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RESEARCH ARTICLE

Determination of vancomycin pharmacokinetics in critically ill intensive care unit patients in Malaysia: A population pharmacokinetic analysis with a nonparametric approach

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ABSTRACT

Background: The pharmacokinetics (PK) of vancomycin in critically ill intensive care unit (ICU) patients is difficult to predict due to the scarcity of data and the variable physiology of the patient cohort. **Aims and Objectives:** Since there are limited studies worldwide, this study is, therefore, intended to explore vancomycin population PK parameters in critically ill ICU patients in Hospital Raja Perempuan Zainab II, Kelantan, Malaysia. **Materials and Methods:** Vancomycin population PK in ICU patients was modeled with Pmetrics. A total of 92 samples from 45 ICU patients were included in the model building and validation. The median observations per patient were three with a range of one to four observations. The median parameters estimates obtained from the final model were used to predict individual vancomycin clearance (CL) in the validation dataset. **Results:** The PK of vancomycin was adequately described with a two-compartment model. Parameters included CL of 1.64 L/h, volume of distribution in central compartment of 20.0 L, rate of constant from central out to the peripheral compartment of 2.92/h, and the rate constant back from the peripheral to central compartment of 7.17/h. The developed model adequately estimated CL in the validation dataset. **Conclusion:** A model to describe the PK of vancomycin was developed which adequately describes vancomycin population PK in critically ill ICU patients in Kelantan. The model might be used in initiating a vancomycin dosage regimen in the type of patients similar to the present study.

KEY WORDS: Pharmacokinetics; Vancomycin; Intensive Care Unit; Critically ill; Nonparametric

INTRODUCTION

Vancomycin still remains the most common first-line option for treating healthcare-associated severe infectionssince methicillin-resistant *Staphylococcus aureus* (MRSA) is the major pathogen.[1,2] MRSA incidence in East Asia and Western Pacific regions was documented between 2.3% and 69%.[3] In Malaysia, the MRSA infections rate was reported as 10.0/1000 hospital admissions over a period of 6 years from 2002 to 2007 with 16.4% of the infections coming from the intensive care unit (ICU).[4] Vancomycin is also the most widely used antibiotic for MRSA in Malaysia.[5]

Achievement of pharmacokinetic/pharmacodynamic (PK/PD) indices associated with a maximal bacterial kill is recommended to increase the likelihood of clinical cure. To achieve target serum concentrations in life-threatening infections, such as sepsis, infective endocarditis,

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osteomyelitis, and hospital-acquired pneumonia, current guidelines recommend trough serum concentrations of vancomycin (Cmin) ranging 15–20 mg/L.[6]

<30% of patients in a Saudi Arabian Medical Center received an inappropriate vancomycin dose regimen based on weight, age, and creatinine clearance (CL).[7] Extensive PK studies in a variety of patient populations such as in elderly, obese patients, children, and neonates have allowed physicians and pharmacists to target serum vancomycin concentrations precisely in a relatively narrow range. However, the CL of vancomycin reduced significantly in patients with renal insufficiency.[8]

However, in critically ill patients with sepsis or septic shock the target concentrations may be difficult to achieve due to the increased distribution volume and the presence of augmented renal CL, and thus may lead to reduced trough concentrations and underdosing, leading to the inadequate bacterial killing and possible treatment failure. Furthermore, insufficient dosing may facilitate the development of multidrug resistance. Despite the vital role of vancomycin in the treatment of MRSA infections, a complete consensus has not been reached regarding the optimum dosing regimens and PK/PD goals in critically ill patients.

Since there are limited studies worldwide, this study is, therefore, intended to explore the vancomycin population PK parameters in critically ill ICU patients in Hospital Raja Perempuan Zainab (HRPZ) II, Kelantan, Malaysia.

MATERIALS AND METHODS

Subjects

This is a cross-sectional study that involved ICU patients treated with vancomycin in HRPZ II, Kelantan, Malaysia. All adult ICU patients regardless of diagnosis who required vancomycin therapy were included in the study. Patients with myeloma, cystic fibrosis, and burn injury on >20% of the body surface were excluded from the study.

Informed consent was obtained from the patient or their care provider before recruitment. Data collected on each patient included gender, age, weight, serum creatinine, albumin, alanine transaminase (ALT), alkaline phosphatase (ALP), and AST levels. Creatinine CL was calculated using the Cockcroft–Gault equation. Accurate dosing history of vancomycin and serum sampling including date, time, dose, and infusion time was also recorded.

Forty-five ICU patients from HRPZ II, Kelantan, were included in the model building and validation analysis. For the model building and validation, 30 patients and 15 patients were prospectively recruited, respectively. One steady-state sample was obtained from 15 patients for validation analysis.

The study was approved by the Medical Research Ethics Committee, Ministry of Health, Malaysia (NMRR-16-2229–33111). The protocols were in accordance with the Helsinki Declaration of 1975–1983.

Blood Sample Collection

Vancomycin was administered as a slow intravenous (IV) infusion not >1000 mg per hour. A pre-level sampling of the medication is routine ICU management. For the PK study, sparse blood samplings were taken with of at least one post-level additionally for each patient. Times of sampling were recorded. Blood samplings were taken after the third dose of vancomycin or after the first maintenance dose with a loading dose (steady-state achieved).

Measurement of Vancomycin Serum Concentrations

The blood samples were centrifuged and frozen at –20ºC until analysis could be performed. Determination of vancomycin was performed using the COBAS INTEGRA analyzer available in the pharmacy therapeutic drug monitoring unit according to the instructions provided in the manufacturer's manual.

Vancomycin PK Analysis

Vancomycin population PK was modeled with a non-parametric approach using Pmetrics software (version 5.0, Laboratory for Applied PK, Los Angeles, CA, USA) using the algebraic model solver.[9] Candidate models which included 1 - and 2 - compartment were fitted to vancomycin concentrations to determine the best structural models. The structural model was selected on the basis of minimizing Akaike information criterion (AIC). Bias (mean weighted predicted-observed error) and imprecision (bias-adjusted and mean weighted squared predicted-observed error) were also factored into the selection of the structural model.

Covariate Analysis

Once an appropriate structural model was obtained, influences of covariates were then investigated in the analysis. Changes in vancomycin PK can occur due to high individual variation. This variation can be described using a set of related covariates. Thus, covariate analysis processes help to detect the relationship between PK parameters and covariates of interest.

For screening and selection purpose, a multiple linear regression test was performed to explore the potential relationship between the following covariates with individual PK parameters: Age, weight, estimated creatinine CL Estimated creatinine clearance (eCLCr) calculated using the Cockcroft and Gault equation, aspartate aminotransferase (AST) level, ALT level, ALP level, albumin level, and

gender. PM-step is a function used in the Pmetrics program to estimate the linear regression of multivariate *P*-values for each covariate versus posterior parameter values. The covariates that were significantly associated with PK parameters were then introduced into the structural model.

In this study, weight and eCLCr were significantly associated with the volume of distribution (V) and CL, respectively. Both covariates were applied to V and CL parameters using the non-inverse approach according to the following equations:

For V parameter estimate:

V=V0*(Weight/average weight)

For CL parameter estimate:

CL = CL0*(eCLCr/average eCLCr)

The relevance of the covariates in the final model depended on comparing the values of AIC as well as the evaluation of the visual diagnostic scatterplots of goodness-of-fit that detects the observed versus predicted concentration based on bias, and imprecision.

Model Validation

Assessing and checking the effectiveness of the final model was carried out by applying internal and external validity techniques. The internal validation method used in the study is normalized prediction distribution errors (NPDE).

In the external validation group, the median of the individual Bayesian posterior distribution was obtained using the prior building dataset and was used to predict individual vancomycin CL. The reference vancomycin CL in this study was calculated using a single trough level based on the following equations[10] with the volume of distribution (Vd) of 0.41L/Kg: [11]

$$Ke=\ln\left(\frac{Dose/Vd + Cmin}{Cmin}\right) / Tau$$

CL=KeVd.

The Bland-Altman plot was used to compare the difference between predicted vancomycin CL with reference CL against the mean of both vancomycin CL.

RESULTS

Social Demographic and Clinical Characteristic of the Patients

The demographic and clinical characteristic of the patients for model building and validation groups are shown in Table 1.

Population Model

A total of 73 observations from 30 patients were included in the model building, while 19 observations from 15 patients were included in the validation analysis. The median observations for model building per patient were three with a minimum of one observation and a maximum of four observations per patient. Vancomycin PK in the critically ill patient was best described by a two-compartmental model [Figure 1].

Covariates Analysis

The covariates identified in the screening analysis, eCLCr and weight were incorporated into the structural model. However, it does not contribute to the decrement of the models' statistics compared to the structural model. Although the model with weight reduced the AIC value, the run, however, did not converge even after 10,000 cycles. Therefore, the structural model was chosen as the final model. The AIC, bias, and imprecision of the structural model and covariates models are shown in Table 2. The observation-prediction scatterplot for population and individual of the selected final model is shown in Figure 2. The full marginal distributions are shown in Figure 3. The scatterplot indicates no major bias in the model.

Internal Validation

The plot illustrating the NPDE is shown in Figure 4. The *t*-test was different from 0 (0.223), indicating a non-0 mean, the fisher variance test was 0.547, indicating a variance different from 1, and the Shapiro–Wilks test of normality was not significant (0.457), indicating that normality of data was not rejected and the distribution presents a normal distribution in the final model. These results testify the validity of the model.

External Validation

Validation of the model was performed from a total of 19 observations from 15 patients. The Bland-Altman plot

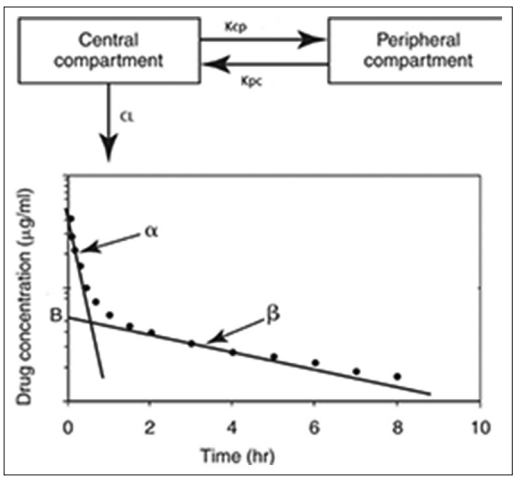

Figure 1: Plasma concentration versus time graph after intravenous administration of vancomycin. A two-compartment demonstrated with clearance from the central compartment

Table 1: Social demography and clinical characteristic of the patients

Variables	Model development group *n*=30		Validation group *n*=15		*P*-value
	n (%)	Mean±SD	*n* (%)	Mean±SD	
Gender					
Male	7 (23.33)		3 (20.0)		1.0[a]
Female	23 (76.67)		12 (80.0)		
Age (years)		49.29±15.89		47.27±17.10	0.697[b]
Weight (Kg)		72.43±20.28		73.73±25.92	0.854[b]
Serum creatinine		208.87±147.91		212.95±173.0	0.935[b]
eCLCr		56.16±49.47		53.82±44.84	0.878[b]
Alb level		19.15±4.09		21.0±3.74	0.149[b]
ALP level		415.25±661.21		179.43±120.83	0.180[b]
AST level		190.85±252.66		164.57±227.48	0.736[b]
ALT level		64.50±95.01		17.43±7.37	0.064[b]

[a]Fisher exact test, [b]Independent sample *t*-test. ALP: Alkaline phosphatase, AST: Aspartate aminotransferase, ALT: Alanine transaminase

Table 2: Statistics between models

Model	Covariates	AIC value	Likelihood	Population prediction		Individual prediction	
				Bias	Imprecision	Bias	Imprecision
1*	No covariates	328.6	317	−0.6882	6.4309	−0.13	0.312
2	eCLCr	386.7	375	0.1013	0.1498	3.24	4.75
3[#]	Weight	328.2	316.6	−0.4551	7.4151	−0.23	−0.38

*Structural model was chosen as the final model, [#]The run did not converge, AIC: Akaike information criterion

Table 3: Population parameter of vancomycin in the ICU patients

Parameter	Value	
	Mean±SD	Median
Volume of distribution of central compartment, V (L)	20.05±11.63	14.96
CL, CL (L/h)	1.64±0.68	1.72
Rate of constant from central out to the peripheral compartment, Kcp/h	2.92±1.67	2.81
Rate constant back from the peripheral to central compartment, Kpc/h	7.17±10.59	0.99

CL: Clearance, SD: Standard deviation, ICU: Intensive care unit

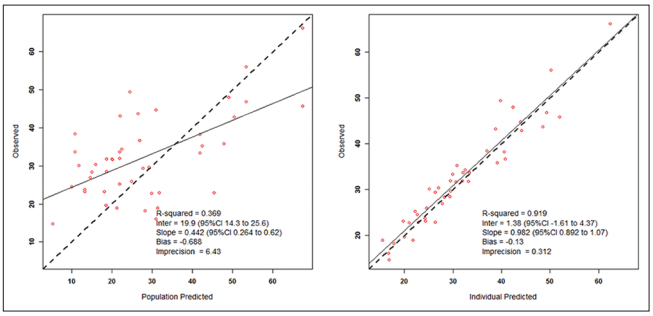

Figure 2: Observed-predicted plot of the final model

showed no structural bias because the plots are equally distributed within a 95% limit of agreement with calculated vancomycin CL [Figure 5].

Population estimates of the volume of distribution for central compartment (V), CL of vancomycin CL, the rate of constant from central out to the peripheral compartment (Kcp), and rate constant back from the peripheral to the central compartment (Kpc) are presented in Table 3. A summary of the PK data from previous studies investigating vancomycin in ICU is shown in Table 4.

DISCUSSION

Critically ill patients in ICU are those with any severe conditions that may cause deterioration, impairment or deficiency of at least one internal organ or physiology requiring invasive devices and progressive treatment with close monitoring and are at high risk of bacterial infections, including MRSA.[14] Current guidelines recommend that vancomycin trough serum concentration at a steady state should be maintained between 15% and 20 mg/L in critically ill ICU patients. In this study, with a standard dose given according to guidelines, approximately 70% of the ICU patients did not attain the recommended vancomycin trough concentration. Similarly, Dedkaew *et al*. found that 80% did not achieve the recommended trough in their Thai population. The changes in PK characteristics caused by pathophysiological changes are often seen in critically ill patients, which are a challenge for health-care providers to provide appropriate vancomycin dosage.

The published vancomycin reference PK parameters were derived from Western population data and occasionally

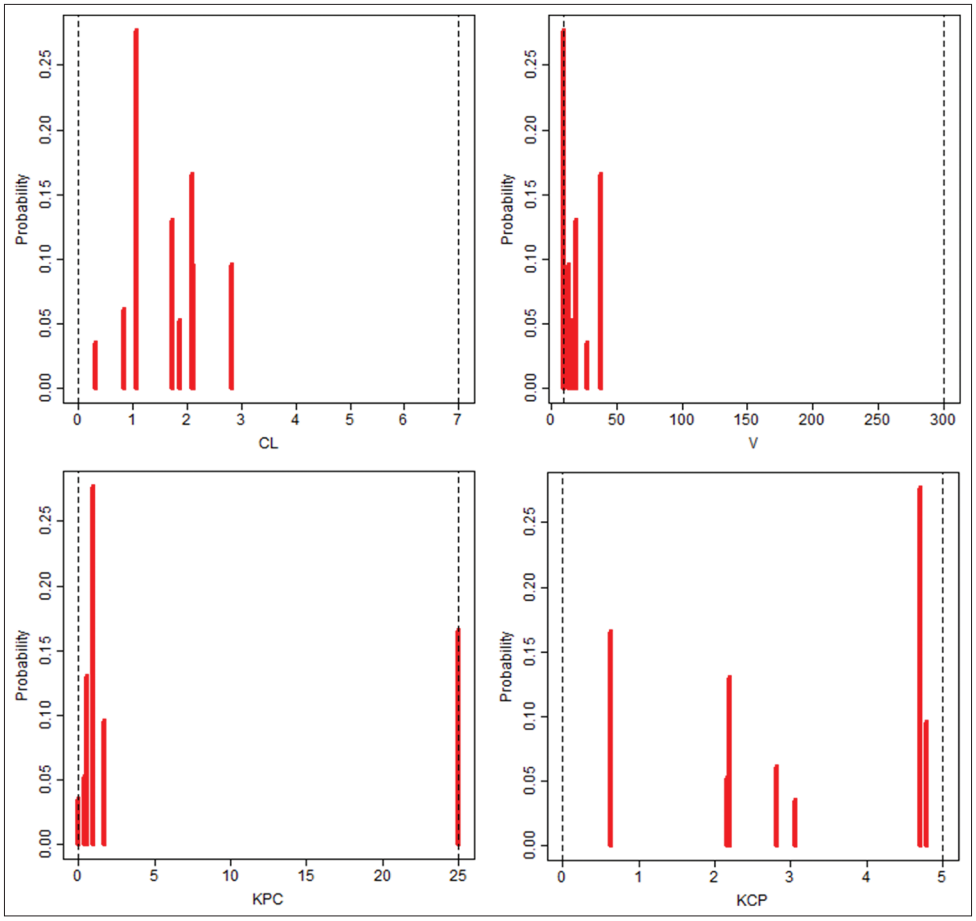

Figure 3: Marginal of parameter values in the final model

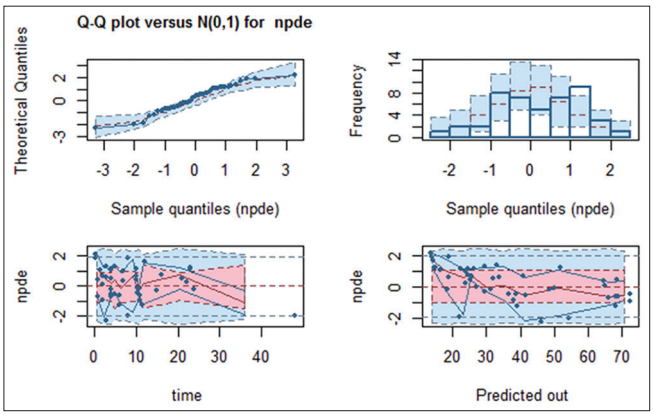

Figure 4: Graphs plotted by the package normalized prediction distribution errors for the final model. *t*-test: 0.223; Fisher variance test: 0.547; SW test of normality: 0.457; global adjusted $P = 0.67$.

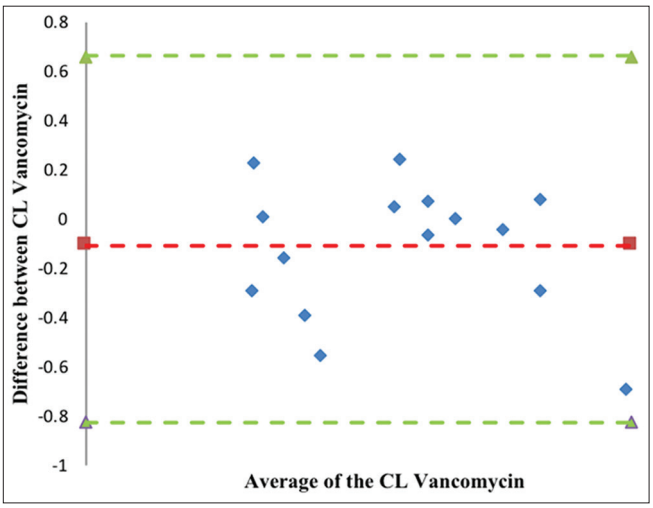

Figure 5: The Bland-Altman plot showing the difference between predicted vancomycin clearance (CL) with reference CL against the mean of both vancomycin CL. The dotted line showed a 95% limit of agreement between the CL vancomycin

constructed using computer-aided software and based on a multiple-compartment PK model.[12] Therefore, there is no certainty that the manual calculation is adequate to assist in the dosage adjustment. This study is the first vancomycin population PK modeling conducted in critically ill ICU patients in Malaysia. It was best described with the two-compartmental model, in agreement with other populations with a parametric approach.[11,15] The nonparametric approach permits the use of multiple model dosage design that develops maximally precise dosage regimens which hit a desired target serum concentration. However, the parametric approach is unable to do this because it does not use the entire model parameter distributions. Therefore, it cannot evaluate and maximize the expected precision with which the dosage regimen hits a clinically selected target goal. Moreover, Pmetrics calculates the likelihood

Table 4: Comparison of vancomycin PK parameters with previously published study in critically ill patients

Population	Study setting	Pkinetic analysis	Pkinetic Model	*n*	Age (years) mean±SD	Weight (kg) mean±SD	CLCr (ml/min) mean±SD	CL Vanco (L/h) mean±SD	V (L)	Vd (L/kg)	Reference
Malaysia	ICU	Nonparametric	2-compartment	30	49.3±15.9	72.4±20.3	56.2±49.7	1.64 (0.68)	20.05 (Vc)	0.31 (Vc)	Present study
Malaysia	ICU, HDU, CCU	Manual calculation	1-compartment	37	50.0±16.6	66.1±12.7	74.9±25.5	4.12±2.20		1.04	[12]
Thailand	ICU	Parametric	2-compartment	138	65.7±69	62.1±13.7	54.5±29.1	3.39	24.92 (Vc) 24.6 (Vp)	0.8	[13]
Spain	ICU	Parametric	2-compartment	30	67±27	75.0±12.5	70.2±33.3	3.46		0.41 (Vc) 1.32 (Vp)	[11]

Vc: Volume of central compartment, Vp: Volume of peripheral compartment, ICU: Intensive care unit, CCU: Coronary care unit, HDU: High dependency unit

function exactly and thus possesses statistical consistency in contrast to parametric approaches.[16,17] This is one of the significant strength regarding the clinical application of the approach in therapy. Multivariate analysis for covariates selection showed that weight and estimated creatinine CL contributed to the differences in the volume of distribution and CL of vancomycin, respectively. However, it was not significant enough to be retained in the final model.

The mean estimate of the vancomycin CL in this study was 1.64 L/h, approximately 2-time lower than reported by other studies in ICU patients. These may be explained by lower creatinine CL observed in the study population, which accounted for about 30% lower than other populations. Vancomycin undergoes glomerular filtration as the important route of excretion, and the rate of renal glomerular filtration is acceptably estimated by the creatinine CL.[18] Since the renal pathway is the major one for vancomycin excretion, this is not surprising to elicit creatinine CL as a significant factor for vancomycin CL. The CL is known to be positively correlated with the CL of creatinine.[19] This study observed a similar relationship (r^2 = 0.23, P = 0.01). Other than creatinine CL, the variability in the volume of IV fluid resuscitation and the administration of hemodynamic active drugs, such as dopamine, dobutamine, and diuretics, may explain the differences of the vancomycin CL.[20]

The vancomycin volume of distribution observed in the present study is lower than reported in the Malaysian and Thai populations, but similar to the reported Vc in Spain. However, it is still higher compared to Vc estimates for non-ICU patients with various degrees of renal function.[8] It is speculated that differences in the patient's body weight may have contributed to this observation. The body weight in the current study is similar to Spain but higher than other studies. It is known that vancomycin volume of distribution is associated with body weight[21,22] and the association was also detected in the current study (r^2 = 0.26, P = 0.005). However, the higher volume of distribution of vancomycin may also correspond to age or as a surrogate of their underlying disease.[23]

The differences of vancomycin PK parameters observed in the current study compared to other local populations by Makmor-Bakryi *et al.*, 2011, can be explained by the differences in the study design and PK analysis used. The present study is an observational study where sampling is obtained during routine therapeutic care and population PK modeling using software were employed, while Makmor-Bakryi *et al*. collected samples retrospectively and utilized manual calculation for PK parameters. Furthermore, the differences in the study settings may have contributed to this observation. The current study has

included subjects only from the ICU, but Makmor-Bakryi *et al*. had also recruited patients from the cardiac care and high dependency units.

CONCLUSION

Vancomycin PK profile in critically ill ICU patients in Malaysia was best described by a two-compartment model. However, vancomycin CL and volume of distribution were lower compared to other ICU populations due to differences in patients' demographic and clinical parameters. Significant covariates affected vancomycin PK identified include body weight and estimated creatinine CL, but both covariates were not significant enough to be retained in population modeling. The model might be used in initiating a vancomycin dosage regimen in the type of patient similar to the present study.

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