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Vancomycin Pharmacokinetics in Patients with Peritonitis on Peritoneal Dialysis

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Vancomycin pharmacokinetics were studied in four patients with peritonitis undergoing chronic intermittent peritoneal dialysis. Serum levels exceeding 4.0 μg/ml were maintained for 8 and 13 days after a single 1-g intravenous dose. Vancomycin serum concentrations measured before, during, and upon completion of dialysis revealed no appreciable decline. Peritoneal fluid concentrations in two patients exceeded 4.0 μg/ml for more than 12 days.

The clinical effectiveness of vancomycin against staphylococci is well documented (3, 6, 8, 9). The minimum inhibitory concentrations of vancomycin range from 0.63 to 3.12 μg/ml for *Staphylococcus aureus* and from 1.56 to 3.12 μg/ml for *Staphylococcus epidermidis* (3, 5, 7, 9, 11, 14). Maintenance of vancomycin fluid concentrations equal to or greater than 4.0 μg/ml has been correlated with prevention (11) and treatment (2, 7, 8) of staphylococcal infections.

We report vancomycin serum, peritoneal, and dialysate fluid concentrations after administration of a single intravenous (i.v.) dose. Values for the elimination rate, elimination half-life, and total body clearance were determined in four patients. Peritoneal clearance values were determined in two patients.

(This work was previously presented in part [B. E. Magera, J. Arroyo, S. Rosansky, and B. Postic, Abstr. Annu. Meet. Am. Soc. Microbiol. 1982, A91, p. 16].)

MATERIALS AND METHODS

Patients. Four chronic intermittent peritoneal dialysis patients with end-stage renal failure were admitted for management of severe uremia and acute peritonitis. The patients' age ranged from 49 to 87 years, and the patients had residual creatinine clearances ranging from 2.35 to 10.25 ml/min. Peritoneal cultures revealed *S. epidermidis* in three patients and a sterile eosinophilic peritonitis in one patient. All patients had greater than 300 leukocytes per ml of peritoneal fluid.

Drug administration and tissue sampling. Patients received a single 1- or 2-g i.v. dose of vancomycin. Vancomycin was diluted in normal saline or 5% dextrose solution to a concentration not exceeding 50 mg/ml and was administered as a 30- to 60-minute infusion. Blood and dialysate fluid were sampled simultaneously at selected time intervals before, during, and upon completion of dialysis. Peritoneal fluid was collected from patients 2 and 4 before initiation of six to eight cycles of dialysis.

Dialysate, peritoneal fluid, and blood samples were collected in Vacutainer separation tubes. Blood samples were centrifuged, and the serum was withdrawn. All samples were kept frozen until assayed.

Dialysate fluid is the fluid which drains from the peritoneum after the 15-min dwell time of each dialysis cycle. The total volume of dialysate outflow was measured, and a 20- to 30-ml sample was obtained. Peritoneal fluid was defined as the fluid which is present in the peritoneum after an overnight rest period from dialysis.

Vancomycin assays. Determination of vancomycin concentrations was performed by Eli Lilly Laboratories, Indianapolis, Ind., using a radioimmunoassay (Monitor Science Corp.). Each specimen was analyzed in duplicate. Serum and peritoneal fluid samples were diluted 1:100 in a 0.01 M solution of phosphate-buffered saline. Dialysate samples were diluted 1:10 in buffered saline. Phosphate-buffered saline solution contains 1.0% human serum. Vancomycin standards were prepared in normal serum at concentrations of 0.1, 0.5, 1, 2, 4, 8, 16, 32, and 64 μg/ml. The radioimmunoassay is specific for vancomycin, and cross-reactivity or interference with other antimicrobial agents does not occur (4).

Samples from patient 4 were analyzed in triplicate by a microbiological assay (2, 3) described by Sabath et al. (13). The indicator strain used was *Bacillus subtilis*. Vancomycin standards were prepared in normal serum at concentrations of 2.5, 5, 10, 20, 40, and 80 μg/ml. To ensure the inactivation of β-lactam derivatives possibly present, without affecting vancomycin measurements (13), samples and standards were pretreated for 15 min with 50,000 U of *Bacillus cereus* 569, a commercial penicillinase, per ml.

Dialysis procedure. A volume of 2,000 ± 50 ml of dialysate, containing either 1.5 or 4.25% dextrose (Dianeal; Travenol, Deerfield, Ill.), was instilled through a permanent peritoneal catheter. The fill, dwell, and drainage times were preset for 5, 15, and 25 min, respectively, with an automated peritoneal dialyzer (Peritoneal Dialysis System; American Medical Products Corp.).

Pharmacokinetic analysis. By means of a Hewlett-Packard 85 computer program, serum vancomycin concentrations were fitted to a regression line by the

method of least mean squares according to the equation $\ln C = \ln C_0 + \beta \cdot t$. C equals the vancomycin concentration in serum at time t (micrograms per milliliter), and C_0 equals the back-extrapolated theoretical serum drug concentration at time zero (micrograms per milliliter). The quantity β equals the hybrid or overall elimination rate constant and is obtained from the slope $-\beta/2.303$ of a semilogarithmic plot of drug concentration in serum versus time or slope of the log linear regression line (day^{-1}). The elimination half-life of vancomycin was calculated by dividing $\ln_2$ by the slope. The apparent volume of distribution (V_d), systemic clearance (Cl_s), and peritoneal clearance (Cl_p) were calculated by the following equations: $V_d = \text{dose/AUC} \cdot \beta$, $Cl_s = \text{dose/AUC}$, and $Cl_p = D \cdot V/t \cdot C_{\text{midpt}}$. Dose is the intravenous dose administered (grams); AUC is the total area under the serum concentration-versus-time curve obtained by using the trapezoidal rule (from time 0 to time t of the last sample) and extrapolated to infinity using β; D is the concentration of drug in the dialysis fluid (micrograms per milliliter); V is the total volume of dialysate outflow (milliliters); t is the time required to complete the exchange (fill + dwell + drainage times in minutes); and C_{midpt} is the vancomycin serum concentration at the midpoint of the dialysis procedure (micrograms per milliliter).

RESULTS

Serum concentrations. Figure 1 depicts the vancomycin serum concentrations after a single 1-g (patients 1, 2, and 3) or 2-g (patient 4) dose. The straight line portion of the graph describes the β (elimination) phase, and the curved part represents the α (distribution) phase. After a 1-g dose, serum vancomycin concentrations obtained 30 and 60 min postinfusion were 24.0 and 18.5 μg/ml, respectively. The last serum determinations from patients 1, 2, and 3 were obtained 8.1, 3.8, and 13.2 days postinfusion and measured 5.8, 8.6, and 4.6 μg/ml. The duration of peritoneal dialysis was 8 h (patient 1), 45.1 h (patient 2), and 98 h (patient 3).

Approximately 12 h after a 2-g dose to patient 4, a vancomycin serum concentration was 66.0 μg/ml. On day 20, a serum level of vancomycin measured 6.5 μg/ml despite a total of 107 h of peritoneal dialysis.

Patients 3 and 4 are representative of peritoneal dialysis effects upon vancomycin serum concentrations (Table 1). In patient 3, a comparison of pre- and postdialysis serum levels obtained on study days 5, 6, 11, and 12 revealed no more than a 0.1% decline. Vancomycin serum concentrations measured before and upon completion of 72 h of continuous peritoneal dialysis (days 7 through 10) decreased less than 0.2%.

After a 2-g vancomycin dose to patient 4, pre- and postdialysis serum levels measured on day 9 varied 0.05%. On day 12, midpoint and postdialysis serum concentrations declined 0.2%. On days 13 and 20, vancomycin serum concentrations obtained before and at the midpoint of dialysis revealed no change.

Peritoneal fluid levels. Figure 2 depicts the vancomycin elimination profiles in serum and peritoneal fluid as determined in patients 3 and 4. Three days after a 1-g dose to patient 3, vancomycin concentrations in serum and peritoneal fluid were 8.9 and 7.6 μg/ml, respectively. Subsequent vancomycin peritoneal fluid concentrations exceeded 5.0 μg/ml for nearly 12 days. On day 12, a serum level measured 4.5 μg/ml, and the corresponding peritoneal fluid level was 4.0 μg/ml.

At 12 h after a 2-g dose to patient 4, vancomy-

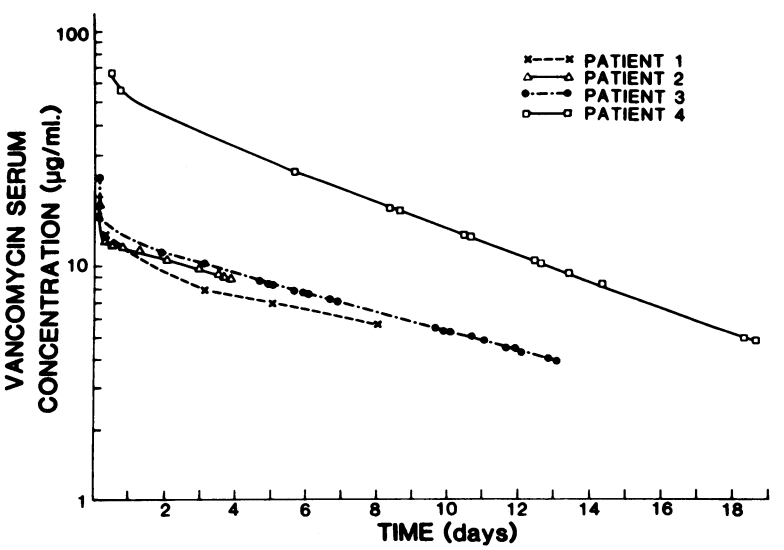

FIG. 1. Semilogarithmic plot of vancomycin serum concentration versus time after a single i.v. 1-g (patients 1, 2, and 3) or 2-g (patient 4) dose.

TABLE 1. Effect of peritoneal dialysis upon vancomycin serum concentrations after 1-g (patient 3) or 2-g (patient 4) dose

Patient no.	Study day	Sampling time[a]	Vancomycin concn (μg/ml) in serum
3	5	Pre	7.9
	5	Mid	7.3
	5	Post	7.1
	6	Pre	7.0
	6	Mid	6.8
	6	Post	6.8
	7	Pre	6.5
	10	Post	5.5
	11	Pre	5.2
	11	Post	5.0
	12	Pre	5.0
	12	Mid	4.9
	12	Post	4.5
4	9	Pre	19.0
	9	Post	18.0
	12	Mid	12.0
	12	Post	10.0
	13	Pre	10.0
	13	Mid	10.0
	20	Pre	6.5
	20	Mid	6.5

[a] Pre, Predialysis; Mid, dialysis midpoint; Post, after dialysis.

cin concentrations were 66.0 μg/ml in serum and 37.0 μg/ml in peritoneal fluid. Sequential vancomycin levels in serum and peritoneal fluid obtained simultaneously were 12 and 10 μg/ml (day 10); 10 and 9.6 μg/ml (day 12); 7.0 and 6.0 μg/ml (day 14); and 6.5 and 6.0 μg/ml (day 18).

Pharmacokinetic parameters. The mean pharmacokinetic parameters were calculated as shown in Table 2.

Peritoneal clearance values were determined in two patients by the equations described above. Data used for the peritoneal clearance value calculations are shown in Table 3. The mean peritoneal clearance values reported represent the average value of three determinations from data obtained on three separate days. Mean peritoneal clearance values were calculated as 1.04 ± 0.285 ml/min for patient 3 and 3.64 ± 1.147 ml/min for patient 2.

The amount of vancomycin cleared by peritoneal dialysis can be calculated. Assuming vigorous peritoneal dialysis (up to 100 h), a serum concentration of 4.0 μg/ml, and a peritoneal clearance equal to 2.4 ml/min, less than 60 mg of a 1-g dose is removed by peritoneal dialysis: (2.4 ml/min) (60 min/h) (100 h) (4 μg/ml) (1 mg/1,000 μg) = 57.6 mg. Thus, only a small fraction of a single 1-g i.v. vancomycin dose is cleared during a week of peritoneal dialysis at 14 h/day.

DISCUSSION

The average elimination half-life of vancomycin in normal subjects is 6 to 8 h (3, 8–11) with a wide interpatient variability ranging from 4.7 to 11.2 h (10). In four chronic intermittent peritoneal dialysis patients, the mean half-life of vancomycin was 8.55 ± 2.601 days. The shortest calculated half-life was determined in patient 4 and may be attributed to his improved creatinine clearance during the study. The calculated peritoneal clearance of vancomycin was less than

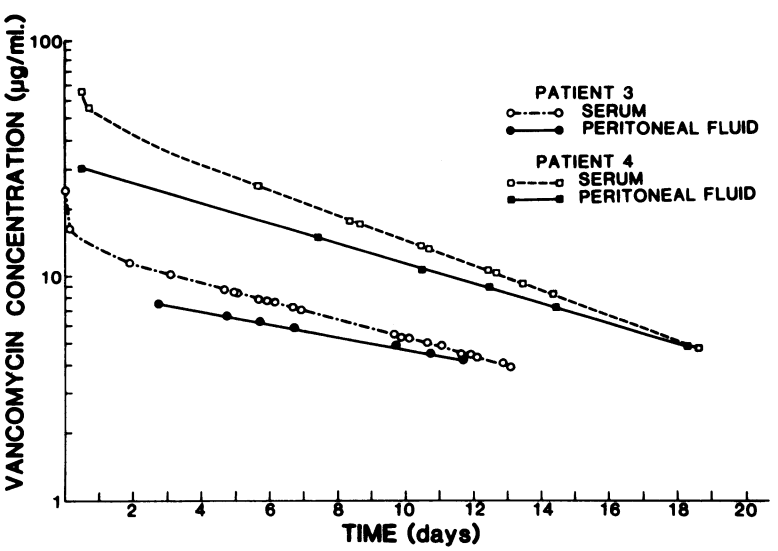

FIG. 2. Vancomycin elimination profiles in serum and peritoneal fluid after a single 1-g (patient 3) or 2-g (patient 4) i.v. dose.

TABLE 2. Vancomycin pharmacokinetic parameters in patients with peritoneal dialysis and associated peritonitis[a]

Patient no.	β (days^{-1})	$t_{1/2\beta}$ (days)	AUC (μg/ml · h)	V_d (liters/kg)	Cl_s (ml/min)
1	0.064	10.79	3,715.57	1.23	4.48
2	0.095	7.34	3,529.81	1.12	4.72
3	0.065	10.63	4,047.39	1.40	4.12
4	0.127	5.47	4,525.98	0.53	3.68
Mean ± SD	0.087 ± 0.0295	8.55 ± 2.601	3,954.69 ± 436.91	1.07 ± 0.377	4.25 ± 0.616

[a] See text for definitions of parameters.

4.0 ml/min. The mean volume of distribution was 1.07 liters/kg, nearly identical to values reported in normal subjects (0.92 liter/kg) (10).

Two reports (1, 12) addressing vancomycin peritoneal clearance cite values less than 10 ml/min; however, the authors' conclusions and dosing recommendations are conflicting. After a single 1-g i.v. dose to one patient, Ayus et al. (1) reported vancomycin concentrations exceeding 5.0 μg/ml in serum and peritoneal fluid for more than 16 days after 40 h of peritoneal dialysis per week. These authors concluded that vancomycin is not rapidly eliminated by peritoneal dialysis and recommended the administration of a single 1-g i.v. vancomycin dose every 7 to 19 days for the treatment of staphylococcal peritonitis.

After a single 1-g i.v. dose of vancomycin to 11 anuric patients, Nielsen et al. (12) calculated a mean peritoneal clearance of 6.1 ml/min. These authors based their calculations on three serum determinations obtained 1, 8, and 15 h after drug administration. Samples were obtained while patients were undergoing 15 h of peritoneal dialysis. During the 15-h sampling interval, a 39.7% decline in serum vancomycin concentrations was noted. These authors concluded that vancomycin was significantly cleared by peritoneal dialysis and that supplemental dosing upon completion of dialysis was necessary to maintain effective tissue drug concentrations. We do not concur with their conclusions. Although Nielsen et al. (12) observed an approximate 40% decline in serum drug levels, vancomycin serum concentrations remained greater than 15 μg/ml at the completion of 15 h of dialysis. In patients 2 and 3 of our study, we also noted a near 50% decline in serum vancomycin concentrations which occurred within 10 and 44 h, respectively, after drug administration. Nevertheless, serum drug concentrations exceeding 4.0 μg/ml were maintained for 8 and even up to 13 days. On several occasions, we compared serum drug levels obtained before, during, and upon completion of dialysis and found no appreciable differences in values. Thus, it is unlikely that the initial decline in serum drug levels that Nielsen et al. observed 15 h after drug administration was due to enhanced drug elimination by peritoneal dialysis.

In the setting of bacterial peritonitis complicating intermittent peritoneal dialysis, a single 1-g i.v. dose of vancomycin achieves effective blood and peritoneal fluid levels which are maintained for at least 7 days despite 6 to 8 h of daily peritoneal dialysis. After vancomycin administration, all patients exhibited clinical improvement, a decrease in total peritoneal fluid cell count, negative posttherapy cultures, or some or all of these. In anuric patients, supplemental intraperitoneal or i.v. dosing of vancomycin upon completion of peritoneal dialysis appears unnecessary. Whether the peritoneal clearance rate of vancomycin may be enhanced during dialysis procedures which utilize a longer dwell time (i.e., continuous ambulatory peritoneal dialysis or continuous cycle peritoneal dialysis) was not determined by this study. If improve-

TABLE 3. Peritoneal clearance of vancomycin in peritonitis[a]

Patient no.	Study day	D (μg/ml)	V (ml)	t (h)	C_{midpt} (μg/ml)	Cl_p (ml/min)
2	1	1.3	15,800	8.3	9.4	4.37
	2	1.2	22,800	10.75	10.0	4.24
	3	1.1	18,575	12.25	12.0	2.32
3	3	0.45	32,820	30.08	6.5	1.26
	4	0.36	31,920	51.41	5.2	0.72
	6	0.33	32,240	67.99	5.0	1.15

[a] See text for definitions of parameters.

ment in renal function occurs after vancomycin administration, additional doses may be necessary depending upon actual vancomycin serum and peritoneal fluid concentrations.

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LITERATURE CITED

1. **Ayus, J. C., J. F. Eneas, T. G. Tong, N. L. Benowitz, P. Y. Schoenfeld, K. L. Hadley, C. E. Becker, and M. H. Humphreys.** 1979. Peritoneal clearance and total body elimination of vancomycin during chronic intermittent peritoneal dialysis. Clin. Nephrol. 11:129–132.
2. **Barcenas, C. G., T. J. Fuller, J. Elms, R. Cohen, and M. G. White.** 1976. Staphylococcal sepsis in patients on chronic hemodialysis regimens. Arch. Intern. Med. 136:1131–1134.
3. **Cook, F. V.** 1978. Vancomycin revisited. Ann. Intern. Med. 88:813–818.
4. **Crossley, K. B., J. C. Rotschafer, M. M. Chern, K. E. Mead, and D. E. Zaske.** 1980. Comparison of a radioimmunoassay and a microbiological assay for measurement of serum vancomycin concentrations. Antimicrob. Agents Chemother. 17:654–657.
5. **Ein, M. E., N. J. Smith, J. F. Aruffo, M. S. Heeremа, M. W. Bradshaw, and T. W. Williams.** 1979. Susceptibility and synergy studies of methicillin-resistant *Staphylococcus epidermidis*. Antimicrob. Agents Chemother. 16:655–659.
6. **Esposito, A. L., and R. A. Gleckman.** 1977. Vancomycin: a second look. J. Am. Med. Assoc. 238:1756–1757.
7. **Eykyn, S., I. Phillips, and J. Evans.** 1970. Vancomycin for staphylococcal shunt site infections in patients on regular hemodialysis. Br. Med. J. 3:80–82.
8. **Fekety, R.** 1982. Vancomycin. Med. Clin. North Am. 66:175–181.
9. **Geraci, J. E.** 1977. Vancomycin. Mayo Clin. Proc. 52:631–634.
10. **Krogstad, D. J., R. C. Moellering, and D. J. Greenblatt.** 1980. Single-dose kinetics of intravenous vancomycin. J. Clin. Pharmacol. 20:197–201.
11. **Morris, A. J., and R. T. Bilinsky.** 1971. Prevention of staphylococcal shunt infections by continuous vancomycin prophylaxis. Am. J. Med. Sci. 262:87–92.
12. **Nielsen, H. E., I. Sorensen, and H. E. Hansen.** 1979. Peritoneal transport of vancomycin during peritoneal dialysis. Nephron 24:274–277.
13. **Sabath, L. D., J. I. Casey, R. A. Ruch, L. L. Stumpf, and M. Finland.** 1971. Rapid microassay of gentamicin, kanamycin, neomycin, streptomycin and vancomycin in serum or plasma. J. Lab. Clin. Med. 78:457–463.
14. **Schaad, U. B., G. H. McCracken, and J. E. Nelson.** 1980. Clinical pharmacology and efficacy of vancomycin in pediatric patients. J. Pediatr. 96:119–126.