Correlation of Initial Dose Option With Plasma Vancomycin Exposure and Safety in Older Chinese Patients: a Cohort Retrospective Study

Cuifang Wu
Central South University Third Xiangya Hospital
Yulu Zhou
Central South University Third Xiangya Hospital
Shengfeng Wang
Central South University Third Xiangya Hospital
Sujie Jia
Central South University Third Xiangya Hospital
Yueliang Xie
Central South University Third Xiangya Hospital
Zhenzhen Deng (dengzhen2008.love@163.com)
Central South University Third Xiangya Hospital https://orcid.org/0000-0003-3045-1710

Research Article

Keywords: Vancomycin, Serum trough concentration, older adults, initial dose

Posted Date: October 20th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-977291/v1

Abstract

Background: The option of initial vancomycin dose for older patients is still controversy.

Methods: Vancomycin trough concentrations in older patients who received vancomycin initial dose of ≥1.5g/day or dosing recommended by package insert (≤1g/day) were compared. The relationship between independent covariate variables and trough concentration were identified, and changes in renal function and vancomycin-related nephrotoxicity was evaluated.

Results: About 187 vancomycin trough samples were obtained from 97 older patients (56.7% males, median age of 70 (IQR=8) years). Significant difference was observed in vancomycin trough concentration between the two groups (17.22±7.52 vs. 13.78±6.90 mg/L; p=0.037). The proportion of VCM trough concentration within the therapeutic target concentration was 55% in group A and 48% in group B. Subsequent dose adjustment should be taken in 54 (65.9 %) patients in group A and 9 (60%) patients in group B to reach the target trough levels. SCr after medication, baseline eGFR, eGFR after medication and death had a significant effect on VCM trough concentrations in group A. The incidence of AKI was 8.5% in group A and 20.0% in group B, logistic regression model showed positive correlation between vancomycin trough level and the incidence of AKI.

Conclusion: Compared with the recommended dose by package insert, the daily dosing recommendation of ≥1.5g/d for older patients result in a higher incidence of target trough concentration. Yet, the incidence of nephrotoxicity has not increase significantly. Prospective studies with large sample size are needed to define the optimal vancomycin dose in older patients.

Impacts On Practice

- Since there are no recommendations of dosing specific for the geriatric population in the current vancomycin therapeutic guidelines, vancomycin dose option for older patients is mainly based on clinician's experience.
- Although the kidney function of the older patients is reduced, older patients with vancomycin dose of more than 1.5g/d had significantly higher incidence of target trough concentration compared with the recommended dose by package insert, and it did not translate to increase AKI.
- Prospective studies with large sample size are needed to define the optimal vancomycin dose for older patients.

Introduction

Vancomycin is a glycopeptide antibiotic that has a strong effect on gram-positive bacterial infections[1]. As a first-line treatment option for methicillin-resistant Staphylococcus aureus (MRSA) infection, it is clinically used for the treatment of osteomyelitis, hospital acquired pneumonia, skin and soft tissue infections and endocarditis[2]. The efficacy of vancomycin is dependent on appropriate dosing, which

should aim to achieve a target serum trough level[3]. Routine therapeutic drug monitor (TDM) of vancomycin is recommended in clinical practice to optimize drug exposure. According to the clinical guidelines, a vancomycin dosing of 15–20 mg/ kg of actual body weight every 8-12 h is recommended, not to exceed 2 g per day in patients with normal renal function, the trough concentration should be maintained above 10 mg/L to improve the clinical outcome and avoid the development of resistance, and less than 20 mg/L to reduce the risk of nephrotoxicity[4–6].

A variety of factors are known to affect the pharmacokinetics and serum trough concentrations of vancomycin, including age, body weight, serum albumin, etc [7, 8]. For geriatric patients, the increased volume of distribution as well as more likely to have combination of multiple illnesses and take complicated medications have also been identified as variables that influence vancomycin concentrations[9, 10]. With renal function being the primary route of elimination for intravenous vancomycin, there is an increased risk of dose accumulation and vancomycin-induced nephrotoxicity in the older population due to prolonged t1/2, likely attributable to decreased renal function[11]. These unique characteristics make dosing vancomycin a challenge for clinicians.

There are no recommendations of dosing specific for the geriatric population in the current vancomycin therapeutic guidelines[12]. In previous research, optimal administration based on Bayesian method or population pharmacokinetic (PPK) analysis might help to predict accuracy dosing[13–16], but little is known concerning vancomycin dosing in older patients. The package insert for vancomycin recommends that the daily dosing for the older patients should be half of the dosing for younger adults with normal renal function(1g/day). Theoretically, lower empiric maintenance doses and monitor vancomycin serum concentrations earlier than steady state for older patients was needed to accurately calculate drug elimination and make appropriate dose adjustments for them[17]. However, the pharmacokinetics of vancomycin in older patients followed the lower daily dosing have not been explored and safety of vancomycin treatment in these patients were still unknown.

Aims of the study

This retrospective study had the following aims: (1) to explore the vancomycin concentration of older patients who had received the vancomycin dose recommended by package insert (≤1g/d) or dosing regimen for younger adult patients (≥1.5g/day); (2) to investigate clinical factors that affect the vancomycin trough concentration; and (3) to compare the safety of vancomycin treatment of two dosage regimens in older patients.

Ethical Approval

Ethical approval was given by the medical ethics committee of the third Xiangya Hospital, Central South University with the following reference number: 2019-S505. We confirmation that all patients were gave written informed consent.

Methods

Patients

This was a single-center retrospective study performed at The Third Xiangya hospital, Central South University. We recruited all older inpatients treated with vancomycin from January 2016 to December 2019. Patients treated with vancomycin were eligible for inclusion in the following situation: (i)≥65years of age; (ii) receiving four or more doses of vancomycin during treatment period; (iii) with TDM before the fourth or later dose of vancomycin until the steady-state condition was reached. Patients were excluded if: (i) incomplete case information from the medical records; (ii) patients had received a kidney transplant; (iii) patients had stage 5 chronic kidney disease (CKD) or receiving regular dialysis.

Study design

This study was designed to include three steps. First, we recorded the doses of the included patients and separated the latter into two groups: Group A patients were received the initial dose of vancomycin for younger adults patients with normal kidney function (≥1.5g/day); Group B patients had received the recommended initial dosage for older patients based on the vancomycin package insert (≤1g/day). Secondly, we collected data and compared the vancomycin trough concentrations between the two groups. The relationship between independent covariate variables and vancomycin serum trough concentration were also evaluated. Thirdly, changes in renal function and vancomycin-related nephrotoxicity were evaluated. Renal function was assessed by the detection of BUN and SCr before vancomycin use and at least 2 days after vancomycin use. The estimated glomerular filtration rate (eGFR) was calculated by the CKD-EPI (chronic kidney disease-Epidemiology collaboration) equation. The definition of vancomycin induced acute kidney injury (AKI) happen is the development of AKI during vancomycin treatment or within 3 days after withdrawal. The 2012 Kidney Disease[18]: Improvement Global Outcome (KDIGO) definition of AKI was used as the major criterion to identify AKI: SCr levels increase ≥0.3 mg/dl (≥26.5umol/l) within 48h or 50% increase from the baseline level within the prior 7days.

Data collection

We retrospectively reviewed medical records and collected data of every patient on baseline patient characteristics, laboratory variables, hospitalization-related factors and concomitant diseases. The following variables concerning vancomycin therapy and the use of concomitant drugs were also collected as comprehensively as possible: indication for vancomycin therapy (prophylactic, local infection, bacteraemia); variety of vancomycin (Wen kexin, Lai kexin); length of therapy (LOT); vancomycin daily dose (0.5, 1.0, 1.5, 2.0, 3.0g) and dose adjustment; TDM.

Statistical analysis

A vancomycin serum trough concentration ranging from 10 to 20mg/l was identified as therapeutic target. The Wilcoxon two sample test or Kruskal-Wallis test was used to compare vancomycin trough concentration. Categorical variables were expressed as numbers (percentages) and compared with the

chi-squared test or Fisher's exact test. Further, univariate analysis was used to assess the association between vancomycin serum trough concentration and independent covariate variables in the two groups. A forward logistic model was used for the assessment of the relationship between vancomycin serum trough concentration and AKI. Multiple linear regression models were used to identify the effect of multiple independent variables on vancomycin concentration, variables with a P value of less than 0.2 on univariate analysis were further examined in multivariate analysis. The time-to-AKI data were compared by log-rank test using the Kaplan-Meier method. P value of less than 0.05 was deemed significant. Statistical analyses were conducted using IBM SPSS statistic version 18.0(IBM Corp., Armonk, NY, USA).

Results

Patients included and Trough vancomycin concentrations

A total of 97 older patients were included, of which 82 in group A and 15 in group B. Among them, 56.7% (55/97) were male, the median age was 70 years (IQR=8) and the average length of hospital stay was 25 days (IQR=18). Baseline characteristics of the older patients are presented in Table 1. A total of 187 vancomycin serum trough samples were measured. Individual variability was observed in the serum trough concentration of vancomycin in this population, ranging from 3.17 to 45.6 mg/l (**Figure 1A**). The trough concentration of vancomycin was 17.22±7.52 mg/L (range 4.64-45.6 mg/L) in 162 samples obtained from 82 patients in Group A and 13.78±6.90 mg/L (range 3.17-28 mg/L) in 25 samples obtained from 15 patients in Group B. The serum trough concentrations of vancomycin in Group A were significantly higher than those in Group B (p=0.037). The proportion of VCM trough concentration within the therapeutic target concentration (range 10-15 mg/L or 15-20 mg/l) was 55% in Group A and 48% in Group B. The proportion of vancomycin with supratherapeutic level in group A and B was 30.9% and 20.0%, respectively (**Figure 1B**).

To reach the target trough levels, 18 patients (22.0%) had the subsequent vancomycin dose adjustment according to the initial trough concentration in group A, with 5 (6.1%) patients increased the dosage and 13 patients (15.9%) reduced the dosage. Of the remaining 64 (78.0%) patients who maintained the initial dose of vancomycin in group A, the proportion of vancomycin trough concentration outside the range of therapeutic target was up to 56.2% (36/64). In Group B, 3 (20%) patients increased the dosage and 2 (13.3%) reduced the dosage. Of the 10 (66.7%) patients maintained the initial dose, the proportion of vancomycin trough concentration outside the range of therapeutic target was 40% (4/10). The above data indicate that the actual number of patients who need to be subsequent dose-adjusted should be 54 (65.9 %) in group A and 9 (60%) in Group B.

Relationship between vancomycin serum trough concentration and covariate variables

The vancomycin serum trough concentration of <75 years and ≥75 years patients were 16.81±7.84 mg/l and 18.02±6.61 mg/l in group A, and 12.00±7.31 mg/l and 16.1±5.75mg/l in group B, respectively. Although the trough concentration of vancomycin increased with age, no significant difference was observed in the trough concentration among age levels either in group A (p=0.135) or group B (p=0.134)

(**Figure 2A**). The vancomycin serum trough concentration in male and female patients were 16.90±7.44 mg/l and 17.48±7.41 mg/l in group A, 13.97±8.02 mg/l and 13.65±6.34 mg/l in group B, respectively. There was no significant difference in the trough concentration level between male and female in either group A (p=0.626) or group B (p=0.918) (**Figure 2**B).

In the univariate analysis, the covariates included in multiple linear regression analysis in group A were: age (year); length of therapy (days); baseline BUN (mmol/l); baseline SCr (μmol/l); baseline eGFR (mL/(min·1.73 m^2)); BUN after medication (mmol/l); SCr after medication (μmol/l); eGFR after medication (mL/min/1.73 m^2); surgery (yes or no); ICU admittance (yes or no); cancer (yes or no); sepsis (yes or no); hypotension (yes or no); mechanical ventilation (yes or no); death (yes or no); hypertension (yes or no). Finally, SCr after medication (p=0.006), baseline eGFR (p=0.047), eGFR after medication (p<0.001) and death (p=0.031) were independently associated factors. However, there was no covariate significantly associated with the trough concentration of vancomycin in group B.

The safety of vancomycin therapy

A total of 10 (10/97, 10.3%) patients developed vancomycin -related AKI. The incidence of AKI was 8.5%（7/82）in group A and 20.0%（3/15）in group B, there was no significant difference in the incidence of AKI between the two groups (p=0.179). In group A and group B, the trough concentration of vancomycin in patients who developed AKI was 23.60±9.14 mg/l and 15.62±8.82 mg/l, respectively. Significant difference was observed in vancomycin trough level between patients with AKI and those without AKI in group A (p=0.008), no significant difference was found in group B. Vancomycin trough concentration between patients with AKI and those without was significantly difference (21.94±9.48mg/l vs. 15.99±6.89mg/l; p=0.006), the logistic regression model showed significant relationship between vancomycin trough concentration and AKI (p=0.002). Furthermore, Kaplen-Meier curves for the cumulative incidence of AKI showed significant difference between the two groups (p=0.043 by log-rank test) (**Figure 3)**.

For patients who developed AKI, one had renal replace therapy, others do not show severe clinical symptom. The BUN and SCr lever were notably increased after vancomycin treatment in group A (7.45 vs. 9.02mmol/l, p=0.015; 84.67 vs. 96.7 μmol/l, p=0.015), the eGFR level have not shown significant decline (80.41 vs. 76.89 ml/min/1.73m^2, p=0.330). The BUN and SCr lever have not shown significant increase in group B (9.83 vs. 12.19mmol/l, p=0.109; 118.93 vs. 137.73 μmol/l, p=0.101) after vancomycin administration. Renal function recovered in 1 patient in group A and 2 patients in group B, and improved in 4 patients in group A. Thus, 71.4% (5/7) of the total AKI in group A and 66.7% (2/3) in group B showed either recovery or improvement (**Table 2**). These data indicate that the dosage regimen of vancomycin even in group A might have a mild effect on renal function in older patients.

Discussion

Due to frequent multimorbidity, polypharmacy, increased risk of adverse effects, and altered pharmacokinetics and pharmacodynamics associated with aging, pharmacotherapy in older patients is challenging[19]. For vancomycin therapy, the efficacy is dependent on appropriate dosing. Since there are no recommendations of dosing specific for the geriatric population in the current vancomycin therapeutic guidelines, the halved dose is recommended for older patients in vancomycin package insert. However, no study has been conducted on the pharmacokinetic characteristics of the halved vancomycin dose in older patients. This retrospective study aimed to investigate the pharmacokinetic characteristics and safety of older patients who were administrated with dose regimen for younger adult patients with normal kidney function (≥1.5g/day) or with a halved dosing of vancomycin (≤1g/d), to provide some suggestions for vancomycin initial dose selection and prevention of adverse reactions in this crowd of patients.

In this older population, we found a large inter-individual pharmacokinetic of vancomycin exposure between the two groups. Although the dosing for younger adult patients is not recommended for the older, most patients were still prescribed with this dose in clinical practice (84.5%). For older patients who have a certain degree of renal dysfunction, this calls for more attention. We observed more patients in group A met the target trough concentration of 10-20mg/l than in group B (55% vs. 48%), however, the proportion of supratherapeutic concentration (30.9%) was significant higher. The halved initial dose of vancomycin in group B (≤1 g/day) in older patients can still lead to higher drug concentration (20.0%). Thus, clinicians had the initial vancomycin dose adjusted of some patients according to the target concentration and therapeutic effect during the treatment (22% in group A and 33.3% in groups B). Of the patients who did not had the initial dose of vancomycin adjusted, the proportion of vancomycin trough concentration outside the range of therapeutic target was up to 56.2% (36/64) in group A and 40% (4/10) in group B, which means the actual number of patients who need to be dose-adjusted should be 54 (65.9 %) in group A and 9 (60%) in group B. These results suggest that the initial dose either in group A or group B is not appropriate for older patients considering the low incidence of target rate of vancomycin concentrations. It highlighted the fact that clinicians need to develop an understanding of the importance of vancomycin concentration monitoring and concern should be focused on how to choose the initial dose of vancomycin for older patients. Since there are no recommendations specific for the geriatric population in vancomycin guidelines by the Infectious Diseases Society of America (IDSA) [20], pharmacokinetic studies should be performed to optimize the dose regimen in these crowd of patients [21].

Several factors that may influence the pharmacokinetic and pharmacodynamic of vancomycin have been identified to be contributed to the inter-individual variability, such as sex, age, body weight, serum albumin and eGFR. Hypoalbuminemia has been proved to be associated with prolonged vancomycin half-life and higher AUC in older patients [22]. Total body weight may affect the volume of vancomycin distribution [7,23]. The present study showed that the trough concentration of vancomycin increased with age despite no significant difference was observed among age stratified, which was consistent with previous study [24]. The multivariable linear regression models found that SCr after medication ($p=0.006$), baseline eGFR ($p=0.047$) and eGFR after medication ($p<0.001$) were associated with vancomycin trough concentration in group A. There was no covariate associated with vancomycin trough concentration in group B, which

probably owing to the small sample size included in group B have affect the generality of the study results. Nevertheless, this result illustrated that low-dose vancomycin may not cause significant changes in eGFR, so it may be more suitable for older patients.

Calculating the optimal dose in older patients is further complicated by the difficulty to accurately estimate their renal function. Glatard A et al compared the abilities of six different renal function estimation equations (Cockcroft-Gault (CG), Jelliffe (JEL), Modification of Diet in Renal Disease (MDRD), Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) and modified MDRD and CKD-EPI equations) to describe vancomycin pharmacokinetics in older patients, the final analysis showed important differences in parameter distributions and AUC estimation, he concluded that each estimation equations should not be considered interchangeable for model-based estimation of vancomycin concentrations in older patients [25]. In our study, we choose Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) to estimate the creatinine clearance of older patients due to weight information of some older patients being unobtained. Besides, older patients who received the high-strength and long-term vancomycin therapy might results in unstable renal function, CKD-EPI method is more suitable since it can afford suitable dose adjustment [26].

Older patients are considered a population at high risk of nephrotoxicity when using vancomycin according to several studies[27,28]. In our study, significant correlations between vancomycin trough concentration and AKI were observed, the trough concentration in patients with AKI was significantly higher than those without (21.94±9.48mg/l vs.15.99±6.89mg/l; p=0.006). We observed that the overall incidence of AKI is lower than previous studies [29]. Meanwhile, even if the trough concentration of vancomycin in group A was significantly higher than that in group B, there was no significant difference in the incidence of AKI between the two groups, which suggest that the dose regimen of vancomycin in both groups had a mild effect on renal function and it was well tolerated for older patients. Surprisingly, the incidence of AKI in group B is a bit higher than that in group A, the probable reason was that some patients in group B had renal impairment before vancomycin administrated and lower initial dose of vancomycin was chosen for them. It is necessary to monitor vancomycin C_{min} early to help older patients improve treatment efficacy and avoid AKI in the absence of further studies on appropriate initial dosage recommendation.

There are three limitations in the present study. First, due to the limited sample size, the results need to be identified in a wider population. Secord, the study was a retrospective design, the dosage of vancomycin was at physicians' discretion, and the time of first levels collection were variable. Third, some older patients already have renal function damage before vancomycin administration, which can lead to a higher vancomycin trough concentration and higher rate of vancomycin -related adverse events.

Conclusion

Compared with the recommended dose by package insert, applying daily dosing recommendations of ≥1.5g/d across older patients results in higher proportion of patients within the therapeutic target

concentration. Yet, the incidence of nephrotoxicity has not increase significantly compared with the daily dose recommended by package insert. Prospective studies with large sample size are needed to define the optimal dose for using this drug in older patients.

Declarations

Acknowledgements

Open access funding provided by University of Helsinki including Helsinki University Central Hospital. Association of Finnish Pharmacies.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Conflicts of interest

We have no conflicts of interest to disclose.

References

1. Moellering RJ. Vancomycin: a 50-year reassessment. Clin Infect Dis. 2006;42(Suppl 1):3–4.
2. Huang M, Wu H, Zhou J, Xu M, Zhou S. Efficacy of Vancomycin on Gram-Positive Bacterial Infection in Elderly Critical Patients and Risk Factors Associated With Nephrotoxicity. Arch Iran Med. 2018;21:349–55.
3. Jeffres MN. The Whole Price of Vancomycin: Toxicities, Troughs, and Time. Drugs. 2017;77:1143–54.
4. Liu Y, Yin Y, Liu XZ, et al. Retrospective Analysis of Vancomycin Nephrotoxicity in Elderly Chinese Patients. Pharmacology. 2015;95:279–84.
5. Matsumoto K, Takesue Y, Ohmagari N, et al. Practice guidelines for therapeutic drug monitoring of vancomycin: a consensus review of the Japanese Society of Chemotherapy and the Japanese Society of Therapeutic Drug Monitoring. J Infect Chemother. 2013;19:365–80.
6. Ye ZK, Chen YL, Chen K, et al. Therapeutic drug monitoring of vancomycin: a guideline of the Division of Therapeutic Drug Monitoring, Chinese Pharmacological Society. J Antimicrob Chemother. 2016;71:3020–25.
7. Hashimoto M, Iketani O, Ichinose N, et al. Evaluation for optimal dosing of vancomycin in patients with different physical types. J Infect Chemother. 2019;25:735–7.
8. He J, Mao EQ, Feng J, et al. The pharmacokinetics of vancomycin in patients with severe acute pancreatitis. Eur J Clin Pharmacol. 2016;72:697–702.

9. Corsonello A, Pedone C, Incalzi RA. Age-related pharmacokinetic and pharmacodynamic changes and related risk of adverse drug reactions. Curr Med Chem. 2010;17:571–84.
10. Sanchez JL, Dominguez AR, Lane JR, et al. Population pharmacokinetics of vancomycin in adult and geriatric patients: comparison of eleven approaches. Int J Clin Pharmacol Ther. 2010;48:525–33.
11. Glatard A, Bourguignon L, Jelliffe RW, et al. Influence of renal function estimation on pharmacokinetic modeling of vancomycin in elderly patients. Antimicrob Agents Chemother. 2015;59:2986–94.
12. Hall RN, Blaszczyk AT, Thompson KA, et al. Impact of empiric weight-based vancomycin dosing on nephrotoxicity and mortality in geriatric patients with methicillin-resistant Staphylococcus aureus bacteraemia. J Clin Pharm Ther. 2014;39:653–57.
13. Zhou Y, Gao F, Chen C, et al. Development of a Population Pharmacokinetic Model of Vancomycin and its Application in Chinese Geriatric Patients with Pulmonary Infections. Eur J Drug Metab Pharmacokinet. 2019;44:361–70.
14. Nunn MO, Corallo CE, Aubron C, et al. Vancomycin dosing: assessment of time to therapeutic concentration and predictive accuracy of pharmacokinetic modeling software. Ann Pharmacother. 2011;45:757–63.
15. Sansot C, Kalbacher E, Lemoine S, et al. A Bayesian Model to Describe Factors Influencing Trough Levels of Vancomycin in Hemodialysis Patients. Nephron. 2015;131:131–37.
16. Neely MN, Kato L, Youn G, et al. Prospective Trial on the Use of Trough Concentration versus Area under the Curve To Determine Therapeutic Vancomycin Dosing. Antimicrob Agents Chemother. 2018;62.
17. Suchankova H, Lecbychova K, Strojil J, Furst T. Individualized dosing of vancomycin in geriatric patients. Epidemiol Mikrobiol Imunol. 2020;69:172–80.
18. Khwaja A. KDIGO clinical practice guidelines for acute kidney injury. Nephron Clin Pract. 2012;120:c179–84.
19. Yahav D, Abbas M, Nassar L, et al. Attention to age: similar dosing regimens lead to different vancomycin levels among older and younger patients. Age Ageing. 2019;49:26–31.
20. Liu C, 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. Clin Infect Dis. 2011;52:e18–55.
21. Bourguignon L, Cazaubon Y, Debeurme G, et al. Pharmacokinetics of Vancomycin in Elderly Patients Aged over 80 Years. Antimicrob Agents Chemother. 2016;60:4563–67.
22. Mizuno T, Mizokami F, Fukami K, et al. The influence of severe hypoalbuminemia on the half-life of vancomycin in elderly patients with methicillin-resistant Staphylococcus aureus hospital-acquired pneumonia. Clin Interv Aging. 2013;8:1323–28.
23. Barber KE, Bell AM, Stover KR, Wagner JL. Intravenous Vancomycin Dosing in the Elderly: A Focus on Clinical Issues and Practical Application. Drugs Aging. 2016;33:845–54.

24. Qian X, Du G, Weng C, Zhou H, Zhou X. Evaluation of the variability and safety of serum trough concentrations of vancomycin in patients admitted to the intensive care unit. Int J Infect Dis. 2017;60:17–22.
25. Glatard A, Bourguignon L, Jelliffe RW, et al. Influence of renal function estimation on pharmacokinetic modeling of vancomycin in elderly patients. Antimicrob Agents Chemother. 2015;59:2986–94.
26. Kim DJ, Lee DH, Ahn S, et al. A new population pharmacokinetic model for vancomycin in patients with variable renal function: Therapeutic drug monitoring based on extended covariate model using CKD-EPI estimation. J Clin Pharm Ther. 2019;44:750–59.
27. 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;57:734–44.
28. Mergenhagen KA, Borton AR. Vancomycin nephrotoxicity: a review. J Pharm Pract. 2014;27:545–53.
29. Pan KM, Wu Y, Chen C, et al. Vancomycin-induced acute kidney injury in elderly Chinese patients: a single-centre cross-sectional study. Br J Clin Pharmacol. 2018;84:1706–18.

Tables

Table 1 Personal demographic and clinical characteristics of patients with difference initial dosage of vancomycin.

Variable	Group A (n=82)	Group B (n=15)	P-Value*
Demographic factors:			
Age, median (IQR)	70(8)	73(10)	0.273
65-74y, n(%)	62(75.6)	9(60)	
75-84y, n(%)	18(22.0)	5(33.3)	
≥85y, n(%)	2(2.4)	1(6.7)	
male, n(%)	46(56.1)	9(60.0)	0.779
Payment methods:			
Basic national medical insurance, n(%)	57(69.5)	11(73.3)	0.766
Self-paying, n(%)	25(30.5)	4(26.7)	
In-patient department:			
Medical, n(%)	22(26.8)	5(33.3)	0.747
Surgical, n(%)	47(57.3)	7(46.7)	
ICU, n(%)	13(15.9)	3(20.0)	
Laboratory variables:			
Baseline BUN, mmol l^{-1}	7.45±4.87 (1.92-28.9)	9.83±4.94 (3.83-18.57)	0.051
Baseline SCr, μmol l^{-1}	84.7±65.0 (32.0-386.0)	118.9±86.4 (51.0-392.0)	0.019
Baseline eGFR, ml min^{-1} 1.73 m^{-2}	80.41±25.09 (9.83-126.67)	60.00±29.05 (12.11-95.85)	0.017
Serum albumin, g l^{-1}	31.0±5.1 (15.6-45.4)	30.4±5.3 (25.0-40.8)	0.682
Hyperuricaemia, n(%)	9 (11)	4 (26.7)	0.092
Hopitalizatiom-related factors:			
LOS, median (IQR)	25 (18)	27 (18)	0.34
ICU admittance, n (%)	23(28)	3(20)	0.518
Cancer, n (%)	16(19.5)	1(6.7)	0.229

Sepsis, n (%)	10(12.2)	1(6.7)	0.535
Hypotension, n (%)	8(9.8)	1(6.7)	0.705
Shock, n (%)	8(9.8)	0(0)	0.207
Surgery, n (%)	48(58.5)	7(46.7)	0.394
Mechanical ventilation, n (%)	15(18.3)	3(20)	0.876
Death, n (%)	1(1.2)	0(0)	0.667
Indication for VAN therapy, n (%):			
Prophylactic, n (%)	6(7.3)	0(0)	0.40
Local infection, n (%)	62(75.6)	12(80.0)	
Bacteraemia, n (%)	14(17.1)	3(20.0)	
Variety of VAN:			
Wen kexin, n(%)	57(69.5)	13(86.7)	0.173
Lai kexin, n(%)	25(30.5)	2(13.3)	
Length of therapy, median (IQR)	9(8)	8(8)	0.572
Therapeutic drug monitoring:			
Serum Trough concentration (mg dl^{-1})	17.22±7.52 (4.64-45.6)	13.78±6.90 (3.17-28.00)	0.037
<5mg dl^{-1}, n(%)	1(0.6)	1(4.0)	0.164
5-10 mg dl^{-1}, n(%)	22(13.6)	7(28.0)	
10-15 mg dl^{-1}, n(%)	45(27.8)	7(28.0)	
15-20 mg dl^{-1}, n(%)	44(27.2)	5(20.0)	
>20 mg dl^{-1}, n(%)	50(30.9)	5(20.0)	
Concomitant disease:			
Hypertension, n (%)	42(51.2)	8(53.3)	0.880
Diabetes, n (%)	20(24.4)	3(20)	0.713
CHD, n (%)	12(14.6)	4(26.7)	0.248
CKD, n (%)	1(1.2)	4(26.7)	<0.001

CLD, n (%)	5(6.1)	1(6.7)	0.933
COPD, n (%)	2(2.4)	1(6.7)	0.385

CHD, coronary heart disease; CKD, chronic kidney disease; CLD, chronic lung disease; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; LOS, length of stay; BUN, blood urea nitrogen; SCr, serum creatinine; eGFR, estimated glomerular filtration rate IQR, interquartile range; VAN, vancomycin.

*$p < 0.05$ considered significant

Table 2 Treatment characteristics for vancomycin

Variable	Group A	Group B	P-value*
VAN on renal function:			
Nephrotoxicity (%)	7(8.5)	3(20.0)	0.179
BUN after medication, mmol l^{-1}	9.02±7.20 (1.92-39.55)	12.19±7.76 (5.06-31.84)	0.056
SCr after medication, μmol l^{-1}	96.7±94.7 (34.0-587.0)	137.7±79.0 (48.0-302.0)	0.010
eGFR after medication, ml min^{-1} 1.73 m^{-2}	76.89±26.94 (7.38-112.88)	56.46±31.89 (16.6-108.4)	0.023
Serum Trough concentration (mg dl^{-1}) in AKI patients	23.60±9.14 (11.4-45.6)	15.62±8.82 (7.0-28.0)	/
Length of therapy in AKI patients, median (IQR)	10(10)	11(6)	/
BUN after medication in AKI patients, mmol l^{-1}	11.89±7.87 (7.51-39.55)	11.08±6.21 (5.82-21.01)	/
eGFR after medication in AKI patients, ml min^{-1} 1.73 m^{-2}	34.74±10.80 (7.61-54.28)	39.16±10.73 (20.04-44.83)	/
Outcome of nephrotoxicity:			
No treatment, n(%)	1(14.3)	2(66.7)	/
Termination of VAN, n(%)	4(57.1)	1(33.3)	
Dose adjustment, n(%)	1(14.3)	0(0)	
RRT, n(%)	1(14.3)	0(0)	
AKI outcome:			
Recovery, n(%)	1(14.3)	2(66.7)	/
Improvement, n(%)	4(57.1)	0(0)	
Nonrecovery, n(%)	2(28.6)	1(33.3)	

IQR, interquartile range; VAN, vancomycin; BUN, blood urea nitrogen; SCr, serum creatinine; eGFR, estimated glomerular filtration rate; AKI, acute kidney injury; RRT, renal replacement therapy.

*$p < 0.05$ considered significant

Figures

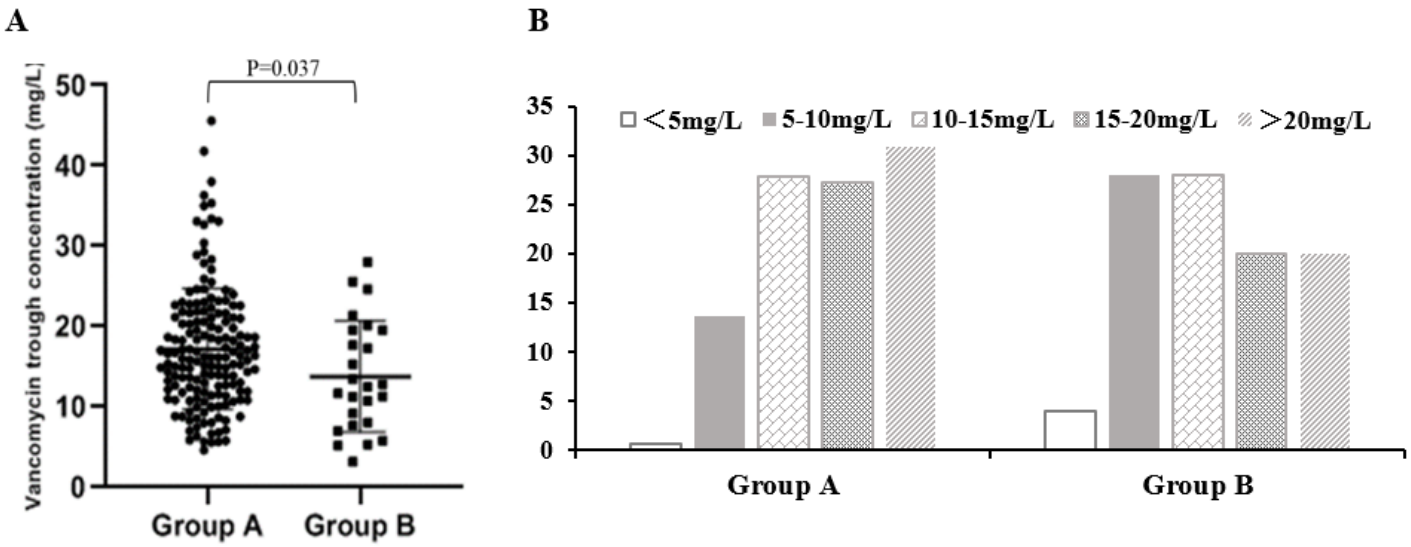

Figure 1

Distribution of vancomycin trough concentrations: 187 samples were obtained from 97 elderly patients.

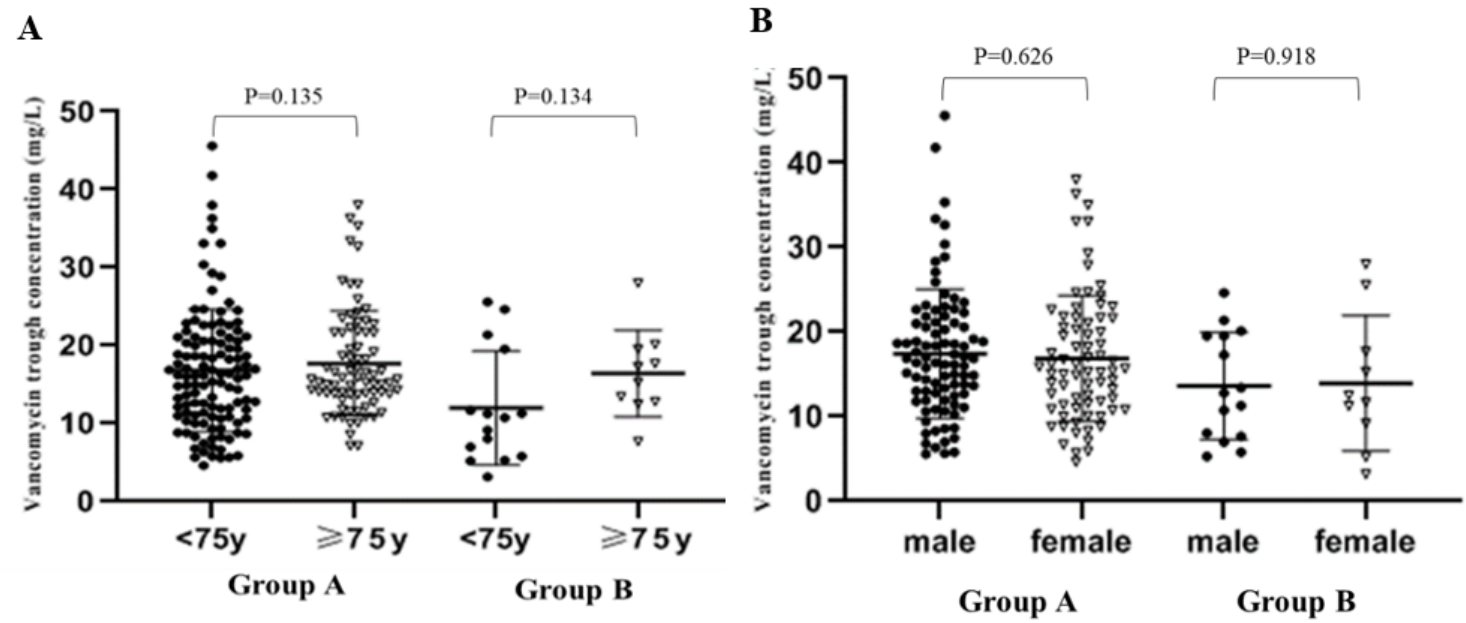

Figure 2

(A). Comparisons of vancomycin trough concentrations in patients younger than 75 years old or older than 75 years old in group A and group B. (B). Comparisons of vancomycin trough concentrations in male and female patients in group A and group B.

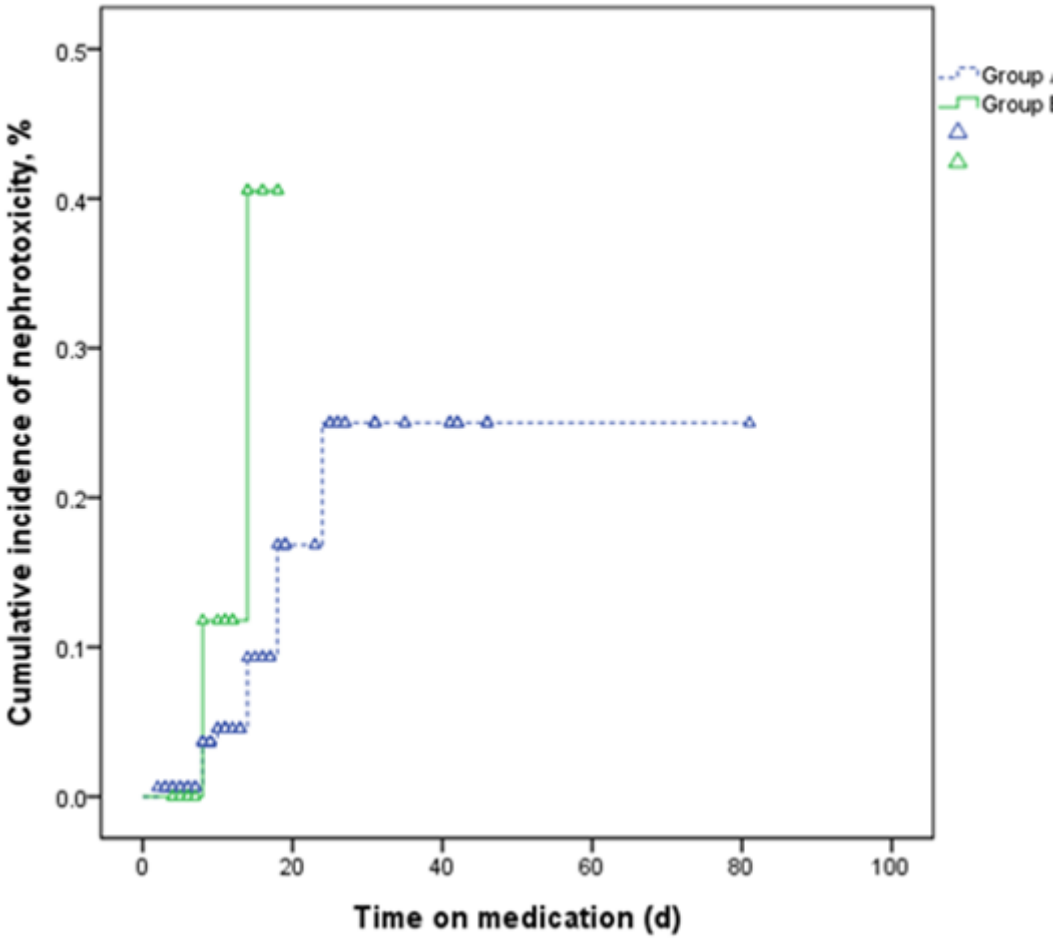

Figure 3

Time to vancomycin-related nephrotoxicity in group A and group B.