Initial Dosage Regimen of Vancomycin for Septic Shock Patients: A Pharmacokinetic Study and Monte Carlo Simulation

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Objective: *To evaluate the pharmacokinetic parameters of vancomycin in septic shock patients and to determine the vancomycin dosage to achieve requisite pharmacokinetic/pharmacodynamic (PK/PD) target against methicillin resistant Staphylococcus aureus (MRSA) in patients with septic shock.*

Material and Method: *Pharmacokinetic parameters of vancomycin in 12 septic shock patients were assessed. Then, the Monte Carlo simulation was performed to calculate the probabilities of target attainment (PTAs) to reach target AUC_{0-24}/MIC of 400 and 450 mg•h/L.*

Results: *The total clearance (CL) and the volume of the central compartment (Vc) of vancomycin was 3.34±1.39 L/h and 0.14±1.43 L/kg, respectively. For Staphylococcal spp. with low MICs of 0.125 and 0.5 mg/L, the administration of vancomycin 30 mg/kg as the loading dose, followed by the maintenance dose of 20 mg/kg every six, eight, 12, and 24 hours achieved >90% PTAs to reach target AUC_{0-24}/MIC. For pathogens with MIC of 1, and 1.5 mg/L, the vancomycin maintenance dose of 20 mg/kg every six, eight, and 12 hours and every six and eight hours respectively to achieve >90% PTA.*

Conclusion: *High dose of vancomycin is required to achieve PK/PD target for treatment of MRSA septic shock, especially if MRSA MIC is higher than 1 mg/L.*

Keywords: *Monte Carlo simulation, Vancomycin, septic shock, Pharmacokinetics/pharmacodynamics, Loading dose*

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Septic shock is associated with high morbidity and mortality[1]. Methicillin-resistant *Staphylococcus aureus* (MRSA) is among the common nosocomial pathogens that cause septic shock. Currently, vancomycin is the drug of choice for invasive MRSA infections[2]. The pharmacokinetics/pharmacodynamics (PK/PD) index that best correlated with the good clinical efficacy of vancomycin for treatment of invasive MRSA infections is AUC_{0-24}/MIC ratio of ≥400 mg•h/L[3].

The early initiation of appropriate empirical antimicrobial therapy is crucial for septic shock patients. A retrospective study conducted in 2,154 septic shock patients found that delays in the initiation of appropriate antimicrobial therapy had a strong correlation with in-hospital mortality[4]. Septic shock has been known to cause sudden changes in patient pathophysiology, including increase in capillary permeability, edema formation, vasodilation, and hypotension[5]. The pharmacokinetics of vancomycin may be altered in response to septic shock even without significant organ dysfunction. The volume of distribution (Vd) and clearance (CL) may increase, and consequently the serum concentration may decrease. Decreasing the vancomycin serum concentration could diminish the chances of achieving the target AUC_{0-24}/MIC ratio of ≥400 mg•h/L, consequently, may lead to the development of antibiotic resistance and/or therapeutic failure[6]. To our knowledge, limited data is available

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concerning the pharmacokinetic profiles and the dosage requirements of this drug in this specific group of patients. Therefore, the authors conducted the present study to evaluate the pharmacokinetic parameters of vancomycin in septic shock patients and to assess, by Monte Carlo simulation, the vancomycin dosages required to achieve the probability of attaining a target PK/PD index in septic shock patients.

Material and Method

Subjects

The present study was conducted in patients under septic shock admitted to Songklanagarind Hospital, an 850-bed university-affiliated hospital located in Southern Thailand between October 2012 and January 2013. The research protocol was approved by the Ethic Committee of Songklanagarind Hospital and written informed consent was obtained from each patient. The patients were included in the present study if they met the following criteria, (1) older than 18 years, (2) have more than two of the following four clinical findings: (i) heart rate >90 beats/minute; (ii) respiratory rate >20 breaths/minute or arterial partial pressure of carbon dioxide (PCO_2) <32 mmHg; (iii) core temperature <36°C or >38°C; and (iv) white blood cell (WBC) count <$4x10^9$ or >$12x10^9$ cells/L or >10% immature (band) forms, (3) develop persistent hypotension, which was defined as SBP <90 mmHg, MAP <60 mmHg or decreasing of SBP 40 mmHg from baseline despite adequate volume resuscitation, (4) absence of other causes for hypotension, and (5) require empirical vancomycin in the setting of suspected MRSA infection. The patients that had prior exposure (within seven days) to iv vancomycin, were on hemodialysis or other renal replacement therapy, were pregnant, had suffered burns, had hematologic malignancy, or had a history of hypersensitivity to vancomycin were excluded from the study.

Data collection

The data carefully recorded for each patient were age, gender, main diagnosis and the Sequential Organ Failure Assessment (SOFA) score within 24 hours after admission to the hospital. The total body weight, mechanical ventilation status, nutritional support, fluid balance, serum albumin, and creatinine clearance (CL_{CR}) estimated according to the Cockroft and Gault[7]. Concurrent administration of diuretics and vasoactive drugs were recorded within 24 hours of the onset of the shock.

Drugs and chemicals

Vancomycin (Vancin-S®) used in this study was manufactured by Siam Pharmaceuticals, Thailand.

Study design

This was a pharmacokinetic and pharmacodynamic study.

Drug administration and dosage

Vancomycin was reconstituted according to the manufacturer's guidelines. It was diluted into preparations of 1 g in 100 mL of normal saline solution. Each subject received vancomycin-loading dose of 30 mg/kg based on actual body weight via central line (2-hour-infusion). A subsequent dose was calculated according to patient renal function and given 12 hours apart from the loading dose. Those patients with CL_{CR} ≥80 mL/min received 1 g of vancomycin (2-hour-infusion). Those patients who had CL_{CR} <80 mL/min received the reduced subsequent dose according to the nomogram suggested by Moellering et al[8].

Blood sampling

For the loading dose regimen, blood samples of approximately 2.5 mL were obtained by direct venepuncture at 0, 30, 60, 120, 130, 140, 160, 180, 210, 240, 360, 540, and 720 minutes. For the maintenance regimen, blood samples of approximately 2.5 mL were obtained by direct venepuncture at 0, 120, 180, 360, and 720 minutes. All the blood samples were allowed to clot and then centrifuged at 2,000 rpm. The serum was stored at -80°C until analysis time.

Vancomycin assays

Serum concentrations of vancomycin were determined by fluorescence polarization immunoassay (AxSYM; Abbott Laboratories, Abbott Park, IL60064, USA). A quantitative control of vancomycin was done in the hospital laboratory in October 2012. The lower limit of detection of vancomycin was 1.29 mg/L and the controls used in this assay had mean vancomycin concentration of 6.94 (low), 19.74 (medium), and 36.45 (high) mcg/mL, respectively. The controls were run 20 times in one day of yielded within run coefficients of variation (CV). The intra-assay reproducibility values characterized by CVs were 3.34%, 3.24%, and 2.37%, respectively. The inter-assay reproducibility precision values, calculated by CVs, were 6.77%, 4.86% and, 4.64%, respectively.

Pharmacokinetic data analyses

Pharmacokinetic parameters were derived from a two-compartment infusion model. The differential equations used in the study were solved numerically by using the Taylor series expansion method[9] until convergence. The vancomycin pharmacokinetic parameters were obtained by non-linear regression to minimize the sum square errors (SSEs) objective function by random heuristic optimization algorithm, as described elsewhere[10,11].

$$\text{Obj} = \text{minimize} \sum_{i=1}^{n} (Y(i)_{actual} - Y(i)_{calc})^2$$

where $Y(i)_{actual}$ and $Y(i)_{calc}$ are the observed and calculated concentrations, respectively. n is the number of data points.

All the calculations were performed in Microsoft Excel spreadsheets (Microsoft Corp., Redmond, WA).

Pharmacodynamic assessment using Monte Carlo simulation

The simulation of the two-compartment model was performed according to the following protocol:

A set of pharmacokinetic parameters was generated by Box-Muller transform[12] as normal distribution generator and was transformed into log-normal distribution and selected numerically to ensure that their averages, standard deviations, and covariance were comparable with the actual parameter, with no statistical significance.

Such generated parameters were used to simulate the concentration-time profile by using the Runge-Kutta order 4 algorithm[13] in BASIC language and compiled with QB compiler version 3.0 (QB is a product of Microsoft Corporation) to create an executable program.

We used 10,000 simulations to identify the behavior of AUC_{0-24}/MIC ratio at 400 and 450 mg•h/L. The probability of the target attainment (PTA) was reported from the simulated result.

The nephrotoxicity risk related to C_{trough}, described in a retrospective study by Bosso et al[14] was empirically modeled in our study by using the logistic regression model, as follows:

$$R = \text{Log (odd ratio of risk)}$$
$$= 0.6835293\text{-}19.98727/C_{trough} \text{ (mg/L)}$$
$$C_{trough} \text{ risk probability} = 10^R/(1+10^R)$$

This risk-describing model was used in modeling the simulated concentration time profile of vancomycin. The trough concentration of the third dose was used in the calculation of the nephrotoxicity risk in each simulated patient. The overall risk was averaged from all the 10,000 simulations.

Results

Twelve patients were enrolled in the present study (nine males and three females), with a mean age of 57.25±18.75 years (range 26-86 years), a mean body weight of 62.42±8.84 kg (range 50-80 kg) and a mean CL_{CR} of 58.08±33.83 mL/min (range 22-109 mL/min). Two patients died during therapy received only the loading dose. All patients required vasopressor support. The characteristics of all the patients and the regimens of vancomycin were shown in Table 1. The population pharmacokinetic parameters of vancomycin were presented in Table 2. All of the tested covariates had no identifiable influence on the pharmacokinetic parameters, except between k_{12} and k_{el} of vancomycin (Appendix A). The PTAs of vancomycin to reach the target AUC_{0-24}/MIC of 400 and 450 mg•h/L at specific MICs were presented in Table 3, 4, and 5. Administration of 30 mg/kg loading of vancomycin, followed by maintenance dose of 20 mg/kg every 6, 8, 12, and 24 hours in patients with CL_{CR} of 0-120 mL/min achieved >90% PTAs against MRSA isolates with MIC of 0.125-0.5 mg/L. For MRSA isolates with MIC of 1 mg/L, the maintenance dose needed to be 20 mg/kg every 6, 8, and 12 hours to achieve >90% PTAs in patients with CL_{CR} of 0-120 mL/min. Administration of maintenance dose of 20 mg/kg every six and eight hours was required in patients with CL_{CR} of 0 to 120 mL/min to achieve >90% PTAs for MRSA with MIC of 1.5 mg/L. For pathogens with high MIC of 2 mg/L, to achieve >90% PTAs the maintenance dose needed to be 20 mg/kg every six hours in only those patient with CL_{CR} of 0-30 mL/min; the other regimens were not able to reach the target at 90%.

Discussion

The total clearance (CL) of vancomycin in septic shock patients presented in the present study (CL = 3.34±1.39 L/h) was higher than that obtained from non-septic shock patients from other studies (CL = 1.46±0.88 L/h)[15] even though the majority of the patients in the present study (seven out of 12 patients) had acute kidney injury. Our data is supported by the study that was conducted on critically ill patients with acute kidney injury[16]. The results from that study (the CL of vancomycin ranged from 17.1 to 36.6 ml/min) suggested that in the early phase of acute

Table 1. Patient characteristics

Patient	Gender	Age (years)	Weight (kg)	Serum creatinine (mg/dL)	CL_{CR} (mL/min)	SOFA score	Loading dose (mg)	Maintenance dose (mg)	Diagnosis
1	M	79	50	1.28	33	9	1,500	500	Infected wound
2	M	86	50	1.26	30	15	1,500	500	HAP
3	M	41	80	4.01	27	19	2,400	300	Deep neck infection
4	M	57	67	0.99	78	13	2,000	1,000	VAP
5	F	66	65	1.52	34	10	2,000	500	Bacteraemia
6	F	55	60	0.62	96	13	1,800	-	Bacteraemia
7	M	50	68	1.61	53	9	2,000	700	Infected wound
8	M	26	57	0.83	109	10	1,700	1,000	VAP
9	F	81	57	1.59	25	18	1,700	500	Carotid space abscess
10	M	61	60	3.01	22	18	1,800	-	VAP
11	M	52	62	0.71	100	13	1,800	1,000	VAP
12	M	33	73	1.19	90	13	2,200	1,000	Meningitis

F = female; M = male; VAP = ventilator-associated pneumonia; HAP = hospital acquired pneumonia; CL_{CR} = creatinine clearance (determined by the Cockcroft-Gault method)[12]; SOFA = sepsis-related organ failure assessment

Table 2. Comparison of actual and simulated pharmacokinetic (PK) parameters of vancomycin in 12 septic shock patients

PK parameter	Geometric mean	Geometric SD	Median (95% CI)	Geometric %CV
Actual PK parameter				
k_{12} (h^{-1})	2.393	1.603	2.695 (1.063-4.269)	66.987
k_{21} (h^{-1})	0.665	1.300	0.657 (0.484-1.140)	195.489
k_{el} (h^{-1})	0.374	1.666	0.436 (0.131-0.666)	445.455
CL (L/h)	3.339	1.392	3.695 (1.916-5.540)	41.689
V_c (L)	8.526	1.502	8.363 (4.532-16.754)	17.617
V_c (L/kg)	0.138	1.433	0.133 (0.087-0.262)	1,038.406
Simulated PK parameter				
k_{12} (h^{-1})	2.399	1.604	2.399 (0.954-6.109)	66.861
k_{21} (h^{-1})	0.666	1.300	0.666 (0.401-1.107)	195.195
k_{el} (h^{-1})	0.375	1.669	0.373 (0.136-1.039)	445.067
CL (L/h)	2.579	1.514	2.570 (1.156-5.816)	58.705
V_c (L)	6.883	1.432	6.897 (3.440-13.940)	20.805

SD = standard deviation; CI = confidence interval; k_{12} = intercompartmental transfer rate constant from compartment X_1 to X_2; k_{21} = intercompartmental transfer rate constant from compartment X_2 to X_1; k_{el} = elimination rate constant from X_1; CL = total clearance; V_c = volume of distribution central compartment

kidney injury, a substantial portion of the non-renal clearance of vancomycin was preserved[16]. The volume of the central compartment (Vc) (Table 2) in the present study (Vc = 0.14 L/kg) seemed to be less than that determined by Llopis-Salvia et al[17] (Vc = 0.41 L/kg). However, Polard et al[18] reported a similar result as the present study with the vancomycin Vc of 0.19 L/kg in population of critically ill patients. Moreover, Polard et al[18] found that a significant increase (around 30%) in vancomycin Vc was observed between the first day of vancomycin administration (Day 1) and at steady-state (Day 3). The different value of Vc between the present study and Llopis-Salvia et al[17] can be explained by the reason that their study obtained Vc at the steady state whereas, the present study investigated the vancomycin pharmacokinetic during the first 24 hours of vancomycin therapy. The data of vancomycin pharmacokinetic parameter in Thai population, especially critically ill patients is limited. Purwonugroho et al[19] conducted the study to determine pharmacokinetic parameters of vancomycin in Thai adult patients (about one third of patients were in ICU).

Table 3. Probability of target attainment (PTA) to reach the target vancomycin AUC_{0-24}/MIC of 400 and 450 mg•h/L for treatment of MRSA infection with MIC 0.5 mg/L

CL_{CR} (ml/min)	Predicted C_{trough} (mg/L)	Predicted nephrotoxicity (%)	PTA of AUC/MIC ≥400 (%)	PTA of AUC/MIC ≥450 (%)	Dosing interval (hour) after LD*
0-15	48.80	62.27	100	100	6
	36.08	52.37	100	100	8
	23.05	33.80	100	100	12
	6.44	3.25	97.27	94.24	24
	1.42	0.12	62.97	50.71	48
15-30	49.68	62.51	100	100	6
	36.23	52.09	100	100	8
	24.27	36.03	100	100	12
	6.37	3.16	96.63	92.99	24
	1.57	0.14	73.38	61.89	48
30-60	49.11	61.85	100	100	6
	37.93	53.74	100	100	8
	21.16	30.73	100	99.99	12
	9.40	8.16	99.82	99.48	24
	1.49	0.13	66.56	54.96	48
60-120	40.70	57.46	100	100	6
	37.71	53.55	100	100	8
	21.38	30.90	99.99	99.97	12
	6.96	4.07	97.79	95.67	24
	1.69	0.18	78.00	68.23	48

PTA = probabilities of target attainment; MRSA = methicillin resistant *Staphylococcus aureus*; LD = loading dose
* 30 mg/kg loading, followed by 20 mg/kg subsequent dose to complete 24 hours of treatment

Table 4. Probability of target attainment (PTA) to reach the target vancomycin AUC_{0-24}/MIC of 400 and 450 mg•h/L for treatment of MRSA infection with MIC 1.0 mg/L

CL_{CR} (ml/min)	Predicted C_{trough} (mg/L)	Predicted nephrotoxicity (%)	PTA of AUC/MIC ≥400 (%)	PTA of AUC/MIC ≥450 (%)	Dosing interval (hour) after LD*
0-15	48.80	62.27	100	100	6
	36.08	52.37	99.91	99.74	8
	23.05	33.80	98.05	95.69	12
	6.44	3.25	47.20	33.48	24
	1.42	0.12	6.02	2.97	48
15-30	49.68	62.51	100	99.99	6
	36.23	52.09	99.85	99.55	8
	24.27	36.03	98.95	97.53	12
	6.37	3.16	44.40	31.28	24
	1.57	0.14	10.53	5.52	48
30-60	49.11	61.85	99.99	99.96	6
	37.93	53.74	99.95	99.79	8
	21.16	30.73	96.77	93.43	12
	9.40	8.16	83.28	74.24	24
	1.49	0.13	8.71	4.66	48
60-120	40.70	57.46	100	99.92	6
	37.71	53.55	99.92	99.72	8
	21.38	30.90	96.53	93.01	12
	6.96	4.07	55.29	41.70	24
	1.69	0.18	15.45	9.05	48

PTA = probabilities of target attainment; LD = loading dose
* 30 mg/kg loading, followed by 20 mg/kg subsequent dose to complete 24 hours of treatment

Table 5. Probability of target attainment (PTA) to reach the target vancomycin AUC_{0-24}/MIC of 400 and 450 mg•h/L for treatment of MRSA infection with MIC 1.5 mg/L

CL_{CR} (ml/min)	Predicted C_{trough} (mg/L)	Predicted nephrotoxicity (%)	PTA of AUC/MIC ≥400 (%)	PTA of AUC/MIC ≥450 (%)	Dosing interval (hour) after LD*
0-15	48.80	62.27	99.76	99.08	6
	36.08	52.37	97.05	93.22	8
	23.05	33.80	80.56	69.64	12
	6.44	3.25	9.37	4.34	24
	1.42	0.12	0.33	0.10	48
15-30	49.68	62.51	99.72	99.07	6
	36.23	52.09	96.05	91.69	8
	24.27	36.03	86.75	77.46	12
	6.37	3.16	8.53	3.90	24
	1.57	0.14	0.76	0.24	48
30-60	49.11	61.85	99.21	97.98	6
	37.93	53.74	97.52	94.34	8
	21.16	30.73	74.15	60.74	12
	9.40	8.16	43.36	30.18	24
	1.49	0.13	0.61	0.21	48
60-120	40.70	57.46	98.44	95.81	6
	37.71	53.55	97.27	93.67	8
	21.38	30.90	73.07	60.15	12
	6.96	4.07	13.82	7.49	24
	1.69	0.18	1.74	0.71	48

PTA = probabilities of target attainment; LD = loading dose
* 30 mg/kg loading, followed by 20 mg/kg subsequent dose to complete 24 hours of treatment

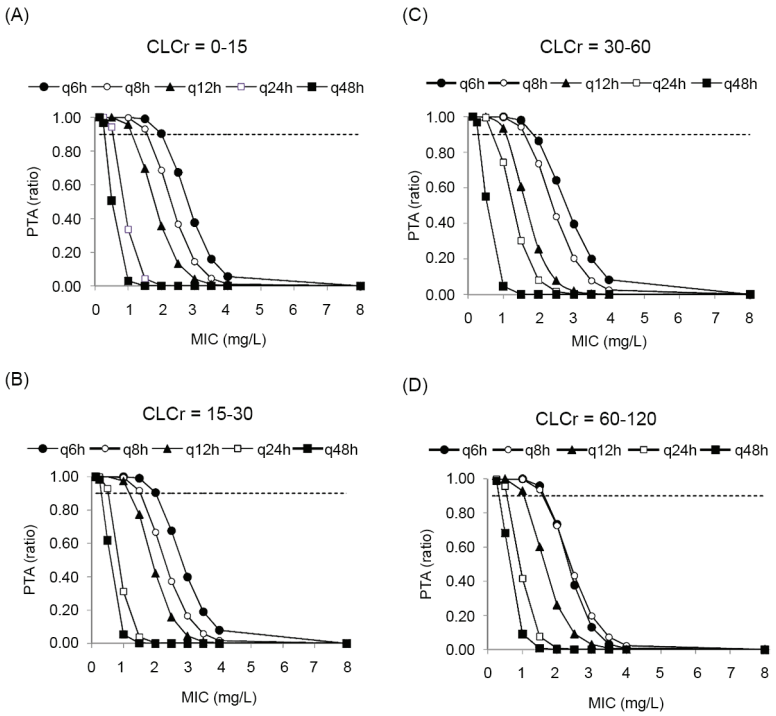

Fig. 1 Probability of target attainment (PTA) of reaching the target vancomycin AUC_{0-24}/MIC of 450 mg•h/L classified according to CL_{CR}: (A) CL_{CR} = 0-15 mL/min; (B) CL_{CR} = 15-30 mL/min; (C) CL_{CR} = 30-60 mL/min; and (D) CL_{CR} = 60-120 mL/min following 30 mg/kg loading, and 20 mg/kg subsequent dose every 6, 8, 12, 24, and 48 hours.

This study obtained Vc at the steady state concentration. The vancomycin Vc was estimated 0.63 L/kg, which was higher than vancomycin Vc obtained from the present study.

Achieving the PK/PD target was likely to be very important for optimizing the clinical efficacy of vancomycin. The PK/PD parameter that is best correlated with the efficacy of vancomycin is the AUC_{0-24}/MIC. A study conducted by Moise-Broder et al[3] showed that in patients with lower respiratory tract infections, vancomycin AUC_{0-24}/MIC values of ≥400 mg•h/L correlated well with good clinical and bacteriological response. A more recent investigation by Zelenitsky et al[20] reported increased survival rates in patients with MRSA-associated septic shock who had AUC_{0-24}/MIC ≥451 mg•h/L compared to those with AUC_{0-24}/MIC <451 mg•h/L. Similar to the result of our study, the results of the several Monte Carlo simulation studies reveal that higher than standard dosage of vancomycin (15-20 mg/kg every 8-12 hours or approximately 2,000 mg/day) may be necessary to reach the highest probability of efficacy when the vancomycin MICs of susceptible *S. aureus* strains increase[2,21]. The simulation data by Roberts et al[22] shown that a loading dose of at least 35 mg/kg would have been necessary to rapidly achieve vancomycin concentrations of 20 mg/liter within a few hours from the onset of infusion. A study conducted in adult critically ill patients found that to achieve the target AUC_{0-24}/MIC ≥400 mg•h/L, the recommended dose of the vancomycin-susceptible *S. aureus* needed to be high. Initial dose of 2,000 mg/day was required for patients with CL_{CR} <60 ml/min[21]. In the patients with better kidney function, the corresponding doses must be increased to 3,000 and 3,500 mg/day[21]. Further investigations conducted in the ICU patients revealed that, doses of 3,000 mg or even 4,000 mg daily may be necessary to reach the highest probability of AUC_{0-24}/MIC ≥400 mg•h/L[2].

The present study differed from those previous studies in several aspects. First, we recruited only specific group of critically ill patients with septic shock. Second, this was the first PK study of vancomycin in Thai septic shock patients, which may display altered PK behavior from the previous study conducted in other patient group. Third, the authors performed vancomycin PK/PD study in the first 24 hours of the septic shock. This was probably the first article that specifically investigated PK during the first 24 hours of therapy. In addition, the authors used AUC_{0-24}/MIC value of 450 mg•h/L as our target to reach more than 90% PTA which was one of the prime reasons that could explain why the recommended dose was higher than that suggested in the previous studies. In fact, the application of high dose, as recommended by the present study, should be practiced only when the patient was in the early phase of the septic shock.

An in vitro study of 96 *S. aureus* isolates at Songklanagarind Hospital collected between 2011 and 2012 demonstrated vancomycin MIC_{90} of 1 mg/L. Based on this data, we recommend the dosage for empirical treatment of patients under septic shock who are suspected of infection with MRSA to be 30 mg/kg loading, followed by a maintenance dose of 20 mg/kg every 12 hours in patients with CL_{CR} 0 to 120 mL/min. This recommended dosage should be weighed for risk, and it will be beneficial to conduct a close monitoring of the drug level. The authors suggest that 24 hours after this, the dosage and the interval should depend on the drug level and must be repeated throughout the patient's hospital course, especially for patients with acute renal failure. In the institutes that serum vancomycin concentration cannot be measured, vancomycin subsequent dosing should be adjusted based on the renal function for each patient. As for the other teaching hospitals in our country, a large tertiary-care university hospital demonstrated that the MIC_{90} of vancomycin against MRSA was 2 mg/L; hence, based on our PK/PD data, we do not recommend the use of vancomycin for empirical therapy in patients who are suspected to have invasive MRSA infections.

Since a very high dose of vancomycin is required to achieve a PTA of more than 90%, it is not free of a high risk of developing nephrotoxicity. In the present study, the percentages of the incidence of nephrotoxicity calculated by using the logistic regression model were approximately 60%, 50%, 30%, 3%, and 0.10%, which correlated with C_{trough}, following the administration of vancomycin 30 mg/kg loading followed by a maintenance with 20 mg/kg every 6, 8, 12, 24, and 48 hours, respectively. The present study has some limitations that must be considered. First, the small sample size could be considered a potential limitation. The patients under septic shock who had complicated conditions and unstable hemodynamics might confound the result since the sample size was not large enough to elucidate such effect. Secondly, the Cockcroft-Gault method used for estimating CL_{CR} in our study was known to have certain limitations in critically ill patients with acute kidney injury[23-25]. A study conducted in adult critically ill patients found that all the GFR estimating

equations used in the present study, the Cockcroft Gault (CG), the Modification of Diet in Renal Disease (MDRD), and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equations, performed poorly when compared to infusion clearance of Cr-EDTA in this group of critically ill patients with early acute kidney injury (AKI)[26]. However, the utilization of the Cockcroft-Gault equation as used clinically results in more accurate predictions of glomerular filtration rate in the critically ill patient than urine creatinine clearance measure[27]. Third, the risk model for nephrotoxicity in the present study was projected from limited data from only one study, which was conducted by Bosso et al[14], and only a few conditions were available for performing logistic regression. Fourth, the present study was conducted in patients with septic shock. The implementation should be generalizable for the same type of population elsewhere. Fifth, the limitation was in using a two-compartment model. From our limited data set, some patient data showed that a two compartment was not the best model. However, in order to obtain consistency, a two compartment was used. This did mean that the prediction of concentration in the terminal phase might not be very reliable. However, since the parameter of interest was AUC which was robust, i.e., could be described by the non-compartmental method, the authors believe that this limitation is not severe[9].

Conclusion

The total clearance of vancomycin was increased in the early phase of septic shock. The dosage of vancomycin for the treatment of septic shock patients should be higher than the standard dosage regimen in order to achieve the expected therapeutic result if the MRSA MIC is higher than 1 mg/L. Alternative therapies such as linezolid or daptomycin should definitely be considered in MRSA with high vancomycin MIC of ≥2 mg/L.

What is already known on this topic?

The previous study conducted in adult critically ill patients and evaluated at steady-state drug concentrations found that, to achieve the target AUC_{0-24}/MIC ≥400 mg•h/L, the recommended dose of the vancomycin-susceptible *S. aureus* needed to be high. Initial dose of 2,000 mg/day was required for patients with CL_{CR} <60 ml/min. In the patients with better kidney function, the corresponding doses must be increased to 3,000 and 3,500 mg/day[21]. Further investigations conducted in the ICU patients revealed that, doses of 3,000 mg or even 4,000 mg daily may be necessary to reach the highest probability of AUC_{0-24}/MIC ≥400 mg•h/L[2]

What this study adds?

The majority of pharmacokinetic/pharmacodynamic (PK/PD) discussions have focused on PK/PD relationships, evaluated at steady-state drug concentrations. However, a concern with reliance on steady-state drug concentrations is that it ignores events occurring while the pathogen is exposed to intermittent suboptimal systemic drug concentrations prior to the attainment of a steady state.

This study evaluated vancomycin PK/PD data of patients with septic shock to explore optimal dosage in the first 24 hours of the septic shock. We think the data are valuable because we got PK/PD data from very specific population and few paper have evaluated the data of the population.

To our knowledge, limited data is available concerning the pharmacokinetic profiles and the dosage requirements of this drug in this specific group of patients. Therefore, we conducted this study to evaluate the pharmacokinetic parameters of vancomycin in septic shock patients and to assess, by Monte Carlo simulation, the vancomycin dosages required to achieve the probability of attaining a target PK/PD index in septic shock patient

Our study differed from previous studies in several aspects. First, we recruited only specific group of critically ill patients with septic shock. Second, this is the first PK/PD study of vancomycin in Thai septic shock patients, which may display altered PK behavior from the previous study conducted in other patient group. Third, we performed vancomycin PK/PD study in the first 24 hours of the septic shock and this is probably the first article that specifically investigates PK during the first 24 hours of therapy. In addition, we used AUC_{0-24}/MIC value of 450 mg•h/L as our target to reach more than 90% PTA, which was one of the prime reasons that could explain why the recommended dose was higher than that suggested in the previous studies.

This is the pharmacokinetic study of vancomycin in a Thai population. This may be interesting, as the other population pharmacokinetic studies are all performed in Western countries. These patients generally have a larger body weight that may influence volume of distribution, which may influence pharmacokinetic target attainment.

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Potential conflicts of interest

None.

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Appendix A. Comparison of covariance matrices between the actual and the simulated pharmacokinetic parameters[a]

Parameter	Actual	Simulated
k_{12}-k_{21}	0.244	0.244
k_{12}-k_{el}	0.822	0.822
k_{12}-V_c	-0.765	-0.765
k_{12}-CL	-0.059	-0.046
k_{21}-k_{el}	0.234	0.234
k_{21}-V_c	0.023	0.023
k_{21}-CL	0.309	0.309
k_{el}-V_c	-0.577	-0.578
k_{el}-CL	0.235	0.235
V_c-CL	0.159	0.171

k_{12} = intercompartmental transfer rate constant from compartment X_1 to X_2; k_{21} = intercompartmental transfer rate constant from compartment X_2 to X_1; k_{el} = elimination rate constant from X_1; V_c = volume of distribution central compartment; CL = total clearance

[a] The covariances are not statistically different at $\alpha = 0.10$

การให้ยา vancomycin ในขนาดเริ่มต้นในผู้ป่วย septic shock: การศึกษาเภสัชจลศาสตร์ และ Monte Carlo simulation

วสันต์ กาติ๊บ, สุเทพ จารุรัตนศิริกุล, สุทธิพร ภัทรชยากุล, วิบูลย์ วงศ์ภูวรักษ์, อานุไร จิตต์สุรงค์

วัตถุประสงค์: *การศึกษานี้มีวัตถุประสงค์เพื่อศึกษาหาค่าเภสัชจลนศาสตร์ของยา vancomycin และประเมินหาขนาดยา vancomycin เริ่มต้นในการเพิ่มความน่าจะเป็นที่จะได้เป้าหมายที่ต้องการ (proability target attatinment, PTA) ของค่าเภสัชจลนศาสตร์ เภสัชพลศาสตร์ สำหรับการรักษาการติดเชื้อเชื้อ MRSA ในผู้ป่วยที่มีภาวะ septic shock*

วัสดุและวิธีการ: *ทำการศึกษาแบบเภสัชจลนศาสตร์ เริ่มจากการเจาะวัดระดับยา vancomycin ในเลือดของผู้ป่วยจำนวน 12 ราย จากนั้นจึงนำค่าดังกล่าวที่ได้มาคำนวณหาค่าพารามิเตอร์ทางเภสัชจลนศาสตร์ แล้วใช้วิธี Monte Carlo simulation เพื่อหาค่า PTA ให้ได้เป้าหมายของค่าเภสัชพลศาสตร์คือมีค่า AUC24/MIC ≥400 และ ≥450 มิลลิกรัม•ชั่วโมง/ลิตร*

ผลการศึกษา: *พบว่าค่า total clearance (CL) และ volume of the central compartment (Vc) ของยา vancomycin เป็น 3.34±1.39 ลิตร/ชั่วโมง และ 0.14±1.43 ลิตร/ชั่วโมง ตามลำดับ เชื้อ MRSA ที่มี MIC ต่อยา vancomycin เท่ากับ 0.125 ไมโครกรัม/มิลลิลิตร และ 0.5 ไมโครกรัม/มิลลิลิตร จะได้ค่า PTA มากกว่าร้อยละ 90 ที่จะได้เป้าหมาย AUC24/MIC เมื่อให้ยา vancomycin แบบ loading ในขนาด 30 มิลลิกรัม/กิโลกรัม หยดเป็นเวลา 2 ชั่วโมง หลังจากนั้นทุก 6, 8, 12 และ 24 ชั่วโมง กรณีที่มีค่า MIC ของเชื้อเท่ากับ 1 ไมโครกรัม/มิลลิลิตร และ 1.5 ไมโครกรัม/มิลลิลิตร เมื่อให้แบบ maintenance ทุก 6, 8 และ 12 ชั่วโมง และ ทุก 6 และ 8 ชั่วโมง ตามลำดับ จะได้ค่า PTA มากกว่าร้อยละ 90*

สรุป: *แนะนำให้ยา vancomycin ในขนาดสูง เพื่อให้ได้เป้าหมาย PTA ของค่าเภสัชจลนศาสตร์เภสัชพลศาสตร์ โดยเฉพาะอย่างยิ่งหากเชื้อ MRSA มีค่า MIC มากกว่า 1 ไมโครกรัม/มิลลิลิตร*