Optimization of Vancomycin Dosing Regimens in Critically Ill Patients: Focus on Early Individualization

Bita Shahrami[1], Farhad Najmeddin[2], Sarah Mousavi[3], Arezoo Ahmadi[4], Mohammad Reza Rouini[5], Kourosh Sadeghi[2], Atabak Najafi[4], Maryam Namdar Khanzadeh[6], Pirooz Salehian[6],Mojtaba Mojtahedzadeh[7*]

[1] Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.

[2]Clinical Pharmacy Department, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.

[3]Department of Clinical Pharmacy and Pharmacy Practice, Faculty of Pharmacy and Pharmaceutical Sciences, Isfahan University of Medical Sciences, Isfahan, Iran.

[4]Anesthesiology and Intensive Care Department, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

[5]Department of pharmaceutics, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran.

[6]Sarem Cell Research Center, Sarem Women's Hospital, Tehran, Iran.

[7]Clinical Pharmacy Department, Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran

*__Corresponding Author:__ Professor MojtabaMojtahedzadeh

Address: Department of Clinical Pharmacy, Faculty of Pharmacy and Pharmaceutical Sciences, Tehran University of Medical Sciences, Enghelab Square, Tehran, Iran. Tel: +98216695 9090, Fax: +98216646 1178.

E-mail: Mojtahed@sina.tums.ac.ir

Abstract

Background: Despite the current clinical guideline recommendation, the optimal dosing regimen of intravenous vancomycin remains controversial. Achievement of therapeutic trough early in the course of illness may be beneficial.

Objective: Our objective was to assess and validate the effectiveness of first dose adjustment in achieving target recommended goal in critically ill patients.

Methods: Twenty critically ill patients with sepsis received loading dose of 25 mg/kg of vancomycin and then randomly assigned to 2 groups. Group 1 received maximum empirical doses of vancomycin as 15 mg/kg every 8 hours for a maximum of 24 hours. In the group 2, the doses were individualized based on serum concentrations of vancomycin. First dose non-steady state sampling was used to calculate pharmacokinetic parameters of the patients within 24 hours. Vancomycin doses were adjusted to achieve AUC=400−600 mg·hr/L and avoiding peak serum concentration higher than 40 mg/L.

Results: Significantly more patients in group 2 had a trough higher than 15mg/L in day-3 and day-5, compared with group 1 (P=0.043, P=0.015). Also trough serum concentrations in day-3

was significantly higher in group 2 (19.4 ± 4.4) comparing group 1 (14.4 ± 4.3) respectively while it was not statistically significant in day-5 between two groups (12.3 ± 5.6 vs. 17.1 ± 1.8). AUCs in day-3 were significantly higher in group 2 (665.9 ± 136.5) comparing group 1 (490.7 ± 101.1) while it was just marginally higher in day-5 (606.1 ± 76.0 vs. 484.0 ± 130.4).

Conclusions: With early individualized dosing (within 48 hours) significantly more patients achieved peak and trough steady state concentrations without additional venous sampling. Also in the context of pharmacokinetic/pharmacodynamic goal of AUC/MIC ≥400, it seems if pharmacokinetic goal is achievement to trough serum concentration ≥15 mg/L and AUC ≥400 mg.hr/L, maximum empirical doses of vancomycin can be used to achieve these goals. However, according to the differences of MIC in various centers, it is necessary to individualize doses of vancomycin in critically ill patients if pharmacokinetic target is to obtain trough serum concentration of vancomycin of ≥15 mg/L and AUC ≥600 mg.h/L.

Keywords: Vancomycin, Critical Care, Therapeutic Drug Monitoring, Pharmacokinetic, Early Individualization

Introduction

Infections inintensive care unit (ICU) continue to be one of the maincauses of mortality and morbidity in critically ill patients [1-2]. Sepsis is defined as a life-threatening infection which has ability to damage multi organ systems and cause to fail them. Optimizing effective antimicrobial therapy as soon as possible is necessary in order to prevent multiple organ failure disorder and bacterial resistance [3-4]. Recent studies have emphasized on the increasing prevalence ofgram-

positivemicroorganisms, especially methicilin-resistant Staphylococcus aureus (MRSA)[5-7]. Due to the increase in prevalence of antimicrobial resistance, efforts to treat gram-positive microorganisms led to reconsidering traditional antibiotics regimens like vancomycin.Vancomycin is a large glycopeptide antibacterial agent that inhibits bacterial cell wall synthesis by blocking glycopeptide polymerization through binding tightly to D-alanyl-D-alanine portion of cell wall precursor. It has been wildly used for treatment of serious gram-positive infections involving MRSA[8]. In the absence of consequences about the indication of vancomycin initiation in sepsis, depending on center base guidelines, it can be used as a first line of treatment for septic patients with un-known etiology, sepsis associated with un-stable hemodynamic, ventilation associated pneumonia (VAP), high clinical suspected for skin soft tissues or abdominal source of infection and catheter related infection [9-11]. Despite thevital roleofvancomycinin the treatment ofMRSAinfections, a completeconsensushas not been reached to therecommendeddose adjustmentofthis antibioticincritically ill patients. Traditional therapeutic regimens of vancomycin was administrated 1 g every 12 hours or 15 mg/kg every 12 hours in order to set trough serum concentration of vancomycin in the range of 5-10 mg/L[12]. Following the reports of increase in incidence of vancomycin-resistant S.aureus strains (VRSA) and germs with higher minimum inhibitory concentrations (MICs) for vancomycin, a large number of studies have performed to identify the determinants that influence bacterial resistance against vancomycin. Optimum area under the time concentration curve/minimum inhibitory concentration (AUC/MIC) and variety of trough concentration ranges has been studied. Finally the studies concluded that AUC/MIC ≥400 of vancomycin is the best factor in the success of treatment and prevention of vancomycin-resistant [13-14]. Considering that implementation of AUC/MIC in the setting of therapeutic drug monitoring requires expertise clinicians to adjust the

dose regarding calculated volume of distribution and clearance of the drug, a shift in the identified target trough concentrations of vancomycin of 5-10 mg/L to 15-20 mg/L has been recommended. American Society of Health-system Pharmacists (ASHP) therapeutic guidelines recommend that "For a pathogen with an MIC of 1 mg/L, the minimum trough serum vancomycin concentration would have to be at least 15 mg/L to obtain the target AUC/MIC ≥400" [14]. It seems that majority of fixeddose regimensof vancomycinhavenot been successful inachieving these goals. On this basis, we planned a randomized two-arm prospective study to assess the role of therapeutic drug monitoring (TDM) in dose adjustment of vancomycin following maximum fixed doses and individualized therapeutic regimens in tailoring vancomycin dosing regimen in maintaining recommended targets of pharmacokinetic/pharmacodynamic (PK/PD) parameters in critically ill patients.

Methods

Study design and participants

This study was designed as a randomized clinical trial. It was performed in two phases. In the first phase (cross sectional), in order to ensure avoidance of toxic serum concentrations following maximum empirical dosing of vancomycin and finding standard clinical laboratory to assay vancomycin levels, serum concentrations of vancomycin measured without any intervention in 10-bed ICU patients. Patients admitted to general and emergency ICU ward of “Sina” Hospital affiliated to Tehran University of Medical Sciences (TUMS), Tehran, Iran, from October 2012 to August 2014 were screened for the study eligibility during ICU stay.In all cases informed consent was obtained from patients or their closest relatives. The study procedure and protocol

were approved by the ethical committee of TUMS.Our clinical trial has been registered in Iranian Registry of Clinical Trials with code number of (IRCT201209291497N2).

Inclusion in the study required that the patients to be older than 18 years old, normal renal function (defined as eGFR≥60 ml/min estimated with Cockcroft-Gault equation), evidence of sepsis following systemic inflammatory response syndrome (SIRS) (body temperature less than 36_C or greater than 38_C, heart rate more than 90 beats per minute, respiratory rate more than 20 breaths per minute or an arterial partial pressure of carbon dioxide less than 32 mmHg, white blood cell count less than 4000 cells/mm^3 or more than 12000 cells/mm^3), survival prognosis more than 72 hours, recent onset of vancomycin administration and no vancomycin sensitivity.Patients with the following conditions were excluded from the study:patient died within first 72 hours, acute renal injury development during the study (according to the criteria of RIFLE[15]), adverse reaction of vancomycin, change in treatment of vancomycin during the first 72 hours, discontinuation of vancomycin during the first 72 hours of treatment, loss of the samples of the first 48 hours and failure of individualization due to pharmacokinetic, physicians and nurses miscommunication.In the second phase (clinical trial) 20 patients who had indication of treatment with vancomycin following sepsis, received loading dose of 25 mg/kg based on actual body weight at a rate of 1000 mg/hr and then maximum empirical doses of vancomycin as 15 mg/kg every 8 hours was administrated for all patients. Then the patientswererandomlydivided into two groups and depending on the group, treatment was continued. One of the groups (group 1) received the same maximum empirical doses of vancomycin as 15 mg/kg every 8 hours for a maximum of 24 hours. In the other group (group 2), the doses were individualized based on serum concentrations of vancomycin.

Demographic and clinical data were obtained from the medical notes of patients. These included sex, age, body weight, height and estimated glomerular filtration rate (eGFR) upon initiation of vancomycin. Sepsis workup and SIRS criteria exploration was performed for every patient at the baseline. All relative routine critical care laboratory tests are followed and documented by daily visits.

Patients were blinded to antibiotic regimen during the experiment. Serum concentrations of vancomycin in patients receiving fixed doses regimen were not available for the medical team for dose adjustment of vancomycin. Serum concentrations of vancomycin were taken at 6 times included: 1- 1 hour after the end of first dose infusion, 2- 4-6 hours after the first sample, 3- 1 hour after the end of fifth dose infusion (fifth dose peak), 4- 1 hour before the sixth dose infusion (fifth dose trough), 5- 1 hour after the end of ninth dose infusion (ninth dose peak) and 6- 1 hour before the tenth dose infusion (ninth dose trough), within during 5-days of study. After centrifugation, plasma samples were analyzed within 2 hours by means of fluorescence polarization immunoassay (Siemens Healthcare Diagnosis, United Kingdom, EMIT).

Pharmacokinetic calculation and early individualization

By measuring both of trough and peak serum concentration of first dose of vancomycin, we calculated pharmacokinetic parameters such as elimination rate (K_{el}), volume of distribution (V_d), half-life ($t_{1/2}$), clearance of vancomycin (Cl_{vanco}) and AUC individually for each patient. These parameters were calculated based on Andrew DeRyke et al., methods [13]. Early individualization of vancomycin was performed with dose adjustment to achieve AUC=400−600 mg·hr/L while avoiding peak serum concentration higher than 40 mg/L,within first 24 hours in divided doses of every 6 to 12 hours daily. Calculations were performed by the clinical pharmacists but the results were not communicated to the ICU physicians.

According to doses of 15 mg/kg every 8 hours as usual empirical doses of vancomycin in our center, we frequently observe patients with AUC less than 400 mg.hr/L. Regarding the pharmacokinetic goal of AUC ≥400 mg.hr/L, we estimated that less than %70 of patients may achieve AUC ≥400 mg.hr/L. Considering the study power %80 and level of significance of 0.05, the sample size of study calculated to be 42 patients (21 patients in each groups).

Data analysis

Trough and peak serum concentration of vancomycin and AUC were compared in two groups during 5-days of study. The AUC/MIC was calculated based on the assumption that MICs were 1−1.5 mg/L for all cases. Goal target of pharmacokinetic was defined as AUC/MIC ≥400. All the analyses were performed using SPSS statistical package, version 20 for windows. All variables were tested for normality of distribution with Kolmogorov-Smirnov test. Levene's test for equality of variances was used to compare the means and the results were analyzed based on Independent t-test. Pearson chi square test or Fisher's exact test was used for ordinal and nominal data. Odds ratio was used when results were statisticallysignificant or marginally significant. P-value of <0.05 was considered statistically significant for all tests.

Results

In the middle of the study due to achievement of significant differences in our primary outcome of frequency of patients who failed achieve to AUC ≥400 mg.hr/L on 20 patients (10 patients in each group), we stopped the study to avoid wasting of resources. 108 samples of vancomycin serum concentrations were assayed. A total of 25 patients were assigned to the second phase, 5 cases excluded based on the exclusion criteria. Demographic information and pharmacokinetic

parameters of the included patients are shown in table 1. The difference between study groups was not significant regarding gender, age, body weight and eGFR at the baseline.

Trough serum concentrations in day-3 was significantly higher in group 2 (19.4 ± 4.4 mg/L) comparing with group 1 (14.4 ± 4.3 mg/L) (P=0.029) while it was not statistically significant in day-5 between two groups (12.3 ± 5.6 mg/Lvs. 17.1 ± 1.8 mg/L) (P=0.137).AUCs in day-3 were significantly higher in group 2 (665.9 ± 136.5) comparing with group 1 (490.7 ± 101.1) respectively (P=0.008) while it was just marginally higher in day-5 (606.1 ± 76.0 vs. 484.0 ± 130.4) (P=0.054). There are no significant differences regarding average vancomycin dosage between two groups in day-3(44.9 ± 3.8 mg/kg vs. 49.4 ± 13.1 mg/kg) and day-5 (46.3 ± 3.3 mg/kg vs. 47.1 ± 12.5 mg/kg)respectively (P=0.33, P=0.87).

Table 2 describes frequencies of patients who failed to achieve pharmacokinetic goals of trough serum concentrations of more than 15, 12.5 and 10 mg/L and AUC of less than 400 and 600 mg.hr/L. Frequencies of trough serum concentration less than 15 mg/L in day-3 and day-5 were significantly lower in group 2 (%10, %0) comparing with group 1 (%62.5, %66.7) respectively (P=0.043, P=0.015). Frequencies of AUC less than 400 mg.hr/L in day-3 and day-5 were significantly lower in group 2 (%0, %0) comparing with group 1 (%14.3, %40) respectively (P=0.041, P=0.012) while frequencies of AUC less than 600 mg.hr/L in day-3 and day-5 did not differ between two groups (P=0.05, P=1).

According to serum concentrations of vancomycin, %80 of patients in group 2 required individualization. It means the need to increase or decrease the dose of 250 mg or to change in dosing interval from 8 hours to 6 or 12 hours. There are no significant differences in frequencies

of patients with vancomycin toxicity regarding trough and peak serum concentrations more than 25 and 40 mg/L respectively between two groups during the study (P=1, P=1) (Table 3).

Discussion

This study describes the evaluation of dose adjustment of vancomycin in critically ill patients. The results demonstrate that an individualized regimen of vancomycin is more likely to result in PK/PD targets of AUC/MIC ≥400. Patients received individualized regimen, are 14 and 15 times more likely to have AUC ≥600 and trough serum concentration ≥15 mg/L than patients received maximum empirical doses regimen respectively.

According to consensus review of ASHP, IDSA and SIDP guideline, empirical doses of vancomycin as 15-20 mg/kg every 8-12 hours can be used for most patients with normal renal function to achieve therapeutic serum concentration of 15-20 mg/L and AUC/MIC ≥400 when MIC is less than 1 mg/L [14]. But the results of present study show that considerable percentage of patients treated with almost fixed doses of vancomycin of 15 mg/kg every 8 hours fails to achieve these goals, while individualized regimen of vancomycin could put the patients in achieving therapeutic serum concentrations.

Recommendations of individual pharmacokinetic adjustments and verification of achievement of target serum concentrations is recently highlighted by IDSA led to improve clinical outcomes of patients [16].Unlike the methods of individualization of vancomycin noted in clinical guidelines that recommend to measure serum concentration at steady state conditions [13-14], we found that early individualization and first dose monitoring of vancomycin let the patients to achieve therapeutic serum concentrations earlier. The results in 3th and 5th day of study show that the first dose monitoring of vancomycin within the first 24 hours of initiation of treatment has been

effective in achieving pharmacokinetic goals in less than 48 hours. In other words, by calculation of pharmacokinetic parameters at non-steady state conditions, there is no need for waiting to reach steady state and delaying interventions for at least 72 hours, especially in terms of MIC ≥1 mg/L. Crumby et al. [17]performed a similar study in 108 patients and compared nomogram-based and individualized vancomycin regimens in neonates. Significantly more patients achieved peak and trough steady state concentrations after first dose pharmacokinetic dose adjustment. This study also confirmed the benefits of early individualized dosing without additional venous sampling.

Nephrotoxicity associated with vancomycinmonotherapy is uncommon, but recent studies demonstrate that excessive serum concentrations can led to nephrotoxicity[18-19]. Lodis et al.,[20] concluded that high doses regimens of vancomycin of more than 4 g/day are related to higher incidence of nephrotoxicity exacerbated by some factors including ICU residence. In other hand another study showed that vancomycin doses greater than 2 g/dose did not show a significant increase in serum creatinine[21]. Therapeutic monitoring of serum concentrations would allow interventions that reduce toxicity[13-14]. The results of present study did not show a statistically significant in toxic trough and peak serum concentrations between two groups. In other words maximum empirical doses vancomycin as did not show increase in toxicity. Therefore due to the lack of efficacy of fixed dose regimens to achieve targets of pharmacokinetic and the risk of vancomycin toxicity with higher empirical doses, individualized regimens are necessary for patients to achieve specific pharmacokinetic goals.

Due to MICs of vancomycin against S.aureus were commonly 1 mg/L or less, trough serum concentrations of vancomycin of 5-10 mg/L were considered acceptable [22]. These results show that patients who receive maximum empirical doses of vancomycin may almost achieve this

trough serum concentration. However according to increased vancomycin MICs and guidelines suggestion of trough serum concentration of 15-20 mg/L, it seems that individualized regimens are preferred. Lodise et al. [23]found vancomycin MIC ≥1.5 mg/L to be associated with a 2.4-fold increase in treatment failure in MRSA bacteremic patients when compared with patients isolate with MICs of ≤1 mg/L (%36.4 vs. %15.4 respectively, P=0.049). In addition, failure or success did not correlate with attainment of primary trough of at least 15 mg/L irrespective of MIC[13].

Conclusion

Although maximum empirical doses of vancomycin have low risk of toxicity and can be used in all septic patients with normal renal function under therapeutic drug monitoring, PK/PD targets of AUC/MIC ≥400 may not to be achieved in terms of relative antimicrobial resistance. Therefore according to the increase in the incidence of VRSA and germs with higher MICs, it is necessary to individualize doses of vancomycin in critically ill patients. In addition delay in pharmacokinetic parameters calculation to reach the steady state condition may put the patients in the risk of under-treatment for at least 72 hours. In summary, our study suggests that first dose pharmacokinetic monitoring and early individualization of vancomycin should be considered for critically ill patients in order to achieve pharmacokinetic goals of trough serum concentration more than 15 mg/L and AUC ≥400 mg.hr/L.

Acknowledgment

This study is received research grant from Tehran University of Medical Sciences. We would like gratefully to acknowledge all the patients who agreed to contribute with us and also all the

physicians and nurses of “Sina” Hospital who helped us during this study. Serum samples of vancomycin measured by laboratory of “Sarem” Hospital and we also thank for their cooperation.

References

1. Brun-Buisson C. ICU-acquired infections and sepsis: more of a deadly duo. Intensive Care Med 2008;34(5) 793-5.
2. Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009; 302(21): 2323-9.
3. Dellinger RP, Levy MM, Rhodes A, Annane D, Gerlach H, Opal SM,et al. Surviving Sepsis Campaign: International Guidelines for Management of Severe Sepsis and Septic Shock: 2012. Intensive Care Med 2013 ;39(2):165-228.
4. Gaieski DF, Mikkelsen ME, Band RA, Pines JM, Massone R, Furia FF et al. Impact of time to antibiotics on survival in patients with severe sepsis or septic shock in whom early goal-directed therapy was initiated in the emergency department. Crit Care Med 2010;38(4):1045-53.
5. National Nosocomial Infections Surveillance System.National Nosocomial Infections Surveillance (NNIS) System Report, data summary from January 1992 through June 2004, issued October 2004. Am J Infect Control 2004;32(8): 470-85.
6. Rice LB. Antimicrobial resistance in gram-positive bacteria. Am J Infect Control 2006 ;34(5 Suppl 1):S11-9; discussion S64-73.

7. Hancock RE. Mechanisms of action of newer antibiotics for Gram-positive pathogens. Lancet Infect Dis 2005;5(4):209-18.

8. Moellering RC Jr. Vancomycin: A 50-Year Reassessment. Clin Infect Dis 2006;42 Suppl 1:S3-4.

9. Fridkin SK, Hageman JC, Morrison M, Sanza LT, Como-Sabetti K, Jernigan JA,et al. Methicillin-resistant Staphylococcus aureus disease in three communities.N Engl J Med 2005;352(14):1436-44.

10. Miller LG, Perdreau-Remington F, Rieg G, Mehdi S, Perlroth J, Bayer AS, et al., Necrotizing fasciitis caused by community-associated methicillin-resistant Staphylococcus aureus in Los Angeles.N Engl J Med 2005;352(14):1445-53.

11. McDonald JR, Friedman ND, Stout JE, Sexton DJ, Kaye KS. Risk factors for ineffective therapy in patients with bloodstream infection. Arch Intern Med 2005; 165(3):308-13.

12. Duffull SB, Begg EJ, Chambers ST, Barclay ML. Efficacies of Different Vancomycin Dosing Regimens against Staphylococcus aureus Determined with a Dynamic In Vitro Model. Antimicrob Agents Chemother 1994;38(10):2480-2.

13. DeRyke CA, Alexander DP. Optimizing Vancomycin Dosing Through Pharmacodynamic Assessment Targeting Area Under the Concentration-Time Curve/Minimum Inhibitory Concentration. Hospital Pharmacy 2009;44(9):751-65.

14. 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(1):82-98.

15. Venkataraman R, Kellum JA. Defining acute renal failure: the RIFLE criteria. Intensive Care Med 2007; 22(4):187-93.

16. Liu C, Bayer A, Cosgrove SE, Daum RS, Fridkin SK, Gorwitz RJ, et al. Clinical Practice Guidelines by the InfectiousDiseases Society of America for the Treatment of Methicillin-Resistant Staphylococcus aureus Infections in Adults and Children: executive summary. Clin Infect Dis 2011;52(3):285-92.

17. Crumby T, Rinehart E, Carby MC, Kuhl D, Talati AJ. Pharmacokinetic comparison of nomogram-based and individualized vancomycin regimens in neonates. Am J Health Syst Pharm 2009; 66(2):149-53.

18. Hidayat LK, Hsu DI, Quist R, Shriner KA, Wong-Beringer A. High-dose vancomycin therapy for methicillin-resistant Staphylococcus aureus infections: efficacy and toxicity. Arch Intern Med 2006; 166(19): 2138-44.

19. Lodise TP, Patel N, Lomaestro BM, Rodvold KA, Drusano GL. Relationship between initial vancomycin concentration-time profile and nephrotoxicity among hospitalized patients. Clin Infect Dis 2009;55(12): 5475-79.

20. Lodise TP, Lomaestro B, Graves J, Drusano GL.Larger Vancomycin Doses (at Least Four Grams per Day) Are Associated with an Increased Incidence of Nephrotoxicity. Antimicrob Agents Chemother 2008;52(4):1330-6.

21. Mansour H, Bush J, Brito M, Novotny P, Courtney C, MustonenJ,et al.The effect of vancomycin doses greater than 2 grams on serum creatinine and vancomycin trough levels. Int J Pharm Pharm Sci 2014;6(8): 621-5.

22. Cantú TG, Yamanaka-Yuen NA, Lietman PS. Serum vancomycin concentrations: reappraisal of their clinical value. Clin Infect Dis 1994;18(4):533-43.

23. Lodise TP, Graves J, Evans A, Graffunder E, Helmecke M, Lomaestro BM, et al. Relationship between vancomycin MIC and failure among patients with methicillin-resistant Staphylococcus aureus bacteremia treated with vancomycin. Antimicrob Agents Chemother 2008;52(9): 3315-20.

Table 1. Patients' demographics and pharmacokinetic parameters in two groups.

	Measures	Group 1	Group 2	Sig. (2-tailed)
		Mean ± **S.D**	Mean **±** **S.D**	
	Number of patients	10	10	–
	Sex (male/female)	8/2	8/2	0.610
Baseline	Age (year)	48.5 ± 18.3	47.7 ± 20.9	0.933
	Body weight (kg)	66.0 ± 12.1	73.0 ± 12.2	0.245
	Height (cm)	170.1 ± 9.1	171.5 ± 13.9	0.784
	eGFR (ml/min)	99.8 ± 49.8	112.4 ± 45.7	0.586
	Number of patients	8	10	–
	eGFR (ml/min)	111.1 ± 57.2	113.2 ± 45.9	0.933
	Total dose (mg/kg)	44.9 ± 3.8	49.4 ± 13.1	0.328
	Trough (mg/L)	14.4 ± 4.3	19.4 ± 4.4	0.029
Day-3	Peak (mg/L)	28.1 ± 6.0	33.7 ± 6.7	0.076
	V_d (L/kg)	0.65 ± 0.12	0.68 ± 0.10	0.609
	Cl_{vanco} (ml/min)	45.1 ± 54.8	79.3 ± 53.7	0.202
	AUC (mg.hr/L)	490.7 ± 101.0	665.9 ± 136.5	0.012
	Number of patients	5	8	–

	eGFR (ml/min)	115.5 ± 72.3	125.2 ± 51.2	0.764
	Total dose (mg/kg)	46.3 ± 3.3	47.1 ± 12.5	0.873
	Trough (mg/L)	12.3 ± 5.6	17.1 ± 1.8	0.137
Day-5	Peak (mg/L)	21.8 ± 2.7	31.4 ± 4.9	0.002
	V_d (L/kg)	0.97 ± 0.58	0.68 ± 0.11	0.330
	Cl_{vanco} (ml/min)	111.2 ± 39.9	103.6 ± 32.0	0.712
	AUC (mg.hr/L)	484.0 ± 130.4	606.1 ± 76.0	0.054

eGFR: Estimated Glomerular filtration rate, AUC: Area Under the Curve, Cl: Clearance, V_d: Volume of distribution, Vanco: Vancomycin.

Table 2. Frequencies of patients who have sub therapeutic levels regarding specific pharmacokinetic goals.

	Frequencies	Group 1	Group 2	Sig. (2-sided)	Odds Ratio
		%	%		
	Number of patients	8	10	–	–
	Trough <15 (mg/L)	62.5	10	0.043	15
	Trough <12.5 (mg/L)	50	0	0.023	–
Day-3	Trough <10 (mg/L)	12.5	0	0.444	–
	AUC <400 (mg.hr/L)	14.3	0	0.041	–
	AUC <600 (mg.hr/L)	85.7	30	0.050	14
	Number of patients	5	8	–	–

	Trough <15 (mg/L)	66.7	0	0.015	−
	Trough <12.5 (mg/L)	50	0	0.055	−
Day-5	Trough <10 (mg/L)	50	0	0.055	−
	AUC <400 (mg.hr/L)	40	0	0.012	−
	AUC <600 (mg.hr/L)	80	62.5	1	−

AUC: Area Under the Curve.

Table 3. Frequencies of patients who have toxic levels regarding specific pharmacokinetic goals during the study.

Frequencies	Group 1	Group 2	Sig. (2-sided)	Odds Ratio
	%	%		
Trough >25 (mg/L)	12.5	20	1	−
Peak >40 (mg/L)	0	10	1	−