Vancomycin Dosing Regimen by Monte Carlo Simulation in Patients on Intermittent High-Efficiency Hemodialysis (HEHD)

Daraporn Rungprai B Pharm*,**, Sutep Jaruratanasirikul MD***,
Wibul Wongpoowarak MSc****, Sutthiporn Pattharachayakul Pharm D, BCPS*,
Usanee Wanakamanee MSc, BCP*, Phongsak Dandecha MD***, Arnurai Jitsurong MSc*****

** Department of Clinical Pharmacy, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkhla, Thailand*
*** The College of Pharmacotherapy of Thailand, The Pharmacy Council of Thailand, Bangkok, Thailand*
**** Department of Medicine, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand*
***** Department of Pharmaceutical Technology, Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Songkhla, Thailand*
****** Department of Pathology, Faculty of Medicine, Prince of Songkla University, Hat Yai, Songkhla, Thailand*

Objective: *To evaluate the effective vancomycin dosing regimens by Monte Carlo simulation among patients on intermittent high-efficiency hemodialysis (HEHD).*
Material and Method: *The present study was conducted on eight end-stage renal disease patients receiving HEHD. The patients received an initial dose of vancomycin 1 g followed by 500 mg immediately after HEHD session for a supplementation. Blood samplings were obtained to investigate vancomycin pharmacokinetic parameters. A Monte Carlo simulation was performed to determine the percentage of probability of target attainment (PTA) achieving AUC_{24}/MIC ratio greater than or equal to 400 as the target of achievement of antimicrobial activity.*
Results: *A loading dose (LD) of vancomycin of 20 mg per kilogram of dry weight (DW) with or without a supplementation had the optimum effectiveness for pathogens with MICs not greater than 0.5 mg/L. For pathogens with an MIC of 1.0 mg/L, the LD of 25 mg/kgDW followed by 20 or 25 mg/kgDW supplementation was achieved the target in some cases. Therefore, the LD of 30 mg/kgDW followed by 25 mg/kgDW or the LD of 35 mg/kgDW with 10, 20 or 25 mg/kgDW supplementation was required to achieve the target of antimicrobial activity.*
Conclusion: *From the present study, the lowest vancomycin dosing regimen that had the optimum effectiveness was a 35 mg/kgDW LD followed by 10 mg/kgDW supplementation. This regimen is recommended to treat pathogens with MICs not greater than 1.0 mg/L.*

Keywords: *Vancomycin, Dosing regimen, Monte Carlo simulation, High-efficiency hemodialysis (HEHD)*

J Med Assoc Thai 2015; 98 (6): 606-15
Full text. e-Journal: *http://www.jmatonline.com*

Vancomycin, a glycopeptide antibiotic, is active against the vast majority of Gram-positive bacteria especially methicilin-resistant *Staphylococcus aureus* (MRSA)[1]. Published studies among populations with end-stage renal disease (ESRD) receiving hemodialysis have found that this group of patients have a strongly increased risk for morbidity and mortality from infection and the leading pathogen that causes severe infection in dialysis patients is *S. aureus* (27.7-50%)[2]. In addition, patients undergoing hemodialysis have a 100-fold higher risk for invasive MRSA infections than the general population. For this reason, vancomycin has played an important role in the treatment of dialysis-related Gram-positive bacterial infections. Generally, vancomycin is exclusively excreted via the kidney. Therefore, in anuric patients the half-life of vancomycin is extremely increased to approximately 100 to 200 hours. Not only for the half-life but some other pharmacokinetic (PK) parameters of vancomycin are also changed in patients with renal insufficiency. The volume of distribution (V_d) of vancomycin varies over quite a wide range because it is affected by the volume overload or fluid removal via dialysis[1,3-5]. Therefore, determining an appropriated dose of vancomycin in such patients on hemodialysis is quite difficult because the serum vancomycin concentration-time profile is complex and

Correspondence to:
Rungprai D, Department of Pharmacy, Faculty of Pharmacy, Silpakorn University, Nakhon Pathom 73000, Thailand.
Tel: +66-34-253910-19 ext. 24263, Fax: +66-34-255801
E-mail: daraporn.r@su.ac.th, d.rungprai@gmail.com

has been characterized as a one-, two-, and three-compartment pharmacokinetic models[3]. In addition, the pharmacokinetic properties of vancomycin in the hemodialysis population are still unclear due to various factors of the hemodialysis mode for individual patients e.g., type of dialysis membranes, duration of dialysis, blood flow rate (BFR), dialysate flow rate (DFR) and dialysis frequency. Besides, other patient variables such as weight, number of dialyzer reuse and residual renal function also impact on PK and vancomycin dosing[1,6,7]. A consideration of the pharmacokinetics/pharmacodynamics (PK/PD) is necessary to determine the optimum effectiveness for vancomycin treatment. Previous animal experiments and human studies found that the PK/PD index that was best correlated to vancomycin effectiveness was the steady-state 24-hour area under the concentration-time curve divided by the minimum inhibitory concentration (AUC_{24}/MIC). An AUC_{24}/MIC value of greater than or equal to 400 was associated with a successful outcome[3,4,8]. Nowadays, the PK/PD study in ESRD patients, especially those who are undergoing intermittent high-efficiency hemodialysis (HEHD) is still limited. The present study is the first PK/PD study of vancomycin in HEHD patients using the Monte Carlo simulation (MCS). The aim of the study was to evaluate the effective vancomycin dosing regimens by Monte Carlo simulation among patients on HEHD.

Material and Method

The study protocol and statement of informed consent were approved by the Ethics Committee of Songklanagarind Hospital (Faculty of Medicine, Prince of Songkla University, Hat Yai, Thailand) on 16 July 2012. Judgement reference No. EC: 55-315-14-1-1. Prior to participation in the study, written informed consent was obtained from all patients or their legally acceptable representative.

Subjects and study design

The present study was a prospective, open-labelled study conducted at Songklanagarind Hospital between September 2012 and April 2013. Individuals considering for enrollment in the study included ESRD patients who were at least 18 years old, those who had experienced HEHD for at least three months and were treated with intermittent HEHD two to three times per week with vancomycin used as empirical therapy for MRSA infection. All patients were admitted to Songklanagarind Hospital. Patients were excluded if they had a history of vancomycin allergy or received vancomycin within six weeks before their enrollment. Patient demographic data, allergic and medical history including dialysis data and history of dialysis experiences were obtained by patient interview and some data were retrieved from the computerized patient database of Songklanagarind Hospital.

Renal replacement therapy procedure

All patients underwent intermittent HEHD with a cellulose triacetate hollow-fiber dialyzer (model: Sureflux-150E_{GA}, Nipro Corp., Osaka, Japan) with a surface area of 1.5 m^2 and an ultrafiltration coefficient (K_{uf}) of 20.50 ml/hr/mmHg. Blood flow rate, dialysate flow rate and duration of each hemodialysis session were determined by a nephrologist as a dialysis prescription. Different kinds of vascular access for hemodialysis were allowed among patients e.g., double-lumen catheter, permanent central venous catheter, arteriovenous fistula (AVF) or arteriovenous graft (AVG).

Dosing regimen and drug administration

A 1 g dose of vancomycin (Vancocin-S®; Siam Pharmaceutical Co. Ltd.) was given to the patients via intravenous infusion over two hours; a supplemental dose of 500 mg of vancomycin was administered to the patients via a 2-hour intravenous infusion immediately after a hemodialysis session. Most of the patients in the study had a dialysis free period for a few days after the initial vancomycin dose; therefore, the timing of the supplemental dose that was given to the patients depended upon the dialysis schedule for each individual.

Blood samplings

Blood samples were obtained at three phases, the initial dose infusion phase, during an HEHD session and the infusion of the supplemental dose. For the initial dose, venous blood samples (approximately 2.5 mL) were subsequently obtained at times: 0 (before vancomycin administration), 0.5, 1, 2 (end of vancomycin infusion), 2.5, 3, 4, 5, 8, and 10 hours. Blood samplings were not needed on the dialysis free days. For the dialysis day, patients who were on HEHD for 4 hours had blood samples collected at times: 0 (before starting HEHD), then at 1, 2, and 3 hours after starting HEHD. In a similar way, patients who were on 3-hour or 3.5-hour HEHD session, blood samples would be collected at times 0, then at 1 and 2 hours after starting HEHD. Blood samplings for the third phase were done immediately at the end of the

hemodialysis session. After the HEHD was completed, blood samples were gathered from the patients at times: 0 (immediately after the hemodialysis was completed and the infusion of the vancomycin supplemental dose was started), then at 2 (end of vancomycin infusion), 4, 6, and 8 hours.

Serum samples preparation and analytical methods

All blood samples were collected into non-heparinized blood collection test tubes, allowed to clot for at least 1 hour then stored in the refrigerator at 4°C until all phases of blood sampling were completed. After that, the blood samples were centrifuged at 8,000 to 10,000 relative centrifugal force (RCF) for 10 minutes. All serum samples were stored at -20°C until vancomycin serum level analysis was performed. Serum vancomycin concentrations were determined by fluorescence polarization immunoassay (AxSYM; Abbott Laboratories, Abbott Park, IL 60064 USA). A quantitative vancomycin immunoassay for AxSYM analyzer was done in the hospital laboratory in October 2012. The controls used in this assay had mean vancomycin concentrations of 6.94, 19.74, and 36.45 mcg/mL as low, medium, and high controls, respectively. The three level of controls were run 20 times in one day to yield within run coefficients of variation (CV). For between run CV, each level of controls was run once on a time point of the day for 20 days. The within run CV for the three level of controls were 3.34, 3.24, and 2.37%, respectively and the between run CV were 6.77, 4.86, and 4.64%, respectively. The lower limit of detection of vancomycin of this assay was 1.29 mg/L.

Pharmacokinetic analysis

Vancomycin serum concentration-time curves were analyzed using Microsoft Excel (Microsoft Corp., Redmond, WA) spreadsheets. A two-compartment model was used to obtain the best fit between the PK parameters and the vancomycin serum concentrations in each patient. Non-linear regression was used to obtain the PK parameters and the Taylor series expansion method was performed to solve a differential equation that described the pharmacokinetic model used in the study[9]. The algorithm used for minimization of the sum of squares errors (SSE) in the present study was heuristic random optimization[10]. This method has a good convergence speed and can be easily executed in a spreadsheet. To explain this method concisely, various random sets of parameters were generated and used for the SSE calculation and vancomycin serum concentration-time curves were generated in Microsoft Excel spreadsheet and the SSE objective function was assessed from the actual and calculated concentrations. The parameters were randomly walked from the previously best-spot to find a better SSE. This process was repeated continuously until convergence was achieved[11].

Pharmacodynamic assessment by Monte Carlo simulation

Since the parameter values obtained from the pharmacokinetic analysis were not normally distributed, their behavior could be presented more appropriately by using a logarithmic scale. For that reason, the obtained PK parameters were expressed in the form of a geometric mean and geometric standard deviation (SD) (Table 1) and a logarithmic scale was used for all PK parameters in the MCS.

From the PK parameters obtained in the study, the MCS was performed. The simulation software was written in BASIC language and compiled with Microsoft QuickBASIC (QB) compiler version 3.0 (product of Microsoft Corporation) to create an executable program. The PK parameters were simulated to obtain the set of parameters that had the statistical behavior (mean, SD, and covariance) harmonized with the actual PK parameters acquired from the patients who had participated in the study and these parameters were used to simulate the concentration-time profiles using the Runge-Kutta order 4 algorithm according to the differential equations that described a two-compartment model[12]. The simulated PK parameters and actual PK parameters were compared. The choice of significance level of type I error (alpha or α) is arbitrary. The range of alpha between 0.01 and 0.1 was generally accepted. In the present study, the alpha level at 0.1 was used for statistical analysis to make the analysis stricter and more challenging than the general alpha level at 0.05. The values of simulated and actual PK parameters should not statistically different (p-value >0.1). Therefore, the simulated PK parameters could be used for a further process to predict the effectiveness of vancomycin treatment.

Simulation sizes of 10,000 were performed to predict the effectiveness of the vancomycin treatment in the ESRD patients undergoing intermittent HEHD. PK parameters and vancomycin dosing regimens used in the simulations were calculated based on the patient's dry weight (DW). Four loading doses (LD) (20, 25, 30, and 35 mg/kgDW) and four

Table 1. Comparison of actual and simulated PK parameters of vancomycin in eight ESRD patients undergoing intermittent HEHD

Parameter	Geometric mean	Geometric SD	Median	90% CI
Actual PK parameter				
k_{12} (h^{-1})	2.295	1.664	2.514	1.299-4.453
k_{21} (h^{-1})	0.523	1.626	0.583	0.232-0.929
k_e (h^{-1})	0.057	1.612	0.049	0.034-0.139
$k_{intraHD}$ (h^{-1})	0.480	1.976	0.423	0.226-1.434
V_c (L)	9.522	1.714	9.457	3.831-18.458
V_c (L/kgDW)	0.171	1.591	0.190	0.080-0.278
Simulated PK parameter				
k_{12} (h^{-1})	2.294	1.662	2.516	0.852-6.237
k_{21} (h^{-1})	0.521	1.627	0.582	0.199-1.344
k_e (h^{-1})	0.057	1.607	0.049	0.022-0.145
$k_{intraHD}$ (h^{-1})	0.481	1.972	0.424	0.129-1.835
V_c (L/kgDW)	0.170	1.588	0.189	0.069-0.423

PK = pharmacokinetic; ESRD = end-stage renal disease; HEHD = high-efficiency hemodialysis; SD = standard deviation; CI = confidence interval; k_{12} = intercompartment transfer rate constant from central compartment (X_1) to peripheral compartment (X_2); k_{21} = intercompartment transfer rate constant from compartment X_2 to X_1; k_e = elimination rate constant from X_1; $k_{intraHD}$ = elimination rate constant from X_1 during hemodialysis session; V_c = volume of distribution in the central compartment

The mean and SD of actual and simulated PK parameters were not statistically different (p>0.1).

supplemental doses (0, 10, 20, and 25 mg/kgDW) of vancomycin were used. The AUC_{24}/MIC ratio and the probability of target attainment (PTA) were computed and recorded using MIC values of 0.125, 0.25, 0.375, 0.5, 1.0, 1.5, and 2.0 mg/L. The MIC distributions were derived from vancomycin MICs for 50% (MIC50) and 90% (MIC90) of the organisms. MIC range obtained from vancomycin MIC against MRSA by the E-test method during the year 2011-2012 of Songklanakarind Hospital (Prince of Songkla University, Hat Yai, Thailand). The analysis of the AUC_{24}/MIC ratio and PTA were done in three phases by using the AUC of vancomycin in each phase; the AUC of vancomycin after the loading dose (represented by AUC_x), the AUC of vancomycin during hemodialysis session (represented by AUC_y) and the AUC of vancomycin after the supplemental dose (represented by AUC_z). The dialysis duration (represented by t_y) used in the 10,000 simulations was fixed as the common standard duration of 4 hours. The model used for the analysis is shown in Fig. 1. The vancomycin dosing regimen was considered to have the optimum effectiveness when the PTA was not less than 90% at the target of AUC_{24}/MIC that is greater than or equal to 400.

Results

Eight patients were enrolled in the study (five males and three females), with a mean age of 70±16.90 years (range 41-89 years). The patients had a mean dry weight of 57.33±14.76 kg (range 39-75 kg) and their weight gain per day was 2.24±0.69% (range

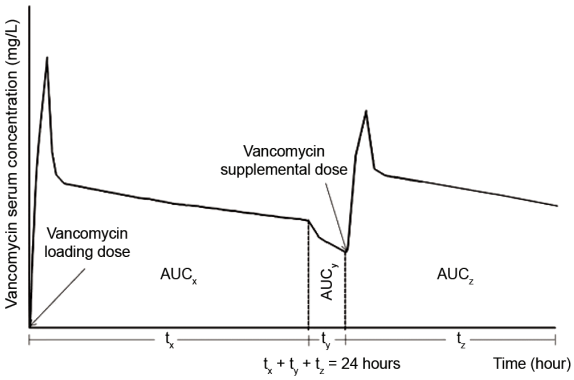

Fig. 1 Model of a vancomycin serum concentration-time profile in ESRD patients undergoing HEHD used in the analysis for the AUC_{24}/MIC ratio and PTA which were done in three phases. t_x, time since the initiation of infusion of the loading dose until starting a hemodialysis session; t_y, dialysis duration; t_z, time since the initiation of infusion of the supplemental dose until 24 hours of vancomycin use was completed; AUC_x, the total amount of vancomycin in the body after infusion of the loading dose until the initiation of hemodialysis; AUC_y, the total amount of vancomycin in the body during the hemodialysis session; AUC_z, the total amount of vancomycin in the body after infusion with the supplemental dose until 24 hours of vancomycin use was completed.

0.81-3.21). All patients received a prescription for a 4-hour HEHD. Five of the eight patients completed hemodialysis at four hours. One patient received a 3.5 hour-dialysis because of a poor BFR and the formation of a blood clot in the circuit, anyway blood samplings were completed for all three phases. Another patient received the HEHD for only one hour and 10 minutes, then needed to stop the hemodialysis process early because of AVF thrombosis. Blood samplings for one patient were missed during the hemodialysis session, so there were six patients whose blood samplings were completed for all three phases. Blood samplings of the others were obtained only during the initial dose of vancomycin and the vancomycin concentrations of these two patients were used to simulate the PK parameters only in the first phase of the study. The characteristics and dialysis data of each patient described as above are shown in Table 3. The geometric mean, SD and median of simulated vancomycin PK parameters were not statistically different from the actual values as shown in Table 1. All of the tested covariates had no identifiable influence on the PK parameters (Table 2). Vancomycin clearance among eight ESRD patients undergoing intermittent HEHD is shown in Table 4.

Table 2. Comparison of covariance matrix between the actual and simulated PK parameters

Parameter	Actual	Simulated
k_{12}-k_{21}	0.019	-0.047
k_{12}-k_e	-0.386	-0.455
k_{12}-V_c	-0.327	-0.201
k_{12}-$k_{intraHD}$	0.512	0.536
k_{21}-k_e	0.061	0.142
k_{21}-V_c	0.821	0.750
k_{21}-$k_{intraHD}$	-0.701	-0.611
k_e-V_c	0.161	0.300
k_e-$k_{intraHD}$	-0.768	-0.683
V_c-$k_{intraHD}$	-0.780	-0.725

k_{12} = intercompartment transfer rate constant from central compartment (X_1) to peripheral compartment (X_2); k_{21} = intercompartment transfer rate constant from compartment X_2 to X_1; k_e = elimination rate constant from X_1; $k_{intraHD}$ = elimination rate constant from X_1 during hemodialysis session; V_c = volume of distribution in the central compartment

The covariances were not statistically different at $\alpha = 0.1$.

Results for the PTA that achieved the target of AUC_{24}/MIC greater than or equal to 400 for each vancomycin dosing regimen were categorized by the duration of t_x, t_y, and t_z (for details, see the model of the analysis in Fig. 1). The study results were presented in three situations which included the patients who received the loading dose of the vancomycin infusion and might get early HEHD 8 hours later (t_x = 8 hours, t_y = 4 hours, and t_z = 12 hours), patients who received HEHD 12 hours after the loading dose of vancomycin (t_x = 12 hours, t_y = 4 hours, and t_z = 8 hours) and patients who received the loading dose of vancomycin infusion and received HEHD in the next 16 hours (t_x = 16 hours, t_y = 4 hours, and t_z = 4 hours). For patients receiving the hemodialysis within 24 hours, the study results for the PTA for vancomycin regimens

Table 3. Characteristics and dialysis data of eight ESRD patients undergoing intermittent HEHD

Patient	Age (years)	Sex	DW (kg)	Weight gain/day (%)	Estimated residual urine (mL/day)	Dialysis frequency (times/week)	Dialysis duration (hours)	BFR (mL/minute)	DFR (mL/minute)
1	72	F	54.0	2.31	500	2 (Tue, Fri)	4.0	350	500
2	58	M	71.6	2.37	285	2 (Tue, Fri)	3.5	290.48*	500
3	77	M	71.0	2.46	50	2 (Tue, Fri)	4.0	350	500
4	89	F	41.0	0.81	50	3 (Mon, Thurs, Sat)	4.0	300	500
5	79	M	44.0	1.89	200	3 (Tue, Thurs, Sat)	4.0	300	500
6	56	M	63.0	2.65	0	3 (Mon, Wed, Fri)	4.0	350	500
7	88	F	39.0	3.21	0	2 (Mon, Thurs)	N/A**	N/A**	N/A**
8	41	M	75.0	2.22	100	3 (Tue, Thurs, Sat)	N/A**	N/A**	N/A**

M = male; F = female; DW = dry weight; BFR = blood flow rate; DFR = dialysate flow rate; N/A = not applicable

* Average values of BFR during hemodialysis session

** No data because of incomplete blood sampling

Table 4. Vancomycin clearance in eight ESRD patients undergoing intermittent HEHD

Patient	$CL_{interHD}$ (L/hour)	$CL_{intraHD}$ (L/hour)	CL_{HD} (L/hour)
1	0.397	4.483	4.086
2	0.377	3.141	2.764
3	0.924	3.886	2.962
4	0.594	4.243	3.649
5	0.107	5.505	5.398
6	0.861	7.296	6.435
7	0.553	N/A*	N/A*
8	1.722	N/A*	N/A*
Median	0.574	4.363	3.878

CL_{NR} = non-renal clearance; CL_{RR} = residual renal clearance; CL_{HD} = clearance by hemodialysis process; $CL_{interHD}$ = clearance during interdialytic period ($CL_{RR} + CL_{NR}$); $CL_{intraHD}$ = clearance during hemodialysis session ($CL_{RR} + CL_{NR} + CL_{HD}$); N/A = not applicable

* No data because of incomplete blood sampling

achieving AUC_{24}/MIC ratio greater than or equal to 400 are shown in Table 5.

In the case of patients who did not received the hemodialysis within 24 hours after the loading dose of vancomycin (t_x = 24 hours, t_y = 0 hour, and t_z = 0 hour), the loading dose of 20, 25, and 30 mg/kgDW gave the percentage of PTA that achieved the AUC_{24}/MIC greater than or equal to 400 at 96.00%, 98.99% and 99.69%, respectively in pathogens with an MIC of 0.5 mg/L, but the percentage of PTA was less than 90% (52.51%, 72.52% and 84.53%, respectively) when the MIC reached 1.0 mg/L. Only the loading dose of 35 mg/kgDW achieved the percentage of PTA for the AUC_{24}/MIC greater than or equal to 400 at 92.06% in pathogens with the MIC of 1.0 mg/L, but the percentage of PTA dropped to only 65.96% and 38.00% when the MIC reached 1.5 mg/L and 2.0 mg/L, respectively (data not shown in the table).

Discussion

There have been numerous studies aimed to determine the vancomycin dosing regimen that were concerned with the pharmacokinetics in the hemodialysis patients[13-17]. Most studies have rarely emphasized one aspect of the vancomycin PK/PD index that was important for determining the effectiveness of antibiotic treatment[3,4,8]. The current consensus recommends that a serum vancomycin trough concentration of 15-20 mg/L should be maintained assuming that concentrations in this range should achieve the AUC_{24}/MIC of greater than or equal to 400 if the MICs of the pathogens were not greater than 1 mg/L. However, the clinical evidence that supports the use of this guideline in hemodialysis patients is lacking[3]. A previous study about PK/PD of vancomcyin was published in 2010. The study performed the PK/PD simulations in short daily hemodialysis (SDHD) patients to evaluate vancomycin dosing strategies to develop a rational dosing method. The authors found that the LD of 20 mg/kg followed by 10 mg/kg after every other SDHD provided an adequate exposure for pathogens with MICs not greater than 1 mg/L[18].

From the current study, the authors found that the LD of vancomycin of 20 mg/kgDW with or without a supplemental dose after HEHD session could achieve the target only in pathogens with MICs not greater than 0.5 mg/L. For pathogens with the MIC equal or higher than 1.0 mg/L, the higher LD and supplemental dose were necessary for the effective treatment. Although the high LD of vancomycin could achieve the target of treatment, the important aspects that were of concern were nephrotoxicity and ototoxicity due to the high vancomycin serum concentration. In humans, nephrotoxicity due to vancomycin monotherapy with typical dosage regimens even the use of a high LD for vancomycin have not been common[3]. The most documented risk factors that could accelerate vancomycin nephrotoxicity were a high trough vancomycin serum concentration (especially which was greater than 20 mg/L) or a dosage that was greater than 4 g/day, concomitant treatment with nephrotoxic agents, prolonged therapy (greater than 7 days), and admittance to an intensive care unit for an especially prolonged stay[19].

Nephrotoxicity from vancomycin could result in a deterioration of residual renal function (RRF) in hemodialysis patients. Among these patients, RRF helped to improve the middle molecule clearance. It also offered a better fluid balance and blood pressure control, better hemoglobin values, serum electrolyte levels, enhanced nutritional status and quality of life scores[20]. For those reasons, vancomycin induced nephrotoxicity should be of great concern and be continuously monitored in hemodialysis population, especially patients who still have residual urine to preserve their RRF. For ototoxicity, previous studies have shown that ototoxictiy was associated with peak vancomycin serum concentration greater than 40 mg/L and the frequency of ototoxicity in humans was

Table 5. The percentage of probability of target attainment (PTA) for vancomycin regimens that achieved AUC_{24}/MIC ratio greater than or equal to 400

MIC (mg/L)	Percentage of PTA that achieved AUC_{24}/MIC greater than or equal to 400											
	No supplemental dose			Supplemental dose 10 mg/kgDW			Supplemental dose 20 mg/kgDW			Supplemental dose 25 mg/kgDW		
	T1	T2	T3	T1	T2	T3	T1	T2	T3	T1	T2	T3
Loading dose 20 mg/kgDW												
0.125	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
0.25	99.95	99.94	99.95	100.00	99.99	99.99	100.00	100.00	99.98	100.00	100.00	100.00
0.375	98.56	98.90	99.04	99.75	99.66	99.57	99.94	99.93	99.71	99.98	99.94	99.88
0.5	92.81	94.46	94.59	98.20	97.78	96.88	99.60	99.11	97.77	99.66	99.45	98.85
1.0	36.56	45.24	45.90	64.91	60.98	56.78	82.57	73.56	61.03	86.70	79.86	68.35
1.5	7.18	11.10	12.48	25.64	23.16	20.32	46.81	35.71	23.99	54.92	44.33	29.69
2.0	0.88	1.91	2.28	7.34	6.16	5.01	20.39	13.36	7.17	27.48	19.30	9.84
Loading dose 25 mg/kgDW												
0.125	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
0.25	99.99	99.98	99.99	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
0.375	99.67	99.74	99.80	99.95	99.94	99.87	99.99	99.98	99.93	100.00	99.96	99.96
0.5	97.76	98.10	98.49	99.43	99.29	99.10	99.83	99.77	99.52	99.91	99.80	99.61
1.0	59.15	62.61	66.05	79.38	77.58	74.52	90.38	86.50	79.31	92.72	89.02	83.99
1.5	20.41	23.11	26.99	42.89	40.27	37.60	63.24	54.61	42.83	67.90	59.56	52.12
2.0	4.80	6.08	8.28	17.43	15.62	13.87	35.06	27.10	18.29	40.49	32.33	24.73
Loading dose 30 mg/kgDW												
0.125	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
0.25	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
0.375	99.93	99.97	99.94	99.98	99.98	99.95	99.99	100.00	99.99	100.00	100.00	99.99
0.5	99.22	99.49	99.46	99.77	99.80	99.65	99.94	99.94	99.78	99.98	99.96	99.93
1.0	75.12	78.56	81.67	87.83	87.47	84.50	93.44	91.39	86.93	96.73	94.68	90.97
1.5	36.89	40.79	45.71	55.66	55.30	50.41	68.48	64.42	54.41	78.34	73.53	62.52
2.0	13.36	15.98	19.44	27.96	27.16	23.27	39.80	37.13	27.20	52.52	46.70	34.43
Loading dose 35 mg/kgDW												
0.125	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
0.25	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00	100.00
0.375	99.97	100.00	99.99	100.00	100.00	99.99	100.00	99.98	100.00	100.00	100.00	100.00
0.5	99.76	99.83	99.89	99.94	99.94	99.90	99.98	99.95	99.95	99.99	99.97	99.94
1.0	84.79	87.83	89.17	92.96	93.00	91.43	96.16	95.10	94.20	97.66	96.46	95.03
1.5	48.55	56.53	59.18	67.95	68.83	63.80	77.76	74.36	71.54	82.89	78.46	74.60
2.0	21.93	29.16	31.49	40.72	41.33	35.91	52.34	48.02	43.66	58.86	52.90	48.70

AUC_{24}/MIC = 24-hour area under the concentration-time curve/minimum inhibitory concentration
T1: t_x = 8 hours, t_y = 4 hours, t_z = 12 hours; T2: t_x = 12 hours, t_y = 4 hours, t_z = 8 hours; T3: t_x = 16 hours, t_y = 4 hours, t_z = 4 hours

reported as 1%-9%. Vancomycin was rarely ototoxic as a single agent. In addition, ototoxic was fully reversible when other ototoxic agents were not used concurrently[3,21]. Therapeutic monitoring of the vancomycin serum concentration is recommended in every HEHD patients using those high dose regimen for vancomycin.

The results of the vancomycin dosing in the present study were higher than the previous studies. That might be because the PK parameters and vancomycin dosing regimens used in the simulations were calculated based on patient's DW, which was the ideal body weight at the end of a dialysis session. Using the DW for calculation of the vancomycin dose might not be the most suitable method because the body weight of hemodialysis patients has a dynamic property. The total body weight usually dropped on the commencement of dialysis therapy due to fluid removal[22]. However, it increased on the dialysis-free day because of fluid retention. Although, the current recommendation from the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists and a recent study in hemodialysis patients were that vancomycin dosages should be calculated based on actual body weight (ABW), there have been

only a small number of the studies about vancomycin weight-based dosing in patients with hemodialysis[3,23]. Patients enrolled in the present study were first seen and their clinical status was assessed at an emergency room (ER). Most of the patients were unable to be weighed nor able to communicate information on their body weight themselves because of their symptoms (e.g., high-graded fever, chills, weak, or alteration of consciousness). Thus, routinely, the clinicians made a visual estimation of the patient's ABW that might be inaccurate and might have caused dosing errors. The authors decided to use patient's DW to indicate vancomycin doses because the ABW of hemodialysis patients were considerably variable. Therefore, DW is the most accurate documented BW of the patients that the authors could obtain from patient's hemodialysis data sheets. Moreover, the healthcare professionals could communicate with the hemodialysis nurses to retrieve the latest accurate patient's DW. Therefore, the authors recommended a clinical application use of the study results should be based on the hemodialysis patient's DW.

The lack of data from a larger sample size could be considered as a potential limitation in the study. Generally, most of the PK/PD studies had a small number of patients as same as the current study and some of the previous studies[16,18]. However, the MCS based on a small sample size could be instructive in illuminating the effects of different dosing approaches[24]. Besides, there were a few confounders that could affect intradialytic vancomycin clearance such as dialyzer reuse, dialysis efficiency (Kt/V) that could not control well enough, but previous studies and reviews stated that these factors had only a small impact on intradialytic vancomycin clearance with unclear clinical importance[1,7].

Conclusion

In summary, it was found that the LD of vancomycin of 30 mg/kgDW followed by a 25 mg/kgDW supplemental dose after the HEHD session or the LD of 35 mg/kgDW with a 10, 20, or 25 mg/kgDW supplemental dose could provide the effective treatment in pathogens with an MIC of 1.0 mg/L. To avoid vancomycin toxicity and to achieve the optimum treatment effectiveness, the authors would recommended the use of the lowest effective vancomycin dosing regimen at the LD of 35 mg/kgDW followed by 10 mg/kgDW supplementation after the HEHD session for empirical therapy. Anyway, monitoring of vancomycin serum concentrations was still necessary among these patients. After the culture and susceptibility results of the suspected pathogens were reported, the dose could be adjusted on the basis of the MIC for the pathogen. For pathogens with MICs greater than or equal to 1 mg/L, treating with vancomycin might give a suboptimal clinical outcome in ESRD with HEHD patients, therefore, alternative antibiotic therapy should be considered as well[25,26].

What is already known on this topic?

The pharmacokinetic (PK) parameters of vancomycin in the ESRD patients receiving hemodialysis have been reported from many previous studies. Most of them used a high-flux hemodialysis, so only a limited number of studies have been evaluated for the PK of vancomycin in HEHD patients. There have been numerous studies aimed to determine the vancomycin dosing regimen that were concerned with the pharmacokinetics in the hemodialysis patients. However, most of them have rarely emphasized one aspect of the vancomycin PK/PD index that was important for determining the efficacy of antibiotic treatment.

What this study adds?

The present study is the first PK/PD study of vancomycin in HEHD patients using the MCS to forecast the efficacy of the vancomycin dosing regimens. The aim was to assess the PK/PD of vancomycin in patients on intermittent high-efficiency hemodialysis (HEHD) in order to predict the efficacy of treatment and determine the congruity of the vancomycin dosing regimen among these patients.

Acknowledgements

The authors wish to thank the fund providers (the Faculty of Medicine and Faculty of Pharmaceutical Sciences, Prince of Songkla University, Hat Yai, Thailand) for the study grants and support. Thanks to all the patients who participated in the study, the nurses who helped for the blood samplings, and Hemodialysis Unit staffs for their support. Thanks also to Dr. Brian Hodgson for assistance with the English manuscript.

Potential conflicts of interest

None.

References

1. Vandecasteele SJ, De Vriese AS. Vancomycin dosing in patients on intermittent hemodialysis. Semin Dial 2011; 24: 50-5.

2. Li PK, Chow KM. Infectious complications in dialysis--epidemiology and outcomes. Nat Rev Nephrol 2012; 8: 77-88.
3. Rybak M, Lomaestro B, Rotschafer JC, Moellering R Jr, Craig W, Billeter M, et al. Therapeutic monitoring of vancomycin in adult patients: a consensus review of the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Diseases Pharmacists. Am J Health Syst Pharm 2009; 66: 82-98.
4. Rybak MJ. The pharmacokinetic and pharmacodynamic properties of vancomycin. Clin Infect Dis 2006; 42 (Suppl 1): S35-9.
5. Launay-Vacher V, Izzedine H, Mercadal L, Deray G. Clinical review: use of vancomycin in haemodialysis patients. Crit Care 2002; 6: 313-6.
6. Pai AB, Pai MP. Vancomycin dosing in high flux hemodialysis: a limited-sampling algorithm. Am J Health Syst Pharm 2004; 61: 1812-6.
7. Pallotta KE, Manley HJ. Vancomycin use in patients requiring hemodialysis: a literature review. Semin Dial 2008; 21: 63-70.
8. Moise-Broder PA, Forrest A, Birmingham MC, Schentag JJ. Pharmacodynamics of vancomycin and other antimicrobials in patients with *Staphylococcus aureus* lower respiratory tract infections. Clin Pharmacokinet 2004; 43: 925-42.
9. Jaruratanasirikul S, Wongpoowarak W, Kositpantawong N, Aeinlang N, Jullangkoon M. Pharmacodynamics of doripenem in critically ill patients with ventilator-associated Gram-negative bacilli pneumonia. Int J Antimicrob Agents 2012; 40: 434-9.
10. Li J, Rhinehart RR. Heuristic random optimization. Comput Chem Eng 1998; 3: 427-44.
11. Jaruratanasirikul S, Limapichat T, Jullangkoon M, Aeinlang N, Ingviya N, Wongpoowarak W. Pharmacodynamics of meropenem in critically ill patients with febrile neutropenia and bacteraemia. Int J Antimicrob Agents 2011; 38: 231-6.
12. Wylie CR, Barrett LC. Finite differences. In: Wylie CR, Barrett LC, editors. Advanced engineering mathematics. Singapore: McGraw-Hill; 1982: 247-97.
13. Ariano RE, Fine A, Sitar DS, Rexrode S, Zelenitsky SA. Adequacy of a vancomycin dosing regimen in patients receiving high-flux hemodialysis. Am J Kidney Dis 2005; 46: 681-7.
14. Castellano I, Gonzalez Castillo PM, Covarsi A, Martinez SJ, Suarez Santisteban MA, Gallego S, et al. Vancomycin dosing in hemodialysis patients. Nefrologia 2008; 28: 607-12.
15. Pollard TA, Lampasona V, Akkerman S, Tom K, Hooks MA, Mullins RE, et al. Vancomycin redistribution: dosing recommendations following high-flux hemodialysis. Kidney Int 1994; 45: 232-7.
16. Touchette MA, Patel RV, Anandan JV, Dumler F, Zarowitz BJ. Vancomycin removal by high-flux polysulfone hemodialysis membranes in critically ill patients with end-stage renal disease. Am J Kidney Dis 1995; 26: 469-74.
17. Klansuwan N, Ratanajamit C, Kasiwong S, Wangsiripaisan A. Clearance of vancomycin during high-efficiency hemodialysis. J Med Assoc Thai 2006; 89: 986-91.
18. Decker BS, Kays MB, Chambers M, Kraus MA, Moe SM, Sowinski KM. Vancomycin pharmacokinetics and pharmacodynamics during short daily hemodialysis. Clin J Am Soc Nephrol 2010; 5: 1981-7.
19. Elyasi S, Khalili H, Dashti-Khavidaki S, Mohammadpour A. Vancomycin-induced nephrotoxicity: mechanism, incidence, risk factors and special populations. A literature review. Eur J Clin Pharmacol 2012; 68: 1243-55.
20. Chandna SM, Farrington K. Residual renal function: considerations on its importance and preservation in dialysis patients. Semin Dial 2004; 17: 196-201.
21. Saunders NJ. Why monitor peak vancomycin concentrations? Lancet 1994; 344: 1748-50.
22. Purcell W, Manias E, Williams A, Walker R. Accurate dry weight assessment: reducing the incidence of hypertension and cardiac disease in patients on hemodialysis. Nephrol Nurs J 2004; 31: 631-6.
23. Brown M, Polisetty R, Gracely EJ, Cuhaci B, Schlecht HP. Weight-based loading of vancomycin in patients on hemodialysis. Clin Infect Dis 2011; 53: 164-6.
24. Roberts JA, Kirkpatrick CM, Lipman J. Monte Carlo simulations: maximizing antibiotic pharmacokinetic data to optimize clinical practice for critically ill patients. J Antimicrob Chemother 2011; 66: 227-31.
25. Itani KM, Dryden MS, Bhattacharyya H, Kunkel MJ, Baruch AM, Weigelt JA. Efficacy and safety of linezolid versus vancomycin for the treatment of complicated skin and soft-tissue infections

proven to be caused by methicillin-resistant *Staphylococcus aureus*. Am J Surg 2010; 199: 804-16.
26. Watkins RR, Lemonovich TL, File TM Jr. An evidence-based review of linezolid for the treatment of methicillin-resistant *Staphylococcus aureus* (MRSA): place in therapy. Core Evid 2012; 7: 131-43.

การกำหนดขนาดยาแวนโคมัยซินโดยแบบจำลองมอนติ คาร์โล ในผู้ป่วยที่ได้รับการบำบัดทดแทนไตด้วยวิธี intermittent high-efficiency hemodialysis (HEHD)

ดาราพร รุ้งพราย, สุเทพ จารุรัตนศิริกุล, วิบุล วงศ์ภูวรักษ์, สุทธิพร ภัทรชยากุล, อุษณีย์ วนรรฆมณี, พงศ์ศักดิ์ ด่านเดชา, อานุไร จิตต์สุรงค์

วัตถุประสงค์: *เพื่อประเมินประสิทธิผลของการกำหนดขนาดยาแวนโคมัยซินโดยแบบจำลองมอนติ คาร์โล ในผู้ป่วยที่ได้รับการบำบัดทดแทนไตโดยการฟอกเลือดด้วยเครื่องไตเทียมแบบ intermittent high-efficiency hemodialysis (HEHD)*
วัสดุและวิธีการ: *การศึกษานี้ทำในผู้ป่วยโรคไตเรื้อรังจำนวน 8 ราย ที่ได้รับการฟอกเลือดด้วยเครื่องไตเทียมแบบ HEHD โดยผู้ป่วยจะได้รับยาแวนโคมัยซินในขนาดเริ่มต้นจำนวน 1 กรัม ตามด้วยขนาดเสริม 500 มิลลิกรัม ทันทีภายหลังจากการฟอกเลือด ทำการเก็บตัวอย่างเลือดผู้ป่วย เพื่อตรวจสอบพารามิเตอร์ทางเภสัชจลนศาสตร์ของยาแวนโคมัยซิน จากนั้นใช้หลักการของแบบจำลองมอนติ คาร์โล เพื่อหาร้อยละความน่าจะเป็นที่จะได้ระดับยาเป้าหมาย (probability of target attainment, PTA) ที่ AUC_{24}/MIC มากกว่าหรือเท่ากับ 400 ซึ่งเป็นเป้าหมายการออกฤทธิ์ของยาต้านจุลชีพที่ต้องการ*
ผลการศึกษา: *พบว่าการบริหารยาแวนโคมัยซินขนาดโถม (loading dose) 20 มิลลิกรัมต่อกิโลกรัมของน้ำหนักแห้ง ทั้งในกรณีที่มีหรือไม่มีการให้ยาในขนาดเสริม จะสามารถให้ประสิทธิผลที่ดีในการรักษาการติดเชื้อก่อโรคที่มี MIC ไม่เกิน 0.5 มิลลิกรัมต่อลิตร สำหรับเชื้อก่อโรคที่มี MIC เท่ากับ 1 มิลลิกรัมต่อลิตร การบริหารยาแวนโคมัยซินขนาดโถม 25 มิลลิกรัมต่อกิโลกรัมของน้ำหนักแห้ง ตามด้วยขนาดเสริม 20 ถึง 25 มิลลิกรัมต่อกิโลกรัมของน้ำหนักแห้ง จะให้ประสิทธิผลที่ดีตามเป้าหมายได้ในผู้ป่วยบางรายเท่านั้น ดังนั้นจึงอาจมีความจำเป็นในการใช้ยาแวนโคมัยซินขนาดโถม 30 มิลลิกรัมต่อกิโลกรัมของน้ำหนักแห้ง ตามด้วยขนาดเสริม 25 มิลลิกรัมต่อกิโลกรัมของน้ำหนักแห้ง หรือ ขนาดโถม 35 มิลลิกรัมต่อกิโลกรัมของน้ำหนักแห้ง ร่วมกับขนาดเสริม 10, 20 หรือ 25 มิลลิกรัมต่อกิโลกรัมของน้ำหนักแห้ง เพื่อให้บรรลุเป้าหมายการออกฤทธิ์ของยาต้านจุลชีพตามต้องการ*
สรุป: *จากการศึกษานี้ ขนาดยาแวนโคมัยซินต่ำสุดที่สามารถให้ประสิทธิผลที่ดีในการรักษา ได้แก่ แวนโคมัยซินขนาดโถม 35 มิลลิกรัมต่อกิโลกรัมของน้ำหนักแห้ง ตามด้วยขนาดเสริม 10 มิลลิกรัมต่อกิโลกรัมของน้ำหนักแห้ง โดยแนะนำให้ใช้ขนาดยานี้เพื่อรักษาการติดเชื้อก่อโรคที่มี MIC ไม่เกิน 1.0 มิลลิกรัมต่อลิตร*
