Research Article

Therapeutic Drug Monitoring of Vancomycin and Guidance for Dosing Optimization in Patient with End Stage Renal Disease

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Abstract

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IJPS, 2025; 21(1) : 64-77

Received: 18 February 2025 **Revised:** 10 March 2025 **Accepted:** 18 March 2025

Vancomycin is primarily eliminated from the body through the kidneys and exhibits pharmacokinetic variability. Due to its narrow therapeutic range, monitoring drug concentrations is essential during treatment. Impaired kidney function in end stage renal disease (ESRD) patients affects pharmacokinetics, influencing drug distribution and elimination. Currently, there is insufficient pharmacokinetic data in Thai patients with ESRD to determine appropriate dosing. **Objective:** This retrospective study aimed to analyze the pharmacokinetic parameters of vancomycin in ESRD patients and determine the appropriate dosage regimen of vancomycin for ESRD patients. **Methods:** The data of ESRD patients who used vancomycin from medical records including dosage regimen, and serum vancomycin concentrations after administration of the first dose were analyzed by using the linear pharmacokinetics of one-compartment, short infusion model equation to derive pharmacokinetic parameters. Subsequently, the trough concentrations of vancomycin were calculated based on the administered dose, and the number of patients with subtherapeutic drug levels was assessed. The patient's pharmacokinetic parameters were then used to perform a Monte Carlo simulation to determine the appropriate initial vancomycin dosing for ESRD patients. **Results:** Pharmacokinetic parameters of 211 ESRD patients were calculated from measured serum vancomycin concentration. Volume of distribution (Vd) was 41.42 ± 8.56 liters, elimination rate constant (Ke) was 0.017 ± 0.013 hour-1, Clearance (CL) was 0.410 ± 0.288 L/hr, and elimination half-life was 58.62 ± 52.54 hours. At 24 hours after the first dose administration, 42.7% of patients had vancomycin levels less than 15 mg/L, and 14.6 % of patients had vancomycin levels less than 10 mg/L. From Monte Carlo simulation, it revealed that the appropriate loading dose of vancomycin to achieve the trough serum concentration above 10 mg/L is 20-30 mg/kg, and 25-30 mg/kg for those who need serum concentration above 15 mg/L. Monitoring drug level should be performed within 24 hours after the loading dose to evaluate individualized pharmacokinetic parameters and design the maintenance dosage regimen. **Conclusion:** From this study, giving a loading dose of 25 - 30 mg/kg vancomycin, then measuring serum drug concentration at 24 hours after administration to evaluate pharmacokinetic parameters and design the appropriate individualized maintenance dose may be useful to enhance treatment efficacy and reduce the risk of drug resistance.

Keywords: Vancomycin Dosing, Therapeutic Drug Monitoring, End-stage renal disease (ESRD), Monte Carlo Simulation

Introduction

Vancomycin, a glycopeptide antibiotic, effectively targets Staphylococcus, Streptococcus, and other gram-positive bacteria (Wilhelm *et al.*, 1991). It is a first-line therapy for methicillin-resistant Staphylococcus aureus (MRSA) infections (Cataldo *et al.*,2012), which are the most common antibiotic-resistant infections in the world (Ye *et al.*, 2014). These infections can cause diseases such as pneumonia, skin and soft tissue infections, septicemia, endocarditis, osteomyelitis, and central nervous system infections. Vancomycin is primarily eliminated by the kidneys. In ESRD patients, impaired renal function leads to reduced clearance and fluctuating serum concentrations. Therapeutic drug monitoring (TDM) or the measurement of drug concentrations is essential in determining the optimal dosage of vancomycin for individual patients. Even monitoring the area under the concentration versus time curve is for 24 hours (AUC24hr) is presently widely preferred since improving outcome of treatment in complicated skin and soft tissue infections due to MRSA (Alosaimy S, *at al.*, 2021), the limitation of using AUC24hr is the evidence is strong only in MRSA infections not for infections caused by others vancomycin susceptible microorganism such as Enterococcal infection. In addition, when the adjusted dosing interval longer than 24 hr is needed, especially in the patients who have renal insufficiency, AUC24 hr monitoring might not be able to be performed. The trough concentration monitoring, therefore, in Therapeutic Drug Monitoring, is still necessary in such cases. The recommended therapeutic vancomycin serum trough concentration is 10-15 mg/L for non-sever infection or superficial infections (such as soft tissue infections), while the higher range of trough concentration 15 - 20 mg/L is recommended in case of severe or deep-seated infections (such as bacteremia, endocarditis, osteomyelitis, prosthetic joint infections, pneumonia requiring hospitalization, central nervous system infections, or infections causing critical illness) (Rybak *et al.*, 2020). This is because vancomycin has a narrow therapeutic window. Patients with End Stage Renal Disease (ESRD) who receive vancomycin will have serum drug levels that fluctuate, resulting in levels that may not reach the therapeutic range and thus fail to provide the desired therapeutic effect. Therapeutic Drug Monitoring (TDM) is crucial for these patients to monitor Serum vancomycin concentrations and adjust the dosage appropriately for each individual to ensure that the Serum vancomycin concentrations are within the therapeutic range. The obtained drug concentrations are used to calculate the patient's pharmacokinetic parameters. These pharmacokinetic parameters are subsequently utilized to determine the appropriate dosage to ensure the patient's serum vancomycin concentration remains within the therapeutic range. The analysis for pharmacokinetic parameters is calculated using equations from the short infusion model, employing the volume of distribution of 0.7 L/kg. This value represents the average population volume of distribution, which ranges from 0.4 to 1 L/kg (Rodvold *et al.*, 1988). Using population pharmacokinetic parameters for analysis does not provide the true pharmacokinetic parameters of individual patients. Consequently, the calculated dosage may not align with the patient's pharmacokinetics, and the target serum concentration after administration may deviate from the predicted values. This study aimed to determine the proportion of ESRD patients with subtherapeutic serum vancomycin concentrations, to investigate the pharmacokinetics of vancomycin in ESRD patients, and determine the appropriate dosage regimen of vancomycin for ESRD patients. This information would be useful in clinical practice of the Therapeutic Drug Monitoring Service.

Materials and Methods

Study design

This retrospective descriptive study aimed to evaluate the number of ESRD patients who have serum vancomycin concentrations out of therapeutic range, analyze the pharmacokinetic parameters of vancomycin in ESRD patients, and determine the appropriate dosage regimen of vancomycin for ESRD patients to be a guidance in Therapeutic Drug Monitoring Service. The study population consisted of end-stage renal disease (ESRD) patients who received vancomycin therapy at Srinagarind Hospital, Faculty of Medicine, Khon Kaen University, from 2012 to 2023.

Ethics

This study has been approved by the Center for Ethics in Human Research at Khon Kaen University (Reference No. HE651123) and conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice (ICH GCP) guidelines. Strict confidentiality measures have been implemented to safeguard participant privacy and protect patient records.

Patients and Data

The retrospective descriptive study of ESRD patients' data using vancomycin included in this study were 18 years or older, had been diagnosed with end-stage renal disease, had 1 or 2 obtained serum vancomycin concentrations after receiving the first dose of the medication, and did not undergo renal replacement therapy (RRT).

Data of serum vancomycin concentrations after administration of the first dose in ESRD patients were collected to determine individual pharmacokinetic parameters. Patient characteristics, age, weight, height, gender, and main reasons for hospital admission were collected as baseline data. Clinical data, including medication administration, laboratory values included serum creatinine (SCr) to calculate the estimated glomerular filtration rate (eGFR) and Creatinine Clearance (CrCL) were also collected.

All data were collected from the medical records of Srinagarind Hospital during the year 2012 to 2023. The data storage and analysis were conducted using Microsoft Excel software version 2021.

Assay

Vancomycin serum concentration assays were performed as part of routine clinical monitoring. Vancomycin concentrations were measured using Chemiluminescent Microparticle Immunoassay (CMIA) by ARCHITECT i1000SR (Abbott Laboratories) at Therapeutic Drug Monitoring Service, Pharmaceutical Sciences, Khon Kaen University.

Data Analysis

Pharmacokinetic Analysis

Calculation of pharmacokinetic parameters and drug concentration at various times by first-order pharmacokinetics, one compartment model used in the routine Therapeutic Drug monitoring Service was used in this study (Rodvold KA *et al.*, 1995, Brit JK, *et al.*, 1990, Michael JR., 2006). For patients who have had two obtained serum vancomycin concentrations taken after receiving the first dose, the elimination rate constant (Ke) was calculated by

$$K_e = \frac{\ln C_2 - lnC_1}{T_1 - T_2}$$

Ke = Elimination rate constant

T = time

C1 and C2 = Concentration at time (T)

Then the one-compartment, first-order pharmacokinetic short infusion model equation as described below was used to calculate Volume of distribution (Vd)

$$V_d = \left(\frac{Dose}{\frac{t'}{C_t \times K_e}} \right) \left(1 - e^{-K_e t'}\right) e^{-K_e t}$$

Ke = Elimination rate constant (hr-1)

Cl = Clearance (L/hr)

τ = Dosing Interval

t = Time after end of infusion

t' = Infusion time

The volume of distribution (Vd) for patients with two obtained serum drug levels was converted to liters per kilogram (L/kg) based on each patient's weight. These values were averaged to determine the mean volume of distribution (L/kg), which represented the volume of distribution for the patients in this study. These average values were used to calculate pharmacokinetic parameters and vancomycin serum levels for patients with single-point drug level measurements.

Predicted Serum vancomycin concentrations at various time points, including 12, 24, 48, 72, 96, 120, 144, and 168 hours were calculated from the Ke value of each patient by using the short infusion model equation described below. The calculated serum vancomycin concentrations of all patients were presented in the serum concentration-time profiles. The serum vancomycin concentrations for all patients were then used to count and assess the trend of therapeutic concentrations.

Dosing Regimen Optimization

The calculated pharmacokinetic parameters, calculated from the group of patients who had obtained two serum vancomycin concentrations, were applied using the short infusion model equation to estimate serum drug levels under various vancomycin dosage regimens. These regimens were divided into maintenance doses and loading doses. A Monte Carlo simulation (on 1,000 virtual patients was generated) then was conducted to analyze the percentage of patients whose serum drug levels fall below the target concentration (< 10 mg/L and < 15 mg/L). The goal was to identify the optimal dosage regimen that results in a percentage of target attainment and to determine the appropriate timing for monitoring serum drug levels after administration. The simulation aimed to find the serum concentration, calculated from the short infusion model equation, by varying different parameters in the formula, including Vd and Ke, patient's weight, and dose. Once the serum concentration was obtained from the simulation, the percentage of target attainment was determined based on the serum concentration, categorized as subtherapeutic (< 10 mg/L and < 15 mg/L), on therapeutic (15-20 mg/L), and supratherapeutic (>20 mg/L). The most appropriate dose, then, would be determined based on the percentage of target attainment. Dosage regimens were considered optimal when their percentage of target attainment was more than or equal to 80% (Bradley JS, *et al.*, 2003)

Results

1. Demographic Data

Serum vancomycin concentrations were collected from a total of 211 patients. The mean eGFR and CrCl values were 10.16 and 9.33 mL/min, respectively. The demographic and clinical characteristics of patients are presented in Table 1.

Table 1 Overview of demographic and clinical characteristics of total patients (n=211)

Characteristic	Mean ± Standard Deviation or n (%)
Gender	
Male	115 (53.99%)
Female	96 (46.01 %)
Age (year)	65.45 ±15.27 (20-101)
Weight (Kg)	53.79 ±11.09 (26.0-82.9)
eGFR CKD-EPI (mL/min/1.73m^2)	10.18±5.69
CrCL (mL/min)	9.36±4.07

2. Pharmacokinetic Parameters of Vancomycin in ESRD

The mean Vd in these ESRD patients, 0.77 ± 0.35 L/kg, from 26 patients who have 2 obtained-serum vancomycin concentrations in various times of the first dose. The calculated Vd 0.77 L/kg was then used in calculation of pharmacokinetic parameters and the predicted serum vancomycin concentration in data simulation by the short infusion model's equation for all ESRD patients. The pharmacokinetic parameters from all patients are shown in Table 2.

Table 2 Pharmacokinetic parameters of vancomycin in ESRD patients (n=211)

Pharmacokinetic parameters	Median (Range)
V_d (L)	39.89 (20.02-63.83)
K_e (hr^{-1})	0.015 (0.001-0.059)
CL (mL/min)	0.577 (0.003–2.963)
$T_{1/2}$ (hr)	47.8 (11.77-529.54)

3. Serum Vancomycin Concentration - Time Profile in ESRD Patients

Pharmacokinetic parameters of each individual were used in calculation of the serum vancomycin concentration at different times (0-168 hours) of the first dose for individual patients and observed the results if patients would have vancomycin level below the target therapeutic concentration (15 mg/L and 10 mg/L). The relationship between vancomycin concentration and time in all patients with ESRD is shown in Figure 1.

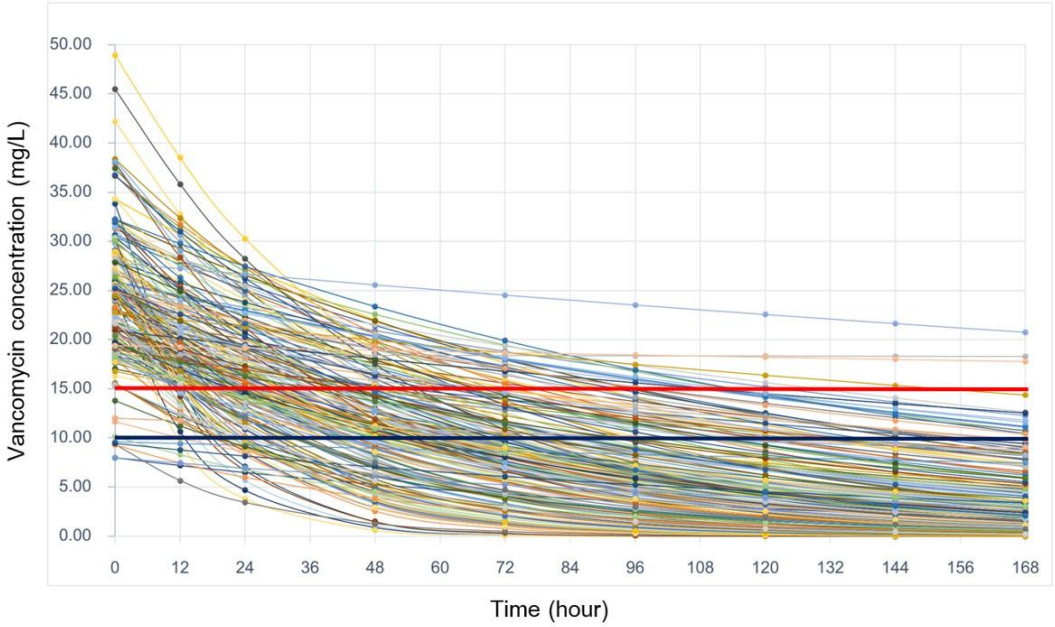

Figure 1 Predicted vancomycin concentration - time profile after first dose in patients with ESRD (n=211). The blue and red straight lines are target of trough vancomycin concentrations (10 mg/L and 15 mg/L respectively)

Table 3 Mean predicted serum vancomycin concentration after administering the first dose at different times. (n=211)

Time (hour)	Serum vancomycin concentration (Mean ± SD)
0	24.08±6.47
12	19.63±5.49
24	16.31±5.40
48	11.73±5.37
72	8.79±5.13
96	6.78±4.81
120	5.35±4.47
144	4.31±4.14
168	3.53±3.84

From the data, it is found that after 24 hours of the first vancomycin dose, many patients began to have serum vancomycin concentrations below target concentration, resulting in subtherapeutic concentrations. At 24 hours after receiving the initial dose, concentrations lower than 10 mg/L and 15 mg/L were observed in 31 patients (14.6%) and 91 patients (42.7%) respectively. In addition, at 48 hours, the number of patients with serum vancomycin concentrations below 10 mg/L increased to 76 (35.7%), and those with concentrations below 15 mg/L increased to 156 (73.2%), as shown in Table 4

Table 4 Number of patients with ESRD who had concentrations lower than 10 and 15 mg/L at different times. (n=211)

Time (hour)	Number of patients with ESRD: n (%)	
	<10 mg/L	<15 mg/L
12	8 (3.8%)	27 (12.7%)
24	31 (14.6%)	91 (42.7%)
48	76 (35.7%)	156 (73.2%)
72	135 (63.4%)	183 (85.9%)
96	163 (76.5%)	197 (92.5%)
120	176 (82.6%)	207 (97.2%)
144	188 (88.3%)	209 (98.1%)
168	197 (92.5%)	210 (98.6%)

4. Monte Carlo Simulation for Vancomycin Dosage Regimen Design

A Monte Carlo simulation of 1,000 virtual patients was generated by using patients' data from medical records and pharmacokinetic parameters in this study with various dosage regimen of vancomycin.

Table 5 Percentage of patients and serum vancomycin minimum concentration by various dosage regimens (mg/kg) of the first dose from the Monte Carlo simulation. (n=1000)

Regimen	Percentage of patients (%)			
	Subtherapeutic <10 mg/L	%Target Attainment (>10 mg/L)	Subtherapeutic <15 mg/L	%Target Attainment (>15 mg/L)
15 mg/kg (At 24 hr)	8.5	91.5	9.9	90.1
15 mg/kg (At 48 hr)	18.2	81.8	34.2	65.8
15 mg/kg (At 72 hr)	44.7	55.3	58.7	41.3
15 mg/kg (At 96 hr)	55.1	44.9	66.8	33.2
20 mg/kg (At 24 hr)	7.7	92.3	7.8	92.2
20 mg/kg (At 48 hr)	11.6	88.4	19.3	80.7
20 mg/kg (At 72 hr)	30.5	69.5	45.7	54.3
20 mg/kg (At 96 hr)	47.8	52.2	60.5	39.5

According to Table 5, for patients targeting concentrations above 10 mg/L, subtherapeutic concentrations increased significantly at 72 hours, with 44.7% of those receiving 15 mg/kg and 30.5% of those receiving 20 mg/kg falling below this threshold. For patients targeting concentrations above 15 mg/L, 34.2% of those receiving 15 mg/kg had subtherapeutic concentrations at 48 hours, while 45.7% of those receiving 20 mg/kg were subtherapeutic at 72 hours.

Table 6 Percentage of target attainment at steady state (10 mg/L and 15 mg/L) in various dosage regimens (mg/kg) of vancomycin from the Monte Carlo simulation. (n=1000)

Regimen (Steady State)	Percentage of patients (%)			
	Subtherapeutic <10 mg/L	%Target Attainment (>10 mg/L)	Subtherapeutic <15 mg/L	%Target Attainment (>15 mg/L)
15 mg/kg q 24 hr (At dose 10)	8.5	91.5	8.5	91.5
15 mg/kg q 48 hr (At dose 5)	11	89	16.9	83.1
15 mg/kg q 72 hr (At dose 4)	33	67	44.6	55.4
15 mg/kg q 96 hr (At dose 3)	58.6	41.4	70	30.0
20 mg/kg q 24 hr (At dose 10)	7.7	92.3	7.7	92.3
20 mg/kg q 48 hr (At dose 5)	8.9	91.1	11.5	88.5
20 mg/kg q 72 hr (At dose 4)	22.4	77.6	32.9	67.1
20 mg/kg q 96 hr (At dose 3)	38.5	61.5	50.8	49.2

At steady-state concentration, a significant proportion of patients receiving 15 mg/kg every 72 hours (dose 4 which is achieved steady stage) had subtherapeutic levels, with 33.0% below 10 mg/L and 44.6% below 15 mg/L. Similarly, for those receiving 20 mg/kg every 72 hours (dose 4), 22.4% had concentrations below 10 mg/L, while 32.9% were below 15 mg/L (Table 6).

This finding highlighted the importance of incorporating a loading dose into the dosing regimen. A loading dose is intended to rapidly achieve therapeutic concentrations, thereby increasing the probability of successful treatment. A Monte Carlo simulation was conducted for patients receiving various initial dose of vancomycin to determine the optimized loading dose by percentage of target attainment. The results of the simulation are presented in Table 7.

Table 7 Percentage of patients and predicted minimum serum vancomycin concentration at various time by loading doses of vancomycin from the Monte Carlo simulation. (20, 25, and 30 mg/kg). (n=1000)

Regimen	Percentage of patients (%)			
	Subtherapeutic <10 mg/L	%Target Attainment (>10 mg/L)	Subtherapeutic <15 mg/L	%Target Attainment (>15 mg/L)
20 mg/kg at 12 hr	2.6	97.4	16.0	84.0
20 mg/kg at 24 hr	5.3	94.7	27.4	72.6
20 mg/kg at 48 hr	24.7	75.3	50.1	49.9
20 mg/kg at 72 hr	42.7	57.3	64.3	35.7
20 mg/kg at 96 hr	55.8	44.2	71.8	28.2
25 mg/kg at 12 hr	1.1	98.9	4.4	95.6
25 mg/kg at 24 hr	1.5	98.5	13.4	86.6
25 mg/kg at 48 hr	14.2	85.8	36.3	63.7
25 mg/kg at 72 hr	33.6	66.4	53.1	46.9
25 mg/kg at 96 hr	47.6	52.4	64.0	36.0
30 mg/kg at 12 hr	1.7	98.3	2.3	97.7
30 mg/kg at 24 hr	1.9	98.1	5.5	94.5
30 mg/kg at 48 hr	7.2	92.8	23.4	76.6
30 mg/kg at 72 hr	22.0	78	42.6	57.4
30 mg/kg at 96 hr	37.6	62.4	56.6	43.4

To achieve more than 80% of target attainment, for a target concentration greater than 10 mg/L, many patients who received loading doses of 20 mg/kg, 25 mg/kg, and 30 mg/kg experienced subtherapeutic concentrations at 48, 72, and 72 hours, respectively. Obtained vancomycin concentration at 24 hours after loading dose might be useful to avoid risk of subtherapeutic concentration. For a target concentration above 15 mg/L, many patients who received the same loading doses experienced subtherapeutic concentrations at 24, 48, and 48 hours, respectively. Obtaining vancomycin concentration after loading dose in therapeutic drug monitoring before 24 hr, however, might be inconvenient in clinical practice, the loading dose of 25-30 mg/kg seems to be more appropriate for those who need target concentration above 15 mg/L.

The calculated vancomycin concentrations at various times after receiving loading doses of 20, 25, and 30 mg/kg by using the short infusion model equations were presented in Table 8.

Table 8 Predicted vancomycin concentration from various loading doses. (n=211)

Time (hour)	Mean vancomycin concentration (Mean ± SD)		
	20 mg/kg	25 mg/kg	30 mg/kg
0	25.53 ± 0.32	31.92 ± 0.41	38.30 ± 0.49
12	21.01 ± 3.09	26.26 ± 3.86	31.52 ± 4.63
24	17.6 ± 4.48	22.01 ± 5.62	26.41 ± 6.74
48	12.9 ± 5.56	16.08 ± 6.97	19.29 ± 8.36
72	9.8 ± 5.72	12.21 ± 7.18	14.65 ± 8.61
96	7.7 ± 5.7	9.54 ± 6.99	11.45 ± 8.39

These findings indicate that a loading dose may help achieve therapeutic levels and monitoring after the loading dose is crucial to prevent subtherapeutic concentrations and assess individual pharmacokinetic parameters, enabling appropriate dosage adjustments for effective treatment.

For patients with non-severe infections or superficial infections (soft tissue infection) requiring a target serum vancomycin concentration of more than 10 mg/L, those receiving a loading dose of 20 mg/kg should have their serum vancomycin concentration monitored within 24 hours and in case of patients receiving a loading dose of 25 mg/kg or 30 mg/kg should have their serum levels monitored within 48 hours.

For patients with severe infections or deep-seated infections (such as bacteremia, endocarditis, osteomyelitis, prosthetic joint infection, pneumonia warranting hospitalization, infection involving the central nervous system, or infection causing critical illness) requiring a target serum vancomycin concentration of more than 15 mg/L, those receiving a loading dose of 25 - 30 mg/kg should have their serum levels monitored within 24 hours.

Discussion

Many studies have investigated the pharmacokinetics of vancomycin and therapeutic drug monitoring (TDM) in patients with chronic kidney disease (CKD). However, no studies have specifically examined the pharmacokinetics of vancomycin especially in Thai patients with end stage renal disease (ESRD). The pharmacokinetic parameters in this study are close to those reported in other studies or sources. The half-life of vancomycin in ESRD patients was 133.34 hours close to a previous study that reported a half-life of 146.7 hours in patients with kidney disease (Matzke *et al.*, 1984). Additionally, study employing two-compartment pharmacokinetic models had found a half-life of 121.3 hours (Tan *et al.*, 1990), which is close to the results of this study that used a one-compartment model. The volume of distribution in this study was 0.77 ± 0.35 L/kg. Some studies have examined populations with creatinine clearance less than 10 mL/min, indicative of end-stage renal disease, and reported a mean volume of distribution (Vd) of 0.9 L/kg (Matzke *et al.*, 1984). Other studies examining vancomycin pharmacokinetics in ESRD patients undergoing hemodialysis have reported similar Vd values of 0.9 L/kg (Ariano *et al.*, 2005). In previous studies examining pharmacokinetic parameters in Thai patients,

the volume of distribution was found to be 0.78 L/kg (Soontornpas *et al.*, 2008), which is similar to the findings in this study. However, the patients compared in the study may have different health conditions from those in this study, such as not all patients having ESRD, some patients having Congestive heart failure, which may affect vancomycin clearance due to reduced cardiac output (Shimamoto *et al.*, 2012). While the pharmacokinetic parameters, including Vd, were similar across studies, the methods used to analyze pharmacokinetic data may differ. Computational models and equations used to calculate pharmacokinetics parameters may not be identical to those in this study, where the Vd was 0.77 L/kg, calculated using the short infusion model equation. Other studies have reported a Vd ranging from 0.4 to 1 L/kg. Some studies used standard compartmental pharmacokinetics equations, finding a steady-state Vd of 0.64 L/kg for patients with CrCL less than 10 mL/min. One study found a steady-state Vd of 0.39 to 0.97 L/kg, but it was conducted in patients with normal kidney function (Matzke *et al.*, 1986). In patients undergoing hemodialysis, a Vd of 0.87-0.9 L/kg was reported. (Hartinger *et al.*, 2022) (Lewis *et al.*, 2021) The results from different studies may be affected by variations in patient characteristics or differences in research methodologies.

The study determining the appropriate dose for patients undergoing high-efficiency hemodialysis, serum vancomycin concentrations were measured at various time points between hemodialysis sessions, and the optimal dose was determined using Monte Carlo simulation. The study recommended that loading doses of 25 mg/kg and 30 mg/kg could provide effective treatment for pathogens with an MIC of 1.0 mg/L (Rungprai *et al.*, 2015). This finding recommended loading dose is similar to our study.

Based on data in this study, two vancomycin dosage regimens are recommended for vancomycin loading doses to achieve the target serum concentration; 1) For patients with non-severe or superficial infections (such as soft tissue infections) requiring a target serum vancomycin concentration above 10 mg/L, a loading dose of 20–30 mg/kg is recommended, 2) For patients with severe or deep-seated infections (such as bacteremia, endocarditis, osteomyelitis, prosthetic joint infections, pneumonia requiring hospitalization, central nervous system infections, or infections causing critical illness) requiring a target serum vancomycin concentration above 15 mg/L, a loading dose of 25–30 mg/kg is recommended. In addition, by Monte Carlo Simulation we found that a dose of vancomycin 15–20 mg/kg every 24–48 hours as maintenance dosage regimen might be effective to maintain steady state serum concentrations above 10–15 mg/L.

This finding aligns with the recommendations from the "Therapeutic Monitoring of Vancomycin for Serious Methicillin-Resistant Staphylococcus aureus (MRSA) Infections: A Revised Consensus Guideline," by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists. For critically ill patients with suspected or confirmed serious MRSA infections, a recommended loading dose is 20 to 35 mg/kg for intermittent infusion administration of vancomycin. For patients with suspected or definitive serious MRSA infections, the guidelines also recommend an appropriate maintenance dose of 15 to 20 mg/kg (based on actual body weight), administered every 8 to 12 hours as an intermittent infusion for most patients with normal renal function (Rybak *et al.*, 2020).

Therapeutic drug monitoring (TDM) after the initial dose is essential to ensure that the serum vancomycin concentration remains within the therapeutic range. In this study, patients were divided into two groups: those with non-severe or superficial infections and those with severe or deep infections. These two groups had different target serum concentrations: greater than 10 mg/L for non-severe infections and greater than 15 mg/L for severe infections.

1) For patients with mild infections requiring a target serum vancomycin concentration of greater than 10 mg/L, those receiving a loading dose of 20 mg/kg should monitor their serum drug levels within 24 hours. Patients receiving loading doses of 25 mg/kg or 30 mg/kg should be monitored within 48 hours.

2) For patients with severe infections requiring a target serum vancomycin concentration of greater than 15 mg/L, those receiving loading doses of 20 mg/kg, 25 mg/kg, or 30 mg/kg should have their serum levels monitored within 24 hours.

The appropriate sampling time for therapeutic concentration monitoring presented in this study is align to the recommendations from the American Society of Health-System Pharmacists, which suggests that TDM may begin within 24 to 48 hours of vancomycin therapy for serious MRSA infections. Anyhow, the guidelines for routine serum vancomycin monitoring have been debated and discussed for many years (Rybak *et al.*, 2020).

This study focused on therapeutic drug monitoring and determining the appropriate vancomycin dosage for ESRD patients not undergoing continuous renal replacement therapy (CRRT). There is still a lack of data on therapeutic drug monitoring and dosage adjustment for ESRD patients undergoing CRRT, such as hemodialysis (HD) or continuous ambulatory peritoneal dialysis (CAPD). Further studies on therapeutic drug monitoring, vancomycin dosage adjustments and clinical outcome in ESRD patients receiving RRT could build upon this research. Conducting multicenter studies and developing prospective studies would help gather more comprehensive data, ultimately providing more relevant insights for ESRD patients on dialysis therapies.

Conclusion

A retrospective study was conducted on end-stage renal disease patients who received vancomycin along with therapeutic drug monitoring. Calculated pharmacokinetic parameters, the volume of distribution was 41.42 ± 8.56 L, the elimination rate constant was 0.017 ± 0.013 per hour, the clearance was 0.410 ± 0.288, and the half-life was 133.34 ± 883.42 hours. Patients who had serum vancomycin concentrations below 10 mg/L and 15 mg/L after receiving the medication for 24 hours were 14.6% and 42.7%, respectively. From Monte Carlo Stimulation to enhance treatment efficacy and reduce the risk of drug resistance, the appropriate loading dose of vancomycin to achieve the trough serum concentration above 10 mg/L is 20-30 mg/kg, and 25-30 mg/kg for those who need serum concentration above 15 mg/L. Then monitoring drug level to evaluate individualized pharmacokinetic parameters and design the appropriate maintenance dosage regimen should be performed 24 hours after the loading dose.

Acknowledgments

We very much appreciate Assoc. Prof. Dr. Cheardchai Soontornpas, Division of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Khon Kane University, Thailand for his advice on the research results, and Mr Teerapon Bootprom, Mr Weerapong Thumchotang, Miss Penpimon Sa-ingthong, and Miss Pornlada Thongpanchang for their hard works and support in data collection.

References

Alosaimy S, Murray KP, Zasowski EJ, Morrisette T, Lagnf AM, Lodise TP, *et al.* Clinical experience with vancomycin area under the curve-guided dosing and monitoring: A multicenter study. *Clin Infect Dis*. 2021;73(11):e4560–7.

Ariano RE, Fine A, Sitar DS, Rexrode S, Zelenitsky SA. Adequacy of a vancomycin dosing regimen in patients receiving high-flux hemodialysis. *Am J Kidney Dis*. 2005;46(4):681–7.

Bradley JS, Dudley MN, Drusano GL. Predicting efficacy of anti-infective with pharmacodynamics and Monte Carlo simulation. *Pediatr Infect Dis J*. 2003;22(11):982–92.

Brit JK, Chandler MHH. Using clinical data to determine vancomycin dosing parameter. *Ther Drug Monit*. 1990;12:206–9.

Cataldo MA, Tacconelli E, Grilli E, Pea F, Petrosillo N. Continuous versus intermittent infusion of vancomycin for the treatment of Gram-positive infections: systematic review and meta-analysis. *J Antimicrob Chemother*. 2012;67(1):17–24.

Hartinger JM, Šíma M, Hronová K, Halouzková BA, Szonowská B, Polakovič V, *et al.* Vancomycin pharmacokinetics in patients treated with intermittent haemodialysis based on therapeutic drug monitoring. *J Chemother*. 2022;34(3):149–56.

Lewis SJ, Mueller BA. Evaluation and development of vancomycin dosing schemes to meet new AUC/MIC targets in intermittent hemodialysis using Monte Carlo simulation techniques. *J Clin Pharmacol*. 2021;61(2):211–23.

Matzke GR, McGory RW, Halstenson CE, Keane WF. Pharmacokinetics of vancomycin in patients with various degrees of renal function. *Antimicrob Agents Chemother*. 1984;25(4):433–7.

Matzke GR, Zhanel GG, Guay DRP. Clinical pharmacokinetics of vancomycin. *Clin Pharmacokinet*. 1986;11(4):257–82.

Michael JR. The pharmacokinetic and pharmacodynamic properties of vancomycin. *Clin Infect Dis*. 2006;42 Suppl 1:S35–9.

Tan CC, Lee HS, Ti TY, Lee EJC. Pharmacokinetics of intravenous vancomycin in patients with end-stage renal failure. *Ther Drug Monit*. 1990;12(1):29–34.

Rodvold KA, Blum RA, Fischer JH, Zokufa HZ, Rotschafer JC, Crossley KB, *et al.* Vancomycin pharmacokinetics in patients with various degrees of renal function. *Antimicrob Agents Chemother*. 1988;32(6):848–52.

Rodvold KA, Erdman SM, Pryka RD. Vancomycin. In: Schumacher GE, editor. Therapeutic Drug Monitoring. Norwalk: Appleton & Lange; 1995. p. 587–622.

Rungprai D, Jaruratanasirikul S, Wongpoowarak W, Pattharachayakul S, Wanakamanee U, Dandecha P, *et al.* Vancomycin dosing regimen by Monte Carlo simulation in patients on intermittent high-efficiency hemodialysis (HEHD). *J Med Assoc Thai*. 2015;98(6):606–15.

Rybak MJ, Le J, Lodise TP, Levine DP, Bradley JS, Liu C, *et al.* Therapeutic monitoring of vancomycin for serious methicillin-resistant Staphylococcus aureus infections: a revised consensus guideline and review. *Am J Health Syst Pharm*. 2020;77(11):835–64.

Shimamoto Y, Fukuda T, Tominari S, Fukumoto K, Ueno K, Dong M, *et al.* Decreased vancomycin clearance in patients with congestive heart failure. *Eur J Clin Pharmacol*. 2012;69(3):449–57.

Soontornpas C, Chaichun J, Noimay S. Therapeutic drug monitoring of vancomycin at Queen Sirikit Heart Center of the Northeast. *Isan J Pharm Sci*. 2008;4(1):42–9.

Wilhelm MP. Vancomycin. *Mayo Clin Proc*. 1991;66(11):1165–70.

Winter ME. Winter's basic clinical pharmacokinetics. 5th ed. Philadelphia: Lippincott Williams & Wilkins; 2010. p. 58–72.

Ye ZK, Li C, Zhai SD. Guidelines for therapeutic drug monitoring of vancomycin: a systematic review. *PLoS One*. 2014;9(6):e99044.