



Population pharmacokinetics analysis of vancomycin in critically ill patients

Phumprut Gawmahanil¹, Prawat Chantharit²,
Pakwan Bunupuradah², Supasil Sra-ium²,
Nantaporn Lekpittaya², Wanchai Treyaprasert^{1*}

¹Department of Pharmacy Practice, Faculty of Pharmaceutical Sciences, Chulalongkorn University, Bangkok, Thailand, ²Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Corresponding Author:

Wanchai Treyaprasert,
Department of Pharmacy
Practice, Faculty of
Pharmaceutical Sciences,
Chulalongkorn University,
Bangkok, Thailand.
E-mail: twanchai@chula.ac.th

Received: Oct 18, 2017

Accepted: Apr 4, 2018

Published: May 20, 2018

Keywords:

Critically ill patients,
population pharmacokinetics,
vancomycin

ABSTRACT

Objectives: The aim of this study was to determine population pharmacokinetic parameters of vancomycin in adult critically ill patients and to investigate the covariates affecting population pharmacokinetic parameters. **Methods:** Plasma concentration data from therapeutic drug monitoring were collected from a retrospective study. Vancomycin population pharmacokinetic modeling was analyzed using nonlinear mixed effect model (NONMEM) program. Patient characteristics that could potentially influence vancomycin pharmacokinetic parameters were tested in the pharmacokinetic model. The covariates were analyzed by the forward inclusion and backward elimination method to identify their potential influence on vancomycin parameter. To assess the robustness of the estimated parameter, bootstrap analysis was performed. **Results:** A total of 171 patients with 398 concentrations during clinical routine therapeutic monitoring were analyzed. Vancomycin serum concentration-time profiles were best described by a one-compartmental model with first-order elimination. Creatinine clearance calculated by Cockcroft-Gault equation, diabetes mellitus and sepsis were found significantly influence CL whereas V of vancomycin showed the significant dependence on patient serum creatinine and gender. The mean population parameters were CL = 3.63 L/h and V = 118 L. The inter-individual variability for CL and V was 32.90 and 29.12 %, respectively. A comparison of the population pharmacokinetic parameters of vancomycin in the final model estimated in NONMEM with original data and 1000 bootstrap samples show that both sets of estimates were comparable, thereby indicating the robustness of the proposed model. **Conclusions:** A population pharmacokinetic model of vancomycin for critically ill patients with Gram-positive infections was developed in this study. The population pharmacokinetic parameters and the significant covariates distinguished in the final model can provide helpful information to facilitate individualized vancomycin dosage regimen with similar patient population characteristics.

INTRODUCTION

Vancomycin is a glycopeptide antibiotic generally used for the treatment of Gram-positive infections, especially against those caused by methicillin-resistant *Staphylococcus aureus* and methicillin-resistant *Staphylococcus epidermidis*, *Streptococcus viridans*, and *Streptococcus faecalis*.^[1] Vancomycin pharmacokinetics could be changed by the various factors and physiopathological conditions such as renal function,^[2,3] liver function,^[4] age,^[5] body weight,^[6] critical illness,^[7] and type of infection.^[8] Critically ill patients have several factors that alter pharmacokinetics parameters such as impairment of at least one organ system

or physiology requiring invasive equipment underlying diseases, and complex treatment.^[9,10] Vancomycin is mainly eliminated through glomerular filtration and reported a relationship between creatinine clearance (CrCl) and vancomycin clearance. Differences in vancomycin clearance have been observed in critically ill patients with different degrees of renal function.^[7] Moreover, vancomycin is a hydrophilic antimicrobial, and the distribution volume is limited to the extracellular space. Therefore, it is possible that an increase in the distribution volume is the result of the pathophysiology of bacterial infections, characterized by an inflammatory response associated with increased vascular permeability and the accumulation of extracellular fluid at

the site of infection.^[8] Thus, determining the optimal dosage of vancomycin is complicated by variability in the drug's pharmacokinetics. Understanding the variability associated with pharmacokinetics and identifying subpopulations with special features can provide clinicians and pharmacists with relevant information for dosage individualization. The population pharmacokinetic approach allows the pharmacokinetic characterization of drugs in subpopulations, the associated inter- and intra-individual variability, and the covariates affecting variability using data collected from patients.^[11] To the best of our knowledge, the studies on population pharmacokinetics of vancomycin in critically ill patients are limited.^[12,13] Population pharmacokinetics of vancomycin was studied by Purwonugroho *et al.*^[14] in the type of heterogeneous populations including non-critically ill and critically ill patients. Little is known about the vancomycin pharmacokinetics in Thai critically ill patients since only one population pharmacokinetic analysis has been published previously by Dedkaew *et al.*^[12] We proposed to improve the knowledge on vancomycin pharmacokinetics in critically ill patients based on routine therapeutic drug monitoring data. The objectives of this study were to determine population pharmacokinetic parameters of vancomycin and to evaluate the covariates affecting population pharmacokinetic parameters.

PATIENTS AND METHODS

Patients and Data Collection

All data were collected retrospectively from critically ill patients who received vancomycin for treatment of Gram-positive bacterial infections between January 2014 and December 2016 at Ramathibodi Hospital, Mahidol University, Bangkok, Thailand. The study protocol was approved by Human Research Ethics Committee of Faculty of Medicine, Ramathibodi Hospital, Mahidol University. Vancomycin concentrations were collected during routine therapeutic monitoring. 398 vancomycin concentration-time profiles were collected. Blood sampling was ordered as required clinically. Peak or trough at steady state is usually drawn. Vancomycin was administered by intermittent infusion over 1–2 h, and blood samples were collected at least 1 h after completion of the drug infusion (peak vancomycin levels) and up to 1 h before the next dose (trough vancomycin levels). Patients were included in the present study if they met *al.* of the following criteria:

1. Age ≥ 18 years.
2. Admitted to the intensive care unit or sub-intensive care unit more than 48 h or ≥ 1 character related to critically illness defined as:
 - a. Acute physiology and chronic health evaluation system II (APACHE II) score evaluated before starting vancomycin ≥ 15 points.
 - b. Currently on one or more continuous vasopressors infusions at any dose with vancomycin ≥ 4 h.
 - c. Currently receiving invasive mechanical ventilation with vancomycin ≥ 4 h.
 - d. Diagnosed one or more organ system failure by physician before treatment with vancomycin.
3. Using vancomycin by intravenous infusion for treatment Gram-positive bacterial infection.

4. Complete data regarding dosage regimen, serum drug concentration, and accurate timing of dose administration, and blood collection.

And patients will be excluded if:

1. Currently on hemodialysis, peritoneal dialysis, or kidney transplantation or
2. Incomplete data at least one item or,
3. Pregnant.

The following data were retrieved from each patient's medical records: Sex, age, body weight, serum albumin, and serum creatinine. Clinical data such as fluid balance, invasive mechanical ventilation, underlying diseases, comorbidity, type of infections, and concomitant medication were also recorded. The APACHE II scores^[15] and sepsis organ failure assessment (SOFA) scores^[16] were determined on the 1st day of antibiotic treatment. CrCl was calculated from serum creatinine using the Cockcroft and Gault equation.^[17] CrCl estimated by the Cockcroft and Gault equation was generally used in routine clinical practice and is reported as a significant covariate affecting vancomycin pharmacokinetic parameters.^[8]

Vancomycin Assay

Vancomycin serum concentration assays were performed as part of routine clinical monitoring. Vancomycin concentrations were measured using Chemiluminescent Microparticle Immunoassay by ARCHITECT I (Abbott Laboratories, Abbott Park, Illinois, U.S.A.). The quantification limit of the assay for vancomycin was 0.24 $\mu\text{g/mL}$. The coefficient of variation for this assay was $<10\%$ over the entire calibration range (0.24–100 $\mu\text{g/mL}$).

Population Pharmacokinetic Analysis

Pharmacokinetics modeling was analyzed using nonlinear mixed effect model (NONMEM) software package version 7.3.1 (Icon Development Solutions, Ellicott City, MD, USA). The NONMEM runs were executed with PDx-Pop version 5.1 (Icon Development Solutions, Ellicott City, MD, USA). The first-order conditional estimation method with interaction (FOCE INTERACTION) was used to estimate the mean and the variance of the population pharmacokinetic parameters.

Basic model selection

To determine the appropriate basic compartmental model, data were fitted to both one- and two-compartment models, with first-order elimination by ADVAN1-TRANS2 or ADVAN3-TRANS4 subroutines, respectively. The additive error model, the proportional error model, the exponential error model, and the combined additive, and proportional model were evaluated to describe the inter-individual variability in the pharmacokinetic parameters and the residual variability. Basic model selection was selected by the minimum value of the objective function value (OFV) and the Akaike information criterion.

Model building

After basic model evaluation, the selection of covariates in preliminary screening step was carried out by plotting the pharmacokinetic parameters against demographic factors to assess relationships. If a trend between a covariate and a PK

parameter was found, then it was considered for inclusion in the base model. The covariates including sex, age, body weight, serum albumin, serum creatinine, CrCl (using Cockcroft and Gault equation), fluid balance, invasive mechanical ventilation, underlying diseases (diabetes mellitus (DM), atrial fibrillation, cirrhosis, and heart failure), comorbidity (upper GI bleeding and renal dysfunction), type of infections (sepsis and septic shock), and concomitant medication (dopamine, dobutamine, norepinephrine, epinephrine, furosemide, amikacin, gentamicin, ibuprofen, and diclofenac), APACHE II score, and SOFA scores were analysis. The potential covariates were selected with the stepwise forward addition and backward exclusion method. The forward additional step was conducted to add each covariate one by one into the basic model to build the full model. The covariate was retained in the model if the decrease of OFV was >3.84 ($P < 0.05$, degrees of freedom = 1). The final model was obtained by removing covariates from the full model by the backward elimination method. A covariate causing an increase of OFV smaller than 6.64 ($P < 0.01$, degrees of freedom = 1) was rejected.

Model evaluation

The goodness of fit was evaluated by diagnostic scatter plots as follows: Predicted concentrations versus observed concentrations, individual predicted concentration versus observed concentrations, and conditional weighted residuals versus predicted concentrations. Furthermore, the bootstrap approach was used as internal model evaluation. 1000 bootstrap dataset was generated by resampling from the original dataset. The final model parameter estimates were compared with the median parameter values, and 95% confidence interval of bootstrap replicates.

RESULTS

Patient Characteristics

A total of 171 patients were enrolled in this study. Vancomycin was empirical treatment in 123 patients (71.93%) whereas in 48 patients (28.07%) were initiated treatment as a result of a documented infection. The demographic and clinical characteristics of the patients are shown in Table 1. 398 vancomycin concentration samples were collected. Figure 1 present scatter plots of the observed vancomycin concentration-time data.

Population Pharmacokinetic Analysis

A base model without covariates is defined. A one-compartmental model with first-order elimination was appropriate to describe the vancomycin concentration-time data in this study. In this model, the exponential and additive error models were chosen for inter-individual variability and residual variability, respectively. The base model provided an estimate of mean population value for clearance of 3.04 L/h and volume of distribution of 112 L.

The influence of covariates was evaluated by the stepwise forward addition and backward exclusion method. The model building process is summarized in Table 2. After forward selection and the remaining significant covariates after backward deletion, CrCl estimated by Cockcroft and Gault equation, DM

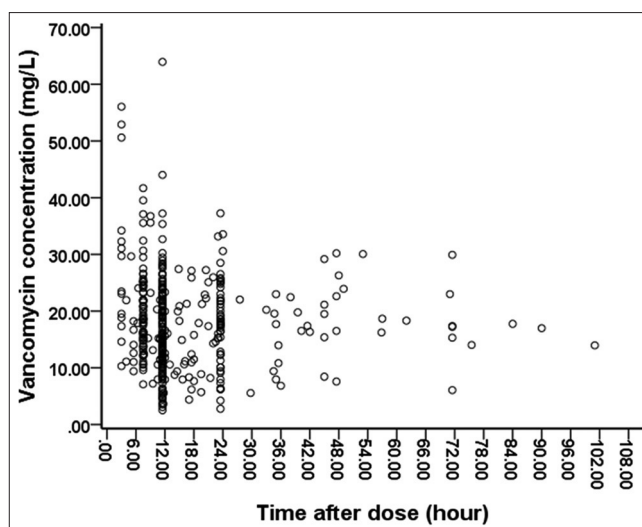


Figure 1: Relationship between vancomycin concentrations and sampling time after intravenous infusion

and sepsis were found significantly influence CL whereas V of vancomycin showed the significant dependence on patient serum creatinine and gender. The final model parameters of vancomycin were described by equations as follows:

$$CL \text{ (L/h)} = 3.63 \times \left(\frac{CRCL}{67.7} \right)^{0.768} \times [1 - (0.243 \times DM)] \times [1 - (0.225 \times SEPS)]$$

where CRCL is CrCl by Cockcroft and Gault equation (mL/min); DM, DM = 0 if no presentation with DM, DM = 1 if presentation with DM; SEPS is sepsis, SEPS = 0 if no presentation with sepsis, SEPS = 1 if presentation with sepsis.

$$V \text{ (L)} = 118 \times \left[\left(\frac{SCR}{0.9} \right)^{-0.209} \right] \times [1 + (-0.237 \times SEX)]$$

Where SCR is serum creatinine (mg/dL); SEX is gender, SEX = 0 if male, SEX = 1 if female.

The goodness-of-fit plots from final model are shown in Figure 2. The scatterplot of population predicted concentrations and individual predicted concentrations versus observed concentrations showed a symmetric distribution around identity line [Figure 2a and b]. In addition, the conditional weighted residuals showed the good distribution of the points around zero line and were within the range of -3 and 3, which indicated that the model was significantly well fit [Figure 2c].

The robustness of the final model was evaluated by bootstrap analysis. The results of the bootstrap analysis are shown in Table 3. The stability of model using bootstrap method for 1,000 re-sampling successfully runs with the success rate of 86.4%. The median and 95% confidence intervals of parameters from the bootstrap procedure were in good agreement with the estimates from the final model. The estimated value of parameters from the bootstrap analysis was very close to the respective value from the final model and was within 95% percentile of bootstrapping intervals.

DISCUSSIONS

A one-compartment pharmacokinetic model with first-order elimination was appropriate to describe the concentration-time

Table 1: Demographic and clinical data on patients

Characteristic	Value ^a
Male (%)	100 (58.48)
Age (years)	62.20±17.96
Total body weight (kg)	56 (29, 125.7)
APACHE II score (point)	20 (16, 22)
SOFA score (point)	12.4±1.64
Serum creatinine (mg/dL)	0.9 (0.19, 12.07)
CrCl by Cockcroft and Gault equation (mL/min)	67.7 (3.67, 405.7)
Serum albumin (g/dL)	3.82 (3, 4.46)
Dosage (mg/kg/day)	30.3 (6.39–87.53)
Duration (days)	3 (1–53)
Number of serum concentrations per patient	2 (1–14)
Invasive mechanical ventilation events (%)	158 (39.7)
Underlying diseases and comorbidity (%)	
Hypertension	59 (34.5)
DM	38 (22.22)
Dyslipidemia	34 (19.88)
Renal dysfunction	24 (14.04)
Cerebrovascular disease	22 (12.87)
Upper gastrointestinal bleeding	5 (2.92)
Heart failure	5 (2.92)
Atrial fibrillation	5 (2.92)
Cirrhosis	4 (2.34)
Type of infections (%)	
Sepsis	42 (24.56)
CNS infection	38 (22.22)
Skin and soft tissue infection	29 (16.96)
Urinary tract infection	27 (15.79)
Intra-abdominal infection	12 (7.02)
Pneumonia	9 (5.26)
Septic shock	3 (1.75)
Others	11 (6.44)
Concomitant medication (%)	
Dopamine	280 (70.35)
Furosemide	272 (68.34)
Norepinephrine	29 (7.29)
Ibuprofen	18 (4.52)
Gentamicin	17 (4.27)
Dobutamine	7 (1.76)
Epinephrine	7 (1.76)
Amikacin	3 (0.75)
Diclofenac	1 (0.25)

^aData are described as mean±standard deviation or median (range)

data on vancomycin in the present study. In agreement with previous studies^[18-20] using a similar model as shown in

Table 4, we found that a one-compartment model can be used to estimate vancomycin pharmacokinetic parameters. Since sparse concentration data obtained from therapeutic drug monitoring, it is usually described by the one-compartment model. However, the two-compartment model provides a better description of the pharmacokinetic process of vancomycin if a large number of data from several sampling time points including post distribution sampling times are analyzed as Llopis-Salvia and Jiménez-Torres study^[13] and Dedkaew *et al.*^[12] In our study, both the one-compartment and two-compartment models were fit to our data. Finally, our data could not support a two-compartment model since a number of data consisted largely of trough concentrations (74%), peak concentration (4%), and other times (22%) so the data are one compartment in nature.

Vancomycin pharmacokinetics is mostly affected by the pathophysiological changes observed in critically ill patients with increased volumes of distribution and altered drug clearance (related to changes in CrCl). The increase in the volume of distribution has been explained on the basis of changes in the body compartments due to fluid overload in attempts to maintain hemodynamics.^[13] Moreover, vancomycin is a hydrophilic antimicrobial, and the distribution volume is limited to the extracellular space. Therefore, it is possible that an increase in the distribution volume is the result of the pathophysiology of bacterial infections, characterized by an inflammatory response associated with increased vascular permeability and the accumulation of extracellular fluid at the site of infection.^[8]

The mean CL and V of vancomycin in the present population [Table 4] was 3.63 L/h and 118 L, respectively. The mean CL value of this study was similar to the value of 3.60 L/h reported by Fernández *et al.*^[20] but was lower than that in the other studies.^[18,19] The value of V was lower than the value of 190.2 L reported by Revilla *et al.*^[18] but was higher than that in the other studies.^[19,20] According to our final model, CL of vancomycin was influenced by CrCl by Cockcroft and Gault equation, diabetes mellitus and sepsis. A significant effect of CrCl on vancomycin clearance is found in most reported studies,^[13,18-20] it could be explained due to vancomycin elimination through glomerular filtration. Differences in vancomycin clearance have been observed in critically ill patients with different degrees of renal function. Besides the major effect of CrCl on vancomycin clearance, the influence of diabetes mellitus and/or sepsis was a possibly influential covariate. The inclusion of both diabetes and sepsis on clearance produced a significant decrease in the objective function and improvement in model building [Table 2]. Diabetes and sepsis had an indirect effect on vancomycin clearance. The effect of diabetes mellitus and sepsis might be explained by the change of a renal function with increased the risk of acute kidney injury in critically ill patients.^[21-24] Mangin *et al.*^[25] reported that diabetes was significantly associated with reduced vancomycin intercompartmental clearance by decreasing the diffusional clearance in accordance with the pathophysiology that diabetic microangiopathy may cause a drug tissue distribution defect. In our results, V of vancomycin was influenced by serum creatinine and gender. In agreement with Revilla *et al.*,^[17] we found that a relationship between V of vancomycin and serum creatinine. This may be due

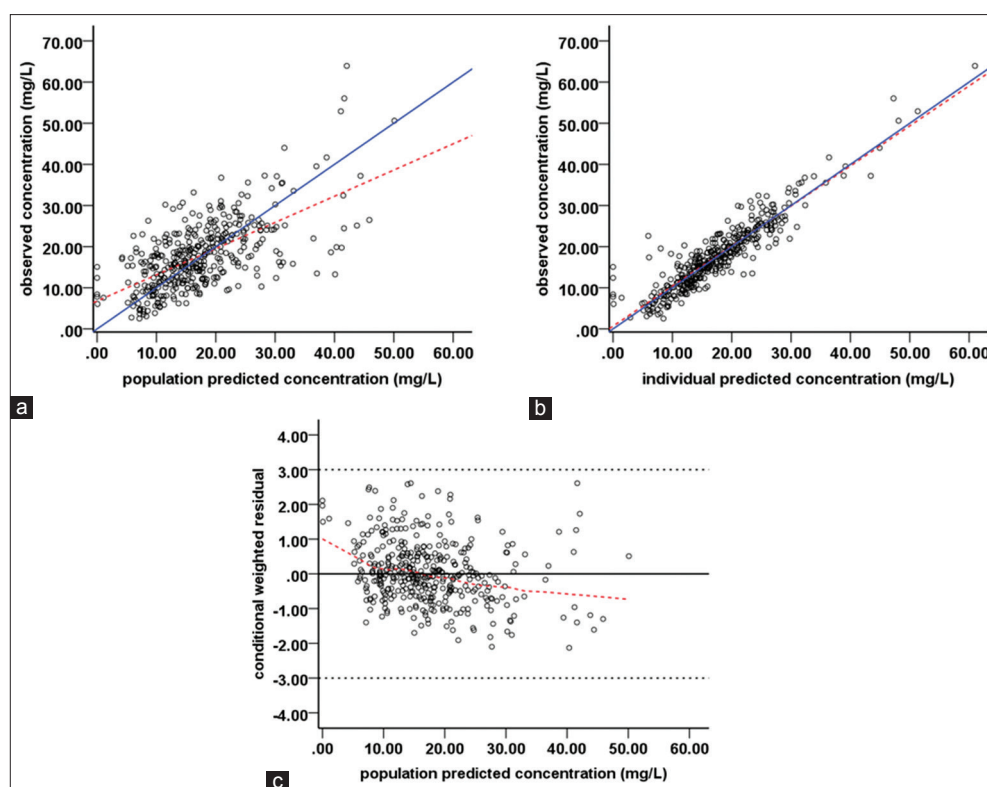


Figure 2: Goodness-of-fit plots from final model: Population prediction concentration versus observed concentration (a), individual prediction concentration versus observed concentrations (b), and conditional weighted residual versus population prediction concentration (c), and identity lines (blue solid line), trend lines (red dotted line), $x = \pm 3$ criteria for good distribution of the conditional weighted residuals (black dotted line)

Table 2: Summary of the covariate models development

Model	Covariate	Model equation	OFV	DOFV	P
Base	-	$CL (L/h) = \theta_1$	1962.16	-	-
Forward	CRCL	$CL (L/h) = \theta_1 \times (CRCL/67.7)^{0.3}$	1778.45	-183.71	<0.05
	DM	$CL (L/h) = \theta_1 \times (CRCL/67.7)^{0.3} \times [1 + (\theta_4 \times DM)]$	1769.69	-8.76	<0.05
Full	SEPS	$CL (L/h) = \theta_1 \times (CRCL/67.7)^{0.3} \times [1 + (\theta_4 \times DM)] \times [1 + (\theta_5 \times SEPS)]$	1762.04	-7.65	<0.05
Backward	CRCL	$CL (L/h) = \theta_1 \times [1 + (\theta_3 \times DM)] \times [1 + (\theta_4 \times SEPS)]$	1935.98	+173.94	<0.01
	DM	$CL (L/h) = \theta_1 \times (CRCL/67.7)^{0.3} \times [1 + (\theta_4 \times SEPS)]$	1772.18	+10.14	<0.01
	SEPS	$CL (L/h) = \theta_1 \times (CRCL/67.7)^{0.3} \times [1 + (\theta_4 \times DM)]$	1769.69	+7.65	<0.01
Base	-	$V (L) = \theta_2$	1962.16	-	-
Forward	SCR	$V (L) = \theta_2 \times [(SCR/0.9)^{0.3}]$	1929.65	-32.51	<0.05
Full	SEX	$V (L) = \theta_2 \times [(SCR/0.9)^{0.3}] \times [1 + (\theta_4 \times SEX)]$	1916.24	-13.41	<0.05
Backward	SCR	$V (L) = \theta_2 \times [1 + (\theta_3 \times SEX)]$	1955.35	+39.11	<0.01
	SEX	$V (L) = \theta_2 \times [(SCR/0.9)^{0.3}]$	1929.65	+13.41	<0.01

DOFV: Difference of objective function values, CL: Clearance, V: Volume of distribution, CRCL: Creatinine clearance by Cockcroft and Gault equation (mL/min), DM: Diabetes mellitus, SEPS: Sepsis, SCR: Serum creatinine (mg/dL), SEX: Gender, θ : Fixed-effect parameters, ω : Inter-individual variability related to each pharmacokinetics parameters, σ : Residual variability

to serum creatinine may be able to be some surrogate that reflects the influence of critical illness. In addition, gender was significantly related to V due to body weight. However, other studies^[8,13] observed that body weight was a significant covariate on V. In our study, V did not associate with total body weight. The narrow range of total body weight on the most patients in our study (75.44% of total body weight values were ranged from 45 to 75 kg) might not be enough to become a

significant covariate in this population. Gender in the present study seemed to be an intermediate factor of total body weight.

These modeling analysis results identified five clinically relevant covariates (CrCl, diabetes mellitus, sepsis, serum creatinine, and gender) that influenced vancomycin pharmacokinetics and might achieve better individualization of vancomycin for critically ill patients. Based on the

results of the current population analysis, we simulated the vancomycin concentration-time curves for a standard patient (male, 65 kg in weight, with a CrCl of 85 mL/min), critically ill patients and critically ill patients with diabetes and sepsis [Figure 3]. The significantly lower concentration predicted with our models in critically ill patients due to the lower CL and higher V values estimated. The results suggested that the initial dose of vancomycin should be increased and the maintenance dose should be decreased preferably by prolonging the dosing interval to prevent vancomycin from accumulating in critically ill patients and critically ill patients with diabetes and sepsis. In addition, initial dose regimens including loading and maintenance doses should be developed to reach target steady-state trough concentration range.

Furthermore, the bootstrap method was used for evaluating the accuracy and robustness of the final model in the present study. The mean values of the bootstrap procedure were comparable to the parameter estimates from the original dataset and the 95% CIs overlapped with those of the original

dataset. These results suggest that the accuracy and robustness of the final model were acceptable.

There were several limitations in our study. First, this was a retrospective study with small sample size. Second, due to insufficient data, we did not perform a proper external validation of the model. A prospective study is being conducted to evaluate the predictive performance and generalizability of this model. Finally, we did not design a dosing recommendation for vancomycin in the target population. In a further study, a Monte Carlo simulation study should be conducted to develop an optimal vancomycin dosage regimen according to PK/PD principles based on the population parameters of the final model, which will be extended to clinical practice.

In conclusion, we have developed a one-compartment model with first-order elimination model for vancomycin in critically ill patients with Gram-positive infections. CrCl and comorbidity with diabetes mellitus and sepsis were the key covariates for CL, while serum creatinine and gender were the most significant predictor for V. The population parameters of the final model can be used to develop a dosage regimen

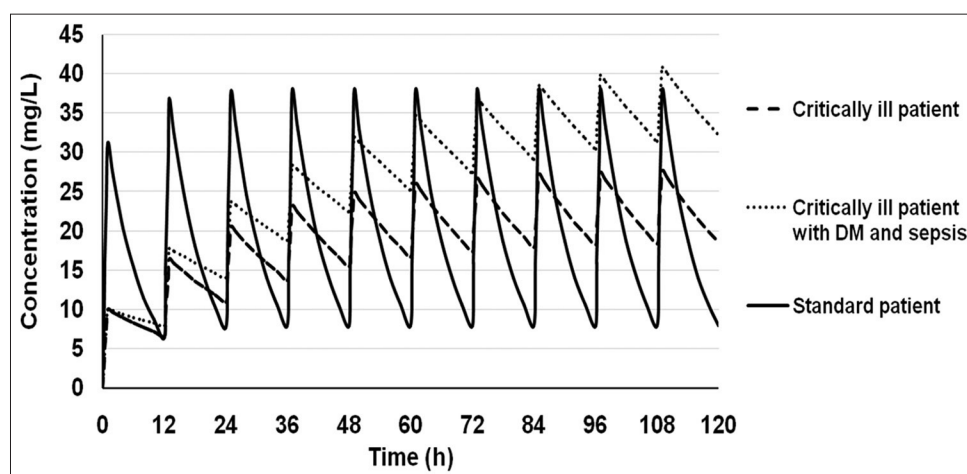


Figure 3: Simulated mean vancomycin serum profiles in a standard patient receiving a conventional dosage regimen of 1,000 mg/12 h versus critically ill patients and critically ill patients with diabetes and sepsis

Table 3: Bootstrap results of the final model

Parameters	Final model		Bootstrap (<i>n</i> =1,000)	
	Estimates value	95% CI	Median	95% CI*
CL (L/h)	3.63	3.32, 3.94	3.59	3.31, 3.94
θCRCL (mL/min)	0.768	0.661, 0.875	0.749	0.573, 0.889
θDM	-0.243	-0.368, -0.118	-0.212	-0.379, -0.063
θSEPS	-0.225	-0.352, -0.098	-0.189	-0.343, -0.079
V (L)	118.00	98.40, 138.00	120.80	98.40, 143.00
θSCR (mg/dL)	-0.209	-0.357, -0.061	-0.218	-0.472, -0.045
θSEX	-0.237	-0.402, -0.072	-0.260	-0.425, -0.072
ω CL (%CV)	32.90	26.30, 38.34	45.16	25.86, 39.49
ω V (%CV)	29.12	5.54, 40.87	22.36	0.22, 41.23
σ (SD)	3.97	3.54, 4.37	4.02	3.27, 4.68

*2.5th percentile and 97.5th percentile. CL: Clearance, V: Volume of distribution, CRCL: Creatinine clearance by Cockcroft and Gault equation (mL/min), DM: Diabetes mellitus, SEPS: Sepsis, SCR: Serum creatinine (mg/dL), SEX: Gender, θ: Fixed-effect parameters, ω: Inter-individual variability related to each pharmacokinetics parameter, σ: Residual variability

Table 4: Previous population pharmacokinetic studies of vancomycin

Authors, population of patient	n (VAN)	Type of data	Structural model	Estimated values	Covariates related to each PK parameter
This study, Thai ICU	171 (398)	Sparse	1 CPM	CL=3.63L/h V=112L	CL: CrCl, DM, Sepsis, V: Scr, Gender
Revilla <i>et al.</i> , Spain ICU ^[18]	191 (596)	Sparse	1 CPM	CL=3.96L/h V=190.2L	CL: CrCl, Age V: Scr
Roberts JA, <i>et al.</i> , Belgium ICU ^[19]	206 (579)	Sparse	1 CPM	CL=4.6L/h V=90L	CL: CrCl, V: TBW
del Mar Fernández de Gatta Garcia <i>et al.</i> , Spain ICU ^[20]	46 (233)	Sparse	1 CPM	CL=3.6L/h V=100.8L	CL: CrCl, Age, Salb, APACHE
Llopis-Salvia and Jiménez-Torres Spain ICU ^[13]	30 (234)	Sparse	2CPM	CL=3.49L/h Q=7.48L/h V1=25.09L V2=79.99L	CL: CrCl, TBW, V1: TBW V2: TBW
Dedkaew <i>et al.</i> , Thai ICU ^[12]	138 (299)	Sparse and dense	2CPM	CL=3.39 L/h Q=10.54 L/h V1=24.92 L V2=24.59 L	CL: CrCl

CL: Clearance, Q: Distributive clearance, V1: Central compartment volume of distribution, V2: Peripheral compartment volume of distribution, CPM: Compartment, CrCl: Creatinine clearance, VAN: Vancomycin concentration, DM: Diabetes mellitus, Scr: Serum creatinine, TBW: Total body weight, Salb: Serum albumin, PK: Pharmacokinetics

and individualize therapy with similar patient population characteristics.

ACKNOWLEDGMENT

This study was partially supported by “CU GRADUATE SCHOOL THESIS GRANT” from Chulalongkorn University. Moreover, the authors thank the staff of Faculty of Medicine Ramathibodi Hospital, Mahidol University for the use of their facilities and collaboration.

REFERENCES

- Sorrell TC, Packham DR, Shanker S, Foldes M, Munro R. Vancomycin therapy for methicillin-resistant *Staphylococcus aureus*. *Ann Intern Med* 1982;97:344-50.
- Tan CC, Lee HS, Ti TY, Lee EJ. Pharmacokinetics of intravenous vancomycin in patients with end-stage renal failure. *Ther Drug Monit* 1990;12:29-34.
- Schaedeli F, Uehlinger DE. Urea kinetics and dialysis treatment time predict vancomycin elimination during high-flux hemodialysis. *Clin Pharmacol Ther* 1998;63:26-38.
- Martí R, Rosell M, Pou L, García L, Pascual C. Influence of biochemical parameters of liver function on vancomycin pharmacokinetics. *Pharmacol Toxicol* 1996;79:55-9.
- Culter NR, Naravag PK, Lesko JL, Ninos M, Power M. Vancomycin disposition: The importance of age. *Clin Pharmacol Ther* 1984;36:803-10.
- Bauer LA, Black DJ, Lill JS. Vancomycin dosing in morbidly obese patients. *Eur J Clin Pharmacol* 1998;54:621-5.
- Roberts JA, Lipman J. Pharmacokinetic issues for antibiotics in the critically ill patient. *Crit Care Med* 2009;37:840-51.
- Yamamoto M, Kuzuya T, Baba H, Yamada K, Nabeshima T. Population pharmacokinetic analysis of vancomycin in patients with gram-positive infections and the influence of infectious disease type. *J Clin Pharm Ther* 2009;34:473-83.
- Álvarez-Lerma F, Grau S. Management of antimicrobial use in the intensive care unit. *Drugs* 2012;72:447-70.
- Abdul-Aziz MH, Lipman J, Mouton JW, Hope WW, Roberts JA. Applying pharmacokinetic/pharmacodynamic principles in critically ill patients: Optimizing efficacy and reducing resistance development. *Semin Respir Crit Care Med* 2015;36:136-53.
- Vinks AA. The application of population pharmacokinetic modeling to individualized antibiotic therapy. *Int J Antimicrob Agents* 2002;19:313-22.
- Dedkaew T, Cressey TR, Punyawoddho B, Lucksiri A. Pharmacokinetics of vancomycin in critically ill patients in Thailand. *Int J Pharm Pharm Sci* 2015;7:232-7.
- Llopis-Salvia R, Jiménez-Torres NV. Population pharmacokinetic parameters of vancomycin in critically ill patients. *J Clin Pharm Ther* 2006;31:447-54.
- Purwongroho TA, Chulavatnatol S, Preechagoon Y, Chindavijak B, Malathum K, Bunuparadah R, *et al.* Population pharmacokinetics of vancomycin in Thai patients. *ScientificWorldJournal* 2012;2012:762649.
- Knaus WA, Draper EA, Wagner DP, Zimmerman JE. APACHE II: A severity of disease classification system. *Crit Care Med* 1985;13:818-29.
- Vincent JL, de Mendonça A, Cantraine F, Moreno R, Takala J, Suter PM, *et al.* Use of the SOFA score to assess the incidence of organ dysfunction/failure in intensive care units: Results of a multicenter, prospective study. Working group on “sepsis-related problems” of the European Society of Intensive Care Medicine. *Crit Care Med* 1998;26:1793-800.
- Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. *Nephron* 1976;16:31-41.
- Revilla N, Martín-Suárez A, Pérez MP, González FM, Fernández de Gatta Mdel M. Vancomycin dosing assessment in intensive care unit patients based on a population pharmacokinetic/pharmacodynamic simulation. *Br J Clin Pharmacol* 2010;70:201-12.
- Roberts JA, Taccone FS, Udy AA, Vincent JL, Jacobs F, Lipman J,

- et al.* Vancomycin dosing in critically ill patients: Robust methods for improved continuous-infusion regimens. *Antimicrob Agents Chemother* 2011;55:2704-9.
20. del Mar Fernández de Gatta Garcia M, Revilla N, Calvo MV, Domínguez-Gil A, Sánchez Navarro A. Pharmacokinetic/pharmacodynamic analysis of vancomycin in ICU patients. *Intensive Care Med* 2007;33:279-85.
 21. Patschan D, Müller GA. Acute kidney injury in diabetes mellitus. *Int J Nephrol* 2016;2016:6232909.
 22. Sykes E, Cosgrove JF. Acute renal failure and the critically ill surgical patient. *Ann R Coll Surg Engl* 2007;89:22-9.
 23. Zarbock A, Gomez H, Kellum JA. Sepsis-induced acute kidney injury revisited: Pathophysiology, prevention and future therapies. *Curr Opin Crit Care* 2014;20:588-95.
 24. Majumdar A. Sepsis-induced acute kidney injury. *Indian J Crit Care Med* 2010;14:14-21.
 25. Mangin O, Urien S, Mainardi JL, Fagon JY, Faisy C. Vancomycin pharmacokinetic and pharmacodynamic models for critically ill patients with post-sternotomy mediastinitis. *Clin Pharmacokinet* 2014;53:849-61.