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

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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 AUC24/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)

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Vancomycin, a glycopeptide antibiotic, is active against the vast majority of Gram-positive bacteria especially methicillin-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 (Vd) 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
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\(_{24}/\text{MIC}\)). An AUC\(_{24}/\text{MIC}\) 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\(_{\text{UF}}\)) 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\(^\text{®}\); 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\cite{9}. The algorithm used for minimization of the sum of squares errors (SSE) in the present study was heuristic random optimization\cite{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\cite{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\cite{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
supplemental doses (0, 10, 20, and 25 mg/kgDW) of vancomycin were used. The AUC24/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 AUC24/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 AUCx), the AUC of vancomycin during hemodialysis session (represented by AUCy) and the AUC of vancomycin after the supplemental dose (represented by AUCz). The dialysis duration (represented by ty) 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 AUC24/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 1.662-1.627). The mean and SD of actual and simulated PK parameters were not statistically different ($p>0.1$).

![Fig. 1](image)

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

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Geometric mean</th>
<th>Geometric SD</th>
<th>Median</th>
<th>90% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Actual PK parameter</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>k12 (h⁻¹)</td>
<td>2.295</td>
<td>1.664</td>
<td>2.514</td>
<td>1.299-4.453</td>
</tr>
<tr>
<td>k21 (h⁻¹)</td>
<td>0.523</td>
<td>1.626</td>
<td>0.583</td>
<td>0.232-0.929</td>
</tr>
<tr>
<td>ke (h⁻¹)</td>
<td>0.057</td>
<td>1.612</td>
<td>0.049</td>
<td>0.034-0.139</td>
</tr>
<tr>
<td>k_{intraHD} (h⁻¹)</td>
<td>0.480</td>
<td>1.976</td>
<td>0.423</td>
<td>0.226-1.434</td>
</tr>
<tr>
<td>Vc (L)</td>
<td>9.522</td>
<td>1.714</td>
<td>9.457</td>
<td>3.831-18.458</td>
</tr>
<tr>
<td>Vc (L/kgDW)</td>
<td>0.171</td>
<td>1.591</td>
<td>0.190</td>
<td>0.080-0.278</td>
</tr>
<tr>
<td><strong>Simulated PK parameter</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>k12 (h⁻¹)</td>
<td>2.294</td>
<td>1.662</td>
<td>2.516</td>
<td>0.852-6.237</td>
</tr>
<tr>
<td>k21 (h⁻¹)</td>
<td>0.521</td>
<td>1.627</td>
<td>0.582</td>
<td>0.199-1.344</td>
</tr>
<tr>
<td>ke (h⁻¹)</td>
<td>0.057</td>
<td>1.607</td>
<td>0.049</td>
<td>0.022-0.145</td>
</tr>
<tr>
<td>k_{intraHD} (h⁻¹)</td>
<td>0.481</td>
<td>1.972</td>
<td>0.424</td>
<td>0.129-1.835</td>
</tr>
<tr>
<td>Vc (L/kgDW)</td>
<td>0.170</td>
<td>1.588</td>
<td>0.189</td>
<td>0.069-0.423</td>
</tr>
</tbody>
</table>

PK = pharmacokinetic; ESRD = end-stage renal disease; HEHD = high-efficiency hemodialysis; SD = standard deviation; CI = confidence interval; k12 = intercompartment transfer rate constant from central compartment (X1) to peripheral compartment (X2); k21 = intercompartment transfer rate constant from compartment X2 to X1; ke = elimination rate constant from X1 during hemodialysis session; Vc = volume of distribution in the central compartment.
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.

Results for the PTA that achieved the target of AUC24/MIC greater than or equal to 400 for each vancomycin dosing regimen were categorized by the duration of tx, ty, and tz (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 (tx = 8 hours, ty = 4 hours, and tz = 12 hours), patients who received HEHD 12 hours after the loading dose of vancomycin (tx = 12 hours, ty = 4 hours, and tz = 8 hours) and patients who received the loading dose of vancomycin infusion and received HEHD in the next 16 hours (tx = 16 hours, ty = 4 hours, and tz = 4 hours). For patients receiving the hemodialysis within 24 hours, the study results for the PTA for vancomycin regimens

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Actual</th>
<th>Simulated</th>
</tr>
</thead>
<tbody>
<tr>
<td>k12-k21</td>
<td>0.019</td>
<td>-0.047</td>
</tr>
<tr>
<td>k12-k3</td>
<td>-0.386</td>
<td>-0.455</td>
</tr>
<tr>
<td>k12 -ve</td>
<td>-0.327</td>
<td>-0.201</td>
</tr>
<tr>
<td>k12-kminHD</td>
<td>0.512</td>
<td>0.536</td>
</tr>
<tr>
<td>k21-k3</td>
<td>0.061</td>
<td>0.142</td>
</tr>
<tr>
<td>k21 -ve</td>
<td>0.821</td>
<td>0.750</td>
</tr>
<tr>
<td>k21-kminHD</td>
<td>-0.701</td>
<td>-0.611</td>
</tr>
<tr>
<td>kve</td>
<td>0.161</td>
<td>0.300</td>
</tr>
<tr>
<td>kve-kminHD</td>
<td>-0.768</td>
<td>-0.683</td>
</tr>
<tr>
<td>vve</td>
<td>-0.780</td>
<td>-0.725</td>
</tr>
</tbody>
</table>

k12 = intercompartment transfer rate constant from central compartment (X1) to peripheral compartment (X2); k21 = intercompartment transfer rate constant from compartment X2 to X1; k3 = elimination rate constant from X3; kminHD = elimination rate constant from X1 during hemodialysis session; ve = volume of distribution in the central compartment

The covariances were not statistically different at α = 0.1.

<table>
<thead>
<tr>
<th>Table 3. Characteristics and dialysis data of eight ESRD patients undergoing intermittent HEHD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
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<tr>
<td>5</td>
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<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
<tr>
<td>8</td>
</tr>
</tbody>
</table>

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
achieving $\text{AUC}_{24}/\text{MIC}$ ratio greater than or equal to 400 are shown in Table 5.

In the case of patients who did not receive 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 $\text{AUC}_{24}/\text{MIC}$ 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 $\text{AUC}_{24}/\text{MIC}$ 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 $\text{AUC}_{24}/\text{MIC}$ 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\(^{18}\). A previous study about PK/PD of vancomycin 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\(^{11}\). 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 ototoxicity was associated with peak vancomycin serum concentration greater than 40 mg/L and the frequency of ototoxicity in humans was

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

<table>
<thead>
<tr>
<th>Patient</th>
<th>$\text{CL}_{\text{interHD}}$ (L/hour)</th>
<th>$\text{CL}_{\text{intraHD}}$ (L/hour)</th>
<th>$\text{CL}_{\text{HD}}$ (L/hour)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.397</td>
<td>4.483</td>
<td>4.086</td>
</tr>
<tr>
<td>2</td>
<td>0.377</td>
<td>3.141</td>
<td>2.764</td>
</tr>
<tr>
<td>3</td>
<td>0.924</td>
<td>3.886</td>
<td>2.962</td>
</tr>
<tr>
<td>4</td>
<td>0.594</td>
<td>4.243</td>
<td>3.649</td>
</tr>
<tr>
<td>5</td>
<td>0.107</td>
<td>5.505</td>
<td>5.398</td>
</tr>
<tr>
<td>6</td>
<td>0.861</td>
<td>7.296</td>
<td>6.435</td>
</tr>
<tr>
<td>7</td>
<td>0.553</td>
<td>N/A*</td>
<td>N/A*</td>
</tr>
<tr>
<td>8</td>
<td>1.722</td>
<td>N/A*</td>
<td>N/A*</td>
</tr>
<tr>
<td>Median</td>
<td>0.574</td>
<td>4.363</td>
<td>3.878</td>
</tr>
</tbody>
</table>

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

* No data because of incomplete blood sampling
were calculated based on patient’s DW, which was the
That might be because the PK parameters and
vancomycin serum concentration is recommended in
reversible when other ototoxic agents were not used
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\(^\text{[121]}\). 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\(^\text{[22]}\). 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\(^\text{23}\). 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\(^\text{16,18}\). However, the MCS based on a small sample size could be instructive in illuminating the effects of different dosing approaches\(^\text{24}\). 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\(^\text{1,7}\).

### 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\(^\text{25,26}\).

### 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.

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### Potential conflicts of interest

None.

### References


การกําหนดขนาดยาแวนโคมัยซินโดยแบบจําลองมอนติ คารโร ในผูปวยที่ไดรับการบําบัดทดแทนไตดวยวิธี intermittent high-efficiency hemodialysis (HEHD)

ภาวะกรูฎการ, สุเทพ หงสูติศรีภู, วิฑูร วงศภูวรักษ, สุเทพ ภัทรชยากุล, พงศศักดิ์ ดานเดชา, อานุไร จิตตสุรงค

วัตถุประสงค์: เพื่อประเมินประสิทธิผลของการกําหนดขนาดยาแวนโคเมซินโดยแบบจําลองมอนติ คารโร ในผูปวยที่ไดรับการ ปบกยทดแทนโดยการฟอกเลือดดวยเครื่องฟอกเลือดแบบ intermittent high-efficiency hemodialysis (HEHD)

วัตถุประสงค์: การศึกษานี้ที่ผูปวยโรคไตเรื้อรังจำนวน 8 ราย ที่ไดรับการฟอกเลือดดวยเครื่องฟอกเลือดแบบ HEHD โดย ผูรับยาจะไดรับยาแวนโคเมซินในขนาดเริมตนจำนวน 1 กรัม ตามดวยขนาดเสริม 500 มิลลิกรัม ทันทีหลังจากการฟอกเลือด ที่เก็บตัวอยางเลือดผูปวย เพื่อตรวจสอบความมีมิติทางเภสัชคติของยาแวนโคเมซิน จากนั้นใชหลักการของแบบจําลอง มอนติ คารโร เพื่อใหความนาจะเปนเปาที่จะใหระดับยาเปาหมาย (probability of target attainment, PTA) ที่ AUC24/MIC มากกวาหรือเทากับ 400 ซึ่งเปาหมายของยาแวนโคเมซินที่ตองการ

ผลการศึกษา: พบวาการบริหารยาแวนโคเมซินขนาดโถม (loading dose) 20 มิลลิกรัมตอกิโลกรัมของนํ้าหนัก ทั้งในกรณี ที่มีหรือไม่มีการใหยาในขนาดเสริม จะสามารถใหประสิทธิผลที่ตองการได ที่ AUC24/MIC ไมเกิน 0.5 มิลลิกรัมตอกิโลกรัม สําหรับขนาดโถมที่ MIC เทากับ 1 มิลลิกรัมตอกิโลกรัม กรณีพรบกยทดแทนโดยการฟอกเลือดธรรมดา 25 มิลลิกรัมตอกิโลกรัมของนํ้าหนัก ตามดวยขนาดเสริม 20 ถึง 25 มิลลิกรัมตอกิโลกรัมของนํ้าหนัก จะใหประสิทธิผลที่ตองการได ที่ AUC24/MIC ไมเกิน 0.5 มิลลิกรัมตอกิโลกรัม แต การใชขนาดเสริม 25 มิลลิกรัมตอกิโลกรัมของนํ้าหนัก ตามดวยขนาดเสริม 25 มิลลิกรัมตอกิโลกรัมของนํ้าหนัก หรือ ขนาดเต็ม 35 มิลลิกรัมตอกิโลกรัมของนํ้าหนัก รวมกับขนาดเสริม 10, 20 หรือ 25 มิลลิกรัมตอกิโลกรัมของนํ้าหนัก เพื่อใหผลการปบกยทดแทนโดยการฟอกเลือดที่ตองการ

สรุป: จากการศึกษาพบวาขนาดยาแวนโคเมซินที่เหมาะสมจะใหประสิทธิผลที่ตองการได ไดแกขนาดโถม 35 มิลลิกรัม ตองการใหแวนโคเมซินตามดวยขนาดเสริม 10 มิลลิกรัมตอกิโลกรัมของนํ้าหนัก ตามที่แนะนําใหใชขนาดนี้เพื่อใหรักษาการ ติดเชื้อที่ MIC ไมเกิน 1.0 มิลลิกรัมตอกิโลกรัม