Original article

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THE PREDICTION OF VANCOMYCIN DOSING REGIMEN IN PATIENTS WITH NORMAL RENAL FUNCTION AND PATIENTS WITH AUGMENTED RENAL CLEARANCE USING POPULATION PHARMACOKINETICS MODEL AND MONTE CARLO SIMULATION METHOD AT BUDDHACHINARAJ PHITSANULOK HOSPITAL

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ABSTRACT

Current literature reports the initial recommended dose of vancomycin may be inadequate to promptly achieve therapeutic concentration in patients with normal renal function, especially the ones with augmented renal clearance (ARC). Our objectives were to describe vancomycin pharmacokinetics and to propose optimal vancomycin dosage regimens that achieve the area under the curve to minimum inhibitory concentration ratio (AUC/MIC) of 400 to 600 in adult patients with normal renal function, including the ones with ARC. This retrospective study collected data from patients with an estimated glomerular filtration rate (eGFR) > 90 mL/min/1.73m^2. Population pharmacokinetics (PPK) analysis was performed using Phoenix NLME. Monte Carlo simulation of the final PPK model using Certara Trial Simulator™ was employed to explore vancomycin dosage regimens that achieve a target AUC/MIC of at least 70%. A total of 172 patients with 222 blood specimen collections were included in the analysis. Data were fitted to one-compartment model with first order rate of elimination. Body weight was the covariate that correlated with volume of distribution, whereas body weight, age, and creatinine clearance (CL_{cr}) calculated by the Cockcroft-Gault equation correlated with vancomycin clearance. Simulation of study populations revealed a usual vancomycin dose, 15-20 mg/kg every 12 hours, could not reach the target AUC/MIC in patients with CLcr more than 90 mL/min. The following regimens were suggested to achieve the target AUC/MIC: 17.5 mg/kg every 8 hours for patients with CLcr of 90 to 130 mL/min and, either 20 mg/kg every 8 hours or 15 mg/kg every 6 hours for patients with CLcr greater than 130 mL/min and those with ARC. However, for patients with CLcr ≥130 mL/min, a higher dose or shorter dosing interval of vancomycin was necessary, along with therapeutic drug monitoring and requires further study.

Keywords: vancomycin, population pharmacokinetic model, Monte Carlo Simulation, normal renal function, augmented renal clearance

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Introduction

Vancomycin is a glycopeptide antibiotic extensively employed for treatment of serious gram-positive bacterial infections, notably those caused by methicillin-resistant *Staphylococcus aureus* (MRSA).[1] Therapeutic drug monitoring (TDM) is recommended throughout vancomycin therapy to optimize dosing with the dual goal of maximizing therapeutic efficacy and minimizing the potential risk for nephrotoxicity.[1] According to consensus guideline by the American Society for Health System Pharmacists (ASHP), Infectious Diseases Society of America (IDSA), and Society for Infectious Diseases Pharmacists (SIDP), the recommended pharmacodynamic target is an area under the concentration–time curve to minimum inhibitory concentration (AUC/MIC) ratio of 400–600[1], replacing the previous reliance on trough concentrations of 15-20 mg/L.[2] This consensus guideline indicates recommends a vancomycin dosage of 15–20 mg/kg administered every 8–12 hours for most patients with normal renal function to attain the target AUC/MIC ratio.[1] However, several studies have shown that an initial regimen of 15–20 mg/kg every 12 hours may be insufficient to achieve therapeutic vancomycin concentrations in patients with normal renal function, particularly in with augmented renal clearance (ARC).[3-8] These findings indicate that shorter dosing intervals, such as every 6 to 8 hours, may be required to maintain adequate therapeutic drug concentration.[3-8] Furthermore, a study conducted by Sima M et al. demonstrated that a 6-hour dosing interval should be considered in patients with an eGFR greater than 110 mL/min/1.73 m^2 to achieve target trough concentrations of 10–20 mg/L.[8]

Despite the importance of AUC/MIC-guided TDM for optimizing vancomycin dosing regimen, the implementation remains limited in several Asian clinical setting, owing to resource limitations and insufficient infrastructure.[2] Consequently, vancomycin dosing regimens are frequently based on trough concentration and creatinine clearance (CL_{cr})–based nomograms. However, these nomograms are supported by limited clinical evidences, particularly in patients with ARC, which compromise dosing accuracy and therapeutic outcomes. To our knowledge, population pharmacokinetic data on vancomycin in patients with normal renal function, including those with ARC, are scarce, especially among Thai populations. Therefore, the objectives of this study were to characterize the population pharmacokinetics of vancomycin and to propose optimal dosing regimens to achieve the target AUC/MIC ratio of 400–600 in adult patients with normal renal function, including those with ARC.

Methods

Patients and data collection

Patient data were retrospectively collected from medical records of individuals hospitalized at Buddhachinaraj Phitsanulok Hospital, Phitsanulok, Thailand, between October 2020 and March 2023. Data of vancomycin serum concentration were from routine TDM service at the hospital. Vancomycin dosage regimens were initiated by physicians. Timing (day after vancomycin initiation) for drug concentration monitoring is individualized and recommended by physicians and pharmacists. Vancomycin peak concentrations were taken at least 2 hours after the end of vancomycin infusion or 30 min before the next dose as trough concentration. The inclusion criteria were as follows: (1) age older than 18 years, (2) eGFR ≥ 90 mL/min/1.73m^2, (3) receiving at least one dose of intravenous vancomycin, and (4) having at least one blood sampling for serum vancomycin concentrations from the TDM service. The exclusion criteria were: (1) patients with acute kidney injury using AKIN criteria[9], (2) hematologic malignancy, and (3) incomplete record of age, body weight (BW), serum creatinine (SCr), eGFR, vancomycin dosage regimen, vancomycin administration time, blood sampling time for TDM, and serum vancomycin concentration. The following data were extracted from patient's medical records, including gender, age, BW, SCr, serum albumin, eGFR using CKD-EPI equation, vancomycin dosage regimen, vancomycin sampling time and vancomycin serum concentrations. We defined ARC using all of the following criteria[10-12] (1) age younger than or equal to 50 years old (2) critically ill status during the use of vancomycin, defined as medical intensive care unit (ICU) or surgical ICU admission, receiving resuscitation fluid (at least 30 ml/kg), receiving vasopressors or inotropes continuously for at least one hour, and (3) CL_{cr}, calculated by Cockcroft-Gault equation, greater than 130 mL/min.[5,13]

The study protocol was approved by Buddhachinaraj Phitsanulok Hospital the Human Research Ethics Committee, with the approval number HREC No.101/2566.

Population Pharmacokinetics Analysis

Population pharmacokinetic analysis was performed using a Phoenix NLME™ (Version 8.4; Certara USA, Inc., 2023). Vancomycin blood collections were from the routine TDM service and the distribution phase of drug was avoided, thus, one-compartmental model with first-order elimination was fitted to the data.

Gender, age, BW, ARC, and CL_{cr} were tested in the covariate model building step using stepwise forward inclusion and backward elimination method.[13-22] Graphical and statistical methods were used for evaluate the final model. The evaluation was processed by Goodness of fit plot (GOF), Visual Predictive Check (VPC), and bootstrap.

Simulation analysis The final population pharmacokinetic model and parameters obtained from the population pharmacokinetic analysis were used for simulation using Monte Carlo method (Certara Trial Simulator™, Version 2.3; Certara USA, Inc., 2023) explore the optimal dosage regimen range 15-20 mg/kg every 6-12 hours.[1,8,14] The probability of target attainment (PTA) to achieved the target AUC/MIC ratio of 400 to 600, assuming a MIC of 1 mg/L was calculated.[1]

Results

Patient characteristic

Data of 172 patients were used in the study (88 males and 84 females), with a mean age of 46.9 ± 14.8 years (range 19 to 84 years), a mean BW of 63.4 ± 13.4 kg (range 38-120 kg) and a mean CL_{cr} of 138.0 ± 42.9 mL/min (range 90.4-296.6 mL/min). Patients with ARC were identified in 26 patients (15.12%). Patient demographic characteristics were summarized in Table 1. Two hundred and twenty-two blood samples for vancomycin concentrations from the TDM service were analyzed.

Population Pharmacokinetics Analysis

Vancomycin serum concentrations data were fitted to one compartment model. The residual error is explained by a multiplicative error model. The effects of covariates on pharmacokinetic parameters were tested by forward addition and backward elimination (p-value < 0.01 and < 0.001 respectively). The significant covariates that influenced vancomycin clearance (CL_v) were age, BW, and CL_{cr}. Additionally, BW significantly affected volume of distribution (Vd). The final model employed in the study were described by equations as follows:

$$Vd\ (L) = 72.12 \times (Wt/63.37)^{0.58}$$

$$CL_v\ (L/min) = 6.73 \times (age/46.90)^{-0.33} \times (Wt/63.37)^{0.40} \times (CL_{cr}/138.01)^{0.35}$$

Where Wt is body weight; CL_{cr} calculated by Cockcroft-Gault equation.

Model Evaluation

The GOF is used to assess how well a model fits the observed data. A good fit typically has points on or scattered around the line of identity (y = x line for predicted vs. observed plots). The GOF from base and final model are presented in Figure 1a, b. The conditional weighted residuals (CWRES) is a diagnostic tool used in population modeling, to assess how well a model fits the observed data. It evaluates the residuals (differences between observed and predicted values) in a way that accounts for the variability and structure of the model. The CWRES homogenously distributed as shown in Figure 2a, b. Figure 3 present the VPC result from 1,000 generated samples showed that the 5th and the 95th percentiles interval of predicted concentration. The diagnostic plots and visual predictive check, indicated that the model adequately described the data.

Table 2 presents the results of internal validation. The 95% confidence intervals (CI) for the pharmacokinetic parameters were obtained by analyzing 1,000 bootstrap samples. These CIs closely match the population pharmacokinetic parameters of the original dataset.

Table 1 Patients' characteristics (n = 172)

Characteristics	Number (%) or mean ± SD (range)
Gender	
Male	88 (51.16)
Female	84 (48.84)
Age (years)	46.90 ± 14.78 (19-84)
Body weight (kg)	63.37 ± 13.43 (38-120)
Serum creatinine (mg/dL)	0.58 ± 0.16 (0.25-1.10)
Creatinine clearance[a] (mL/min)	138.01 ± 42.85 (90.44-296.57)
eGFR[b] (mL/min/1.73m^2)	118.31 ± 15.90 (92-165)
Serum albumin[c] (g/dL)	2.93 ± 0.75 (1.4-4.6)
Number of patients with ARC	26 (15.12)

SD, standard deviation; a = calculated by Cockcroft-Gault equation; b = calculated by CKD-EPI 2009; c = albumin value from 164 patients; eGFR = estimated Glomerular Filtration Rate; ARC = Augmented Renal Clearance.

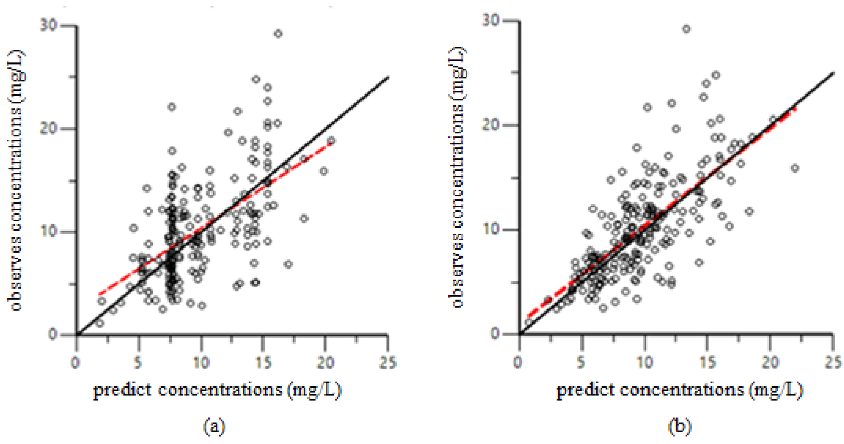

Figure 1 Scatter plot of the observes concentration versus predict concentrations: (a) Base model (b) Final (covariate) model

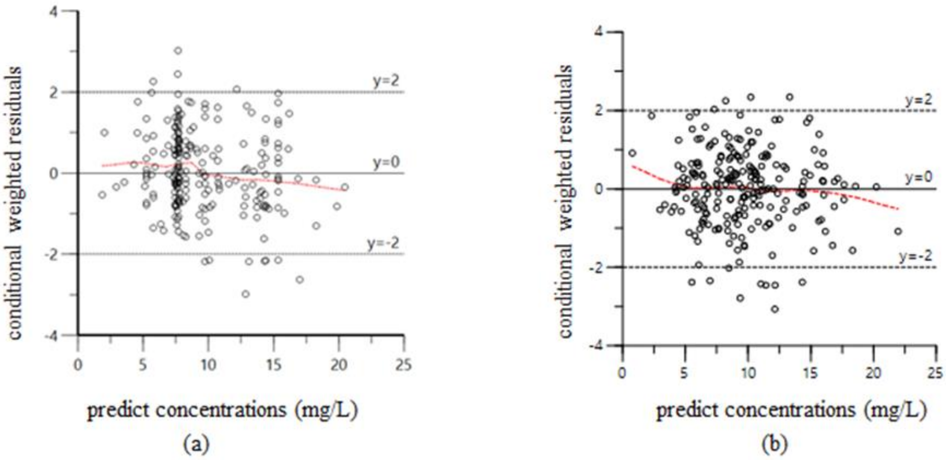

Figure 2 Conditional weighted residuals versus predict concentrations: (a) Base model (b) Final

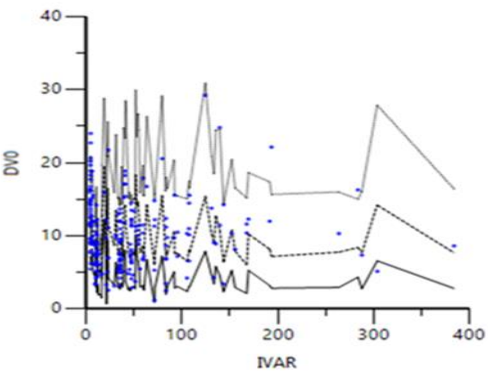

Figure 3 Visual predictive check (VPC) of the final model.

Monte Carlo simulation (MCS) analysis

A total of 10,000 simulated patients for each creatinine clearance range were generated via MCS, using the reference population characteristics outlined in Table 1 and the population pharmacokinetic parameters from Table 2. The simulation results, summarized in Figure 4, show the PTA for all simulated dosing regimens across each CL_{cr} range that achieved the target AUC/MIC ratio of 400–600, assuming an MIC of 1 mg/L. Dosing regimens administered every 8 hours and every 6 hours achieved higher PTAs than less frequent dosing intervals. Figure 4a demonstrates that none of the vancomycin regimens administered every 12 hours achieved PTAs greater than 70%. Conversely, Figures 4b and 4c show that dosing regimens administered every 8 hours and every 6 hours more effectively achieved the PTAs. However, regimens exceeding 60 mg/kg/day resulted in a reduction in PTA due to an AUC/MIC ratio exceeding 600, except in patients with CL_{cr} >150 mL/min. Table 3 illustrates the recommended vancomycin dosage regimens in each CL_{Cr} that achieve a PTA higher than 70. The rationale for selecting a PTA threshold (>70%) is provided in Table 1S in Supplementary data.

Table 2 Population pharmacokinetic parameter of vancomycin estimates from final model and bootstrap validation.

Parameters	Estimates (RSE) [95% CI]	BSV (% RSE)	Bootstrap analysis mean [95% CI]
Vd (L) =		0.043	
THETA-1 x (BW/63.37) $^{(THETA\text{-}2)}$)		(37.209)	
THETA-1	72.12 (4.35%) [65.94-78.30]		67.53 [60.26-75.21]
THETA-2	0.58 (17.71%) [0.37-0.78]		0.56 [0.17-0.92]
CL_v (L/hr) =		0.080	
THETA-3 x (age/46.90) $^{(THETA\text{-}4)}$ x		(5.000)	
(BW/63.37) $^{(THETA\text{-}5)}$ x (CL_{cr} /138.01) $^{(THETA\text{-}6)}$			
THETA-3	6.73 (2.45%) [6.40-7.05]		6.57 [6.17-6.97]
THETA-4	-0.33 (-15.02%)		-0.32
	[-0.43 – (-0.23)]		[-0.44 to -0.20)]
THETA-5	0.40 (20.51%) [0.24-0.56]		0.40 [0.18-0.64]
THETA-6	0.35 (18.57%) [0.22-0.48]		0.35 [0.19-0.51]
multiplicative error	0.15 (12.16%) [0.11-0.18]		0.11 [0.02-0.17]

RSE: relative standard error of the estimate; BSV: between subject variability

Discussion

Our simulation results indicate vancomycin pharmacokinetics were best described by a one-compartment model, with a mean Vd of 72.12 L and a CL_v of 6.73 L/h. These pharmacokinetic parameters were derived from 172 participants with a mean age of 46.9 years, a mean BW of 63.4 kg, and a mean CL_{cr} of 138.0 mL/min. In conjunction with observed vancomycin concentrations obtained through TDM, our findings suggest that the current dosing recommendation for patients with normal renal function (15–20 mg/kg every 8–12 hours) as proposed by the ASHP/IDSA/SIDP consensus guideline may warrant reconsideration.

In our population pharmacokinetic model, CL_v was significantly influenced by age, BW, and CL_{cr}. The identification of CL_{cr} as a significant covariate is consistent with the pharmacokinetic properties of vancomycin, which is primarily eliminated via renal excretion; higher CL_{cr} has been associated with increased vancomycin clearance, as reported in previous studies.[13-18,20,22] Age may further contribute to interindividual variability in clearance, as renal function gradually declines after 40 years of age, with an estimated reduction of approximately 10% per decade between 30 and 80 years.[23] In this study, the mean age of participants was 46.9 years, implying that this relatively young cohorts was more likely to have preserved renal function and, consequently, a higher risk of ARC compared with older populations. Regarding BW, increased vancomycin clearance in individuals with greater BW may be attributed to increase cardiac output, resulting in enhanced renal blood flow and drug elimination.[24] Consistent with the findings of Llopis et al.[19], both CL_{cr} and BW were identified as significant covariates influencing CL_v, whereas Revilla et al.[17] reported CL_{cr} and age as significant predictors. Additionally, our findings demonstrated that increment in BW were associated with corresponding increases in Vd, a finding consistent with previous reports.[19,22]

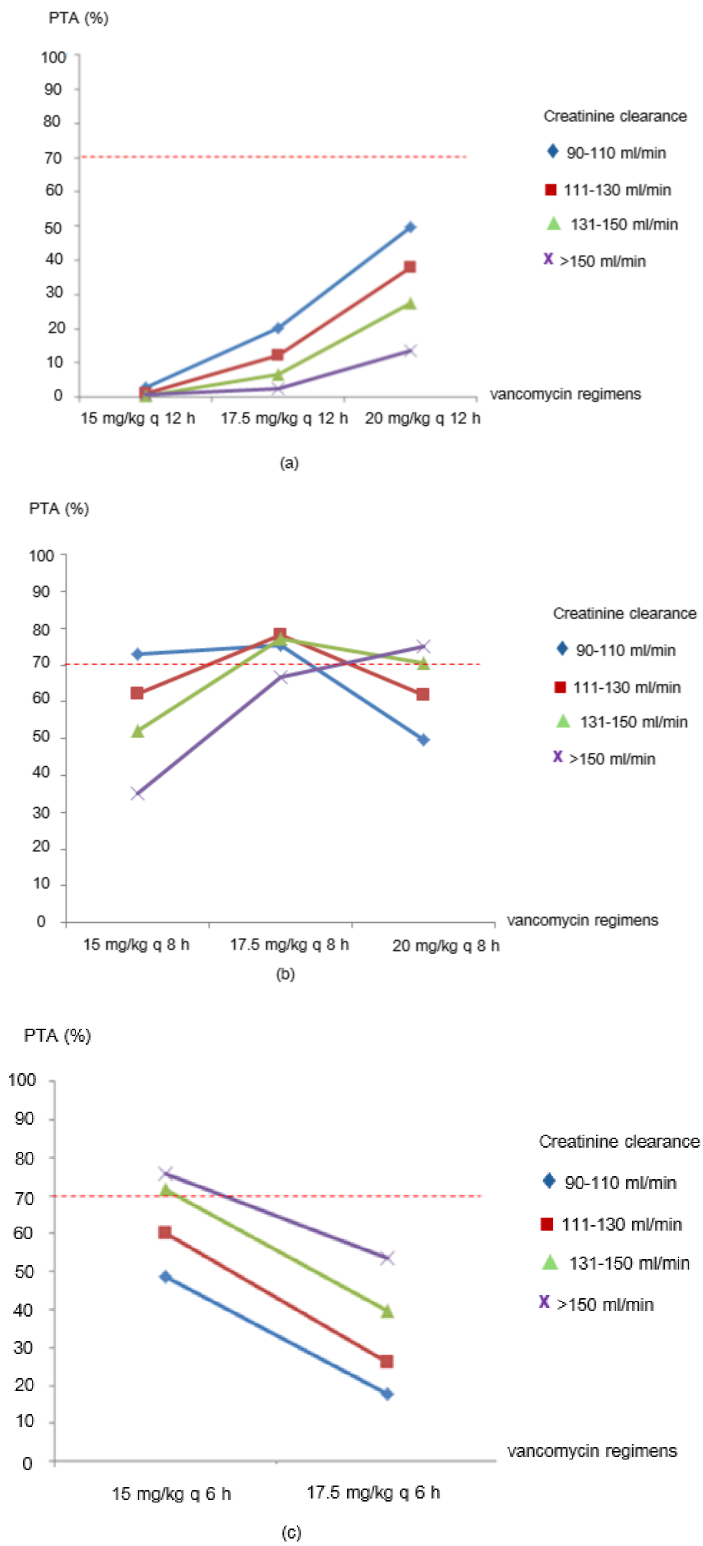

Figure 4 PTA of simulated vancomycin dosing regimens by CL_{cr} category that achieved the target AUC/MIC ratio of 400-600, assuming a MIC of 1 mg/L

Legend: dosing interval every 12 hours (a), every 8 hours (b), every 6 hours (c). Symbols represent CL_{cr} ranges: 90–110 mL/min (blue diamond), 111–130 mL/min (red square), 131–150 mL/min (green triangle), and >150 mL/min (purple cross).

Table 3 Recommended vancomycin dosage regimens that achieved the target AUC/MIC was between 400 and 600 of each range of CL_{cr}

CL_{cr} (ml/min)	Dosage	Dose per day
90 – 110	15 mg/kg every 8 hr	45 mg/kg
	17.5 mg/kg every 8 hr	52.5 mg/kg
111 – 130	17.5 mg/kg every 8 hr	52.5 mg/kg
131 – 150	17.5 mg/kg every 8 hr	52.5 mg/kg
	20 mg/kg every 8 hr	60 mg/kg
	15 mg/kg every 6 hr	60 mg/kg
>150	20 mg/kg every 8 hr	60 mg/kg
	15 mg/kg every 6 hr	60 mg/kg

Our simulation revealed that the ASHP/IDSA/SIDP consensus guideline recommended dosing regimen of 15–20 mg/kg every 12 hours[1] achieved less than a 70% PTA for the target AUC/MIC ratio of 400–600.[1] More frequent dosing intervals of every 6–8 hours were required to achieve the goal, as presented in Table 3. Accordingly, a vancomycin dosing regimen of 17.5 mg/kg every 8 hours or total daily dose of 52.5 mg/kg was proposed for patients with CL_{cr} of 90–150 mL/min. For patients with CL_{cr} greater than 150 mL/min, a total daily dose regimen of 60 mg/kg, divided every 6–8 hours was recommended. These findings are consistent with a previous study by Heffernan AJ et al. in septic patients with normal renal function (CL_{cr} greater than 80 mL/min/1.73 m^2), which suggested administering vancomycin 2 g every 8 hours during the first three days of infection.[14] Notably, the vancomycin dosing regimens proposed in this study were derived primarily from patients with hypoalbuminemia. Therefore, these regimens should be applied with caution, particularly in patients with normal serum albumin concentrations. Moreover, a consistent dosage regimen cannot be universally applied, as renal function and clinical condition could fluctuate throughout hospitalization and substantially affect vancomycin pharmacokinetics. Consequently, renal function and clinical status along with serum vancomycin concentrations should be closely monitored throughout therapy to ensure therapeutic efficacy and safety.

This study has some limitations inherent to its retrospective nature, which should be considered when interpreting the results. First, ARC was identified using CL_{cr} estimated by the Cockcroft–Gault equation, consistent with the methodology employed by Chu Y et al.[5] Direct measurement of 24-hour urinary creatinine, which is considered the standard method for ARC detection[25], was not routinely performed. Thus, the prevalence of ARC in this study may have been underestimated.[26] Secondly, serum albumin data were not available for all participants. Albumin measurements were reported for 94% of patients, with a mean value of 2.93 g/dL which may have limited statistical power to detect its effect on vancomycin pharmacokinetics. Although previous population pharmacokinetic studies have not consistently identified serum albumin as a significant covariate for either Vd or CL_v, hypoalbuminemia has been associated with increased Vd and CL_v due to a higher fraction of unbound vancomycin available for distribution and elimination.[27] Finally, the selection of a PTA threshold greater than 70% represented another limitation of this study. This criterion implied that up to 30% of patients may not achieve the target AUC/MIC range with the recommended dosing regimens (Table 3). Therefore, close monitoring of SCr and clinical response remain essential to ensure both efficacy and safety during vancomycin therapy. Prospective studies are warranted to better characterized key covariates influencing vancomycin population pharmacokinetics and to improve the identification of patients with ARC using standard method[25]. In addition, further prospective validation is required to confirm the treatment efficacy and safety of proposed dosing regimens and other covariates on vancomycin pharmacokinetics in diverse patient populations.

Conclusion

Our study revealed an average Vd of 72.12 L and a CL_v of 6.73 L/hr in a cohort of 172 adults with normal renal function, in participants with a mean age of 46.9 years, CL_{cr} of 138.0 mL/min, and BW of 63.4 kg. These findings suggest that both BW and CL_{cr} significantly influence vancomycin pharmacokinetics. The proposed dosage regimen based on CL_{cr}: a dosage of 17.5 mg/kg every 8 hours for patients with CL_{cr} between 90–150 mL/min and 60 mg/kg/day divided every 6–8 hours for those with CL_{cr} exceeding 150 mL/min.

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