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Amikacin Pharmacokinetics during Continuous Ambulatory Peritoneal Dialysis

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The pharmacokinetics of amikacin were investigated in five stable patients undergoing continuous ambulatory peritoneal dialysis (CAPD). Each patient was studied after the administration of 7.5 mg of amikacin per kg by both the intravenous (i.v.) and intraperitoneal (i.p.) route, allowing a 1-month washout period between doses. No differences in amikacin half-life, volume of distribution, total body clearance, or time-averaged peritoneal clearance were noted between the two routes of administration. After a 5-h dwell period, bioavailability as calculated by the area under the curve for i.p. amikacin was 53 ± 14.0%. Amikacin pharmacokinetics parallel those of other aminoglycosides in CAPD patients when the drug is administered either i.v. or i.p. Single loading doses of amikacin administered i.v. to uninfected CAPD patients provided therapeutic serum and dialysate levels for many aerobic gram-negative organisms for up to 72 h. Because of the variability of absorption of i.p. administered amikacin, single i.p. doses are not recommended.

The development of continuous ambulatory peritoneal dialysis (CAPD) is recognized as a major advance in the treatment of chronic renal failure (9). CAPD peritonitis continues to be a major problem; approximately 60% of patients develop peritonitis within the first year of CAPD (11). Peritonitis represents the single greatest factor in CAPD dropout. In addition, exit site and tunnel infections cause significant morbidity. It is estimated that 20 to 25% of episodes of peritonitis in CAPD patients are caused by aerobic gram-negative organisms (11, 13). Consequently, aminoglycosides continue to be an important class of antibiotics for CAPD peritonitis (7). Controversy exists, however, regarding the ideal route of administration (7).

Standard clinical practice in patients with CAPD peritonitis has been to administer intraperitoneal (i.p.) loading doses of one or two antibiotics, followed by i.p. maintenance dosing (7). The resulting steady-state concentrations in plasma omit the usual peak and trough concentrations seen during intermittent intravenous (i.v.) therapy. Unfortunately, ototoxicity occurs, and expressions of concern regarding the need to develop alternate dosing strategies have been raised (7). Suggested alternate regimens include intermittent i.p. or i.v. dosing. However, no randomized, prospective controlled clinical trials comparing continuous i.p. dosing with either of these alternatives have been performed. Clinical experience and recently published expert recommendations suggest an advantage for continuous i.p. dosing (7). One clinical trial (6) suggested higher cure rates with i.p. rather than i.v. dosing for combined vancomycin and tobramycin therapy, although control for equivalency of infecting organisms and various patient-related factors cannot be assured, which may have affected the outcome.

Initial therapy for patients with CAPD peritonitis generally includes an aminoglycoside when dialysate Gram stain reveals gram-negative rods (7, 13). At the present level of knowledge, continuous i.p. dosing for known gram-negative peritonitis may be preferred. Empiric use of aminoglycosides pending culture results if Gram staining indicates gram-negative infection or if no organisms are identified may be justified. Knowledge of the local frequencies of various pathogens and their susceptibilities guides antibiotic selection in this situation (7).

Data regarding aminoglycoside concentrations in dialysate after single i.v. or i.p. doses over a 72-h period, the usual interval over which definitive culture results are available, are scant for gentamicin and tobramycin and lacking for amikacin (1, 2, 10, 12, 15). Amikacin has the advantage of relatively low MICs against many gram-negative organisms while attaining relatively high concentrations in serum (3, 4).

The purpose of this investigation was to elucidate the pharmacokinetics of amikacin in CAPD patients. In addition, the study was designed to determine the time period over which amikacin concentrations in serum and peritoneal fluid could be maintained in a therapeutic range after single i.v. or i.p. doses of 7.5 mg/kg.

MATERIALS AND METHODS

Subjects. Five adult patients with end-stage renal disease who were participating in the CAPD program at The Mary Imogene Bassett Hospital, Cooperstown, N.Y., were enrolled in the study. The study was approved by the Committee for the Protection of Human Subjects. Written informed consent was obtained from each patient. All patients had received CAPD treatment for at least 1 month and were medically stable prior to initiation of the study. All patients had achieved a stable dry weight. Patients were excluded if they had received amikacin within 1 month prior to the study, had severe cardiovascular or pulmonary disease, or had evidence of volume excess. No patient developed peritonitis during or between study periods. On the day of the study, both a visual inspection and a cell count of the dialysate was performed to rule out acute peritonitis prior to the amikacin dose.

Study design. A crossover study design was used so that each patient received i.v. and i.p. amikacin with no less than 4 weeks between doses. For i.v. drug administration, a single dose of amikacin (7.5 mg/kg) was administered, followed by a saline flush via venous cannula over a 2- to 4-min period, following the i.p. infusion of 2.0 liters of fresh Delflex peritoneal dialysate containing 2.5% glucose (DelMed, Inc., Canton, Mass.) over 10 min. For i.p. drug administration, a single dose of amikacin (7.5 mg/kg) was infused in 2.0 liters

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of fresh Delflex peritoneal dialysate (2.5% glucose) over a 10-min period.

Venous blood samples were collected in nonheparinized tubes from an indwelling cannula placed in the arm opposite the infusion site. Blood samples were obtained at 0, 5, 10, 15, and 30 min and at 1, 2, 3.5, 5, 6, 8, 24, 48, and 72 h after the administration of amikacin during each study period. Samples of dialysate were collected by first draining and then reinstilling approximately 200 ml of dialysate from the peritoneal cavity to clear the transfer set tubing. A second 200-ml volume was then drained into the dialysate bag, and a 10-ml sample was taken from the dialysate bag injection port by using sterile techniques. Dialysate samples were collected at 0, 5, 15, and 30 min and at 1, 2, 3, and 5 h during the first dialysate dwell period (5 h). In addition, all spent dialysate was saved in separate bags over a 72-h period. Directly after the infusion of the second exchange, a sample of dialysate was collected to allow calculation of the residual i.p. volume and amikacin content.

All studies commenced at the start of the first daily dialysate exchange period (8 a.m.). During the study, patients adhered to their usual schedule of four exchanges per day, with daytime dwell periods of 4 to 6 h and overnight dwell periods of 8 to 12 h. All urine voided during the 72-h study period was collected, the volume was recorded, and a sample was taken for determination of amikacin concentration.

All serum, dialysate, and urine samples were stored at −70°C prior to analysis.

Drug analysis. Serum, dialysate, and urine samples were analyzed by using the fluorescence polarization immunoassay technique (Abbott Laboratories, Diagnostics Division, North Chicago, Ill.). This assay is sensitive from 0.2 to 50 μg/ml, with between-run coefficients of variation of 4.27, 2.22, and 2.01% at 5, 15, and 30 μg/ml, respectively (Abbott, *TDx Operators Manual*).

Pharmacokinetic analysis. Noncompartmental analysis (5, 8) was used to determine pharmacokinetic parameters from the following equation: $CL = F\text{Dose}/AUC_{0-\infty}$, where $AUC_{0-\infty}$ is the area under the curve from 0 h to infinity determined by integration, CL is the total body clearance corrected for 1.73 m^2, and F is the fraction of the dose absorbed (bioavailability). F is determined by the following equation: $F = (AUC_{0-\infty}$ i.p. · i.v. dose · $t_{1/2}$ i.v.)/($AUC_{0-\infty}$ i.v. · i.p. dose · $t_{1/2}$ i.p.). In this equation, $t_{1/2}$ i.v. and $t_{1/2}$ i.p. are determined by linear regression analysis of the terminal portion of the concentration (in serum)-time curve for the i.v. and i.p. portions of the study. The results of this calculation were used in further equations using F.

Since all dialysate was collected in each phase of the study, a mass balance approach was also used to calculate F^* from the i.p. data for comparison to the F calculation. The equations used here were as follows: F^* = i.p. dose −RD −D5h/i.p. dose, where i.p. dose is the initial i.p. dose, RD is the amount of drug undrained at 5 h (residual drug calculated from equation below), and D5h is the amount of drug recovered in the dialysate at 5 h. The results of this calculation were compared with the standard F calculation. Residual drug (RD) was calculated by the following formula: RD = 2,000 ml · [COH/(C5h − COH)] · C5h, where COH is the measured amikacin concentration in dialysate immediately after infusion of 2 liters of fluid (cycle 2) and C5h is the measured concentration in dialysate at the end of cycle 1.

The volume of distribution at steady state (V_{ss}) was determined by the following equations: for i.p. administration, $V_{ss} = F\text{Dose}(AUMC_{0-\infty}/AUC_{0-\infty}) - (F\text{Dose}/k_a \cdot AUC_{0-\infty})$ and for i.v. administration, $V_{ss} = CL(AUMC_{0-\infty}/AUC_{0-\infty})$, where $AUMC_{0-\infty}$ is the area under the first moment of the concentration-time curve from 0 to infinity and k_a is the i.p. absorption rate constant calculated by the method of Wagner and Nelson (14).

The time-averaged peritoneal clearance ($CL_{P\ net}$) was calculated for the i.v. dose from 0 to 72 h by using the following equation (5, 8): $CL_{P\ net} = XD(t_1 - t_2)/AUC(t_1 - t_2)$, where $XD(t_1 - t_2)$ is the amount of drug recovered in the dialysate from 0 to 72 h after administration and $AUC(t_1 - t_2)$ is the area under the curve from 0 to 72 h.

The $CL_{P\ net}$ for the i.p. dose was calculated for comparison in two ways. The equation used was that of Janicke et al. (5) (shown above). However, in method 1, XD and AUC values were used from 10 to 72 h only (t_1 = 10 h) to account for residual i.p. drug absorption during the second exchange. This method is similar to that of Morse et al. (8). In the second method, the residual drug absorbed during exchange 2 was estimated by determination of RD after exchange 1 multiplied by F. Thus XD and AUC calculations were made from 5 to 72 h (t_1 = 5) by using the equation $CL_{P\ net} = [XD(t_5 - t_{72}) + (RD \cdot F)]/AUC(t_5 - t_{72})$.

Statistical analysis was performed by using the paired Student t test. $P \leqq 0.05$ was considered significant. All data are reported as the mean ± the standard deviation.

RESULTS

The characteristics of the five patients who completed both the i.v. and the i.p. portions of the study are shown in Table 1. Three of the five patients had never experienced an episode of peritonitis while on CAPD, and no patient had experienced peritonitis within 20 months of study. Patient 5 had an endogenous creatinine clearance of 8 ml/min; no other patient had residual renal creatinine clearance greater than 5 ml/min.

The pharmacokinetic parameters derived from the i.v. portion of the study are presented in Table 2. As expected, this group had a prolonged amikacin half-life (42.2 ± 14.2 h) compared with the normal half-life of 2 to 3 h (3). $CL_{P\ net}$ accounted for approximately 50% of the total body clearance. The concurrent serum and peritoneal fluid concentra-

TABLE 1. Patient characteristics[a]

Patient no.	Sex	Age (yr)	TBW (kg)	BSA (m^2)	Duration of CAPD (mo)	Time from last previous peritonitis episode (mo)	Underlying disease
1	F	56	88.3	1.88	65	20	Polycystic kidney disease
2	F	59	66.1	1.68	7	None	Cystinuria
3	M	61	70.3	1.76	45	25	Renovascular disease
4	M	44	75.3	1.89	10	None	Heriditary nephritis
5	F	27	53.2	1.55	12	None	Membranous nephropathy

[a] F, Female; M, male; TBW, total body weight; BSA, body surface area.

TABLE 2. i.v. amikacin pharmacokinetics

Patient no.	$t_{1/2}$ (h)	V_{ss} (liter/kg)	CL (ml/min per 1.73 m^2)	$CL_{P\ net}$ (ml/min per 1.73 m^2)
1	38.9	0.17	4.1	3.3
2	43.8	0.20	3.5	2.8
3	64.7	0.25	3.0	2.4
4	26.0	0.19	5.5	2.1
5	37.8	0.19	3.3	1.2
Mean ± SD	42.2 ± 14.2	0.2 ± 0.03	3.9 ± 1.0	2.0 ± 1.0

tions after the i.v. dose are shown for a representative patient (patient 2) in Fig. 1. In general, amikacin was detectable in peritoneal dialysate almost immediately after i.v. injection, with peak dialysate concentrations at 4.4 ± 0.8 h averaging 14.4 ± 4.6 μg/ml. Following the single i.v. dose, immediate postdistribution concentrations in serum ranged from 30 to 45 μg/ml. The average amikacin concentrations in serum and dialysate at 24, 48, and 72 h postdose are given in Table 3.

The data obtained from i.p. administration of amikacin are summarized in Table 4. No significant differences in half-life, volume of distribution, or total body clearance were seen between i.p. and i.v. dosing. The concentration in serum versus time curves for i.p. and i.v. administration of a representative patient (patient 2) are shown in Fig. 2. The mean absorption rate from peritoneal dialysate was 1.4 ± 0.23 h, with amikacin detectable in serum after 0.05 ± 0.08 h following the i.p. dose. The mean peak concentration in serum was 19.6 ± 6.1 μg/ml and occurred at 5.6 ± 0.5 h after the i.p. dose. The average amikacin concentrations in serum and dialysate at 24, 48, and 72 h postdose are shown in Table 5. The concentration curves in peritoneal fluid and serum of a representative patient (patient 2) following the i.p. dose are illustrated in Fig. 3.

Two different methods of calculating $CL_{P\ net}$ were used, and no significant differences were found (Table 4). Additionally, no significant difference was seen between the i.p. $CL_{P\ net}$ from 5 to 72 h or from 10 to 72 h and the i.v. $CL_{P\ net}$ values.

A significant difference was seen ($P < 0.05$), however, when the bioavailability was calculated by using the mass balance method versus the area method, with the latter giving a higher value. We would favor the area method since it is the standard method of bioavailability calculation.

As expected, the highest concentrations in peritoneal fluid were achieved during the overnight exchange each day (the last and longest cycle of the day; Fig. 1 and 3) with both i.v.

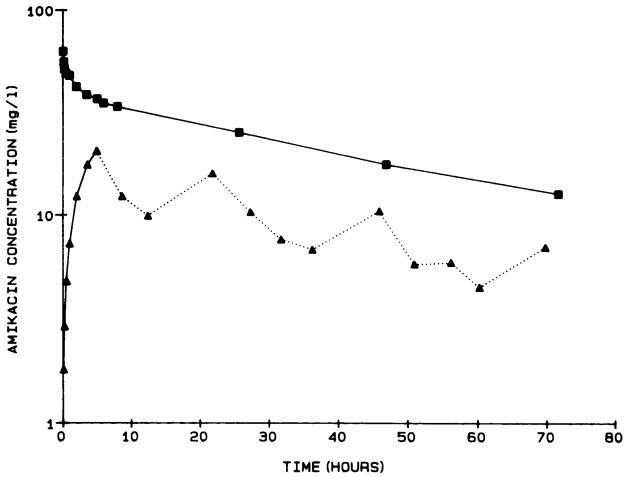

FIG. 1. Amikacin concentrations in serum (■) and peritoneal fluid (▲) following a 7.5 mg/kg i.v. dose. Data are for patient 2. Concentrations connected by the dotted line are those obtained from dialysate at the end of each cycle and indicate the average concentration. Concentrations in dialysate are highest after the overnight, longest exchanges.

and i.p. dosing. Despite the prolonged dwell period during the overnight exchange (8 to 12 h), the ratio of amikacin in peritoneal fluid to amikacin in serum never exceeded 61% (range, 45.4 to 61%) for any patient, indicating that equilibrium was not achieved.

DISCUSSION

While CAPD has advanced the treatment of patients with end-stage renal disease, infection continues to be a major concern (11). Since gram-negative organisms account for approximately 25% of cultured pathogens, aminoglycoside antibiotics continue to be an important therapeutic modality (7, 11, 15). Controversy continues, however, as to what route of administration should be used for the treatment of CAPD-associated peritonitis: i.v. or i.p. (7). There is no doubt that a therapy which could be carried out at home would be advantageous. If a single i.v. dose of a drug could be administered, providing therapeutic concentrations in serum and dialysate for 2 to 3 days, empiric coverage for gram-negative organisms pending cultures could be simplified.

The aminoglycoside antibiotics exhibit a prolonged rate of elimination in patients with chronic renal failure on CAPD (1, 2, 10, 12, 15). Various authors have reported an i.p. bioavailability for gentamicin or tobramycin of between 49

TABLE 3. Amikacin concentrations in serum and dialysate at various times after a single i.v. dose

Patient no.	Concn (μg/ml) at time (h): 24		48		72	
	Serum	Dialysate	Serum	Dialysate	Serum	Dialysate
1	20.1	6.5	16.7	3.0	12.4	1.9
2	25.0	15.9	17.5	10.4	12.6	7.0
3	21.6	10.7	17.4	7.8	14.9	6.1
4	18.6	8.3	9.1	5.4	5.8	3.5
5	26.8	15.5	17.4	10.2	12.0	7.5
Mean ± SD	22.4 ± 3.4	11.4 ± 4.2	15.6 ± 3.7	7.4 ± 3.2	11.5 ± 3.4	5.2 ± 2.4

TABLE 4. i.p. amikacin administration

Patient no.	$t_{1/2}$ (h)	k_a (h^{-1})	V_{ss} (liter/kg)	CL (ml/min per 1.73 m^2)	$CL_{P\ net\ 10-72}$ (ml/min per 1.73 m^2)[a]	$CL_{P\ net\ 5-72}$ (ml/min per 1.73 m^2)[a]	F^*	F
1	42.5	0.51	0.17	3.7	3.2	3.4	0.56	0.62
2	39.4	0.61	0.19	3.8	2.5	2.7	0.44	0.54
3	55.1	0.40	0.24	3.6	2.6	2.6	0.46	0.52
4	27.8	0.52	0.20	6.0	2.2	2.0	0.47	0.68
5	21.1	0.43	0.17	5.9	3.0	3.4	0.28	0.31
Mean ± SD	37.2 ± 13.2	0.49 ± 0.08	0.19 ± 0.03	4.6 ± 1.2	2.7 ± 0.4	2.8 ± 0.6	0.44 ± 0.10	0.53 ± 0.14[b]

[a] $CL_{P\ net\ 5-72}$ and $CL_{P\ net\ 10-72}$, $CL_{P\ net}$ from 5 to 72 h and 10 to 72 h, respectively.
[b] $P < 0.05$ versus F^*.

TABLE 5. Amikacin concentrations in serum and dialysate at various times after a single i.p. dose

Patient no.	Concn (μg/ml) at time (h):					
	24		48		72	
	Serum	Dialysate	Serum	Dialysate	Serum	Dialysate
1	5.9	3.1	5.0	1.4	1.4	1.1
2	13.8	9.2	9.7	5.6	6.5	4.1
3	12.0	6.0	9.1	5.2	6.3	4.2
4	13.4	8.1	7.6	4.6	4.1	2.8
5	18.6	11.5	12.7	7.3	8.8	4.5
Mean ± SD	12.7 ± 4.6	7.6 ± 3.2	8.3 ± 3.8	4.8 ± 2.2	5.4 ± 2.8	3.3 ± 1.4

and 100% in uninfected patients undergoing CAPD (1, 2, 10, 12, 15). It is important to note that bioavailability in our patients receiving i.p. amikacin as calculated by the AUC method (0.53 ± 0.14) was significantly different ($P < 0.05$) than that calculated by the mass balance approach (0.44 ± 0.10). The reason for this difference may be related to the variability in residual volumes in patients and thus variability in the amount of drug undrained following the first exchange. We would support the use of the AUC approach in i.p. bioavailability calculations.

We found no significant difference in $t_{1/2}$, V_{ss}, CL, or $CL_{P\ net}$ following i.p. versus i.v. administration. Additionally, we found that CAPD clearance accounted for approximately 50% of the total body clearance of amikacin. These findings are similar to those of Walshe et al. for tobramycin (16). In any event, both CL and $t_{1/2}$ of amikacin remained significantly prolonged despite CAPD.

It is interesting to note that the administration of amikacin in a single dose of 7.5 mg/kg via the i.v. route resulted in therapeutic concentrations (≧4 μg/ml) in serum and peritoneal dialysate for up to 72 h. This gives the clinician the option of using a single dose of i.v. amikacin to provide empiric gram-negative coverage for many organisms until culture results can be obtained and definitive therapy can be

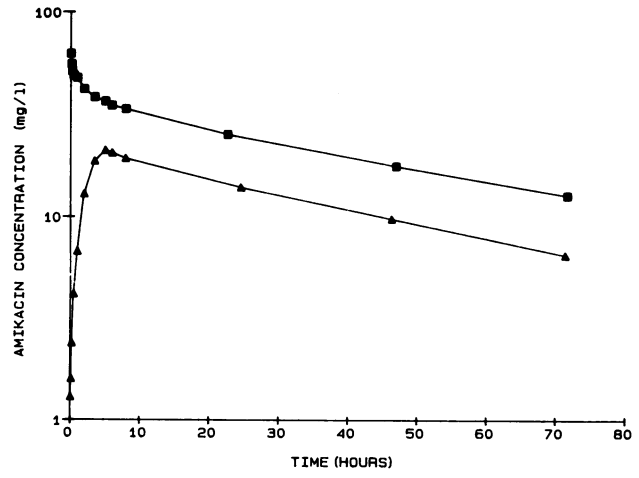

FIG. 2. Concentration in serum versus time curve for amikacin following 7.5-mg/kg i.v. (■) and i.p. (▲) doses. Data are for patient 2.

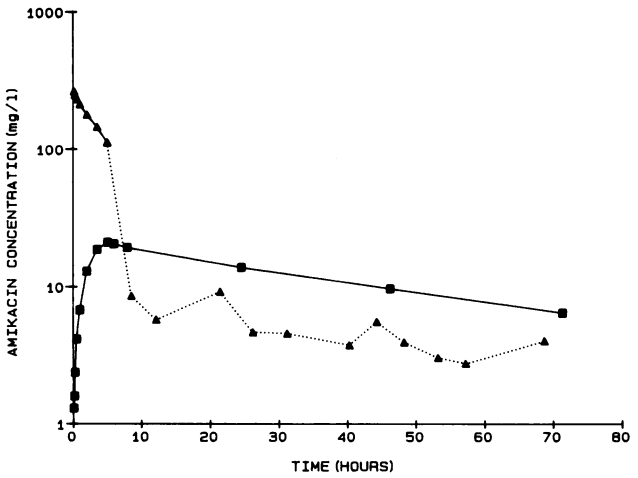

FIG. 3. Amikacin concentrations in serum (■) and peritoneal fluid (▲) following a 7.5-mg/kg i.p. dose. Data are for patient 2. Concentrations connected by the dotted line are those obtained from dialysate at the end of each cycle and indicate the average concentration.

instituted. No studies suggest an advantage of i.v. versus i.p. aminoglycoside used alone in CAPD peritonitis. While some patients maintained therapeutic amikacin concentrations in serum and peritoneal dialysate for 72 h following a single i.p. dose, the variability in bioavailability and the lack of information concerning the bioavailability during peritonitis make the use of this route less certain for single-dose initial therapy.

In conclusion, our data indicate that amikacin elimination is prolonged in end-stage renal disease despite the use of CAPD. On the basis of pharmacokinetic data, a single 7.5 mg/kg i.v. dose of amikacin may provide clinically effective concentrations in serum and peritoneal fluid for up to 72 h, when culture results should be available and definitive therapy can be instituted.

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