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Comparative Study of Intraperitoneal and Intravenous Vancomycin Pharmacokinetics during Continuous Ambulatory Peritoneal Dialysis

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The pharmacokinetic characteristics of vancomycin were investigated in eight patients undergoing continuous ambulatory peritoneal dialysis. A crossover design was used. Four noninfected patients received both a 15-mg/kg (body weight) intravenous dose and a 30-mg/kg intraperitoneal (i.p.) dose. Bioavailability ranged from 0.35 to 0.65 after i.p. administration. i.p. absorption was rapid, with concentrations in serum of 8.8 ± 6 μg/ml noted at 1 h and peak values of 30.4 ± 7 μg/ml at 6 h. A slow distribution phase was apparent, with a terminal elimination phase emerging after 12 to 24 h. Vancomycin was eliminated slowly, with a mean total clearance of 5.0 ± 1.3 ml/min, and concentrations in serum were 7.0 ± 1.2 μg/ml at 168 h. The mean serum half-life was 91.7 ± 28.1 h, and similar pharmacokinetics were noted after intravenous administration. Subsequently, four patients with catheter-related exit site or tunnel infections received a 30-mg/kg i.p. dose of vancomycin and displayed a similar kinetic pattern. This method of administering vancomycin achieved therapeutic serum and end-dwell dialysate concentrations over a 1-week period, represents a simple, cost-effective therapy which avoids the possibility of infusion-related toxicity, and deserves further investigation in patients with continuous ambulatory peritoneal dialysis-related peritonitis.

Continuous ambulatory peritoneal dialysis (CAPD) is growing as an alternative to hemodialysis for the treatment of end-stage renal disease. However, bacterial peritonitis predominantly caused by gram-positive cocci remains a major complication (20). The development of methicillin resistance among staphylococci and the resultant lack of susceptibility to penicillins and cephalosporins has led to an expanded role for vancomycin in the treatment of these infections (23).

Dosing recommendations for vancomycin advocate a loading dose of 1 g intravenously (i.v.) and the addition of 30 mg/liter to subsequent dialysis exchanges (15). Although recent studies investigated an alternative approach which does not require the continuous addition of certain antibiotics to each exchange during the treatment of peritonitis (13, 21, 22), kinetic data to support this approach with vancomycin are lacking. Previous reports on i.v. vancomycin administration to CAPD patients described a low plasma clearance with a prolonged serum half-life (2, 4), and although once-weekly i.v. dosing is advocated by some (10), detailed studies of vancomycin kinetics over a 1-week period after a single dose have not been conducted. Studies on intraperitoneal (i.p.) administration have revealed 50% absorption of drug with low concentrations in serum and subtherapeutic dialysate concentrations over a 72-h period (2, 16). Consequently, on the basis of these data we designed the present study to (i) compare vancomycin pharmacokinetics after a 30-mg/kg (body weight) i.p. dose (to compensate for 50% i.p. absorption) with a 15-mg/kg i.v. dose given in a crossover fashion, and (ii) analyze the vancomycin concentrations in serum and dialysate thus achieved over a 1-week period.

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MATERIALS AND METHODS

Eight adult patients with end-stage renal disease participating in the CAPD program at the Erie County Medical Center were enrolled in the study after giving informed consent. Patients were excluded if they had a history of recent infection, a history of vancomycin allergy, or abnormal coagulation parameters.

An intraindividual crossover study design was used, in which four subjects received both an i.v. and an i.p. dose of vancomycin with a 4-week washout period between doses. In addition, four patients with catheter-related exit site or tunnel infections received an i.p. dose only. The patients were studied in the CAPD unit for the first 12 h and on an ambulatory basis for the remaining sample collection period. Before vancomycin administration, a complete blood count, serum electrolytes, creatinine, glucose, blood urea nitrogen, and prothrombin time were determined.

After a 10-min, gravity-fed infusion of 2 liters of 1.5% Dianeal 137 (Travenol Laboratories, Deerfield, Ill.) into the peritoneal cavity, a single 15-mg/kg dose of vancomycin (lot 9LN59A; Eli Lilly & Co., Indianapolis, Ind.) was administered over 60 min via an indwelling venous catheter. During the initial 24 h, dialysis fluid exchanges were made approximately every 6 h, with subsequent exchanges scheduled every 4 to 8 h throughout the study period. Blood samples (5 ml) were collected in nonheparinized tubes from an indwelling venous catheter in the arm contralateral to the infusion site at 0, 0.5, 1, 2, 3, 4, and 6 h (end of dialysis cycle 1), 7, 9, and 12 h (end of dialysis cycle 2), and 24, 48, 72, and 168 h after the initiation of drug administration. Peritoneal fluid samples (5 ml) were collected at 0, 0.5, 1, 2, 3, 4, 6, 7, 9, and 12 h after drug administration. Dialysis fluid exchanges were continued every 4 to 8 h, with the volume of each exchange recorded and a sample taken. For i.p. administration, a single 30-mg/kg dose of vancomycin was admixed with 2,000 ml of dialysis fluid and introduced into the peritoneal cavity by gravity infusion over 10 min. During the crossover

segment, blood and dialysis fluid were collected as described above; blood samples were obtained at 6, 24, 72, and 144 h from the patients who received i.p. vancomycin only.

Blood was allowed to clot at room temperature, and serum was obtained by centrifugation. Serum and dialysate samples were placed in dry ice within 1 h of collection and then stored at −20°C until assayed. Dialysate samples collected on an ambulatory basis from 96 to 144 h were frozen at home for up to 48 h before transfer to −20°C.

The concentration of vancomycin in serum and dialysate was measured by modification of a previously reported high-performance liquid chromatography assay (12). The mobile phase consisted of 12% acetonitrile and 88% 0.1 M heptanesulfonic acid. Separation was obtained with a Varian Micropak C-18 column (Varian Laboratories, Walnut Creek, Calif.) at a flow rate of 1.0 ml/min. Vancomycin was detected by UV absorption at a wavelength of 210 nm.

The analytical standard of vancomycin used for the assay was provided by Lilly Research Laboratories, Indianapolis, Ind. Serum standards were prepared in blank pooled plasma, and the dialysate standards were prepared in fresh dialysate. Serum standards (1.56 to 100 μg/ml) were run in duplicate, and chromatographic peak heights were determined. Standard curves were linear over the range of 1.56 to 100 μg/ml and typically had correlation coefficients of 0.99. For dialysate samples obtained during the first 6 h after an i.p. dose, standards were prepared from 100 to 800 μg/ml.

Vancomycin was extracted from serum and dialysate as previously described (12). To 500 μl of sample (serum or dialysate), 500 μl of acetonitrile was added, and the mixture was vortexed for 60 s, shaken for 5 min, and centrifuged (1,200 × *g*) for 5 min. After decanting into a polypropylene tube, 2 ml of anhydrous ether was added, and the mixture was vortexted, shaken, and centrifuged as described above. The ether phase was aspirated, and 20 μl of the remaining aqueous phase was injected onto the column.

The intraday relative standard deviations for the 25-μg/ml standard were 3.2% in serum and 5.6% in dialysate. The interday relative standard deviation in serum and dialysate was 7%, and the measured recovery of vancomycin was consistently 75%.

One patient received trimethoprim-sulfamethoxazole before entering the study and subsequently demonstrated interference with the high-performance liquid chromatographic (HPLC) assay. The serum and dialysate samples from this patient were analyzed by fluorescence polarization immunoassay (FPIA) (TDX; Abbott Laboratories, North Chicago, Ill.), which was previously shown not to be interfered with by trimethoprim-sulfamethoxazole (19). Standard curves were prepared using a concentration range of 0 to 100 μg/ml. The intraday and interday variability at 7 and 75 μg/ml was less than 3 and 5%, respectively. Correlation of the two assay methods has been described by the equation $y(\text{FPIA}) = 1.11x\ (\text{HPLC}) + 2.06$ (8).

Pharmacokinetic analysis. Noncompartmental analysis was used to calculate the time-average pharmacokinetic parameters describing the disposition of vancomycin. The total serum clearance (CL), the net peritoneal dialysis clearance ($CL_{P\text{-}net}$), and the steady state volume of distribution (V_{ss}) were determined by the following equations:

$$CL = D/AUC \tag{1}$$

$$CL_{P\text{-}net} = X_D(t_1-t_2)/AUC(t_1-t_2) \tag{2}$$

$$V_{ss} = (AUMC/AUC) \cdot CL \tag{3}$$

where $X_D(t_1-t_2)$ equals the amount of drug recovered in the dialysis fluid from t_1 to t_2 (t_1 = 0 h; t_2 = 168 h). After the i.p. dose, t_1 was 12 h to account for residual drug which was not drained out at 6 h. D is the amount of drug administered, and AUMC is the area under the time multiplied by the concentration-versus-time curve. The area under the curve (AUC) and AUMC were calculated by LaGrange polynomial interpolation and integration (17).

The fraction of vancomycin systematically absorbed after i.p. administration ($F_{i.p.}$) was calculated as the ratio of AUC after i.p. and i.v. dosing with a correction for the dose and with the assumption that clearance remained constant between each part of the study:

$$F_{i.p.} = \frac{AUC_{i.p.} \times D_{i.v.}}{AUC_{i.v.} \times D_{i.p.}} \tag{4}$$

$F_{i.p.}$ was also calculated based on the amount of drug recovered in the dialysate after i.p. administration:

$$F_{i.p.} = \frac{(D_{i.p.} - X_{D(6\,h)})}{D_{i.p.}} \tag{5}$$

where $X_{D(6\,h)}$ is the amount of drug recovered in the dialysate after the initial 6-h dialysis cycle. Serum half-life was determined from the terminal slope by linear least-squares regression analysis.

RESULTS

The serum and dialysate concentration profiles attained after i.v. vancomycin administration are shown in Fig. 1. Vancomycin distributed slowly declined, with a final elimination phase emerging after 12 to 24 h. The mean peak concentration in serum was 57.1 ± 9.3 μg/ml, which decreased to 19.8 ± 4.9 μg/ml at 24 h: it was 8.6 ± 2.7 μg/ml at 168 h. A mean total clearance of 5.0 ± 1.3 ml/min was determined, and the $CL_{P\text{-}net}$ was 1.2 ± 0.5 ml/min. The mean V_{ss} was 0.61 ± 0.2 liter/kg, and the terminal elimination half-life in serum was 111 ± 22 h.

Vancomycin appeared rapidly in peritoneal fluid and increased to a peak of 5.8 ± 2.6 μg/ml at the end of the initial dwell. End-dwell dialysate vancomycin concentrations were >2 μg/ml for most of the dialysate exchanges over the 1-week period, except in patient 4, who had >1 μg/ml in dialysate for 86 h.

The serum and dialysate concentration profiles attained after i.p. vancomycin administration are shown in Fig. 2. Vancomycin appeared rapidly in serum (8.8 ± 6 μg/ml at 1 h) and peak concentrations in serum (30.4 ± 7.2 μg/ml) occurred at the end of the 6-h dwell period in two patients and during the second dwell period in the remaining two patients, suggesting continued absorption of residual drug. A slow decline of concentrations in serum, as described during the i.v. study, was noted. The mean concentration of vancomycin in serum at 24 h was 21.0 ± 1.7 μg/ml and declined to 7.0 ± 1.2 μg/ml at 168 h. Mean total clearance was 5.0 ± 1.3 ml/min, with a mean $CL_{P\text{-}net}$ of 1.7 ± 0.9 ml/min. The mean volume of distribution was 0.56 ± 0.3 liter/kg, and the mean terminal elimination half-life in serum was 91.7 ± 28 h.

Absorption of drug from the peritoneal cavity proceeded in a linear fashion, with mean systemic absorption values of 0.46 ± 0.14 (equation 4). After the 0- to 6-h drug administration dwell period, vancomycin concentrations in dialysate remained quite high, and they ranged from 9.6 to 144 μg/ml

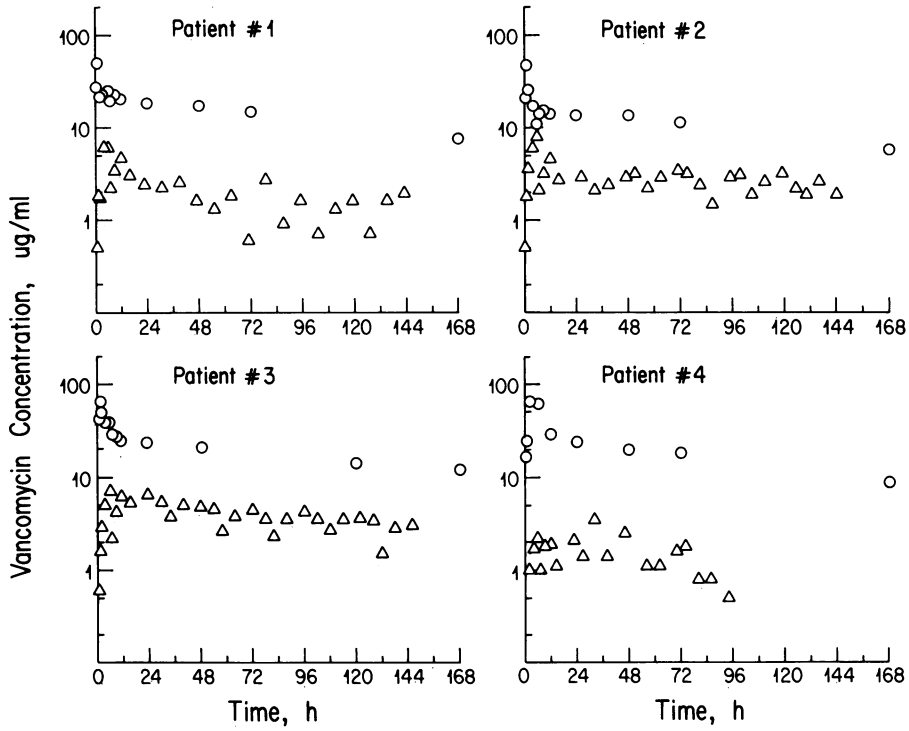

FIG. 1. Serum (○) and dialysate (△) concentration-time profiles after a 15-mg/kg i.v. dose of vancomycin. Dialysate values are end-dwell concentrations which reflect accumulation of vancomycin over the dwell period.

at 12 h. End-dwell vancomycin concentrations in dialysate subsequently remained >2 μg/ml. The serum and dialysate data and individual pharmacokinetic characteristics obtained during the crossover study are shown in Tables 1 and 2, respectively.

Subsequently, four additional patients, who received i.p. vancomycin only, yielded similar serum profiles and kinetic results. The mean concentration in serum at 6 h was 24.9 ± 5.6 μg/ml, which declined to 14.6 ± 2.0 μg/ml at 24 h and 7.5 ± 2.5 μg/ml at 144 h. The mean serum half-life was 104 h.

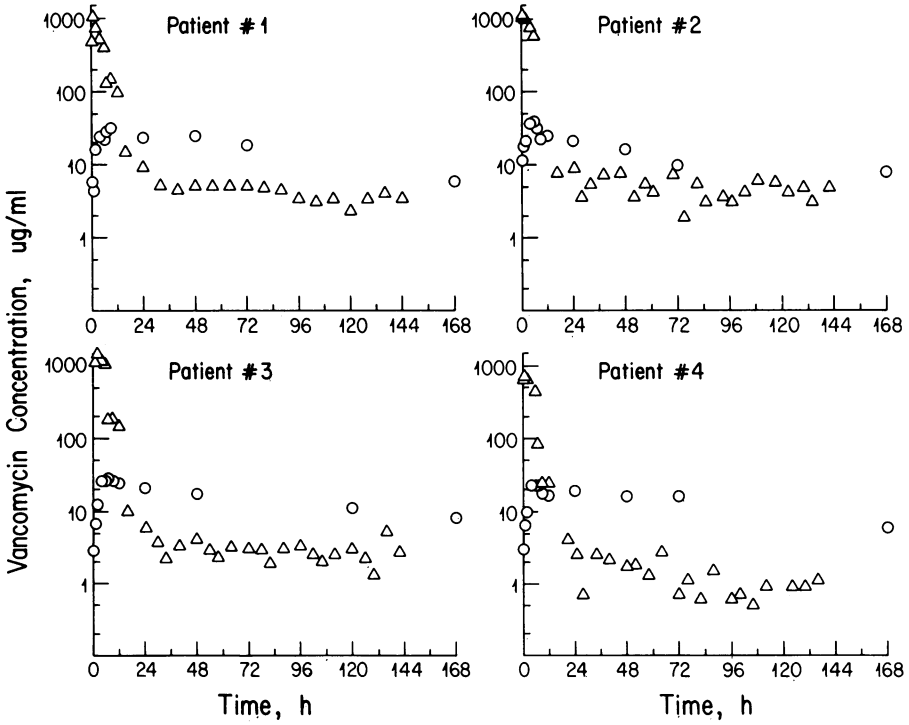

FIG. 2. Serum (○) and dialysate (△) concentration-time profiles after a 30-mg/kg i.p. dose of vancomycin. Dialysate values are end-dwell concentrations which reflect accumulation of vancomycin over the dwell period.

TABLE 1. Serum and end-dwell dialysate vancomycin concentrations after i.v. and i.p. administration during crossover study

Sample and route of administration (dose)	Vancomycin concn (μg/ml; $\bar{x}$ ± SD) at:							
	Peak	6 h	12 h	24 h	48 h	72 h	144 h[a]	168 h
Serum								
i.v. (15 mg/kg)	57.1 ± 9.3			19.8 ± 4.9		15.4 ± 3.1		8.6 ± 2.7
i.p. (30 mg/kg)	30.4 ± 7.2			21.0 ± 1.7		15.0 ± 3.6		7.0 ± 1.2
Dialysate								
i.v. (15 mg/kg)		5.8 ± 2.6	4.3 ± 1.8		3.0 ± 1.4		2.3 ± 0.6	
i.p. (30 mg/kg)		610 ± 295	59.2 ± 73.8		4.7 ± 2.5		3.6 ± 1.1	

[a] Mean values for patients 1, 2, and 3 only.

DISCUSSION

In contrast to the current practice of continuously adding vancomycin to each dialysis exchange, the results from the present study indicate that a single, weekly i.p. dose achieves adequate drug levels in serum and dialysate. Administration of 30 mg/kg i.p. (twice the usual i.v. dose) can overcome the limited i.p. absorption of this drug (Fig. 1 and 2). However, in contrast to the case with i.v. administration, early elevations of vancomycin concentrations in serum are avoided when the drug is given i.p. These high concentrations are thought to elicit histamine-mediated reactions during i.v. vancomycin therapy (9). In addition, i.v. vancomycin has been associated with the occurrence of spasmodic low back pain in CAPD patients (7).

The appearance of vancomycin in serum occurred rapidly after an i.p. dose; therefore, both serum and dialysate attain therapeutic concentrations shortly after instillation of the drug into the peritoneal cavity. However, the overall absorption rate was slow, and the significance of a 6-h dwell period to allow time for adequate absorption must be appreciated. The $F_{i.p.}$ (equation 5) of 0.52 ± 0.16 in the present study is consistent with earlier results which ranged from 0.54 to 0.71 (2, 4, 16, 18). It should be noted that drug which remains in the peritoneal cavity after drainage of dialysate may lead to an overestimation of $F_{i.p.}$ (see comparison of equations 4 and 5 in Table 2) and may also prolong the time to peak in serum secondary to continued absorption during the next dwell period.

After i.v. and i.p. administration of vancomycin, a slow distribution phase was apparent. This delayed period of distribution was previously described in patients with normal renal function (3, 6, 9); however, it seems that patients with end-stage renal disease have an even more prolonged distribution phase (2, 4, 5, 11). This slow distribution could place the patient with end-stage renal disease at risk of developing infusion-related reactions when vancomycin is given too rapidly via the i.v. route.

No previous results on intrapatient variability of vancomycin clearance have been reported in CAPD patients, and we noted almost identical values during this crossover study. The mean value of 5.0 ml/min is similar to that described by Blevins et al. (2) and Pancorbo and Comty (16); however, Bunke et al. (4) determined clearance values of 9.4 and 15.1 ml/min after i.v. or i.p. administration in different patients. The $CL_{P\text{-}net}$ in the present study was also similar to results of previous studies (2, 4, 16). Although vancomycin was removed slowly via CAPD, the end-dwell dialysate concentrations attained were above the MIC for most susceptible bacteria. This may explain the good clinical outcome which was previously noted when a weekly i.v. dose was used for CAPD-related peritonitis (10).

The serum half-life of vancomycin after i.p. administration was 105 ± 36 h, which is similar to what Blevins et al. (2) found (90 h) but longer than that reported by Pancorbo and Comty (16; 67 h) and Bunke et al. (4; 66 h). Both Pancorbo and Bunke et al. appear to have determined the half-life by using serum concentrations obtained at 4 and 6 h when calculating their linear regression; in addition, they sampled for only 48 to 72 h. As a result, the serum half-life was underestimated, because concentrations decline more rapidly during the distribution phase and the entire disposition profile was not characterized. A similar calculation also appears to explain earlier reports of serum half-life values of 18 and 30 h in patients on chronic intermittent peritoneal dialysis (1, 14).

In summary, this study demonstrated that by increasing the i.p. dose of vancomycin to 30 mg/kg per 2 liters of

TABLE 2. Pharmacokinetic characteristics of vancomycin in noninfected CAPD patients during crossover study[a]

Patient	Route of administration	AUC (mg/liter · h)	CL (ml/min)	V_{ss} (liters/kg)	$t_{1/2}$ (h)	$F_{i.p.}$[b]	$F_{i.p.}$[c]	$CL_{P\text{-}net}$ (ml/min)
1	i.v.	3,438	5.9	0.64	100			0.9
	i.p.	3,232	5.9	0.41	58.2	0.47	0.74	1.6
2	i.v.	2,585	6.0	0.82	96.1			1.6
	i.p.	3,277	6.4	0.97	119	0.65	0.46	2.8
3	i.v.	5,368	3.9	0.54	136			1.6
	i.p.	3,572	4.0	0.45	111	0.35	0.35	1.7
4	i.v.	4,562	3.7	0.44	101			0.7
	i.p.	3,086	3.8	0.39	79.1	0.35	0.52	0.7
Mean ± SD	i.v.	3,988 ± 1,225	5.0 ± 1.4	0.61 ± 0.16	111 ± 22			1.2 ± 0.5
	i.p.	3,292 ± 204	5.0 ± 1.3	0.56 ± 0.28	91.7 ± 28	046 ± 0.14	0.52 ± 0.16	1.7 ± 0.9

[a] AUC, Area under the curve; CL, clearance; V_{ss}, volume of distribution at steady state; $t_{1/2}$, half-life; $CL_{P\text{-}net}$, net peritoneal dialysis clearance.
[b] See equation 4.
[c] See equation 5.

dialysate and allowing it to dwell within the peritoneal cavity for 6 h, the problem of limited peritoneal absorption of this drug can be overcome. This dosage of drug also appears to be well tolerated by the patient, and serum and end-dwell dialysate drug concentrations exceed the MIC for susceptible pathogens over a 1-week period. i.p. administration avoids the high concentrations in serum seen after i.v. dosing, thus potentially reducing the risk of adverse reactions. Further evaluation of this convenient dosing regimen is warranted in CAPD patients with peritonitis.

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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. **Blevins, R. D., C. E. Halstenson, N. G. Salem, and G. R. Matzke.** 1984. Pharmacokinetics of vancomycin in patients undergoing continuous ambulatory peritoneal dialysis. Antimicrob. Agents Chemother. **25**:603–606.
3. **Blouin, R. A., L. A. Bauer, D. D. Miller, K. E. Record, and W. O. Griffen, Jr.** 1982. Vancomycin pharmacokinetics in normal and morbidly obese subjects. Antimicrob. Agents Chemother. **21**:575–580.
4. **Bunke, C. M., G. R. Aronoff, M. E. Brier, R. S. Sloan, and F. C. Luft.** 1983. Vancomycin kinetics during continuous ambulatory peritoneal dialysis. Clin. Pharmacol. Ther. **34**:631–637.
5. **Cunha, B. A., R. Quintiliani, J. M. Deglin, M. W. Izard, and C. H. Nightingale.** 1981. Pharmacokinetics of vancomycin in anuria. Rev. Infect. Dis. **3**(Suppl.):269–272.
6. **Cutler, N. R., P. K. Narang, L. J. Lesko, M. Ninos, and M. Power.** 1984. Vancomycin disposition: the importance of age. Clin. Pharmacol. Ther. **36**:803–810.
7. **Gatterer, G.** 1984. Spasmodic low back pain in a patient receiving intravenous vancomycin during continuous ambulatory peritoneal dialysis. Clin. Pharm. **3**:87–89.
8. **Jehl, F., C. Gallion, R. C. Thierry, and H. Monteil.** 1985. Determination of vancomycin in serum by high-pressure liquid chromatography. Antimicrob. Agents Chemother. **27**:503–507.
9. **Krogstad, D. J., R. C. Moellering, and D. J. Greenblatt.** 1980. Single-dose kinetics of intravenous vancomycin. J. Clin. Pharmacol. **20**:197–201.
10. **Krothapalli, R. K., H. O. Senekjian, and J. C. Ayus.** 1983. Efficacy of intravenous vancomycin in the treatment of gram-positive peritonitis in long-term peritoneal dialysis. Am. J. Med. **75**:345–348.
11. **Magera, B. E., J. C. Arroyo, S. J. Ronsanky, and B. Postic.** 1983. Vancomycin pharmacokinetics in patients with peritonitis on peritoneal dialysis. Antimicrob. Agents Chemother. **23**:710–714.
12. **McCain, J. B. L., R. Bongiovanni, and S. Brown.** 1982. Vancomycin quantitation by high-performance liquid chromatography in human serum. J. Chromatogr. **231**:463–466.
13. **Morse, G. D., D. M. Janicke, R. Cafarell, M. A. Apicella, W. J. Jusko, and J. J. Walshe.** 1985. Moxalactam epimer disposition in patients undergoing continuous ambulatory peritoneal dialysis. Clin. Pharmacol. Ther. **38**:150–156.
14. **Nielsen, H. E., I. Sorenson, and H. E. Hansen.** 1979. Peritoneal transport of vancomycin during peritoneal dialysis. Nephron **24**:274–277.
15. **Oreopoulos, D. G., S. Vas, and R. Khanna.** 1981. Treatment of peritonitis, p. 259–264. *In* J. W. Moncrief and R. P. Popovich (ed.), CAPD update. Masson Publishing USA, Inc., New York.
16. **Pancorbo, S., and C. Comty.** 1982. Peritoneal transport of vancomycin in four patients undergoing continuous ambulatory peritoneal dialysis. Nephron **31**:37–39.
17. **Rocci, M. L., and W. J. Jusko.** 1983. LAGRAN program for area and moments in pharmacokinetic analysis. Comput. Programs Biomed. **16**:203–216.
18. **Rogge, M. C., C. A. Johnson, S. W. Zimmerman, and P. G. Welling.** 1985. Vancomycin disposition during continuous ambulatory peritoneal dialysis: a pharmacokinetic analysis of peritoneal drug transport. Antimicrob. Agents Chemother. **27**:578–582.
19. **Schwenzer, K. S., C. J. Wang, and J. P. Anhatt.** 1983. Automated fluorescence polarization immunoassay for monitoring vancomycin. Ther. Drug Monit. **5**:341–345.
20. **Vas, S. I.** 1983. Microbiological aspects of chronic ambulatory peritoneal dialysis. Kidney Int. **23**:83–92.
21. **Walshe, J. J., G. D. Morse, D. M. Janicke, and M. A. Apicella.** 1986. Crossover pharmacokinetic analysis comparing intravenous and intraperitoneal administration of tobramycin. J. Infect. Dis. **153**:796–799.
22. **Walshe, J. J., G. D. Morse, P. E. Lieveld, and M. A. Apicella.** 1985. Treatment of peritonitis in CAPD: rationale for an alternative antibiotic therapy based on kinetic analysis and clinical response. Adv. Peritoneal Dialysis **1985**:66–72.
23. **Watanakunakorn, C.** 1982. Treatment of infections due to methicillin-resistant *Staphylococcus aureus*. Ann. Intern. Med. **97**:376–378.