-test
Fisher's Exact test
Central Nervous System

Table 2- Vancomycin pharmacokinetic parameters

Mean ± SD	Patients with serum vancomycin levels <15 mg/l (n=22)	Patients with serum vancomycin levels≥15 mg/l (n=17)	P value
Trough level in fourth day	13.39 ± 1.10	18.43 ± 2.22	<0.001
Mean total daily dose	3604.76 ± 255.88	3553.33 ± 290.60	0.578

Table 3- Clinical and microbiological responses

Number (%)	Patients with serum vancomycin levels< 15 mg/l (n=22)	Patients with serum vancomycin levels≥ 15 mg/l (n=17)	P value
Clinical response	19 (86.40%)	13 (76.50%)	0.677
Microbiological response	6 (75.00%)	6 (75%)	1

Discussion

In this study, the clinical response and microbiological clearance were not different between patients with serum vancomycin trough levels≥ 15 mg/l and patients with serum vancomycin trough levels< 15 mg/l.

In patients with pneumonia, endocarditis and osteomyelitis due to MRSA, clinical was not different between the two groups with trough concentration less than 15 mg/l and more than 15 mg/l. But the rate of vancomycin induced nephrotoxicity (VIN) was more in patients with higher vancomycin trough concentration (≥15 mg/l). However microbiological clearance was not assessed in this study [11].

In another observational study, found a correlation was not found between serum vancomycin trough concentration and time to normalization of clinical signs and symptoms. However serum trough levels of vancomycin were negatively correlated with CrCl values [12].

In a systematic review and meta-analysis, all-cause mortality was assumed as a main outcome. Mortality was not significantly different between patients with serum trough concentration of vancomycin less than 15 mg/l versus patients with serum vancomycin trough levels≥ 15 mg/l. In sub-group analysis, in patients with pneumonia, the mortality was significantly higher in patients with low

trough levels compared to patients with high trough levels. However this comparison was not statistically significant in patients with bacteraemia. Microbiological failure (persistent bacteraemia≥ 7 days) was significantly higher in patients with vancomycin serum trough levels< 15 mg/l. Also, incidence of VIN was significantly higher in patients with serum vancomycin trough levels≥ 15 mg/l [7-8, 10].

High serum trough level of vancomycin (≥ 15 mg/l) is an independent risk factor for nephrotoxicity [9-10]. Patients in ARC phase need higher doses of vancomycin to reach the therapeutic levels 3). TDM of vancomycin is recommended in these patients. In recent studies, AUC/MIC index was recommended for TDM of vancomycin [13-14]. However there is still no precise correlation between serum trough concentration and AUC/MIC index of vancomycin.

Optimum serum vancomycin level is not defined to predict both efficacy and safety of vancomycin yet. However severity of infection and baseline renal function are two important determinants. Also, the MIC of vancomycin for culprit microorganism is very important to make a decision for treatment strategy.

This study suffered from some limitations. Small sample size, observational design and including patients with different types of infections are main concerns. However this study was the first one that evaluated clinical and microbiological responses in septic patients during ARC phase.

Conclusion

In this study, clinical response and microbiological clearance were comparable in patients with serum vancomycin levels< 15 mg/l and ≥15 mg/l. This finding should be examined in future clinical trials with adequate sample sizes.

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References

1. Sime FB, Udy AA, Roberts JA. Augmented renal clearance in critically ill patients: etiology, definition and implications for beta-lactam dose optimization. Curr Opin Pharmacol. 2015; 24:1-6.
2. Hobbs AL, Shea KM, Roberts KM, Daley MJ. Implications of augmented renal clearance on drug dosing in critically ill patients: a focus on antibiotics. Pharmacotherapy. 2015; 35(11):1063-75.
3. Campassi ML, Gonzalez MC, Masevicius FD, Vazquez AR, Moseinco M, Navarro NC, et al. Augmented renal clearance in critically ill patients: incidence, associated factors and effects on vancomycin treatment. Rev Bras Ter Intensiva. 2014; 26(1):13-20.
4. Mahmoud S, Shen C. Augmented renal clearance in critical illness: an important consideration in drug dosing. Pharmaceutics. 2017; 9(3):36.
5. Rhodes A, Evans LE, Alhazzani W, Levy MM, Antonelli M, Ferrer R, et al. Surviving sepsis campaign: international guidelines for management of sepsis and septic shock: 2016. Intensive Care Med. 2017; 43(3):304-77.
6. Rybak M, Lomaestro B, Rotschafer JC, Moellering Jr R, 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. Ame J Health-Syst Pharm. 2009; 66(1):82-98.
7. Steinmetz T, Eliakim-Raz N, Goldberg E, Leibovici L, Yahav D. Association of vancomycin serum concentrations with efficacy in patients with MRSA infections: a systematic review and meta-analysis. Clin Microbiol Infect. 2015; 21(7):665-73.
8. Bosso JA, Nappi J, Rudisill C, Wellein M, Bookstaver PB, Swindler J, et al. Relationship between vancomycin trough concentrations and nephrotoxicity: a prospective multicenter trial. Antimicrob Agents Chemother. 2011; 55(12):5475-9.
9. Pritchard L, Baker C, Leggett J, Sehdev P, Brown A, Bayley KB. Increasing vancomycin serum trough concentrations and incidence of nephrotoxicity. Am J Med. 2010; 123(12):1143-9.
10. Hale CM, Seabury RW, Steele JM, Darko W, Miller CD. Are vancomycin trough concentrations of 15 to 20 mg/L associated with increased attainment of an AUC/MIC≥ 400 in patients with presumed MRSA infection? J Pharm Pract. 2017; 30(3):329-35.
11. Hermsen ED, Hanson M, Sankaranarayanan J, Stoner JA, Florescu MC, Rupp ME. Clinical outcomes and nephrotoxicity associated with vancomycin trough concentrations during treatment of deep-seated infections. Expert Opin Drug Saf 2010;9(1):9-14.
12. Elyasi S, Khalili H, Dashti-Khavidaki S, Emadi-Koochak H, Mohammadpour A, Abdollahi A. Elevated Vancomycin Trough Concentration: Increased Efficacy and/or Toxicity? Iran J Pharm Res. 2014; 13(4):1241-7.
13. Neely MN, Youn G, Jones B, Jelliffe RW, Drusano GL, Rodvold KA, et al. Are vancomycin trough concentrations adequate for optimal dosing? Antimicrob Agents Chemother 2014;58(1):309-16.
14. Prybylski JP. Vancomycin trough concentration as a predictor of clinical outcomes in patients with Staphylococcus aureus bacteremia: a meta-analysis of observational studies. Pharmacotherapy 2015; 35(10):889-98.