Original Article

PHARMACOKINETICS OF VANCOMYCIN IN CRITICALLY ILL PATIENTS IN THAILAND

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ABSTRACT

Objective: The pharmacokinetics and pharmacodynamics of drugs in critically ill patients are difficult to predict due to complex pathophysiological changes. Vancomycin is an antibiotic commonly used to treat serious gram positive bacterial infections in critically ill patients and the treatment goal is to rapidly achieve and maintain therapeutic concentrations. We assessed the pharmacokinetics of vancomycin in critically ill patients to help guide dosing.

Methods: A total of 138 patients with 299 vancomycin serum concentrations were included in this analysis. Vancomycin serum concentrations were measured using a fluorescence polarization immunoassay. Population pharmacokinetic parameters were estimated using nonlinear mixed effects regression. Age, creatinine clearance (CrCL) and body weight were tested as potential covariates in the pharmacokinetic model.

Results: Vancomycin concentration-time profiles were best described by a two-compartment pharmacokinetic model with an additive error model for between subject variability. Creatinine clearance significantly influenced vancomycin clearance (CL). Mean population pharmacokinetic parameters (% between subject variability) were: CL 3.39 l/h (13%), central compartment volume of distribution (V1) 24.92 l (26%); and peripheral compartment volume of distribution (V2) 24.6 (37%).

Conclusion: Higher clearance and a smaller volume of distribution of vancomycin was observed in critically-ill patients compared to those reported in non-critically ill patients with a similar distribution of renal function and body weight. Close monitoring of vancomycin serum concentrations is warranted in critically ill patients with dose interval adjustments based on the patient's creatinine clearance.

Keywords: Pharmacokinetics, Vancomycin, Critically ill patients, Covariates.

INTRODUCTION

Vancomycin is a tricyclic glycopeptide antibiotic with a different mechanism of action to penicillins and cephalosporins, its bacterial killing property is time-dependent and it has limited post-antibiotic effects [1-3]. Vancomycin is a bactericidal with a narrow-spectrum but is active against most gram-positive organisms [2, 4]. The goal of vancomycin dosing is to rapidly achieve and maintain therapeutic concentrations within the therapeutic range. The ratio of the area under the concentration-time curve at 24 hours to the minimum inhibitory concentrations (AUC_{24}/MIC) is the recommended parameter to evaluate the effectiveness of vancomycin treatment [5-8].

At present, the breakpoint for Methicillin-resistant *Staphylococcus aureus* (MRSA) has been reduced from 4 to 2 mg/l [9]. Lower rates of treatment success due to higher MIC values support the need to revise this therapeutic range. An AUC_{24}/MIC ratio of ≥ 400 has been proposed as the vancomycin therapeutic target for a pathogen with an MIC of 1.0 mg/l [6]. In 2009, the American Thoracic Society proposed a new vancomycin target trough range between 15-20 mg/l in adult patients with complicated infection caused by *Staphylococcus aureus* including hospital-acquired pneumonia (HAP) [10].

After administration, vancomycin is extensively distributed throughout the body [11] and is primarily eliminated through glomerular filtration. Differences in vancomycin clearance (CL) have been observed in patients with different degrees of renal function. Morbidly obese adults have been reported to have significantly higher vancomycin clearance compared to non-obese adults (187.5 ml/min vs 80.0 ml/min) as well as differences in volume of distribution [12].

Vancomycin clearance has been shown to decline in the elderly but this may be the consequence of a reduction in renal blood flow, glomerular filtration rate (GFR) and creatinine clearance [13-14]. Vancomycin apparent volume of distribution was higher in the elderly compared to a younger age group (0.93 l/kg vs 0.64 l/kg) [13].

Therefore, factors which impact renal function and body composition may significantly influence vancomycin pharmacokinetics.

Critically ill patients are those with any severe conditions which may cause deterioration, impairment or deficiency of at least one internal organ or physiology requiring invasive devices and progressive treatment with close monitoring [15]. Critically ill patients in ICU are typically at high risk of bacterial infection which can more than double mortality rates [16].

The prescription of antibiotics in critically ill patients is complicated due to pathophysiological changes in the patient's organs. Understanding the pharmacokinetic and pharmacodynamic (PK/PD) properties of antibiotics in relation to bacterial susceptibility allows the appropriate selection of the initial and maintenance antibiotic dose [17].

Mahoney *et al.* (2006) reported that 61.4% of ICU patients with bacteremia and pneumonia who received vancomycin dosing based on a nomogram did not achieve the optimal trough concentration of>10 mg/l [18]. A study of 14 critically ill patients demonstrated that the penetration of vancomycin into lung tissue is poor [19]. Other studies have shown that using 1.0 gram of vancomycin every 12 hours did not achieve the recommended vancomycin concentrations [11, 20].

Data on the pharmacokinetics of vancomycin in critically ill patients are limited and there are no available guidelines for individualization vancomycin dosing. The vancomycin dose for these patients is based on the clinician's own experience. Often these patients have several pathophysiological conditions which are likely to alter key pharmacokinetics parameters [21-22] making it difficult to ensure target therapeutic drug concentrations are achieved [22].

Our objective was to determine the pharmacokinetics of vancomycin in critically ill patients to help guide antibiotic dosing to rapidly achieve therapeutic target concentrations.

MATERIALS AND METHODS

Study population

A prospective intensive pharmacokinetic study was conducted in critically ill patients who received vancomycin every 24 hours for gram positive bacterial infections in the intensive care unit and sub-intensive care unit at Maharaj Nakorn Chiang Mai Hospital, Chiang Mai, Thailand. The study protocol was approved by the Institution Review Board at the Faculty of Medicine, Chiang Mai University. Informed consent was obtained from all patients. Vancomycin drug concentration data were also collected retrospectively from 134 critically ill patients in the intensive care unit at Bumrungrad International Hospital, Bangkok, who had vancomycin serum concentrations monitored between February, 2003 and July, 2014. This retrospective study was approved by the Institution Review Board at Faculty of Pharmacy, Chiang Mai University.

Blood sample collection

For the intensive PK study serial blood samples were collected at the time of the third vancomycin infusion. Three milliliters (ml) of blood were collected before vancomycin infusion, at the end of the 1-hour infusion (1.0) and then serially at 1.5, 2.0, 2.5, 3.0, 6.0, 12.0 and 24 hours post-infusion.

Retrospective data were extracted from patients' records. Sixty eight patients (50.7%) received 1.0 gram of vancomycin infused intravenously over 2 hours every 12 hours. The other 66 patients (49.3%) received an average vancomycin dose of 15.9±4.5 mg/kg/dose every 12, 24 or 48 hours with an infusion rate of 500 mg/h based upon their renal function. At steady state, peak concentrations were obtained 2 hours after the end of infusion. Vancomycin trough concentrations were measured an hour before the next dose or at least two half-lives after the first blood sample.

Measurement of vancomycin serum concentrations

Blood samples were allowed to clot for 15 minutes then centrifuged at 3,000 RPM for 10 minutes (Spinchron® DLX Centrifuge, Beckman coulter) and the serum stored at -25°C until analysis. Vancomycin serum concentrations were measured using the fluorescence polarization immunoassay (FPIA) by Abbott AxSYM® Vancomycin II (Abbott Laboratories, TX, USA). Controls of 7.0, 35.0 and 75.0 µg/ml of vancomycin were used. The average accuracy was 102.5±2.5% and the precision was less than 7% of the coefficient of variation (%CV). The minimum detectable concentration was 2 µg/ml.

Pharmacokinetic analysis

The population analysis was executed using Phoenix® NLME 1.2 software (Certara™, St. Louis, MO, USA). One-, two-and three-compartmental models with first-order elimination were fitted to the data. First-Order Conditional Estimation with Extended Least Squares (FOCE-ELS) was used for all analyses.

Pharmacokinetic models were assessed using both statistical and graphical methods. The objective function value, OFV (i.e. -2x Log-likelihood, -2LL) was used as a cut-off criteria for model improvement and covariate effect(s) on pharmacokinetic parameter(s). Additive, multiplicative, power and mixed model were investigated to describe the residual variability model.

Individual patient characteristics that could potentially influence vancomycin pharmacokinetic parameters were evaluated for inclusion in the model. Covariates tested was total body weight, age and estimated renal functions using a stepwise forward inclusion and backward elimination model building procedure. Models were compared by observing a decrease of -2LL by 6.63 (p=0.01) for forward inclusion and 10.83 (p=0.001) for backward deletion. A decrease in between subject variability (BSV) was also another criterion for covariate selection.

RESULTS

Patient characteristics

A total of 138 ICU patients with 299 serum vancomycin specimens at steady state (4 patients with 31 observation points from intensive blood samplings and 134 patients with 268 concentrations from sparse blood samplings) were included in this analysis. The patient characteristics data are shown in table 1.

The serum vancomycin concentrations versus time profiles are shown in fig. 1.

Vancomycin serum concentrations were best described by a two-compartmental model with first-order elimination. The residual un explained variability (RUV) was described using an additive error model.
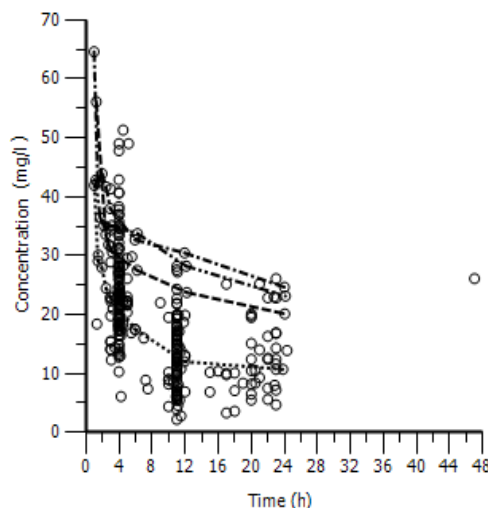

Fig. 1: It shows observed vancomycin serum concentrations versus time profiles in critically-ill patients [4 patients with intensive (dotted line) and 134 patients with TDM samples (299 open circles)]

Among covariates tested for their influence on vancomycin pharmacokinetic parameters, only creatinine clearance was found to significantly influence vancomycin clearance. The degree of between subject variability (BSV %) of CL was 13.0% when creatinine clearance was included in the model. The population pharmacokinetic parameters from the final model are shown in table 3 and goodness of-fit plots are shown in fig. 2.

The final model for vancomycin clearance was achieved using the following equation:

tv Cl (l/hr) = THETA(3) x CrCL$^{(THETA(4))}$

Where tv stands for the typical value and THETA is the final parameter estimate.
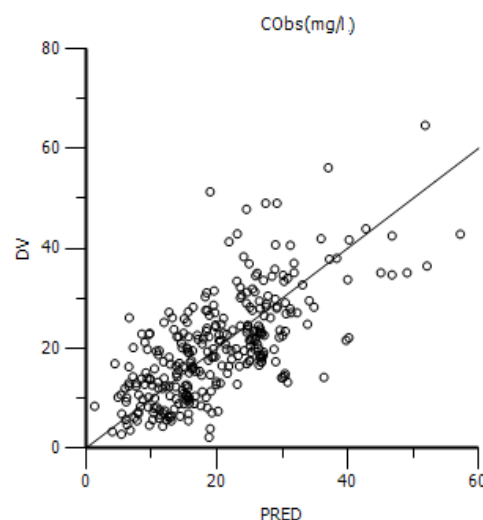

Fig. 2: It shows Observed (DV) versus predicted (PRED) vancomycin concentrations

Table 1: It shows demographic characteristics

Characteristics	Value (mean±SD) [median, range]
Number of subjects	138
Gender (M/F)	72/66
Age (y)	65.7±17.6 [69,18-97]
Body weight (kg)	62.1±13.7 [62.0, 31.7-105.0]
CrCL* (ml/min)	54.5±29.1 [51.4, 10.03-105.00]
Body Mass Index (kg/m2)	23.5±4.4 [23.9, 13.19-34.52]
SAP II score (point)	46.7±5.6 [45.5, 39-52]
Total daily dose (mg/kg/dose)	15.9±4.5[18.2, 6.45-30.0]
Type of infections	
-Bacteremia [n (%)]	55 (39.8)
-Pneumonia [n (%)]	53 (38.4)
-Skin & soft tissue [n (%)]	15 (10.9)
-Meningitis [n (%)]	11 (8.0)
-Others [n (%)]	4 (2.9)
Mechanical ventilation [n (%)]	113 (81.9)
Vasoactive drugs [n (%)]	88 (63.8)

* Estimating by Cockroft and Gault equation

From the retrospective therapeutic drug monitoring (TDM) data, only 18.6% (25 of 134 patients) of the patients achieved the recommended concentrations (15-20 mg/l). After separating these patients based on renal function: Group I: CrCL<30 ml/min, Group II: CrCL 30-60 ml/min and Group III: CrCL>60 ml/min. There was no difference in the percentage of patients who achieved vancomycin trough concentrations (table 2).

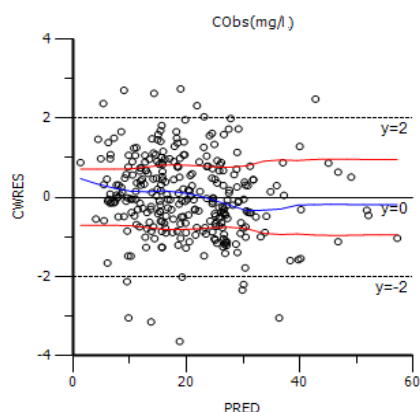**Table 2: It shows vancomycin trough serum concentrations achievement based on renal function**

Group (N)	CrCL (ml/min) mean±SD [range]	Ctrough (mg/l) mean±SD [range]	Ctrough achievement at 15-20 mg/l (n, %)
Group I: CrCL<30 ml/min [n=22]	22.03±4.77 [11.30-29.00]	14.44±6.90 [4.90-25.80]	4 (18.18%)
Group II: CrCL 30-60 ml/min [n= 57]	44.81±8.64 [30.00-59.77]	13.19±6.34 [0.40-26.64]	10 (17.54%)
Group III: CrCL>60 ml/min [n = 55]	81.60±25.61 [60.00-157.50]	9.76±5.56 [1.20-30.64]	11 (20.00%)

CrCL: Creatinine clearance using Cockcroft and Gault equation

Table 3: It shows vancomycin population pharmacokinetic parameters from the final model

Parameters	Estimate (%RSE)	BSV (%RSE)
Cl = THETA(3) x CrCL$^{(THETA(4))}$		13.97 (13.03)
THETA(3)	0.27 (23.97)	
THETA(4)	0.63 (9.65)	
V (l)	24.92 (12.77)	45.97 (25.57)
V2 (l)	24.59 (11.91)	36.54 (36.55)
CL2 (l/h)	10.54(13.38)	109.28 (32.59)
Additive error	1.60μg/l (12.59)	

Cl: systemic clearance; V: central compartment volume of distribution; V2: peripheral compartment volume of distribution; CL2: distributive clearance; RSE: relative standard error of the estimates; BSV: Between subject variability (%CV).

Fig. 3: It shows conditional weighted residuals (CWRES) versus predicted concentrations (PRED) plots for the final pharmacokinetic model

DISCUSSION

The majority of pharmacokinetic studies of vancomycin were performed in healthy volunteers using multi-compartment pharmacokinetics models. Creatinine clearance, body size and age were identified as significant covariates affecting vancomycin pharmacokinetic parameters [23, 26].

In our study, vancomycin serum concentration time profiles were best described by a two-compartmental model with first-order elimination. A strong correlation between creatinine clearance and vancomycin clearance was observed and including creatinine clearance in the model reduced the between subject variability of CL.

Previous studies also reported a relationship between creatinine clearance and vancomycin clearance [23-25]. Llopis-Salvia *et al.*'s also found that body weight influenced vancomycin clearance [26].

It should be noted that the ages of the subjects in these studies were comparable.

Significant variability and changes in both clearance and volume of distribution of vancomycin as well as the plasma vancomycin concentrations in ICU and non-ICU patients during the course of therapy is well documented [21-22, 27].

The mean estimate of the vancomycin clearance in our study was 3.39 l/h. A summary of the pharmacokinetic data from previous studies investigating vancomycin are shown in table 4. A two-compartment pharmacokinetic model was implemented in each of these studies.

Table 4: It shows population pharmacokinetic models of vancomycin

Study (N, Type of patients)	Covariates			Population Estimated Parameters	% BSV
	Age (y)	Wt (kg)	CrCL (ml/min)		
Sanchez *et al.* (141, adult&geriatric) [23]	55±14.6	73.2±17.5	76.13	CL=3.29 V1=20.72 V2=32.2 CL2=8.12	CL: 24.49 V2:6.8
Yamamoto *et al.* (106, gram⊕ infected) [24]	65.4(25.8-99.7)	52.6 (28.7-97.0)	79.6±41.8	CL=2.57a,3.83b V1=25.14 V2=60.6 CL2=8.81	CL: 37.5 V1:18.2 CL2:19.2 V2:72.8
Yasuhara*et al.* (190, MRSA infected) [25]	64.3 (19.3-89.6)	52.3 (25.5-75.0)	77.1±50.9	CL=2.43c,3.51b K12=0.525 K21=0.213 Vss=60.7	CL: 38.5 K12:0(fix) K21:28.6 Vss: 25.4
Purwonugroho*et al.* (246, Thai adult) [28]	66.62±18.38	52.3 (25.5-75.0)	35.07±29.38	CL=1.54 V1=36.11 V2=44.20 CL2=6.950	CL: 35.78 V1:20.93 V2:52.27 CL2:39.50
Thomson *et al.* (398, adult) [29]	66 (16-97)	72 (40-159)	64 (12-216)	CL=3.04 V1=48.6 V2=52.70 CL2=2.28	CL: 27 V1:15 V2:130 CL2:49
Llopis-Salvia *et al.* (50, ICU) [26]	60 (18-81)	60.6 (40-130)	76.3(16.3-120)	CL=3.49 V1=25.09 V2=79.99 CL2=7.48	CL: 29.2 V1:36.2 V2:39.8
Polard*et al.* (19, ICU) [27]	55±18	67±14	136±67	CL=5.88±1.98 V1=13±8 V2=46±32	-
This study (138,Thai ICU)	65.7±17.6(18-97)	62.1±13.7(31.7-105)	54.5±29.1(10-157)	CL=3.39 V1=24.92 V2=24.59 CL2=10.54	CL: 13.97 V1:45.97 V2:36.54 CL2:109.28

CL: Vancomycin clearance (l/h); V1:central compartment volume of distribution of vancomycin (l); V2:peripheral compartment volume of distribution of vancomycin (l); Vss: Estimate of the vancomycin volume of distribution at steady state=MRTINF*Clss; CL2:distributive clearance (l/h); K12:rate constant for the flow between the central and peripheral compartments (h^{-1}); K21:rate constant for the flow between the peripheral and central compartment (h^{-1}); a: group with Creatinine clearance<85 ml/min using Cockcroft and Gault equation; b: group with Creatinine clearance>85 ml/min using Cockcroft and Gault equation; c: group with Creatinine clearance ≤ 85 ml/min using Cockcroft and Gault equation; BSV: Between subject variability

The clearance of vancomycin in our study is comparable to those in infected non-ICU patients, despite the creatinine clearance of our patients being lower than those in non-ICU patients [24-25]. Other patient factors such as the administration of intravenous fluid during the resuscitation and the administration of hemodynamic active drugs (e. g. dopamine, dobutamine and diuretics) may explain these discrepancies and partly dilute the effect of creatinine clearance on the elimination of vancomycin in these critically ill patients [5, 27].

No significant covariates were found to influence the volume of distribution, similar to the results from Yasuhara *et al.*'s study [25]. However, other studies by Yamamoto *et al.*, Thomson *et al.* and Llopis-Savia *et al.* observed that body weight was a significant covariate on vancomycin volume of distribution [24, 26, 29]. Sanchez *et al.* and Purwonugroho *et al.* found that age was an influential covariate on vancomycin volume of distribution [23, 28]. Moreover, Yamamoto *et al.* also found that the patient's status (healthy and infected) as a significant covariate influencing the volume of distribution of vancomycin. The steady state volumes of distribution were larger in infected patients than healthy volunteers. In addition, central compartment volumes of distribution were highest in patients with pneumonia compared to patients with other infections [24].

It has been proposed that increases in capillary or vascular permeability from infections, stress, or sepsis results in fluid leaking from the intravascular compartment or fluid extravasation to the interstitial space or third spacing may result in an increase in vancomycin volume of distribution but, we did not observed increase in the volume of distribution of vancomycin compared with previously report values.

However, it should be noted that the timing of the available vancomycin concentration data in our retrospective study was primarily during the elimination phase and a limitation of our study was that only a few patients had full pharmacokinetic profiles available.

When comparing studies in ICU patients, the vancomycin volume of distribution at steady state (Vdss) observed by Llopis-Salvia and collogues' and Polard *et al.* had the highest values (1.73 l/kg and 0.88 l/kg), while in our study it was 0.80 l/kg [27].

It was also observed that the vancomycin volume of distribution at steady state was larger in non-ICU patients compared to ICU-patients. The study by Purwonugroho *et al.* in infected (non-ICU)-Thai patients also observed a larger volume of distribution for vancomycin at steady state compared to our study (1.54 l/kg

vs0.80l/kg). However, the higher volume of distribution of vancomycin may correspond to older age or as a surrogate of their underlying disease [28].

Current guidelines by the American Thoracic Society (ATS) recommend an initial vancomycin dose of 15 mg/kg every 12 hours in adult patients with normal renal function. Vancomycin trough serum concentration at steady state should be maintained between 15-20 mg/l for pneumonia [30]. In this study, approximately 80% of our ICU patients did not attain the recommended vancomycin trough concentration. Similarly, del Mar Fernandez found that one-third of patients did not achieve the recommended AUC_{24}/MIC breakpoint for *S. aureus* infections using 1 gram of vancomycin. A larger Vd (1.73 l/kg) than the Vd from our study (0.80 l/kg) was found, likely due to sepsis resulting in fluids leaking in to the third space [8].

To determine the maintenance dose and dosing interval of vancomycin in critically ill patients, increasing frequency of vancomycin administration may be necessary comparing to non-ICU patients with the similar degree of kidney functions. A larger loading dose of vancomycin is less likely to be required for these patients as compare to other populations. However, since the vancomycin volume of distribution displays high patient variability, close monitoring of vancomycin serum concentrations may be warranted.

CONCLUSION

Vancomycin pharmacokinetics profiles in critically ill patients were best described by a two-compartment model. Only creatinine clearance was found to significantly influence the systemic clearance of vancomycin. However, vancomycin clearance was higher, and the volume of distribution smaller compared to non-ICU patients with the same degree of renal function and body size. Thus, adjusting the vancomycin dosing interval based on creatinine clearance in critically-ill patients should be practiced with caution. Close monitoring of serum concentrations is recommended due to multiple factors affecting the pharmacokinetics of vancomycin in critically-ill patients.

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CONFLICT OF INTERESTS

Declared None

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