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ORIGINAL RESEARCH

Factors Affecting Vancomycin Trough Concentration; a Population Pharmacokinetic Model in Non-Critical Care Saudi Patients

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Background and Objective: Vancomycin is commonly prescribed in treatment of methicillin-resistant Staphylococcus aureus infections. While, vancomycins' pharmacokinetic vary among older patients, there is a paucity of data regarding specific characteristics influencing pharmacokinetics in Saudi adult patients. This study aims to establish a population-pharmacokinetic (Pop-PK) model for vancomycin in patients admitted to medical wards, with the focus on identification of patient characteristics influencing vancomycin trough concentrations.

Methods: A multicenter retrospective study was conducted involving patients aged ≥40 years admitted to medical wards in the Eastern Province, Saudi Arabia and initiated on vancomycin, between January to December 2022. Non-linear mixed-effects modelling (Monolix) was employed to develop the Pop-PK model. A base model was selected based on the Akaike information criterion. Covariates considered included age, sex, body weight, C-reactive protein (CRP), serum creatinine, creatinine clearance (CrCl), and albumin levels. A *P*-value of <0.05 was considered statistically significant for inclusion of covariates in the final model by stepwise addition. The simulation performance of the model was assessed by visual predictive check plot. The final model was simulated using Simulx software to assess the effect of the included covariates on vancomycin trough concentration.

Results: A total of 172 vancomycin trough concentrations from 124 patients were analyzed. The final Pop-PK model characterized vancomycin trough concentrations was one compartment distribution with linear elimination. CrCl and CRP were the only covariates included in the final model, as they reduced the between-subject variability (BSV) for clearance (from 173% to 81%). The simulated model demonstrated that high CRP value and low CrCl contributed to increased vancomycin trough concentrations.

Conclusion: This study highlights large BSV in trough concentrations among patients and emphasizes the influencing of CrCl and CRP on vancomycin pharmacokinetics in medical care settings.

Keywords: vancomycin trough concentration, C-reactive protein, creatinine clearance, population pharmacokinetics, medical care patients

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Background

Vancomycin is the most effective antibiotic for serious, life-threatening infections caused by antibiotic-resistant gram positive bacteria, particularly methicillin-resistant Staphylococcus aureus (MRSA).[1,2] Due to its narrow therapeutic index, therapeutic drug monitoring (TDM) is essential to reduce adverse drug reactions (ADRs) and assure optimal therapeutic outcomes.[3] Several medical organizations have issued clinical practice recommendations to standardize the TDM for vancomycin.[4] A vancomycin trough concentration of 10–20 mg/L has been recommended for optimal dosing.[5,6] Recently, consensus guidelines recommend a target area under the 24–hour time-concentration curve (AUC24) of 400–600 mg.h/L, aiming to maximize efficacy and minimize the risk of ADRs assuming a minimum inhibitory concentration (MIC) of 1 mg/L.[7]

Vancomycin pharmacokinetic (PK) parameters exhibit significant variability among different cohorts of patients, including elderly, cancer patients, and those with impaired renal function.[8–10] Vancomycin is primarily excreted unchanged in urine, and its clearance (CL) is closely dependent on creatinine clearance (CrCl). Thus, renal function represents the primary determinant influencing variations in vancomycin PK parameters.[11] Reported values for vancomycin CL ranges from 0.334 to 8.75 L/h, while the volume of distribution (V) ranges from 7.12 to 154 L and from 29.2 to 501.8 L in the case of one- and two-compartment models, respectively. The between-subject variability (BSV) has been reported as high as 77% for V and 99% for CL.[2]

The emergence of antimicrobial resistance is one of the main causes of treatment failure in infectious diseases.[12] To avoid this problem, particularly in critically ill patients, several strategies have been employed, including the application of population pharmacokinetic model (Pop-PK) approach.[13] These applications allow healthcare providers to predict the efficacy of antimicrobial treatments based on patient characteristics and the infecting pathogen, thereby providing valuable guidance for the selection of the most appropriate treatment available.

Pop-PK modeling and simulation play a pivotal role in optimizing vancomycin dosing by assessing the inter- and intra-subject variability in PK. Previous studies have developed Pop-PK models for vancomycin in different cohorts of patients.[8,10,14–16] Renal function has been found as a crucial determinant of vancomycin PK profiles,[17,18] highlighting the importance of monitoring both renal function and vancomycin trough levels. Ethnicity can significantly impact drug pharmacokinetics through various mechanisms, including genetic variations, differences in drug metabolism, and variations in protein binding mechanisms.[19] However, as vancomycin is almost exclusively renally eliminated, variability in vancomycin trough levels among different ethnic populations may contribute to genetic polymorphisms affecting renal drug transporters rather than metabolizing enzymes.[17]

According to our preliminary narrative review, no Pop-PK model specifically designed for patients admitted to medical care was identified. Therefore, our study aimed to perform a Pop-PK analysis to determine vancomycin PK parameter in Saudi adult patients and identify specific patient characteristics that clinicians should consider optimizing therapeutic efficacy of vancomycin.

Methodology

Study Design, Subjects, and Sample Collection

This is a multicenter retrospective Pop-PK study conducted in the Eastern region of Saudi Arabia, involving patients admitted to the medical ward of participating hospitals: Al-Mana General Hospital (AGH) in Al-Khobar, Qatif Central Hospital (QCH), and Dammam Medical Complex (DMC)] during the period from January 1st to December 31st, 2022. Eligible participants included patients aged ≥ 40 years who were prescribed systemic vancomycin therapy and had documented vancomycin trough concentration in their medical record. Exclusion criteria included patients treated in the emergency department, the intensive care unit, or surgical wards, those with chronic kidney disease, pregnant women, aged < 40 years, or lacking documentation of vancomycin trough concentration. Data were collected from the patients' computerized medical records.

The age of 40 years was set as the inclusion criteria to assess the impact of aging on the epidemiology of multiple morbidities and facilitates an examination of how changes in comorbidities and co-prescribed medications may influence the antihypertensive drugs prescription.[20] For patients with multiple visits during the study period, only data from their first reported visit was included.

The following patient-specific data were collected: demographic information including age, sex, and body weight (BW), concurrent prescribed medications, number of previous vancomycin doses, and clinical biochemistry and hematology blood test results. CrCl was calculated using the Cockcroft-Gault formula.[21] Dosage details including dosing date, time, and duration in addition to TDM data including sampling time and vancomycin plasma concentrations were collected.

Vancomycin doses were standardized to 500 mg for better visual presentation and comparison of vancomycin trough concentration over time among participants. However, the actual doses were used in the modeling process.

Vancomycin Assay

Vancomycin plasma concentrations were measured using the enzyme-multiplied immunoassay technique (EMIT) according to the manufacturer's instructions.[22] The calibration range was 2–50 mg/L (1.3–34 µmol/L), with a fluctuation of less than 10% observed both between and within days.

Population Pharmacokinetics Model Development

Pop-PK analyses were performed using the non-linear mixed-effect modeling approach with the stochastic approximation maximization (SAEM) algorithm implemented in Monolix software (version 2023, Lixoft).[23,24] All the individual PK parameters were assumed to follow a log-normally distributed (equ.1), where exponential random effects were used to describe BSV.

$$\theta i = \theta pop.e^{\eta i}\eta i \sim \mathrm{N}\left(\mathrm{O}, \omega_{\theta}^{2}\right)$$ [23]

Where θi is the individual parameter value for the *i*th individual, θpop is the population parameter value, and ηi is an independent random variable with a mean of zero and variance of ω^2.

The model building process followed a three-step approach: initially identifying and developing a structural base model that best describe the data without considering covariates, followed by development of the covariate model using statistically significant patient characteristics, and finally evaluation and validation of the final model.[23–25]

First Step; Base Model Selection

Firstly, the base structural model for vancomycin was established. Various models were tested, including those with one, two, or three compartments, with infusion or bolus administration, with no delay or lag-time absorption, and with linear or nonlinear elimination. The PK models estimated the following parameters: CL, volume of distribution in central and peripheral compartments (V1 and V2), and inter-compartmental clearance (Q). For residual unexplained variability, constant, proportional, and combined models were evaluated. Selection criteria for the structural models involved the lower Akaike information criterion (AIC), objective function value [(OFV); known as − 2 log-likelihood value (− 2LL)], precision of parameter estimation expressed as the relative standard error (RSE), final parameter estimate, physiological plausibility, and goodness of fit (GOF) plots such as observed versus predicted concentration, residual plot, and visual predictive check (VPC).[23–25] Outliers were assessed through visual presentation before model building step and from the weighted residuals plots of the model fit. A conditional weighted residuals (CWRES) of the model fit outside – 6 to + 6 was a set limit to determine an outlier, which was excluded and the model refitted accordingly.[23,24]

Covariate Model

After selection of the best base model, potential covariates were tested, including age, sex, BW, number of previous vancomycin doses, serum creatinine levels, serum albumin levels, CrCl, and C-reactive protein (CRP) levels. All covariates were coded as continuous variables except for sex (coded as a categorical variable). The OFV (−2LL) was computed to discriminate between models.[23–25] The covariate was retained in the model if its inclusion resulted in a statistically significant decrease in the OFV (- 2LL) [by at least 3.84 ($\chi 2$ $P < 0.05$)] or increase [by at least 10.83 ($\chi 2$ $P < 0.001$)] for one degree of freedom during stepwise deletion from the full model. The final inclusion of covariates was determined using the Wald test (stochastic approximation), with a significance level set at $P < 0.05$.

Model Evaluation

GOF plots were used as an indicator of suitability, including the representation of model-based individual predictions and population predictions versus observed concentrations.[23–25] The VPC plot was constructed with 1000 simulated data sets to show the time course of the 10th, 50th and 90th percentiles of the observed data to evaluate the simulation performance of the final model. The convergence assessment tool of Monolix was used, with five estimation runs performed, to assess the robustness of the convergence by different randomly generated initial fixed effects values and different seeds.

Simulation of Vancomycin Exposure

Monte Carlo simulations were performed using Simulx (version 2023) with the final Pop-PK model incorporating covariate parameters. The simulation generated 1000 vancomycin PK virtual patients stratified into nine groups based on their levels of CRP (considered low at 20 mg/dL, normal at 80 mg/dL, and high at 180 mg/dL), and CrCl (considered normal at 90 mL/min, moderately low at 60 mL/min, and severely low at 30 mL/min). Simulated trough concentrations were calculated for each simulated scenario after 48 hours of administering 1g of vancomycin every 12 hours.

Overall Statistical Analysis

All analyses, except for Pop-PK, were generated using the statistical package for social statistics (SPSS) software (V. 26). Results are expressed as mean (± standard deviation (SD)), or as median (interquartile range (IQR)). Graphical presentations were performed using R software or generated from Monolix or Simulx software.

Compliance with Ethical Standards

The study was approved by Mohammed Al Mana College for Medical Science IRB (Approval number SR/Rp/79, Date of approval 17/2/2022), Qatif Central Hospital's IRB (Approval number QCH-SRECO 19/2022, Date of approval 8/6/2022) and Dammam Medical Complex's IRB (Approval number PH-26, Date of approval 1/11/2023). As retrospective study, waive to collect informed consent was approved by the IRB. All participants' related data were deidentified to ensure privacy and confidentiality.

Results

Patient Characteristics

This study involved 124 patients receiving vancomycin dose ranging from 500 to 1750 mg (Table 1). The median age of the cohort was 79 years, with most of the patients aged between 60–89 years. Among the cohort, 59% were males, with

Table 1 Characteristics of the Patients (n = 124)

Characteristics	
Age, median (IQR)	79 (50–86)
Age groups	n (%)
40–49 years	8 (7%)
50–59 years	8 (7%)
60–69 years	42 (33%)
70–79 years	31 (25%)
80–89 years	26 (21%)
90–99 years	9 (7%)

(*Continued*)

Table 1 (Continued).

Characteristics	
Sex	n (%)
Male	73 (59%)
Female	51 (41%)
Body weight in kg, mean (±SD)	72 (± 20)
Serum albumin level (g/L), mean (± SD)	29.5 (± 8)
Serum creatinine level (mg/dL), mean (± SD)	183 (±171)
C-reactive protein level (mg/dL), mean (± SD)	80.6 (± 32.5)
CrCl (mL/min), mean (± SD)	61.1 (± 48.2)
CrCl (mL/min)	n (%)
> 120 mL/min	17 (14%)
120–91 mL/min	21 (17%)
90–61 mL/min	14 (11%)
60–31 mL/min	28 (23%)
≤ 30 mL/min	44 (35%)
Vancomycin doses	n (%)
500 mg	31 (25%)
750 mg	20 (15%)
850 mg	2 (2%)
1000 mg	50 (40%)
1200 mg	1 (1%)
1250 mg	11 (9%)
1500 mg	7 (6%)
1750 mg	2 (2%)

Abbreviations: IQR, interquartile range; SD, standard deviation; kg, kilogram; g, gram; mL, milliliter; min, minute.

an average BW of 72 kg (± 20). The average CrCl was 61 mL/min (± 48), and 35% of patients had a CrCl of ≤ 30 mL/min.

Vancomycin Trough Concentration

A total of 172 vancomycin trough concentration readings were collected from 124 subjects. Figure 1 presents substantial variability in vancomycin trough concentrations among the included patients. Vancomycin trough concentrations ranged widely, with some patient exhibiting concentration near 20 µg/mL, while others showed much lower levels below 5 µg/mL.

Further analyses were conducted to identify the correlations between patients' characteristics and the results are depicted in Figure 2. The analysis revealed that increasing CRP levels were positively correlated with advancing age (r =

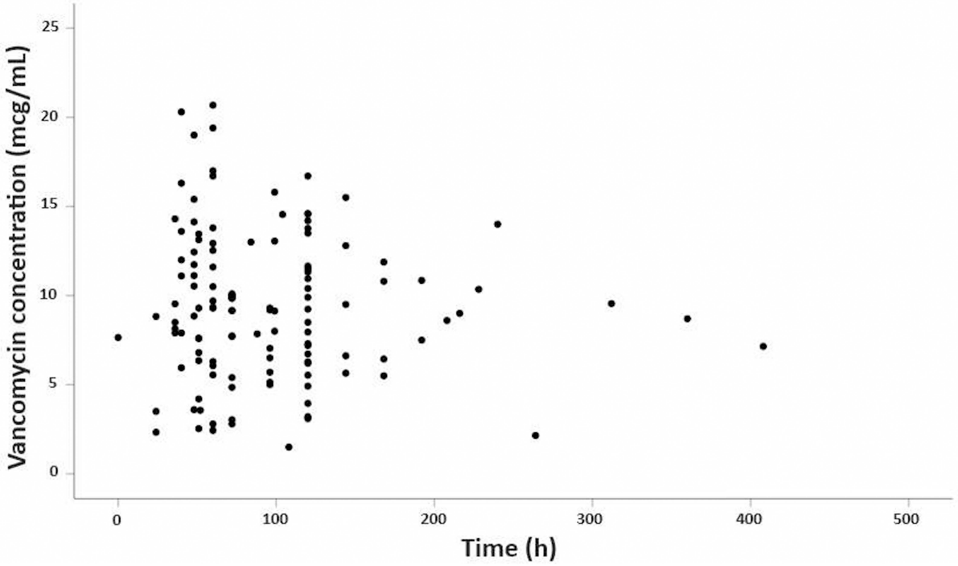

Figure 1 Individual patients' vancomycin trough concentrations over time. Vancomycin dose was standardized to 500 mg.

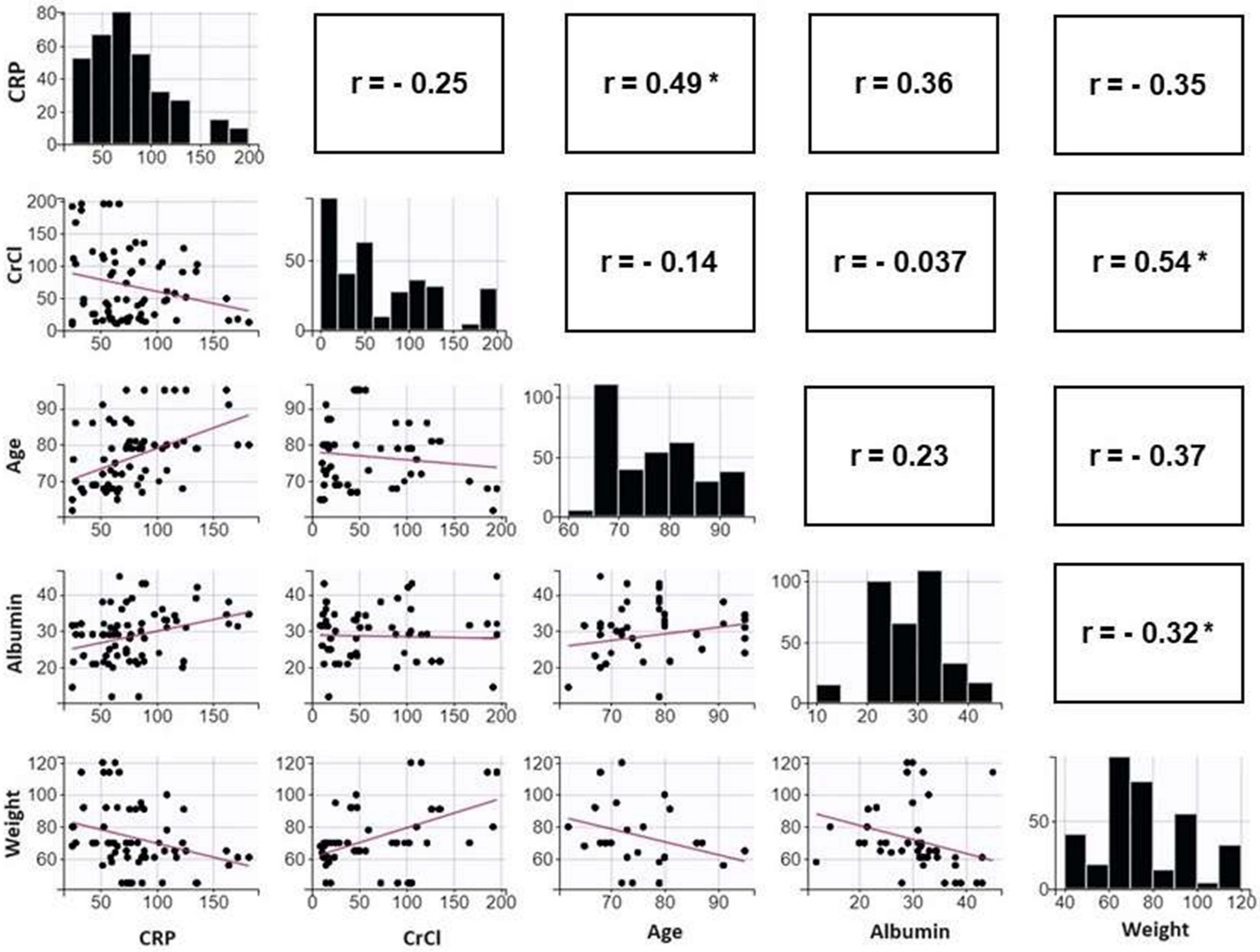

Figure 2 Correlation between patients' characteristics. * = P value < 0.05.
Abbreviations: CRP, C-reactive protein; CrCl, creatinine clearance.

0.49) or increasing albumin levels (r = 0.36), but negatively correlated with increasing CrCl (r = −0.25). In addition, the analysis indicated that higher BW was positively correlated with increasing CrCl (r = 0.54), but negatively correlated with increasing CRP levels (r = −0.35).

Population Pharmacokinetic Parameters of Vancomycin

The development of the based model indicated that vancomycin PK was best described by infusion administration, no-delay absorption, one-compartment distribution, and linear elimination (Supplementary Tables 1–6). This finding was confirmed by GOF plots, and there was a significant decrease in the AIC with respect to bolus administration, delayed (lag-time) absorption, two compartments or three compartments distribution, or non-linear elimination models. A proportional error model with coefficient b = 0.4 was used to describe residual variability (Table 2).

All covariates were tested in a univariate stepwise pattern (Supplementary Tables 7 and 8). Among them, only CrCl and CRP demonstrated a significant decrease in the OFV of the final model (Table 3). These covariates contributed to a notable reduction in BSV for CL from 173% to 81% (Table 2). The final estimated PK parameters for vancomycin are summarized in Table 3. The estimated V was 224.4 L and the estimated CL was 3.52 L/h. The shrinkage values for the estimated parameters ranged from 1.9–14.9% (Supplementary Figure 1). The condition number for the final model was 36.91.

Model Evaluation

The RSE expressed as percentage (Table 2) revealed that all parameters were well estimated, except for CL, which had an RSE of 62.5% in the final model. Diagnostic GOF plots for the final covariate model are shown in Figures 3 and 4.

Table 2 Population Pharmacokinetic Model Estimates for Vancomycin

Parameter	**Base Model**		**Final Model**	
	Population	**RSE (%)**	**Population**	**RSE (%)**
V (L)	224.37	9.48	193.65	7.41
CL (L/h)	0.0035	240	3.52	62.5
CRP effect on CL	–	–	− 0.05	28
CrCl effect on CL	–	–	0.0088	48.4
Omega V	0.37	29.6	0.33	17.2
Omega Cl	1.73	28	0.81	44
Residual error, b (%)	0.38	17.4	0.3	13.7

Abbreviations: RSE, Relative standard error; V, Volume of distribution; CrCl, Creatinine clearance; CL, Clearance; CRP, C-reactive protein; L, Liter; h, Hour; Omega, Inter-individual variability presented as standard deviation.

Table 3 Change in Objective Function Value (−2LL) for the Base and the Final Model

Parameter	**OFV (−2LL)**	**Difference**	**P-value**
Base model	377.5		
CrCl effect on CL	368.5	13	< 0.001
CRP effect on CL	366.5	11.2	< 0.001
Covariates model	355.3		

Abbreviations: CrCl, creatinine clearance; CRP, C-reactive protein; CL, clearance.

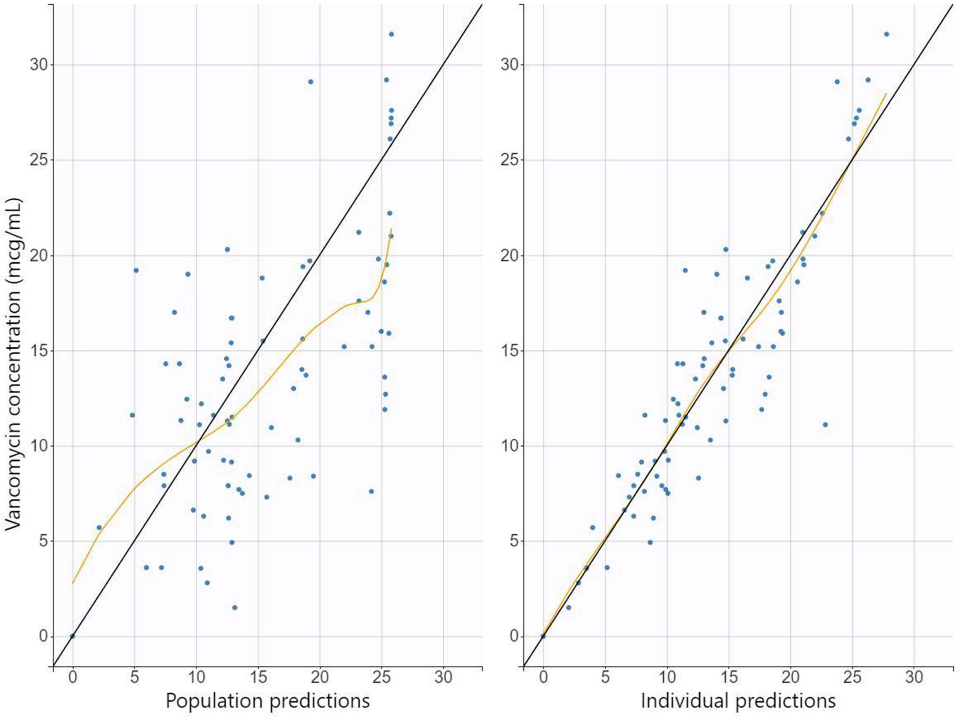

Figure 3 Goodness of fit (GOF) plots of observed versus predicted concentration obtained from the final model for vancomycin. (Right) Individual vancomycin predicted concentrations versus observed concentrations. (Left) Population prediction of vancomycin concentrations versus observed concentrations. The yellow line represents the spline line of the model.

These figures demonstrate that the final PK model adequately describes the measured trough concentrations. However, Figure 3 showed potential outliers in the population model for vancomycin, although this was not confirmed by the residual plots presented in Figure 4, as all the residual values fell within the (6, −6) range, as described in the methodology section.

Moreover, the VPC plot revealed a good agreement between the percentile intervals obtained by simulation of the final model and those of the observed data indicating a good predictive performance of the model (Figure 5). Precisely, the 10th, 50th, and 90th percentiles of observed vancomycin concentrations fell within the predicted 90% confidence interval for these percentiles. The mean estimates closely matched those from the best covariate model, emphasizing the adequacy and stability of the model.

Simulation of Vancomycin Trough Concentration

The results of the Monte Carlo simulation of vancomycin across different patient groups are shown in Figure 6. Precisely, under a fixed CrCl value, increasing CRP levels resulted in an increase in the simulated vancomycin trough concentration, reflecting the influence of CRP on vancomycin clearance (Supplementary Table 9).

Discussion

A Pop-PK model for vancomycin PK was developed to characterize vancomycin PK in adult patients admitted to medical wards in the Eastern region of Saudi Arabia. The findings present that vancomycin PK are best described by a one-compartment model with linear elimination. Although, this finding is consistent with some previously reported models,[15,26] it contradicts the assumption that vancomycin PK is best characterized by a two-, or three-compartment model.[10,16,27] This discrepancy may be attributed to the nature of the current study design, being retrospective, which involved collecting blood samples exclusively for measuring trough concentration as a part of routine TDM. This approach of sample collection limited the interpretation of the absorption and distribution phases. Nevertheless, the base

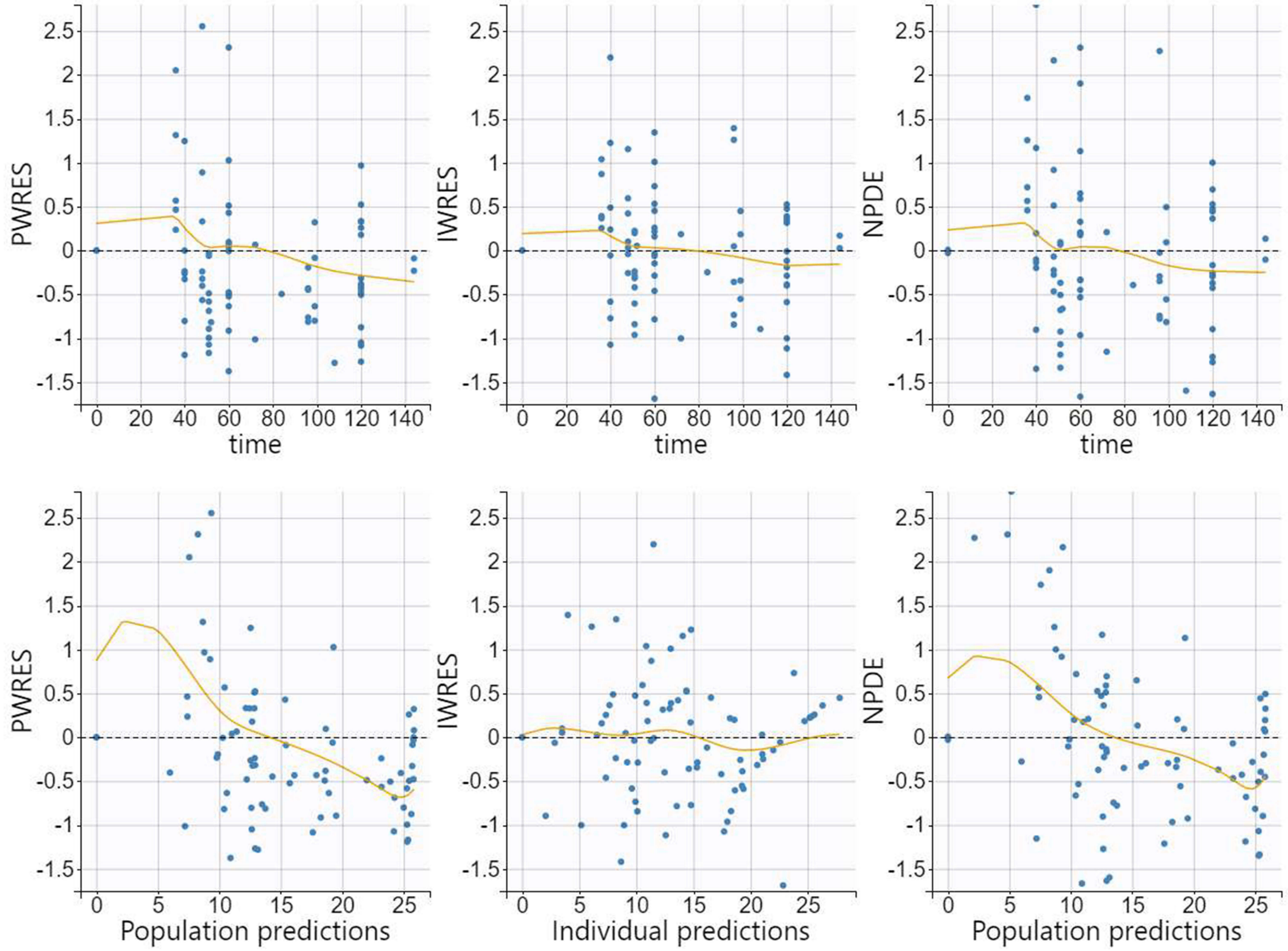

Figure 4 Goodness of fit (GOF) plots of the residual values obtained from the final model for vancomycin. (The top panel shows residual values plotted against time: on left side, population residual; on middle, individual residuals; and on right, normalized prediction distribution error (NPDE). The bottom panel shows a comparison between population residuals versus population predictions on the left, the individual residual versus individual predictions in the middle, and NPDE versus population predictions on the right.

model was selected based on the lowest AIC values compared to other test models. This selection was further validated by the RES value and GOF plots.

Inflammation significantly influences drug PK, increasing plasma drug concentrations and thereby heightening the risk of overdose and ADRs.[28] A key finding of this study is that CRP, a marker of inflammation, significantly influences vancomycin PK (Figure 6, groups 1, 2, and 3). Inflammation is well known to downregulate the expression of various drug-metabolizing enzymes (DME) and transporters, which can alter drug metabolism and clearance (27). In addition, inflammation can suppress receptor activation, resulting in diminished drug efficacy despite elevated plasma drug concentration.[29] Furthermore, elevated levels of pro-inflammatory cytokines contribute to substantial variability in non-renal clearance, particularly in patients with renal impairment.[30] Jalusic et al previously explored the impact of inflammation on vancomycin PK and recommended adjusting dosing based on the inflammatory state.[27] This recommendation is particularly relevant for older patients, and those with renal impairment, as their inflammatory status may further reduce vancomycin clearance, resulting in higher trough concentrations and consequently an increased risk of toxicities. Our study's final simulated model supports this recommendation, highlighting the importance of considering inflammatory status when prescribing vancomycin.

Inflammation is characterized by increased vascular permeability, which enhances the migration of immune cells into interstitium, a crucial process for eradication of pathogen during infection.[30] A recent study reported that acute inflammation and injury enhance the vancomycin penetration into lung tissue.[29] The hydrophilicity of vancomycin, together with the

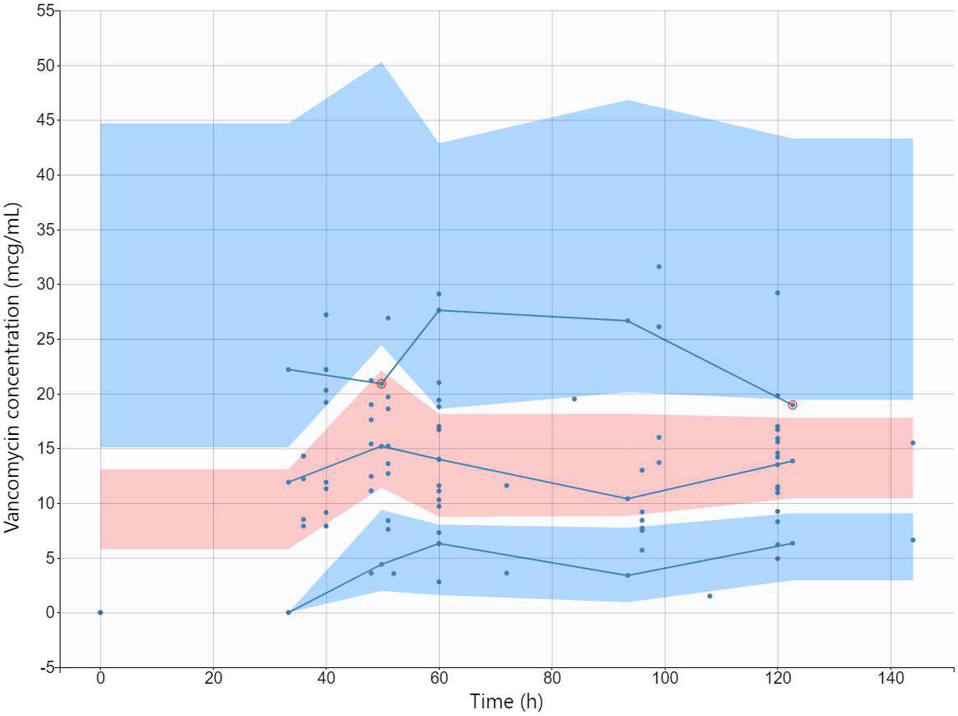

Figure 5 Visual predictive check (VPC) for vancomycin concentration versus time in 1000 Monte Carlo simulation. The solid blue lines represent the 10th, 50th, and 90th percentiles of the observed data. The shaded regions around these lines represent 90% confidence intervals around the 10th, 50th, and 90th percentiles of the simulated data. The blue circles denote the observed concentrations.

increase permeability, may account for the observed high volume of distribution. However, due to the retrospective nature of the study, the early distribution phase of vancomycin was difficult to precisely determine. This limitation may contribute to the observed increase in vancomycin trough concentration associated with increased CRP levels, as the drugs initially escape from circulation and subsequently returns into an equilibrium state between the interstitial and blood circulation. This factor should be considered to precisely evaluate the potential impact of inflammation on vancomycin distribution.

Vancomycin exposure was simulated cross different proposed patient groups and indicated that vancomycin concentrations increase in parallel with increasing CRP levels. It is important to note that the CRP values were measured at the time of vancomycin trough level collection, and they are not reflective to the actual inflammatory state when initiating vancomycin therapy. In patients respond to treatment, inflammation level will decrease leading to normalization of DMEs and transporter genes' expression. This normalization often results in a reduction in plasma drug concentrations over time.[28] Conversely, in patients who do not respond to treatment, persistent inflammation maintains reduced expression of DMEs and transporters, resulting in high plasma drug concentrations. This dynamic is crucial in terms of vancomycin dosage, particularly in the situation of treating drug-resistant bacteria. Uncontrolled infection can further elevate inflammatory markers, thus increasing the risk of ADRs.

CrCl has been previously identified as a significant covariate affecting PK variability in vancomycin CL. This relationship has been confirmed in several models that describe vancomycin PK among different cohorts of patients.[12,14,26,27] In a ligament with these models, the final model indicated that a decrease in CrCl associated with elevated vancomycin trough concentration. Due to its hydrophilic nature, vancomycin mainly relies on renal filtration for excretion.[9] The large variability observed in the actual vancomycin trough concentrations in our study highlights the need for careful monitoring to reduce the risk of overdose.

Several important patient characteristics that could affect the study findings were not addressed. These include the specific vancomycin indications, which are necessary therapeutic targets, bacterial culture results, drug sensitivity profiles, and clinical outcomes. Missing this data represents a limitation of our study. Additionally, only CRP was used as a biomarker

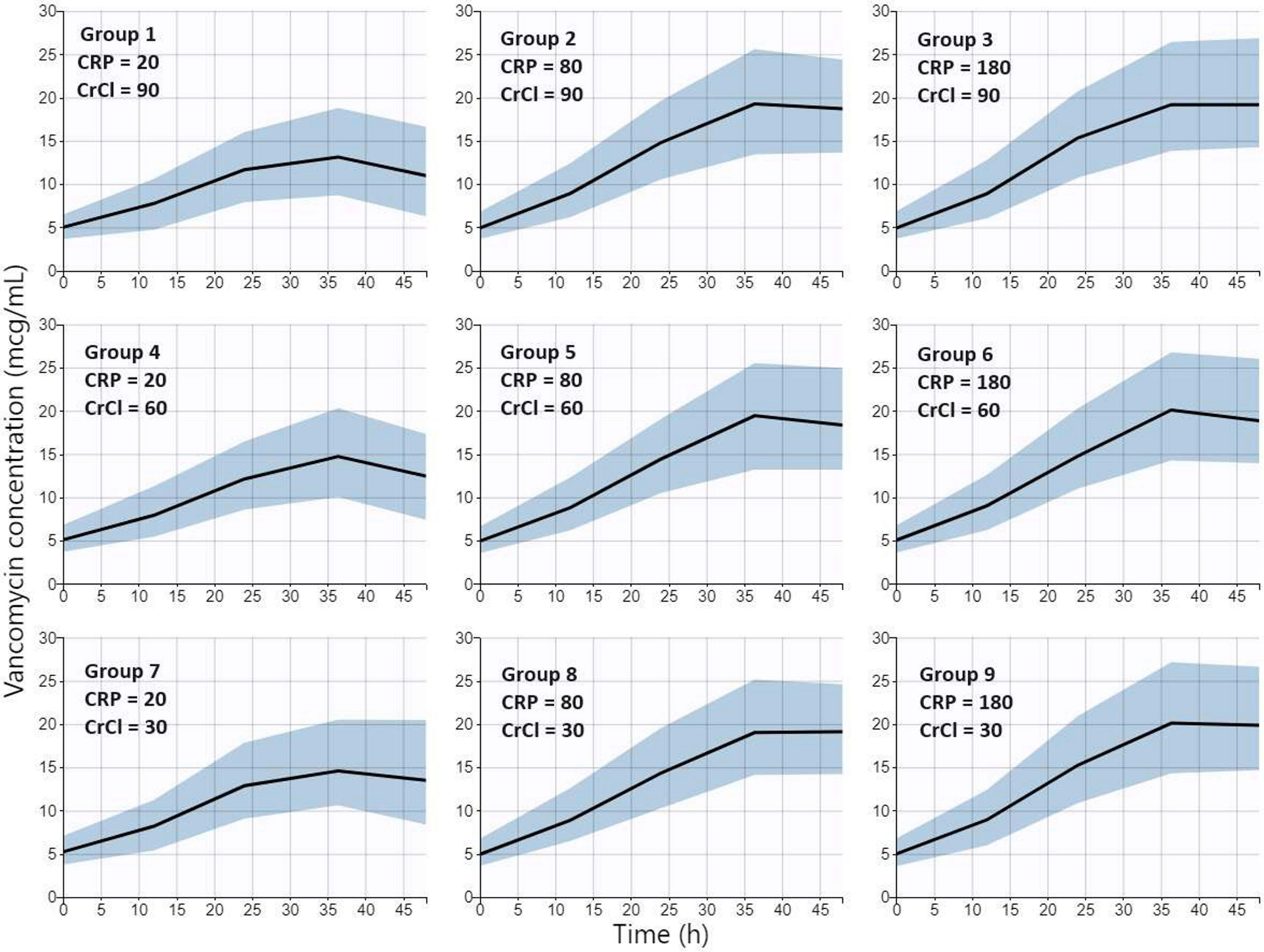

Figure 6 Simulated vancomycin trough concentrations generated by Simulx at a dose of 1 g administered twice daily. CRP levels are measured in mg/dL, CrCl values are expressed in mL/min.

for inflammation as CRP rapidly responds to inflammation process. Nevertheless, Rawson et al reported that CRP can be effectively linked to vancomycin PK and PD.[31] This approach may not fully reflect the patients' inflammatory status. Other markers, such as erythrocyte sedimentation rate, procalcitonin, plasma viscosity, leukocyte count and leukocyte differentiation, and proinflammatory mediator including interleukins one and six and tumor necrosis factor-α should also to be considered.[32] Moreover, as most patients in the study had some degree of renal impairment, the generalizability of the findings may be limited to patients with similar renal characteristics. The findings of this study may not be applicable to patients with augmented renal clearance such as those in critical care settings.[33] Future prospective studies with larger sample sizes and more comprehensive patient data are recommended to investigate these outcomes.

In addition, the use of vancomycin combined with other antibiotics became a field of extreme interest, especially in the treatment of infections caused by MRSA.[34,35] Recent literature underlines that administration of vancomycin in combination with beta-lactam antibiotics enhances the treatment efficiency against MRSA due to the synergistic effect.[35,36] However, the impact of inflammation on vancomycin pharmacokinetics should be investigated when vancomycin was used in combination therapy. The elevated inflammatory markers can alter the pharmacokinetics of both vancomycin and other antibiotics, potentially requiring dosage adjustments. Future studies should aim to evaluate the interactions between vancomycin and other antibiotics in combination therapy under varying inflammatory conditions to better tailor treatment regimens for individual patients.

Conclusion

A one-compartment with a linear elimination model was best fit for vancomycin trough concentration. A large BSV for CL (81%) was best presented by the large variability in vancomycin trough concentrations observed in the actual samples. The final model identified CrCl and CRP as significant covariates. Precisely, increasing CRP levels or decreasing CrCl values were associated with elevated vancomycin trough concentration, affecting vancomycin clearance. The findings from this study can advise clinical practice by highlighting the important patient characteristics to be considered while adjusting vancomycin dosing, thus maximizing efficacy and minimizing the risk of ARDs.

Key Points

1. A large between subject variability for clearance was best presented by the large variability in vancomycin trough concentrations observed in the actual samples.
2. The final model identified CrCl and CRP as significant covariates, as increasing CRP levels or decreasing CrCl values were associated with elevated vancomycin trough concentration, affecting vancomycin clearance.

Data Sharing Statement

The datasets analysed during the current study will be made available at reasonable request from Dr. Aymen A. Alqurain. Data will be made available for scientific purposes for researchers whose proposed use of the data has been approved by the research team.

Ethical Approval and Informed Consent

The study was approved by Mohammed Al Mana College for Medical Science IRB (Approval number SR/Rp/79, Date of approval 17/2/2022), Qatif Central Hospital's IRB (Approval number QCH-SRECO 19/2022, Date of approval 8/6/2022) and Dammam Medical Complex's IRB (Approval number PH-26, Date of approval 1/11/2023) and conducted in accordance with the principles of the Helsinki Declaration on Human Experimentation. As retrospective study, waive to collect informed consent was approved by the IRB. All participants' related data were deidentified to ensure privacy and confidentiality.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

The authors report no conflicts of interest in this work.

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