Pharmacokinetics of Vancomycin in Patients Undergoing Continuous Ambulatory Peritoneal Dialysis

ROGER D. BLEVINS,1 CHARLES E. HALSTENSON,2,3 NANDA G. SALEM,4 AND GARY R. MATZKE2,3*

Department of Medicine, Section of Cardiovascular Diseases, Sinai Hospital of Detroit, Detroit, Michigan 48235; Drug Evaluation Unit, Hennepin County Medical Center, Regional Kidney Disease Program, Minneapolis, Minnesota 554152; College of Pharmacy, University of Minnesota, Minneapolis, Minnesota 554553; and Department of Medicine, William Beaumont Hospital, Royal Oak, Michigan 480724

Received 28 November 1983/Accepted 1 March 1984

The pharmacokinetics of vancomycin were studied in four patients on continuous ambulatory peritoneal dialysis. After a single intravenous infusion of 10 mg/kg of total body weight, multiple blood, urine, and dialysate samples were collected during a 72-h evaluation period. The steady-state volume of distribution was 0.73 ± 0.07 (mean ± standard deviation) liters/kg with a beta half-life of 90.2 ± 24.2 h. The continuous ambulatory peritoneal dialysis clearance of vancomycin was 1.35 ± 0.35 ml/min, and the serum clearance was 6.4 ± 1.1 ml/min. Peritoneal dialysate concentrations of vancomycin were rapidly attained after the intravenous infusion and averaged 2.2 ± 0.7 mg/liter throughout the 72-h observation period. A loading dose of 23 mg/kg followed by a maintenance dose of 17 mg/kg every 7 days should attain and maintain therapeutic serum and dialysate concentrations. More frequent dosing may be necessary for less susceptible organisms.

Continuous ambulatory peritoneal dialysis (CAPD) is a self-dialysis procedure which is now widely used for the management of end-stage renal disease. The most frequent complication of CAPD is peritonitis. Over 65% of these infections are caused by gram-positive organisms, and ca. 50% are due to staphylococcal species (P. K. Peterson, and W. F. Keane, in J. S. Remington and M. N. Swartz, ed., Current Clinical Topics in Infectious Diseases, in press). Clinical effectiveness of vancomycin against staphylococci is well documented (1, 5, 7, 9, 14). The MICs of vancomycin have ranged from 0.63 to 3.12 mg/liter for Staphylococcus aureus and from 1.56 to 3.12 mg/liter for Staphylococcus epidermidis (6, 8, 10, 16). Thus, vancomycin could be an extremely useful antibiotic for the management of infections in the CAPD patient.

The pharmacokinetics of intravenously administered vancomycin in patients undergoing CAPD have, until recently, not been rigorously evaluated (4). The purpose of this study was to assess vancomycin concentrations in serum, peritoneal dialysate fluid, and urine after administration of a single intravenous dose. The pharmacokinetic parameters determined are as follows: elimination rate, elimination half-life, volume of distribution, total body clearance, and peritoneal clearance.

MATERIALS AND METHODS

Patients. Four patients (two males and two females) with end-stage renal disease undergoing CAPD gave written, informed consent to participate in this study. All patients had been on CAPD for at least 2 months (range, 2 to 14 months), and none had experienced peritonitis in the previous 2 months. Patients requiring systemic antibiotic therapy or who had a known allergy to vancomycin were excluded. Each patient had a physical examination and a laboratory screening profile done before and after they were studied. All patients had an indwelling Tenckhoff catheter in place. The CAPD exchange schedule for all patients was 2 liters of 2.5% glucose peritoneal dialysis solution (PD I; Travenol Laboratories, Deerfield, Ill.) four times a day. An intravenous catheter was placed in a forearm vein and was used to infuse the drug. A single dose of 10 mg/kg of total body weight was infused over a 30-min period. A heparin lock was placed in a forearm vein in the contralateral arm, and blood samples were collected before and 0, 1, 2, 3, 4, 5, 6, 7, 24, 32, and 72 h after the end of the intravenous infusion. Urine was collected in three 24-h fractions, beginning with the start of the intravenous infusion. The total dialysate return after each instillation was collected. Dialysate volume was recorded, and a sample was retained for determination of vancomycin concentration.

Concentrations of vancomycin in serum, peritoneal dialysate, and urine were measured in duplicate by radioimmunoassay (American Diagnostics, Newport Beach, Calif.). The minimum quantifiable vancomycin concentration was 1 mg/liter. The interassay coefficients of variation for this procedure were 9, 6.5, and 9.8% at 4, 17, and 32 mg/liter, respectively.

Data analysis. The decline in vancomycin concentration in the serum of each patient was biexponential. Therefore, the data were analyzed in terms of the following equation: 

\[ C = Ae^{-at} + Be^{-bt} \]

where \( C \) is the concentration in serum at time \( t \), \( A \) and \( B \) are the intercepts, and \( a \) and \( b \) are the disposition rates obtained from the first and second phases, respectively, of the plot of log vancomycin concentration in serum versus time.

Initial estimates of the parameters in the above equation were obtained by standard curve stripping procedures. Final estimates were obtained by nonlinear regression analysis with the program KINA on a Control Data digital computer (University Computing Center, University of Minnesota, Minneapolis, Minn.). All vancomycin concentrations were weighted according to their reciprocal squared concentrations during the computer fitted procedure. Since the vancomycin doses were infused over a period of 30 min, results of the computer analyses were analyzed with the appropriate equations for the biphasic decay of log concentration versus time after the termination of an intravenous infusion (19).

* Corresponding author.
The volume of distribution of the central compartment, the steady state volume of distribution, the half-life of the alpha and beta phases, and the serum clearance were calculated by standard techniques (11). The area under the serum concentration-versus-time curve (AUC) to infinity time (AUC∞) was calculated for each subject by the trapezoidal method, and extrapolation of the area to infinity was calculated as: AUC∞ = Ctt/β, where Ct is the last concentration data point.

The CAPD clearance (CLCAPD) and renal clearance (CLR) of vancomycin were calculated by the following methods:

\[ \text{CL}_{\text{CAPD}} = \frac{A_d}{\text{AUC}_{0-72}} \] and \[ CL_R = \frac{A_u}{\text{AUC}_{0-72}} \]

where A_d and A_u equal the amount of drug recovered in the dialysate and urine, respectively, during the 72-h sampling period, and AUC_{0-72} equals the AUC during the 72-h sampling period. The nonrenal clearance (CLNR) was calculated as: \( CL_{\text{NR}} = CL_S - CL_{\text{CAPD}} - CL_R \), where CL_S equals the serum clearance.

The multiple-dose kinetic profile of vancomycin during CAPD was simulated with the mean coefficients and exponentials derived from this population. The following equations were used to predict the steady-state concentrations after repeated doses:

\[ C_n = \frac{X_0 (\alpha - k_{21})}{V_1 (\alpha - \beta)} \left( 1 - e^{-\alpha t} \right) + \frac{X_0 (k_{21} - \beta)}{V_1 (\alpha - \beta)} \left( 1 - e^{-\beta t} \right) \]

and \( X_0 = X_0 \left[ \frac{1}{1 - e^{-\beta t}} \right] \), where C is the serum concentration at any time t, n is the number of doses, \( \tau \) is the dosing interval, \( X_0 \) is the maintenance dose, \( X_0' \) is the loading dose, \( k_{21} \) is the transfer rate constant from the peripheral to central compartment, and \( V_1 \) is the volume of distribution of the central compartment.

### RESULTS

The vancomycin serum concentration time profile of the four subjects is shown in Fig. 1. Biexponential decay of vancomycin serum concentrations is evident in each case. The demographic data and kinetic parameters derived from the two-compartment open model analysis of the serum concentration-time data are shown in Tables 1 and 2, respectively. The serum clearance of vancomycin was 6.42 ± 1.10 ml/min (mean ± standard deviation). This was composed of the CLR of 0.65 ± 0.00 ml/min, CLCAPD of 1.35 ± 0.35 ml/min, and CLNR of 4.74 ± 0.93 ml/min. The CLNR of vancomycin in these four subjects approximates the total body clearance observed in patients with end-stage renal disease maintained on hemodialysis (6).

The peritoneal dialysis concentrations of vancomycin ranged from 1.0 to 4.9 mg/liter during the 72-h observation period (Fig. 1). The mean peritoneal dialysate concentration of vancomycin was 2.2 ± 0.7 mg/liter. Simulation of the multidose serum concentration-time profile of vancomycin was carried out. A loading dose of 23 mg/kg, followed in 7 days with a maintenance dose of 17 mg/kg every 7 days,
TABLE 1. Patient demographic data

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Wt (kg)</th>
<th>Ht (cm)</th>
<th>Duration (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>25</td>
<td>60.9</td>
<td>170</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>77</td>
<td>67.7</td>
<td>168</td>
<td>14</td>
</tr>
<tr>
<td>3</td>
<td>F</td>
<td>78</td>
<td>71.3</td>
<td>168</td>
<td>7</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>73</td>
<td>63.1</td>
<td>155</td>
<td>2</td>
</tr>
<tr>
<td>Mean</td>
<td></td>
<td>63.3</td>
<td>65.8</td>
<td>165</td>
<td>6.5</td>
</tr>
<tr>
<td>SD</td>
<td></td>
<td>25.6</td>
<td>4.7</td>
<td>7</td>
<td>5.4</td>
</tr>
</tbody>
</table>

would be required to attain and maintain peak concentrations (1 h after the end of the infusion) of 30 mg/liter and trough concentrations of 7.5 mg/liter, assuming the results of the study apply to multiple dosing of vancomycin.

**DISCUSSION**

The elimination half-life of vancomycin in subjects with normal renal function has been reported to approximate 8 h with wide interpatient variability (range, from 4.7 to 11.2 h) (3, 5, 13). In patients with end-stage renal disease, i.e., creatinine clearance, <10 ml/min, the elimination half-life of vancomycin is significantly prolonged. The half-life has ranged from 40 to 400 h, with an average of 146.5 h (C. E. Halstenson, W. F. Keane, and G. R. Matzke, Abstr. 13th Int. Congr. Chemotherapy, Vienna, Austria, p. 123/1–123/8, 1983). The mean half-life of vancomycin in these four CAPD patients was 90.2 ± 24.2 h, with a range from 59.4 to 115.4 h. The calculated CL\textsubscript{CAPD} of vancomycin was 1.35 ± 0.35 ml/min. The mean total body clearance of these four patients when corrected for the contribution of CAPD was 5.1 ± 1.0 ml/min, a value nearly identical to that reported in subjects with end-stage renal disease undergoing hemodialysis (5.0 ml/min) (Halstenson et al., Abstr. 13th Int. Congr. Chemotherapy, 1983).

Although the pharmacokinetics and peritoneal dialysis clearance of vancomycin in patients undergoing chronic intermittent peritoneal dialysis have been thoroughly investigated (2, 12, 14, 17), only limited information is available regarding the impact of CAPD on the pharmacokinetics of vancomycin (4, 18). After a single 1-gm intraperitoneal dose was administered to four patients, Pancorbo and Comty (18) reported that ca. 54% of the dose was absorbed into the systemic circulation and that peak serum concentrations of ca. 24 mg/liter were attained. After the peak serum concentration had been attained, the mean elimination half-life was 66.9 h, and the peritoneal dialysis clearance was 2.4 ml/min. The authors concluded that therapeutic serum levels of vancomycin can be achieved after intraperitoneal administration of 1 gm of vancomycin, allowing a 6-h equilibration period. They recommended that after this dose, 10 to 20 mg of vancomycin per liter be added to each bag of dialysate to maintain therapeutic serum levels.

Bunke et al. (4) evaluated the pharmacokinetics of vancomycin after intravenous administration (five patients) and intraperitoneal administration (six patients). The mean CL\textsubscript{CAPD} and half-life of vancomycin after intraperitoneal administration closely approximated the values previously reported by Pancorbo and Comty (18). The mean parameters after intravenous administration closely approximated the result of this investigation. The peritoneal dialysis clearance of vancomycin was 1.4 ± 0.95 ml/min, whereas the elimination half-life was 77 ± 27 h. Bunke et al. (4) concluded that little vancomycin was removed by CAPD and that intraperitoneal levels were subtherapeutic after intravenous vancomycin administration.

Although the results of our pharmacokinetic evaluations are similar to those of Bunke et al. (4), we do not concur with their conclusion that intravenous vancomycin administration may not provide appropriate peritoneal concentrations for the treatment of peritonitis. The peritoneal dialysate fluid concentrations of vancomycin varied more than fourfold in these four patients during the 72-h observation period. However, the peritoneal fluid-to-serum concentration ratio of vancomycin in the four patients at 6 and 72 h after administration was relatively stable (0.23 ± 0.067 and 0.28 ± 0.056). The attainment of therapeutic systemic concentrations of vancomycin, i.e., peak concentrations of 30 mg/liter, should thus result in the attainment of peritoneal dialysate concentrations in the range of 7 to 8 mg/liter. Peritoneal dialysate concentrations of vancomycin in this range have proved adequate for the treatment of many staphylococcal species (8, 9, 14). Thus it is likely that adequate peritoneal dialysate concentrations of vancomycin may be attainable when aggressive systemic vancomycin therapy is used.

In the setting of severe systemic gram-positive infections in patients undergoing CAPD, an initial loading dose of 23 mg/kg of total body weight of vancomycin should achieve concentrations 1 h after the end of the infusion of ca. 30 mg/liter. Subsequent doses of 17 mg/kg administered every 7 days should maintain peak and trough serum concentrations of 30 and 7.5 mg/liter, respectively. Peritoneal dialysate vancomycin concentrations should fluctuate between 7 to 8 and 1.5 to 2 mg/liter while patients are receiving doses on this schedule. The attainment of peak and trough serum

**TABLE 2. Pharmacokinetic data**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Dose (mg)</th>
<th>t\textsubscript{1/2α} (h)</th>
<th>t\textsubscript{1/2β} (h)</th>
<th>k\textsubscript{12} (h\textsuperscript{-1})</th>
<th>k\textsubscript{21} (h\textsuperscript{-1})</th>
<th>V\textsubscript{1} (liters/kg)</th>
<th>V\textsubscript{c} (liters/kg)</th>
<th>CL\textsubscript{S} (ml/min)</th>
<th>CL\textsubscript{CAPD} (ml/min)</th>
<th>CL\textsubscript{S} (ml/min)</th>
<th>CL\textsubscript{CAPD} (ml/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
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<td>0.75</td>
<td>59.4</td>
<td>0.398</td>
<td>0.523</td>
<td>0.35</td>
<td>0.62</td>
<td>7.37</td>
<td>0.65</td>
<td>4.89</td>
<td>1.83</td>
</tr>
<tr>
<td>2</td>
<td>700</td>
<td>0.80</td>
<td>84.3</td>
<td>0.549</td>
<td>0.305</td>
<td>0.26</td>
<td>0.74</td>
<td>6.94</td>
<td>0.65</td>
<td>5.92</td>
<td>1.02</td>
</tr>
<tr>
<td>3</td>
<td>750</td>
<td>1.50</td>
<td>101.8</td>
<td>0.248</td>
<td>0.212</td>
<td>0.37</td>
<td>0.79</td>
<td>6.50</td>
<td>0.65</td>
<td>4.48</td>
<td>1.37</td>
</tr>
<tr>
<td>4</td>
<td>650</td>
<td>2.07</td>
<td>115.4</td>
<td>0.135</td>
<td>0.196</td>
<td>0.45</td>
<td>0.76</td>
<td>4.85</td>
<td>0.65</td>
<td>3.68</td>
<td>1.17</td>
</tr>
<tr>
<td>Mean</td>
<td>675</td>
<td>1.27</td>
<td>90.2</td>
<td>0.332</td>
<td>0.309</td>
<td>0.36</td>
<td>0.73</td>
<td>6.42</td>
<td>0.65</td>
<td>4.74</td>
<td>1.35</td>
</tr>
<tr>
<td>SD</td>
<td>65</td>
<td>0.63</td>
<td>24.2</td>
<td>0.180</td>
<td>0.150</td>
<td>0.08</td>
<td>0.07</td>
<td>1.10</td>
<td>0.00</td>
<td>0.93</td>
<td>0.35</td>
</tr>
</tbody>
</table>

\*Abbreviations for the pharmacokinetic parameters: t\textsubscript{1/2α} and t\textsubscript{1/2β}, half-life of the alpha and beta phases, respectively; k\textsubscript{12}, transfer rate constant from the central to the peripheral compartment; k\textsubscript{21}, transfer rate constant from the peripheral to the central compartment; V\textsubscript{1}, volume of distribution of the central compartment; V\textsubscript{c}, volume of distribution at steady state; and CL\textsubscript{S}, serum clearance.
concentrations within these ranges has been associated with clinical improvement (8–10).

Results of this study suggest that the administration of intravenous vancomycin may provide adequate therapy for the treatment of most systemic and intraperitoneal staphylococcal infections in patients undergoing CAPD. Although peritoneal penetration of vancomycin may be increased in the presence of peritonitis (15), more frequent dosing may be necessary if less-susceptible organisms are suspected. The administration of intraperitoneal vancomycin and the monitoring of peritoneal dialysate vancomycin concentrations may not be necessary.

LITERATURE CITED