Vancomycin clearance during continuous venovenous haemofiltration in critically ill patients

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ABSTRACT

The objective of this study was to determine the pharmacokinetics and dosing recommendations of vancomycin in critically ill patients receiving continuous venovenous haemofiltration (CVVH). A prospective study was conducted in the Intensive Care Unit of a university hospital. Seven patients receiving CVVH with a triacetate hollow-fibre dialyser were enrolled. CVVH was performed in pre-dilution mode with a blood flow rate of 200–250 mL/min and an ultrafiltrate flow rate of 800–1200 mL/h. To determine vancomycin pharmacokinetics, serum and ultrafiltrate were collected over 12 h after a 2-h infusion of 1000 mg vancomycin. The mean (± standard deviation) sieving coefficient of vancomycin was 0.71 ± 0.13, which is consistent with previously reported values. Clearance of vancomycin by CVVH (0.73 ± 0.21 L/h or 12.11 ± 3.50 mL/min) constituted 49.4 ± 20.8% of total vancomycin clearance (1.59 ± 0.47 L/h) and was consistent with previously reported clearances. Approximately one-fifth of the vancomycin dose was removed during the 12-h CVVH (213.9 ± 104.0 mg). The volume of distribution was 24.69 ± 11.00 L, which is smaller than previously reported. The elimination rate constant and terminal half-life were 0.08 ± 0.05 h−1 and 12.02 ± 7.00 h, respectively. In conclusion, elimination of vancomycin by CVVH contributed to ca. 50% of the total elimination in critically ill patients. The maintenance dose of vancomycin, calculated from parameters in patients in this study, would be 500–750 mg every 12 h to provide a steady-state trough concentration of 15–20 mg/L. Owing to alterations in clinical conditions, serum vancomycin concentrations must be closely monitored in critically ill patients.

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1. Introduction

Vancomycin is a glycopeptide antibiotic primarily used to treat Gram-positive infections caused by meticillin-resistant staphylococci and ampicillin-resistant enterococci [1,2]. Vancomycin (molecular weight 1448 Da) is ca. 55% bound to plasma albumin (range 15–75%) and has a volume of distribution (Vd) of ca. 0.7 L/kg (range 0.3–0.9 L/kg) [2]. It is eliminated unchanged in the urine, resulting in a significant increase in the half-life in patients with renal insufficiency. The liver may also be involved to a small extent. Only small amounts appear in bile following intravenous (i.v.) administration, i.e. 5–20% of total clearance [2]. The pharmacokinetics of vancomycin can be markedly changed in patients with severe illness [3]. An elevated Vd owing to extracellular volume expansion, altered protein binding and decreased clearance of some drugs can be expected in critically ill patients [4–6].

Continuous renal replacement therapy (CRRT), particularly continuous venovenous haemofiltration (CVVH), is becoming more commonly used in the routine management of critically ill patients with acute kidney injury [7–9]. Some studies [10–12] demonstrated that vancomycin is removed during CVVH, requiring a dose of 1000 mg every 48 h in these patients. Nevertheless, several of these studies have limited applications owing to inadequate CRRT conditions, e.g. dialysate flow, ultrafiltration rate, blood flow rate, haemofilter type, length of therapy or small sample size [13–19].

From an extensive literature search, there are limited studies on vancomycin dosing in critically ill patients. This study was therefore intended to determine the pharmacokinetics and dosing recommendation for vancomycin in critically ill patients undergoing CVVH.

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2. Patients and method

2.1. Study design

This prospective, open-label study was carried out in the Intensive Care Unit (ICU), Department of Medicine, Songklanagarind Hospital (Hat Yai, Thailand) during September 2009 to August 2010. The study protocol and statement of informed consent were approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University (Hat Yai, Thailand). Critically ill patients with acute kidney injury requiring CVVH and vancomycin therapy were eligible for enrolment. Inclusion criteria also included age ≥18 years, male or female (non-pregnant, non-lactating), and those whose relatives could give written informed consent. Individuals with a known history of vancomycin allergy or who developed an allergic reaction to vancomycin during administration were excluded.

2.2. Dosing regimen

All patients received vancomycin at a dose of 1000 mg via i.v. infusion over 2 h. In addition to vancomycin, patients also received other prescribed drugs based on their conditions.

2.3. Continuous renal replacement therapy procedure

One of three major veins, i.e., internal jugular, subclavian or femoral vein, was accessed by double-lumen dialysis catheterisation. CVVH was performed via blood flow through an extracorporeal circuit at 200–250 mL/min and a Sureflux-F 150 E triacetate hollow-fibre dialyser (Nipro Corp., Osaka, Japan). The total ultrafiltration rate was set at a range of 800–1200 mL/h. Unless contraindicated, heparin was added into the circuit and was titrated to the appropriate activated partial thromboplastin time (APTT).

2.4. Patient assessment

On admission to the ICU, patients were screened by obtaining a complete medical history, physical examination and renal functions. Vital signs were measured according to the ICU protocol throughout the study. Standard haematology, blood chemistry and urine laboratory tests were performed based on the patient’s clinical response.

2.5. Blood sampling and analytical methods

Blood samples and ultrafiltrates were collected at predetermined times over a 12-h period. Blood samples of ca. 5 mL were gathered prior to vancomycin administration (t=0) and at 0.5, 1, 1.5, 2, 3, 4, 7.5 and 10.5 h after dosing. Aliquots of 50 mL of ultrafiltrate fluid were taken hourly at 0–1 h and 1–2 h, at 2-h intervals at 2–4 h and 4–6 h, and at 3-h intervals at 6–9 h and 9–12 h. Both blood and ultrafiltrate samples were subsequently centrifugated at 3000 rpm for 10 min and plasma and clear ultrafiltrates were frozen at −20 °C until analysis could be performed. Determination of vancomycin in plasma and dialysate samples was performed using fluorescence polarisation immunoassay (AxSYM Vancomycin II; Abbott Laboratories, Chicago, IL). The lower limit of detection of the assay was 2 mg/L with a coefficient of variation of <7% at 7.0 mg/L and 75.0 mg/L.

2.6. Pharmacokinetic and statistical analyses

Pharmacokinetic parameters for vancomycin were determined by non-compartmental analysis using the WinNonlin program v.1.1 (Pharsight Corp., Mountain View, CA). A one-compartment model was assumed to calculate the maintenance dose and terminal half-life (t1/2) of vancomycin. All data were gathered and analysed using descriptive statistics, i.e. mean ± standard deviation (S.D.). Vancomycin pharmacokinetic parameters were calculated using the following equations.

Total clearance (CLR) was defined as the sum of CVVH clearance and non-renal clearance, which can be estimated by:

\[ \text{CLR} = \frac{D}{\text{AUC}_{0\rightarrow\infty}} = \frac{D}{\text{AUC}_{0\rightarrow12} + \text{AUC}_{12\rightarrow\infty}} \]  

where D is the dose (mg) and \( \text{AUC}_{0\rightarrow12} \) is the area under the concentration–time curve from time 0–12 h (mg h/L). Extrapolation of AUC from t = 12 h to infinity was obtained by:

\[ \text{AUC}_{12\rightarrow\infty} = \text{vancomycin concentration at } 12 \text{ h} / k_e \]  

where \( k_e \) is the elimination rate constant (h⁻¹).

The apparent volume of distribution (Vd) (L) was calculated by:

\[ V_d = \frac{D}{\text{AUC}_{0\rightarrow\infty} \times k_e} \]  

The sieving coefficient (SC) of vancomycin refers to a measure of the permeability of the haemofilter to a specific compound that can be calculated as follows:

\[ \text{SC} = \frac{C_{UF}}{C_{se}} \]  

where \( C_{se} \) is the serum vancomycin concentration at the midpoint of the ultrafiltrate collection period (mg/L) and \( C_{UF} \) is the average concentration of vancomycin in the ultrafiltrate from a respective collection period (mg/L).

Haemofilter clearance (CLR_CVVH) was calculated as:

\[ \text{CLR_CVVH} = \frac{SC \times Q_b \times Q_b}{(Q_b + Q_{pre})} \]  

where \( Q_b \) is the haemofiltration rate (L/h), \( Q_b \) is the blood flow rate (L/h) and \( Q_{pre} \) is the pre-dilution substitution rate (L/h).

Dose (D) or maintenance dose for the target steady-state concentration (15–20 mg/L) [12] is predicted by the equation:

\[ D = \frac{C_{min,ss} \times \text{CLR}(1 - e^{-k_e \tau})}{(S + F/\tau)(1 - e^{-k_e \tau})} \times e^{-k_e \tau} \]  

where D is the dose (mg), \( C_{min,ss} \) is the minimum vancomycin concentration at steady-state (mg/L), \( \text{CLR} \) is total vancomycin clearance from Eq. (1) (L/h), S indicates the salt form, F is bioavailability, \( \tau \) is the dosing interval (h), \( t' \) is the infusion time (h) and \( k_e \) is the elimination rate constant (h⁻¹).

2.7. Adverse effect monitoring

Patients were carefully monitored for vital signs, standard haematology, blood chemistry and urine laboratory tests during the study. Adverse events were observed and evaluated throughout the study using the adverse drug reaction reporting form and Naranjo’s algorithm according to the website http://www.fda.moph.go.th.

3. Results

A total of seven patients were included in the study. Patients were admitted to the ICU with various complications but all required CVVH. Patient characteristics are given in Table 1. All of the patients were male, with an age range of 37–79 years and a weight range of 50.0–80.0 kg. They were diagnosed with different diseases, including infective endocarditis and heart failure as well as some infections that needed to be treated with vancomycin. Their albumin levels were low compared with the normal range (34–54 g/L).
3.1. Pharmacokinetics evaluation

The pharmacokinetic parameters of vancomycin in the seven CVVH patients are summarised in Table 2. Four of the seven patients completed the study. CVVH interruption was encountered in three patients owing to a clotted circuit, and sample collection up to 6 h was obtained in these patients.

The mean ± S.D. sieving coefficient (SC) of the triacetate hollow-fibre dialyser was 0.71 ± 0.13 and was stable over the entire study period of 12 h. Fig. 1 shows the plasma concentrations and the amount of vancomycin removed by CVVH, revealing that it was removed as early as during the infusion period. Over the 12-h collection period, the amount of vancomycin eliminated by CVVH (Ae) was 213.9 ± 104.0 mg, which is ca. 450 mg in 24 h, representing 21.39 ± 10.40% of the administered dose. This corresponded to CVVH clearance of 0.73 ± 0.21 L/h (or 12.11 ± 3.50 mL/min), which accounts for 49.4 ± 20.8% of the total vancomycin clearance. The estimated Vd was 24.69 ± 11.00 L and t1/2 was 12.02 ± 7.00 h.

To achieve a steady-state trough concentration of 15–20 mg/L, the maintenance dose required for this group of patients determined by Eq. (6) above would be 500–750 mg every 12 h, based on the estimated total vancomycin clearance of 1.59 L/h.

3.2. Adverse effects

None of the patients in this study experienced allergic reactions or adverse events during vancomycin administration.

4. Discussion

The results of this study demonstrate that the sieving coefficient (SC = 0.71 ± 0.13) was comparable with previously reported values [13]. Although SC values (0.88–0.89) indicated by Boereboom et al. [14] were similar to the unbound fraction of vancomycin in normal conditions (0.8–0.9), the value of this study was less than other studies. Drug–membrane interactions and protein binding are considered to be the main factors affecting SC values [8,9]. Differences in SC values of the present study and that of Joy et al. (0.68–0.86) [13] could therefore be explained by the use of different membrane types and ultrafiltration rates. Moreover, alterations in protein binding could be another explanation of diverse SC values of both studies.

Approximately 20% of the vancomycin dose was removed by 12-h CVVH. Elimination via CVVH accounted for nearly one-half of total vancomycin clearance, which indicated a significant contribution of the extracorporeal elimination of vancomycin [9]. As defined above, total clearance is the sum of CVVH clearance and non-renal clearance. Non-renal clearance in this study was ca. 0.87 ± 0.53 L/h (50% of total vancomycin clearance), which was consistent with the reported values of 0.23–1.40 L/h in anuric patients [20]. In fact, decreased non-renal clearance with progressive renal failure could not be ruled out in these patients with prolonged renal failure, i.e. >7–10 days. CVVH clearance depends on several factors, such as the ultrafiltrate flow rate, blood flow rate and type of membrane. Clearance of vancomycin by CVVH in this study (0.73 ± 0.21 L/h) was comparable with those reported in other studies (0.28–1.40 L/h) [8,13,14]. The CVVH technique used in the present study was performed with an ultrafiltration rate of 800–1200 mL/h and haemofiltration vancomycin clearance of 0.73 ± 0.21 L/h. Boereboom et al. [14] reported an ultrafiltration rate of 1600 mL/h and haemofiltration vancomycin clearance in two patients of 1.4L/h and 1.3 L/h. Regarding these data, they recommended that the first dose of vancomycin for critically ill patients receiving CVVH should be 15–20 mg/kg body weight and 250–500 mg every 12 h after 24 h of the first dose [14].

Joy et al. [13] studied the impact of critical factors, including type of haemofilter, ultrafiltration rate, vancomycin clearance and creatinine clearance, in conventional haemodialysis patients receiving CVVH. When a blood flow rate of 100 mL/min (or 6 L/h) and ultrafiltration rate of 500 mL/h or 1000 mL/h were employed, haemofilter clearance was in the range 0.28–0.36 L/h and was independent of membrane type. They proposed a strategy for vancomycin dosing in patients receiving CVVH based on ultrafiltration rate and residual renal function in order to achieve an average plasma concentration of 20 mg/L. However, the vancomycin doses in this study were determined by total clearance and other parameters as shown in Eq. (6). The mean weight (66.39 ± 12.12 kg) of patients in this study was lower than the Western population and this might affect the dosing recommendation for different populations. In order to apply the vancomycin dosing to patients with various body weights, the adjusted total vancomycin clearance of 0.02 ± 0.01 L/kg based on the estimated weight and patient’s actual body weight could be used to calculate the total vancomycin clearance and then substitute the values in Eq. (6).

The mean half-life of vancomycin measured during CVVH was 12.02 ± 7.00 h, which is longer than that reported in patients with normal renal function [2,12]. The half-lives obtained in this study,
Table 2

<table>
<thead>
<tr>
<th>Patient values</th>
<th>Average (mean ± S.D.)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Parameter</strong></td>
<td><strong>Unit</strong></td>
</tr>
<tr>
<td><strong>Sorption coefficient (Ks)</strong></td>
<td>L</td>
</tr>
<tr>
<td><strong>Amount cleared by CVVH (A/C)</strong></td>
<td>mg</td>
</tr>
<tr>
<td><strong>Area under the concentration–time curve (AUC)</strong></td>
<td>mg h/L</td>
</tr>
<tr>
<td><strong>Elimination rate constant (k)</strong></td>
<td>1/h</td>
</tr>
<tr>
<td><strong>Distribution rate constant (k) (Cl)</strong></td>
<td>1/h</td>
</tr>
<tr>
<td><strong>Half-life (t1/2)</strong></td>
<td>h</td>
</tr>
</tbody>
</table>

however, were shorter than those reported by Boereboom et al. [14] who evaluated vancomycin in two critically ill patients receiving CVVH at the same blood flow rate; both studies used different ultrafiltration flow rates. The half-lives they reported for two patients were 15.4 h and 20.3 h, respectively.

The Vd was 24.69 ± 11.01 L (or 0.38 ± 0.18 L/kg), which was smaller than those reported by Boereboom et al. [14]. Increased Vd in critically ill patients, i.e. 1.32 L/kg in critically ill patients without renal impairment [3], can be caused by fluid shifts from capillary leakage to the interstitial space [6]. Accumulation of the fluid in the third space owing to tissue oedema induced by sepsis can be a possible cause of elevated Vd [3]. Since patients in this study were clinically unstable, the steady-state plasma concentration was rarely achievable. However, reduced Vd observed in this study might be attributed to the non-steady-state condition as well as variations in the pharmacokinetics of CVVH patients.

In conclusion, this study determined the pharmacokinetics and vancomycin dosing for critically ill patients with CVVH. Clearance via CVVH accounted for approximately one-half of the total clearance of vancomycin in patients receiving CVVH. Non-renal clearance contributed almost the same extent as CVVH clearance. When considering the CVVH and non-renal clearance, vancomycin doses were recommended as follows: (a) literature-based first dose of 25–30 mg/kg actual body weight [12]; and (b) maintenance dose, calculated from parameters in this study, of 500–750 mg every 12 h to achieve a steady-state trough concentration of 15–20 mg/L.

The recommended vancomycin doses above corresponded to vancomycin elimination of ca. 450 mg by CVVH during 24 h. Additional dosage up to 500–750 mg of vancomycin daily was also recommended in order to compensate for non-renal clearance in 24 h. Owing to rapid changes in clinical conditions of critically ill patients, close monitoring of serum trough concentrations is required on a daily basis.

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Competing interests: None declared.

Ethical approval: The study protocol and statement of informed consent were approved by the Ethics Committee of the Faculty of Medicine, Prince of Songkla University (reference no. SUB. EC 52-175-19-2-3).

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