Influence of Cellulose Triacetate Hemodialyzers on Vancomycin Pharmacokinetics

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ABSTRACT
This study was designed to evaluate the pharmacokinetics of vancomycin during hemodialysis with cellulose triacetate (CT) high-flux dialyzers and to assess the influence of membrane surface area on intradialytic clearance. In a randomized crossover fashion, the pharmacokinetics of vancomycin were evaluated during dialysis with the CT 110 and CT 190 membranes. Six hemodialysis patients received 1 g of vancomycin immediately after the completion of a dialysis session, and subsequently, blood samples were obtained over a 5-day study period. On Day 3 subjects were dialyzed with CT 110 or CT 190 membranes. The mean intradialytic clearance of vancomycin was 56.7 ± 7.5 and 100.70 ± 10.7 mL/min with the CT 110 and CT 190 membranes, respectively (P < 0.05). Significant rebound in vancomycin serum concentrations occurred after dialysis; this rebound appeared to be complete 3 h postdialysis. On the basis of postrebound concentrations, the apparent percent removal of vancomycin was 23.6 ± 1.2 and 25.2 ± 8.6% for CT 110 and CT 190 membranes, respectively (not significant). Vancomycin is significantly cleared during dialysis with cellulose triacetate membranes, and its clearance is dependent on membrane surface area. Although a small supplemental dose of vancomycin could be administered after dialysis to replace drug lost during dialysis, it may be more efficient to give a larger dose of vancomycin after several dialysis periods. The determination of vancomycin removal can be used to estimate vancomycin serum concentrations as well as dosage requirements. This in conjunction with serum concentration monitoring can be used to optimize vancomycin dosing.

Key Words: High flux, dialyzers, kinetics, rebound, antibiotics

Vancomycin is the antibiotic of choice for treating vascular infections in hemodialysis patients. This is primarily because of the bactericidal activity of vancomycin against most gram-positive pathogens that are responsible for such infections, including methicillin-resistant Staphylococcus aureus. The pharmacokinetic profile of vancomycin in hemodialysis patients also contributes to the widespread use of this agent. Vancomycin exhibits a prolonged half-life in the presence of renal failure and has negligible clearance by conventional dialysis membranes, allowing intravenous administration during the hemodialysis treatment and dosing intervals of 7 to 10 days (1–3).

The poor clearance of vancomycin during conventional hemodialysis is primarily a function of molecular weight (1,448 d). Conventional hemodialysis membranes composed of cellulose acetate and cuprophane show limited permeability to molecules the size of vancomycin (1). However, more permeable high-flux membranes have gained widespread acceptance for routine hemodialysis. These high-flux membranes, which include cellulose triacetate (CT), polysulfone (PS), and polyacrylonitrile (PAN) membranes, are designed to optimize clearance and decrease dialysis time. Because high-flux dialysis membranes allow the passage of larger molecules than are cleared with conventional membranes, the enhanced removal of vancomycin could be predicted. Several studies have
demonstrated the significant clearance of vancomycin with PS (4–6), PAN (6–9), and CT (6) membranes. Because vancomycin exhibits two-compartment pharmacokinetics, some of these studies that have omitted consideration of the postdialysis rebound of vancomycin concentrations may have overestimated the extent of vancomycin removal (4,7–9). In contrast, other studies have suggested that although vancomycin is cleared more readily with high-flux membranes, the redistribution of vancomycin from tissues to the vascular compartment after dialysis eliminates the need for any change in the conventional once-weekly vancomycin dosing regimen (5,10). Currently, controversy exists regarding the clinical implications of vancomycin clearance during hemodialysis with high-flux membranes. In addition, specific information regarding the effect of membrane surface area on vancomycin pharmacokinetics and redistribution is lacking.

The purpose of this study was to evaluate the pharmacokinetics of vancomycin during hemodialysis by the use of high-flux CT membranes. Specifically, the influence of membrane surface area on the dialysis clearance of vancomycin, as well as the postdialysis redistribution of vancomycin, was examined to provide a complete characterization of vancomycin clearance in the setting of hemodialysis with CT membranes.

METHODS

Subjects

Six subjects (four men and two women) with chronic renal failure on hemodialysis were enrolled in this randomized crossover trial. Before initiation, the study was approved by the hospital's institutional review board and written informed consent was obtained from each subject. All subjects had been stabilized on hemodialysis for at least 6 months and had baseline hematocrit between 25 and 35 vol%. Subjects with a history of hepatic disease, congestive heart failure, or hypersensitivity to vancomycin were excluded from study participation. Subjects who had evidence of infection or those who had received an antibiotic immediately before study participation were also excluded. All subjects were maintained on their regularly scheduled medications during the study period. None of the subjects received any agent(s) known to alter the pharmacokinetics of vancomycin during the study period.

Study Design

In a randomized, crossover manner, subjects were assigned to undergo hemodialysis with a CT 110 dialyzer (CT 110G; 1.1 m²; Baxter Healthcare, Deerfield, IL) or a CT 190 dialyzer (CT 190G; 1.9 m²; Baxter Healthcare). During each phase, subjects received a 1,000-mg intravenous dose of vancomycin and serial blood samples were obtained over a 5-day study period. A minimum of 2 wk separated each of the two study phases.

On Day 1 of each study phase, immediately after the completion of a routine hemodialysis session, 1,000 mg of vancomycin (Vancocin hydrochloride, Lot #6NM20A; Eli Lilly and Company, Indianapolis, IN) diluted in 250 mL of 0.9% saline was infused intravenously over 1 h. When subjects experienced pruritus or other infusion-related reactions, the infusion rate of vancomycin was decreased. However, the vancomycin infusion rate was standardized for each patient during the two study phases. Heart rate and blood pressure were monitored every 15 min during the vancomycin infusion. Before and 60 min immediately after the completion of the vancomycin infusion, venous blood samples (5 mL) were obtained in vacutainer tubes (Becton Dickinson). In addition, on Day 2 of the study, a venous blood sample was obtained 12 to 26 h after the vancomycin infusion. On the third study day, immediately before hemodialysis, a 5-mL venous blood sample was obtained. Subsequently, subjects underwent 3 to 3.5 h of dialysis with the Baxter SPS 550 dialysis machine (Baxter Healthcare) and the study dialyzer (CT 110 or CT 190). A new dialyzer was used for each study dialysis session. Hemodialysis blood flow rates and dialysate flow rates were maintained at 300 and 500 mL/min, respectively. The duration of each dialysis session (3.0 to 3.5 h) remained constant for each subject during each of the study phases. During hemodialysis, simultaneous arterial and venous blood samples were obtained hourly for the determination of vancomycin concentrations. Subsequently, venous blood samples for the determination of vancomycin concentrations were obtained immediately after the completion of dialysis and hourly for four additional hours postdialysis. On Day 5 of the study, a venous blood sample was obtained immediately before hemodialysis. After a minimum of a 2-wk washout period, subjects were crossed over to the alternate study phase and all study procedures were repeated.

Analytical

All blood samples collected were centrifuged at 2,000 rpm for 10 to 15 min. The serum was subsequently harvested and stored at −20°C until analysis. All samples were frozen within 60 min and were subsequently analyzed within 3 months after sample collection. The vancomycin concentrations were determined by an enzyme multiplied immunoassay technique (EMIT; Syva Company, San Jose, CA). The within-day coefficient of variation and the between-day coefficient of variation were 8.6 and 4.0% at 7 µg/mL, respectively, and 7.5 and 3.0% at 35 µg/mL, respectively.

The intradialytic elimination rate constant (Kd) was determined by linear regression of the natural log vancomycin arterial concentrations obtained hourly during dialysis. An estimate of the intradialytic elimination rate constant (Kd) was determined by linear regression of the terminal phase of the log vancomycin venous concentrations versus time profile during the interdialytic period. The intradialytic and interdialytic half-lives were calculated on the basis of 0.693/Kd and 0.693/Kd, respectively. The interdialytic elimination rate constants and interdialytic half-lives should be interpreted with caution because of the limited sampling duration of the study (e.g., 5 days). The area under the concentration-time curve from 0 to 92 h was calculated by use of the linear trapezoidal method. The plasma clearance of vancomycin during dialysis was calculated by use of the equation: 

\[ CL_s = \frac{Q_d}{1 - HCT(C_s/C_a) / HCT(C_s/C_v)} \]

where: \( CL_s = \) vancomycin clearance during dialysis, \( Q_d = \) blood flow rate, \( HCT = \) patient's hematocrit, and \( C_s \) and \( C_a \) are the vancomycin concentrations measured in samples obtained from the arterial and venous lines of the dialyzer, respectively. The apparent percent removal of vancomycin was calculated on the basis of concentrations obtained immediately postdialysis and 1, 2, 3, and 4 h thereafter by use of the equation: 

\[ \% \text{ removal} = \frac{(C_{\text{pret}} - C_{\text{post}})}{C_{\text{pret}}}/100 \]

where \( C_{\text{pret}} \) = apparent percent removal of vancomycin by hemodialysis.
at a given time (t) postdialysis, \( C_{\text{preHD}} \) = vancomycin serum concentration obtained immediately before dialysis, and \( C_{\text{postHD}} \) = vancomycin serum concentration obtained at a given time (t) postdialysis.

Differences in the pharmacokinetic parameters between the two study phases were examined by the use of a paired t test. In order to determine the time at which rebound was complete, postdialysis serum concentrations were compared by the use of repeated measures analysis of variance. Completion of redistribution was defined as the time at which there was no longer any significant change in vancomycin concentrations postdialysis. Differences between the means were evaluated by use of Tukey's studentized range test. Subsequently, percent rebound was calculated by: % rebound = \( \left( \frac{C_{\text{postHD}} - C_{\text{preHD}}}{C_{\text{preHD}}} \right) \times 100 \), where \( C_{\text{postHD}} \) = vancomycin serum concentration obtained immediately postdialysis, and \( C_{\text{preHD}} \) = vancomycin serum concentration obtained at a given time (t) postdialysis. P <0.05 was considered the critical probability level. Reported data are represented as the mean ± the standard deviation.

RESULTS

Six subjects with ESRD, four men and two women ranging in age from 21 to 68 yr (mean, 39.5 ± 19.9 yr) participated in this study. The precise causes of ESRD varied among the subjects but included: medullary sponge disease (N = 1), polycystic kidney disease (N = 1), hypertension (N = 2), congenital abnormalities (N = 1), and unknown (N = 1). Subjects had been receiving hemodialysis three times per week for an average of 6.0 ± 3.1 yr (range, 3.5 to 12.0 yr). Patients were maintained on all of their chronic medications during the study period, including some or all of the following: aluminum- or calcium-containing phosphate binders, calcitriol, iron, epoetin, ranitidine, renal multivitamins, antihypertensive agents, antihistamines, nonsteroidal anti-inflammatory agents, prednisone, quinine sulfate, codeine, diazepam, levothyroxine, nitrates, and male or female hormones. None of these agents is known to influence vancomycin pharmacokinetics. The average height and dry weight of the subjects were 64.8 ± 4.2 inches and 62.7 ± 6.9 kg, respectively. Therefore, the vancomycin dose ranged from 13.9 to 19.4 mg/kg dry body wt (mean, 16.1 ± 1.9 mg/kg).

Although the vancomycin was to be infused over 1 h, the rate of infusion needed to be decreased in three subjects because of adverse reactions. During the vancomycin infusion, three of the six subjects developed pruritis, which necessitated slowing the infusion rate; intravenous diphenhydramine was also administered to two of these subjects to help alleviate the reaction. In these three subjects, pruritis recurred when vancomycin was administered in the second phase of the study and required that the same measures be taken. In no case was the infusion discontinued because of adverse reactions. Because of the decrease in infusion rate, the mean duration of the vancomycin infusion during the CT 110 and the CT 190 study phases was 1.48 ± 0.18 and 1.39 ± 0.40 h, respectively (not significant [NS]).

As shown in Figure 1, the mean vancomycin concentrations declined over time, with concentrations declining rapidly during hemodialysis. After the discontinuation of dialysis, a significant rebound in concentrations was observed. Serum concentrations obtained 1 h after the completion of the vancomycin infusion ranged from 31.30 to 57.30 and 28.10 to

![Figure 1. Mean vancomycin venous concentration (CONC) versus time profiles during study phases with the CT-110 (open squares) and the CT-190 (closed squares) dialyzers.](image-url)
Concentrations slowly redistributed over time, with redistribution being complete 3 h after the discontinuation of dialysis. The percent rebound in vancomycin serum concentrations ranged from 14.74 to 42.31 and 23.08 to 230.77%, after dialysis with the CT 110 and the CT 190 dialyzers, respectively (NS). Because of the redistribution in concentrations postdialysis, the apparent percent removal of vancomycin is dependent on the time at which it is assessed. Table 2 depicts the apparent percent removal of vancomycin calculated on the basis of concentrations obtained immediately and 1, 2, 3, and 4 h after the completion of dialysis. The apparent percent removal of vancomycin calculated, after redistribution was complete, ranged from 22.5 to 25.9% with the CT 110 and from 10.9 to 35.3% with the CT 190 dialyzers, respectively (NS).

Serum concentrations on Day 5 of the study, immediately before dialysis, ranged from 9.7 to 19.2 and 8.5 to 16.7 μg/mL during the CT 110 and the CT 190 study phases, respectively (NS). The average apparent percent decrease in serum concentrations from immediately before dialysis on Day 3 until immediately before dialysis on Day 5 was 36.39 ± 5.7 and 38.87 ± 7.31% during the CT 110 and the CT 190 study phases, respectively. This time interval included one dialysis treatment day and 1 day between dialysis.

**DISCUSSION**

This study clearly demonstrates that vancomycin is removed during hemodialysis with CT high-flux membranes. The clearance of vancomycin during hemodialysis was dependent on membrane surface area and was dramatically higher than that previously reported with conventional dialysis membranes (1). Although the removal of vancomycin during dialysis with conventional dialysis membranes is minimal, several studies, including this study, demonstrate that vancomycin is removed during dialysis with high-flux membranes (4–10). Previous studies evaluating vancomycin pharmacokinetics during hemodialysis with high-flux membranes have reported intradialytic clearances ranging from 31.1 to 122.6 mL/min and apparent percent removal of vancomycin ranging from 13 to 49.5% (4–8). Differences in study design including type of dialysis membrane used (e.g., PAN, PS, CT), surface area of the membrane, dialysis conditions (e.g., blood flow rate, dialysate flow rate, duration of dialysis, etc.), sampling scheme, the assay used to determine vancomycin concentrations (e.g., fluorescence polarization immunoassay versus enzyme multiplied immunoassay), and the pharmacokinetic equations used have contributed to the variable results that have been reported.

Many previous studies based their estimates of apparent percent removal of vancomycin with high-flux hemodialysis on serum concentrations obtained at the end of or immediately after the completion of dialysis (4,7,8). This study clearly demonstrates that after the discontinuation of dialysis, vancomycin con-
Vancomycin Kinetics During Hemodialysis

![Graph showing vancomycin clearance during dialysis for each subject during dialysis with the CT-110 and the CT-190 dialyzers. Vancomycin clearance during dialysis for Subjects 1, 2, 3, 4, 5, and 6 are represented by open square, asterisk, closed square, triangle, circle, and diamond, respectively. Mean clearance is depicted by the hatched lines.]

Figure 2. Vancomycin clearance during dialysis for each subject during dialysis with the CT-110 and the CT-190 dialyzers. Vancomycin clearance during dialysis for Subjects 1, 2, 3, 4, 5, and 6 are represented by open square, asterisk, closed square, triangle, circle, and diamond, respectively. Mean clearance is depicted by the hatched lines.

### TABLE 2. Apparent percent removal of vancomycin by hemodialysis as a function of time

<table>
<thead>
<tr>
<th>Time Post-HD</th>
<th>CT 110</th>
<th>CT 190</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immediately Post-HD</td>
<td>41.3 ± 4.0</td>
<td>55.7 ± 13.5*</td>
</tr>
<tr>
<td>1 h Post-HD</td>
<td>34.8 ± 10.9</td>
<td>31.8 ± 8.5</td>
</tr>
<tr>
<td>2 h Post-HD</td>
<td>28.1 ± 4.1</td>
<td>28.5 ± 7.9</td>
</tr>
<tr>
<td>3 h Post-HD</td>
<td>23.6 ± 1.2</td>
<td>25.2 ± 8.6</td>
</tr>
<tr>
<td>4 h Post-HD</td>
<td>25.3 ± 2.9</td>
<td>26.6 ± 5.9</td>
</tr>
</tbody>
</table>

*Data are presented as mean ± standard deviation. Apparent percent removal of vancomycin = ((vancomycin serum concentration obtained immediately before dialysis - vancomycin serum concentration obtained at time (t) postdialysis)/vancomycin serum concentration immediately before dialysis) * 100, where t = immediately postdialysis and 1, 2, 3, and 4 h after the completion of dialysis.

This study demonstrates that the clearance of vancomycin during hemodialysis was influenced by the surface area of the dialysis membrane. The CT 110 dialyzer has a membrane surface area of 1.1 m², whereas the CT 190 dialyzer has a membrane surface area of 1.9 m². The 72.7% increase in surface area was associated with an approximately 77.6% increase in vancomycin clearance. Although the increase in clearance was roughly directly proportional to the increase in surface area, it is important to recognize that this is not always a linear function (e.g., doubling the surface area does not always equate with a doubling in clearance). The observation that an increase in membrane surface area results in an increase in vancomycin clearance has also been observed with the polysulfone high-flux membranes (4). Although Lanese and co-

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workers demonstrated that the clearance of vancomycin during hemodialysis with the PS membranes increased in a linear fashion on the basis of membrane surface area, the precise relationship between membrane surface area and vancomycin clearance appears different than that observed in our study (4). Specifically, the clearance of vancomycin during hemodialysis was 44.7 ± 6.7, 73.0 ± 5.0, and 85.2 ± 7 mL/min with the PS F-40 (0.65 m²), F-60 (1.2 m²), and F-80 (1.80 m²), respectively, as compared with 64.3 ± 21.3 and 113.5 ± 35.1 mL/min with the CT 110 (1.1 m²) and the CT 190 (1.9 m²), respectively. The differences observed in vancomycin clearances as well as the relationship between clearance and membrane surface area between the two studies may be attributed to membrane properties (e.g., PS versus CT) and/or study design.

Conversely, the lack of a statistically significant difference in the apparent percent removal of vancomycin between the two treatment phases most likely is the result of the multicompartment distribution of the drug, leading to profound redistribution postdialysis. Hemodialysis with the CT membranes efficiently removes vancomycin from the central (plasma) compartment. However, the volume of distribution of vancomycin (i.e., amount of vancomycin) in the central (e.g., plasma) compartment is relatively small as compared with that in the peripheral (i.e., tissue) compartment. Therefore, during dialysis, the redistribution of vancomycin from the tissues to the plasma becomes a rate-limiting step for vancomycin removal (11). Postdialysis, redistribution occurs and a rebound in plasma concentrations is observed. Thus, the percent removal of vancomycin with the CT membranes, taking into account redistribution, is not significantly influenced by membrane surface area.

Similar kinetic behavior during hemodialysis is observed for substances, such as oxalate, that are removed directly from the vascular pool but that are also present in extravascular stores that exchange slowly with the vascular space. Recent data suggest that the reduction in the circulating level of oxalate during a single hemodialysis treatment approximates that observed with urea (well over 60%). Prominent features of oxalate kinetics include a rebound in circulating concentration as well as a small, effective, acutely exchangeable volume of distribution (12). Thus, the interpretation of total removal for any substance cannot be based solely on the acute reduction in circulating concentration unless the effect of second (or third) spaces is evaluated. The significance of redistribution remains unknown regarding some presumed uremic toxins. For example, the reduction in circulating guanidine compounds has been shown to acutely decrease by more than 70% during hemodialysis (13), but the distribution spaces and rebound phenomenon have not been elucidated.

Overall, the results from this study have several clinical implications: First, on the basis of the redistribution in vancomycin serum concentrations that occurs after the completion of dialysis, it is important not to obtain vancomycin serum concentrations during the redistribution phase (e.g., before 3 h postdialysis). The use of concentrations obtained before the completion of redistribution will lead to an overestimation of vancomycin removal, and this may clinically translate into errors in dosing. Second, although the clearance of vancomycin during dialysis with the CT membranes was influenced by membrane surface area, the actual percent removed was not. Clinically, this means that similar vancomycin serum sampling and/or dosing strategies can be used, regardless of membrane surface area. Third, the apparent percentage of vancomycin removed by hemodialysis can be estimated on the basis of predialysis and postredistribution serum concentrations and taking into account double-pool redistribution effects.

Because it is not always practical to calculate the percentage of vancomycin removed during hemodialysis for an individual patient, one can use our findings to estimate the amount of vancomycin removed during a 3-h dialysis session with a CT membrane. Specifically, we demonstrated that approximately 25% of vancomycin is removed during a 3-h dialysis session with the CT 1.1- and 1.9-m² membranes with blood flow and dialysis flow rates of 300 and 500 mL/min, respectively. Clinically, this estimate (25%) can be used to calculate when vancomycin serum concentrations should be obtained and/or when redosing may be necessary. For example, assuming dialysis conditions similar to those used in this study, if a patient had a vancomycin serum concentration of 20 µg/mL immediately before dialysis, one could anticipate that the serum concentration would be approximately 15 µg/mL after the completion of redistribution postdialysis. Alternatively, because minimal vancomycin is eliminated between dialysis sessions in anephric patients, one could also estimate the vancomycin serum concentration before the next dialysis session. Using our data from functionally anephric subjects, we found that vancomycin serum concentrations decreased by approximately 37% from the beginning of one dialysis session to the next. Clearly, these values should only be used as crude estimates and vancomycin serum concentration should be monitored and individualized on a case-by-case basis. It is important to recognize that many patient conditions including sepsis may alter both the clearance and the distribution of vancomycin. These estimates can, however, theoretically be used to assist the clinician in (1) approximating when vancomycin will reach a given serum concentration, (2) estimating when to obtain serum concentrations, and (3) estimating vancomycin dosing requirements.

In summary, vancomycin is removed during hemodialysis with the CT dialyzers. However, if one takes into consideration the redistribution of vancomycin from the tissues after the discontinuation of dialysis, only approximately 25% of vancomycin is removed during a 3-h dialysis session. Theoretically, a small
supplemental dose of vancomycin (i.e., 25% of the dose) could be administered after dialysis to replace this loss. However, we believe that it is important to adjust vancomycin doses on the basis of serum concentration monitoring. For example, during this study, serum concentrations on Day 5 of the study, immediately before the second dialysis session, ranged from 8.5 to 19.2 μg/mL. This suggests that some patients may only need to be dosed after two or three dialysis sessions. Estimation of the amount of vancomycin removed during dialysis in conjunction with serum concentration monitoring should assist the clinician in optimizing therapy.

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