Pharmacokinetics of Intermittent Intravenous Cefazolin and Tobramycin in Patients Treated with Automated Peritoneal Dialysis

HAROLD J. MANLEY,* GEORGE R. BAILIE,*† REGINALD FRYE,§ LORRAINE D. HESS,‡ and M. DONALD MCGOLDRICK†

**Albany College of Pharmacy, †Albany Medical College, and ‡Albany Dialysis Center, Albany, New York; and §University of Pittsburgh, School of Pharmacy, Pittsburgh, Pennsylvania.*

Abstract. There is increasing use of intermittent dosing of antibiotics to treat peritoneal dialysis (PD)-related peritonitis. The disposition of intravenous cefazolin and tobramycin was studied in automated PD (APD) patients. Ten patients were recruited and received a single intravenous dose of cefazolin (15 mg/kg) and tobramycin (0.6 mg/kg). Blood and dialysate samples were collected at the beginning, middle, and end of dwells 1 to 3 (on cycler), and at the end of dwells 4 to 5 (off cycler) for a 24-h period. Baseline and 24-h urine samples were collected. Pharmacokinetic parameters were calculated using a monoexponential model. Cefazolin and tobramycin half-lives were markedly different on cycler than off cycler (cefazolin on cycler: 10.67 ± 4.66 h; cefazolin off cycler: 23.09 ± 5.6 h; $P = 0.001$; tobramycin on cycler: 14.27 ± 4.53 h; tobramycin off cycler: 68.5 ± 26.47 h; $P < 0.001$). Mean serum and dialysate concentrations were above minimum inhibitory concentrations of susceptible organisms throughout the 24-h period for both drugs with intravenous administration. A model was developed to examine serum and dialysate concentrations after intermittent intraperitoneal administration of 15 mg/kg cefazolin and 0.6 mg/kg tobramycin. Model-predicted intraperitoneal cefazolin provides adequate serum and dialysate concentrations for 24 h. Intermittent intraperitoneal tobramycin doses must be 1.5 mg/kg for one exchange during the first day and then given as 0.5 mg/kg thereafter. It is concluded that the current empiric dosing recommendations for PD-related peritonitis may be adequate for cefazolin (15 to 20 mg/kg); however, tobramycin doses must be changed to 1.5 mg/kg intraperitoneally on day 1, then to 0.5 mg/kg intraperitoneally thereafter in APD patients.

Peritonitis remains a cause of significant morbidity and mortality in peritoneal dialysis (PD) patients (1–3). In 1996, the Ad Hoc Committee on the treatment of peritonitis in PD patients recommended a number of changes in the antibiotic regimens used to treat infections (4). There has been a general move toward the use of intermittent, as opposed to continuous, dosing of antibiotics (5–7). Intermittent antibiotic dosing initiatives have been promulgated because it is thought that this regimen provides specific advantages in PD, including convenience, reduced toxicity, and a decreased risk of accidental contamination of the system by the patient. Reversion to continuous therapy might be appropriate under certain circumstances, such as in patients who maintain significant residual renal function.

First-line agents recommended by the Ad Hoc Committee for the treatment of peritonitis are a first generation cephalosporin (*e.g.*, cefazolin or cephalothin) and an aminoglycoside (*e.g.*, gentamicin or tobramycin) by intraperitoneal administration (4). Two recent studies in continuous ambulatory PD (CAPD) patients demonstrated the effectiveness of these first-line agents (5–6). The pharmacokinetics of intraperitoneal cephalosporins and aminoglycosides given intermittently in CAPD patients demonstrate adequate serum and dialysate concentrations, and thereby help clarify the outcomes observed (7–10).

One further complication is the increasing use of different variants of PD. In 1997, there were about 222,000 end-stage renal disease patients in the United States treated with dialysis (11). Of these, 7.5% (16,630) were treated with CAPD and about 4.4% (9,756) with some type of automated system. Automated PD (APD) patients account for approximately 37% of all PD patients in 1997. In APD, three to four exchanges are carried out automatically at night using a cycler while the patient sleeps. Patients may then have either no daytime dwell ("dry day"), or one or more daytime ambulatory dwells.

These systems involve very different exchange characteristics since there are varying dialysate volumes and dwell durations. It might be expected, then, that the disposition of drugs would differ considerably between CAPD and APD. Although the intermittent regimen has been well studied in CAPD, there are few data for APD systems.

It was hypothesized that the serum and dialysate concentrations of cefazolin and tobramycin, administered using a once

Received June 17, 1999. Accepted October 18, 1999.

Dr. Manley is currently at the College of Pharmacy, University of Missouri-Kansas City, Kansas City, MO.

Correspondence to Dr. George R. Bailie, Professor of Pharmacy Practice, Albany College of Pharmacy, 106 New Scotland Avenue, Albany, NY 12208. Phone: 518-445-7235; Fax: 518-445-7302; E-mail: bailieg@acp.edu

1046-6673/1107-1310

Journal of the American Society of Nephrology

daily, intermittent intravenous regimen to cycler APD patients, will be maintained over a 24-h period at levels adequate to eradicate a bacterial peritonitis.

The two primary objectives were to quantify the pharmacokinetic parameters of cefazolin and tobramycin and to provide cefazolin and tobramycin dosing recommendations based on the pharmacokinetic parameters characterized. Secondary objectives were to characterize and compare the serum, dialysate, and urine concentrations of cefazolin and tobramycin at various times over a 24-h period attained in anuric and nonanuric APD patients and to correlate PD clearance with indices of dialysis adequacy.

Materials and Methods

Patients and Study Design

Inclusion criteria were all PD patients cared for at our dialysis unit, over 18 yr old, who had been on PD for at least 1 mo. The institutional committee on human research approved the protocol, and all patients gave written informed consent. Patients could be anuric or maintain some degree of residual renal function. Patients were ineligible for the study if they had peritonitis within the previous 4 wk or were treated with any β-lactam or aminoglycoside antibiotic within the previous 2 wk. Medications that might interfere with active tubular secretion of creatinine, such as H_2 blockers or probenecid, were discontinued for at least 2 wk before the patient was allowed to participate.

Patients had a peripheral venous catheter placed for drug administration and for blood sampling purposes. The catheter was kept patent with flushes of normal saline.

For the 24 h of this study, APD patients were placed on a standard dialysis prescription of three 2.5%, 2-L dialysate (Dianeal; Baxter Health Corp., Deerfield, IL) exchanges over a period of 8 h during the day using the cycler (to simulate an overnight automated session), followed by two 2.5%, 2-L dwells of about 8 h each over the course of the evening and overnight. For this study, patients commenced the automated component of their exchanges when they arrived at the dialysis unit on the morning of day 1. The late afternoon/evening exchange was infused by the cycler, then the patient disconnected from the cycler. The overnight exchange was conducted manually. Existing APD patients had their pattern shifted by 12 h for 1 d. If patients were on CAPD, they were instructed not to perform their routine dialysis prescription and were then treated in a manner similar to the APD patients for the duration of the study. At the start of day 2, all patients reverted to their previous dialysis prescription (APD or CAPD).

Patients with residual renal function urinated immediately before the study. Spent dialysate from the preceding exchange was drained immediately before the administration of the study drugs. Both the pre-study urine and dialysate were collected and their volumes were measured, and 20 ml were retained for assay purposes. Pre-study samples were assayed to verify the absence of any analytical interferences from endogenous or exogenous sources, which would include undocumented exposure to any β-lactam or aminoglycoside.

The cefazolin and tobramycin were injected intravenously via the peripherally placed catheter, and were flushed through with 10 ml of normal saline. The tobramycin (0.6 mg/kg) was administered as a short-term infusion over 30 min, followed immediately by the cefazolin (15 mg/kg) given over 5 min. Antibiotic doses were based on actual body weight. Thereafter, APD with the cycler commenced, with three 2.5%, 2-L exchanges over 8 h.

At the end of each of cycler dwells 1, 2, and 3, the dialysate was drained and retained. At the end of the third dwell, the cycler then instilled another exchange, using 2.5%, 2-L dialysate, and the patient disconnected. This exchange dwelled from approximately 4 p.m. to midnight. Before going to bed, the patient then performed a manual exchange of 2.5%, 2-L dialysate as an overnight dwell from approximately midnight to 8 a.m. The drained dialysate from the manual exchange was retained. That morning, at the end of the overnight dwell, the patients returned to the study center to drain the overnight dwell, for final blood sampling, and to return the drained dialysate from the midnight exchange. All patients then reverted to their previous dialysis prescriptions.

Time 0 (0 h) was defined as the time immediately after the infusion of cefazolin was complete. Blood samples (7 ml) and dialysate samples (5 ml) were collected at baseline (pre-dose), after the first dialysate was instilled (0 h) and at the midpoint and end of the first exchange, at the midpoint and end of each of exchanges 2 and 3, and at the end of the overnight exchange (24 h) (*i.e.*, nine blood samples). In addition, a dialysate sample was collected from the retained first manual exchange (*i.e.*, 10 dialysate samples). The mid-dwell dialysate samples were collected in a manner described previously to assure thorough mixing of dialysate (8). The total volume of each drained dialysate was recorded. Urine samples (from nonanuric patients) were collected and pooled over the 24-h period. The urine volume was measured and a 10-ml aliquot was retained for drug assay.

Sample Analysis

Blood was permitted to clot in the red-top collection tubes. Samples were centrifuged for 10 min and the serum was collected. All serum, dialysate, and urine samples were split into batches and stored at −70°C until assayed. One batch of samples was packed in dry ice and shipped for tobramycin and cefazolin assay. A second batch of samples was sent to our medical center (Albany Medical Center, Albany, NY) for serum, urine and dialysate creatinine and urea assay. The same clinical laboratory performed all urea and creatinine determinations. Creatinine determinations of dialysate samples were corrected for high glucose concentration by the clinical laboratory.

The samples were assayed for cefazolin in duplicate by HPLC (8) and for tobramycin by enzyme-multiplied immunoassay technique (Syva, Dade Behring Inc., Deerfield, IL). It is known that cefazolin and tobramycin are stable in dialysate (12). It was assumed that cefazolin and tobramycin were stable in urine over the collection period.

Pharmacokinetic Calculations

A monoexponential model was used for all pharmacokinetic calculations. The following equations were used:

a) The serum elimination rate constant (k_{el} [h^{-1}]) for dwells 1 to 3 (on cycler) was obtained by regression of the serum concentrations over the time between the start of the dwell and the end of the dwell. The k_{el} (h^{-1}) for dwells 4 and 5 (off cycler) was determined by extrapolating forward (dwell 4) or backward (dwell 5) the last measured cefazolin or tobramycin serum concentration to determine an approximate serum concentration for the end of dwell 4 or the start of dwell 5. The formula used to determine the approximate serum concentration was $C = C_0 \times e^{-kt}$, where C is concentration (mcg/ml), C_0 is original concentration (mcg/ml), $-k$ is the elimination rate constant obtained from the literature (cefazolin [(8–9)]; tobramycin [(11)]) (h^{-1}), and t is the time (h) between sampling points. The k_{el} (h^{-1}) values for dwells 4 and 5 were then determined by linear regression in a manner similar to dwells 1 to 3, using the mean of the

two calculated serum concentrations and appropriate measured serum concentrations.

b) The serum elimination half-life ($t_{1/2}$) (h) for patients on the cycler was calculated as (0.693)/(mean k_{el} dwells 1 to 3). The serum elimination $t_{1/2}$ (h) for patients off the cycler was calculated as (0.693)/(mean k_{el} (h^{-1}) dwells 4 to 5).

c) The serum area-under-the-curve (AUC) for the first 24 h was calculated by summation of the AUC (mg/L per h) of each dwell using the trapezoid rule, and from 24 h to infinity by extrapolation as the serum concentration at 24 h/k_{el} (h^{-1}) dwell 5.

d) The serum-to-dialysate transfer rate constant (k_{sd}) (h^{-1}) for drug movement from serum into the peritoneal cavity was determined for dwells 1 to 3 using linear regression.

e) The half-life ($t_{1/2\ sd}$) (h) of cefazolin or tobramycin transfer rate from the serum to the peritoneal cavity was calculated as 0.693/k_{sd} (h^{-1}).

f) The total body clearance was calculated as:

$$Cl_T\ (L/h) = \frac{Dose}{AUC_{0-\infty}}$$

g) Renal clearance in nonanuric patients was calculated as:

$$Cl_R\ (L/h) = \frac{mg\ of\ drug\ in\ urine\ from\ 0\ to\ 24\ h}{serum\ AUC_{0-24}}$$

h) Peritoneal dialysis clearance was calculated as:

$$Cl_{PD}\ (L/h) = \frac{mg\ in\ dialysate\ from\ 0\ to\ 24\ h}{serum\ AUC_{0-24}}$$

i) The systemic volume of distribution (V_d) was calculated as:

$$V_d\ (L) = Cl_T/k_{el}.$$

The k_{el} (h^{-1}) used was the mean k_{el} (h^{-1}) off cycler (dwells 4 to 5).

j) Estimated GFR was determined using the mean of the following two formulas:

Creatinine clearance (ml/min)

= (Urine Cr × 24-h urine volume)/

(Serum Cr × 1440); Urea clearance (ml/min)

= (Urine urea × 24-h urine volume)/

(Blood urea nitrogen × 1440).

k) Delivered PD dose was calculated by a determination of urea Kt/V_{PD}, using blood and dialysate urea concentrations, where K is urea elimination rate, V is volume of urea distribution (L), and T is time (h). Urea volume of distribution for each patient was calculated using the Hume method (13).

All clearance calculations and GFR were normalized to a body surface area of 1.73 m^2. Body surface area was determined by the following formula: {[Actual body weight (kg) × height (cm)]/3600}$^{1/2}$.

Model estimates of serum and dialysate cefazolin and tobramycin end of dwell concentrations, post intermittent intraperitoneal administration, were determined for a 70-kg individual. Initial cefazolin and tobramycin serum concentrations were calculated from the following formula: (Intraperitoneal dose × F)/V_d. Antibiotic intraperitoneal bioavailability (F) was obtained from the literature (8–9,11), and antibiotic V_d was determined during this study. Initial cefazolin and tobramycin dialysate concentrations were calculated from the following formula: Intraperitoneal dose/2 L (the volume of dialysate instilled during this study). Serum concentrations at the end of the antibiotic-containing dwell were calculated using the following formula: $C = C_0 \times e^{-kt}$, where C is concentration (mcg/ml), C_0 is initial cefazolin or tobramycin concentration (mcg/ml), $-k$ is the elimination rate constant determined from dwells 4 to 5 for cefazolin or tobramycin (h^{-1}), and t is time (h) (assuming 8-h dwell). The mean percentage decline observed in serum and dialysate concentrations on the cycler (dwells 1 to 3) and off the cycler (dwells 4 to 5) in this study were used to predict subsequent end of dwell concentration values from the initial, estimated serum and dialysate concentrations.

Statistical Analyses

Continuous variables were expressed as means and SD. The differences between the mean values in anuric and nonanuric patients were analyzed using a one-tailed t test (unpaired). Correlations were attempted between GFR and cefazolin and tobramycin clearances, and between Kt/V_{PD} and drug clearances.

Results

Ten patients were enrolled in the study. The mean duration on PD was 20.2 ± 25.5 mo. All 10 patients received tobramycin and eight received cefazolin (two patients had a cephalosporin allergy). The patient demographics are shown in Table 1. The mean GFR was 2.57 ± 1.46 ml/min per 1.73 m^2. The mean cefazolin and tobramycin serum peak concentrations (beginning of dwell 1) were 164.7 ± 36 and 4.1 ± 0.7 mcg/ml, respectively.

Summaries of pharmacokinetic parameters for cefazolin and tobramycin are shown in Table 2. The mean dwell times for dwells 1 to 3 (on cycler) were 2.4 ± 0.2, 2.6 ± 0.3, and 2.5 ± 0.2 h, respectively. The mean dwell times for dwells 4 to 5 (off cycler) were 7 ± 0.3 and 8.4 ± 0.6 h, respectively. The elimination half-life on the cycler was significantly less than off the cycler for both study drugs (cefazolin P value = 0.001; tobramycin P value < 0.001). The mean k_{sd} of dwells 1 to 3 for tobramycin were significantly different between anuric and nonanuric patients: dwell 1, 0.54 ± 0.27 h^{-1} anuric, 0.39 ± 0.09 h^{-1} nonanuric (P = 0.03); dwell 2, 0.57 ± 0.02 h^{-1} anuric, 0.54 ± 0.06 h^{-1} nonanuric (P = 0.05); dwell 3, 0.68 ± 0.08 h^{-1} anuric, 0.55 ± 0.12 h^{-1} nonanuric (P = 0.05). The mean k_{sd} of dwells 1 to 3 for cefazolin were not significantly different between anuric and nonanuric patients.

The mean cefazolin Cl_T was 4.82 ± 0.83 ml/min per 1.73 m^2. There was no significant difference observed in cefazolin Cl_T between anuric and nonanuric patients: 4.59 ± 1.5 and 4.9 ± 0.7 ml/min per 1.73 m^2, respectively (P = 0.34). The mean tobramycin Cl_T was 4.25 ± 0.65 ml/min per 1.73 m^2. There was no significant difference in tobramycin Cl_T between anuric and nonanuric patients: 4.13 ± 0.46 and 4.3 ± 0.75 ml/min per 1.73 m^2, respectively (P = 0.37). Cefazolin and tobramycin Cl_{PD} was 2.22 ± 0.6 and 4.45 ± 1.61 ml/min per 1.73 m^2, respectively. Cefazolin and tobramycin Cl_R was 1.33 ± 0.91 and 1.74 ± 1.37 ml/min per 1.73 m^2, respectively.

The mean cefazolin and tobramycin serum and dialysate concentrations at the end of each dwell (1 through 5) for all patients are shown in Figure 1. For cefazolin, the mean serum

Table 1. Patient demographics[a]

Patient	Gender	Age (yr)	ESRD Dx	Duration on PD (mo)	ABW (kg)	IBW (kg)	Height (cm)	BSA (m^2)	24-Hour Urine (ml)	Cefazolin (mg)	Tobramycin (mg)
A	F	51	DM	59	103	54	162.3	2.2	900	1500	61.8
B	M	41	GN	12	123	72.5	177.3	2.5	Anuric	1800	73.8
C	M	38	GN	36	89	69.8	174.3	2.1	450	1300	53.2
D	M	44	GN	70	116	79.9	185.4	2.4	Anuric	1700	69.6
E	M	47	DM	5	76	59.3	162.6	1.8	600	1100	45.6
F	F	38	PKD	5	78	56.5	165.1	1.9	950	1200	46.8
G	M	50	DM	6	91	63.8	167.6	2.1	650	X	56
H	F	57	DM	3	71	51.9	160	1.8	280	1100	42.6
I	F	31	GN	3	70	49.6	157.5	1.8	80	1100	42
J	M	40	PKD	3	77	91.4	198.1	2.1	Anuric	X	46.2
Mean		43.7		20.2	89.4	64.9	171	2.1	391	1350	53.8
SD		7.7		25.5	18.9	13.5	12.9	0.3	373.8	282.8	11.3

[a] ESRD, end-stage renal disease; Dx, diagnosis; PD, peritoneal dialysis; ABW, actual body weight; IBW, ideal body weight; BSA, body surface area; DM, diabetes mellitus; GN, glomerulonephritis; PKD, polycystic kidney disease; X, no drug given.

Table 2. Mean cefazolin and tobramycin pharmacokinetic parameters on and off cycler[a]

Drug	k_{el} (h^{-1}) Dwell 1 to 3	$t½$ (h) Dwell 1 to 3	k_{el} (h^{-1}) Dwell 4 to 5	$t½$ (h) Dwell 4 to 5	k_{sd} (h^{-1}) Dwell 1 to 3	$t½$ k_{sd} (h) Dwell 1 to 3	V_d (L/kg)
Cefazolin							
mean	0.08	10.67	0.03	23.09	0.56	1.25	0.14
SD	0.03	4.66	0.01	5.60	0.03	0.07	0.03
Tobramycin							
mean	0.05	14.27	0.01	68.50	0.49	1.47	0.21
SD	0.01	4.53	0.00	26.47	0.10	0.28	0.06

[a] k_{el}, serum elimination rate; $t½$, half-life; k_{sd}, serum to dialysate transfer rate; V_d, volume of distribution.

and dialysate concentrations remained in excess of minimum inhibitory concentrations (MIC) for sensitive organisms (approximately 8 mcg/ml) (14) throughout the 24-h period. For tobramycin, the mean serum and dialysate concentrations remained above the MIC for sensitive organisms (approximately 1 to 2 mcg/ml) (15) throughout the 24-h period. Statistical difference was not observed between anuric and nonanuric patients' serum and dialysate drug concentrations at the end of any dwell.

The correlation (r^2) between GFR and cefazolin and tobramycin Cl_R was 36% ($P = 0.05$) and 52% ($P < 0.005$), respectively. The correlation between cefazolin and tobramycin Cl_{PD} and urea Kt/V_{PD} was 31% ($P = 0.08$) and 63% ($P < 0.002$), respectively.

The patients were divided into two groups depending on their duration on PD. The mean duration on PD for group 1 (patients A through D) and group 2 (patients E through J) was 44.3 ± 25.7 and 4.2 ± 1.3 mo, respectively ($P = 0.05$). The urea Kt/V_{PD} values for both groups were as follows: urea Kt/V_{PD} (group 1 = 0.19 ± 0.03; group 2 = 0.26 ± 0.08; $P = 0.05$). The Cl_{PD} values for both study drugs were as follows: cefazolin Cl_{PD} (group 1 = 2.2 ± 0.5 ml/min per 1.73 m^2, group 2 = 2.2 ± 0.9 ml/min per 1.73 m^2; $P = 0.49$); tobramycin Cl_{PD} (group 1 = 3 ± 0.6 ml/min per 1.73m^2; group 2 = 5.4 ± 1.3 ml/min per 1.73 m^2; $P < 0.001$).

Model-predicted serum and dialysate cefazolin and tobramycin end of dwell concentrations for a 70-kg individual post-intermittent intraperitoneal administration are shown in Table 3. The cefazolin and tobramycin intraperitoneal doses used in the model were 1000 and 40 mg, respectively. Intraperitoneal administration would yield an initial serum cefazolin concentration of 71.4 mcg/ml and tobramycin serum concentrations of 1.5 mcg/ml. Initial dialysate concentrations, in a 2-L exchange, would be 500 mcg/ml cefazolin and 20 mcg/ml tobramycin. Intermittent intraperitoneal cefazolin administration during the second ambulatory dwell (dwell 5) yielded adequate end of dwell serum concentrations throughout the 24-h period for sensitive organisms (MIC approximately 8 mcg/ml) (14). Cefazolin administered during the first ambulatory dwell would provide adequate serum, but not dialysate, coverage throughout the 24-h period. Intermittent intraperitoneal tobramycin administration yielded adequate dialysate concentrations (MIC approximately 1 to 2 mcg/ml) (15) for the antibiotic-containing exchange only. The remaining dwells, regardless of first or second ambulatory dwell administration, provided inadequate tobramycin end of dwell dialysate con-

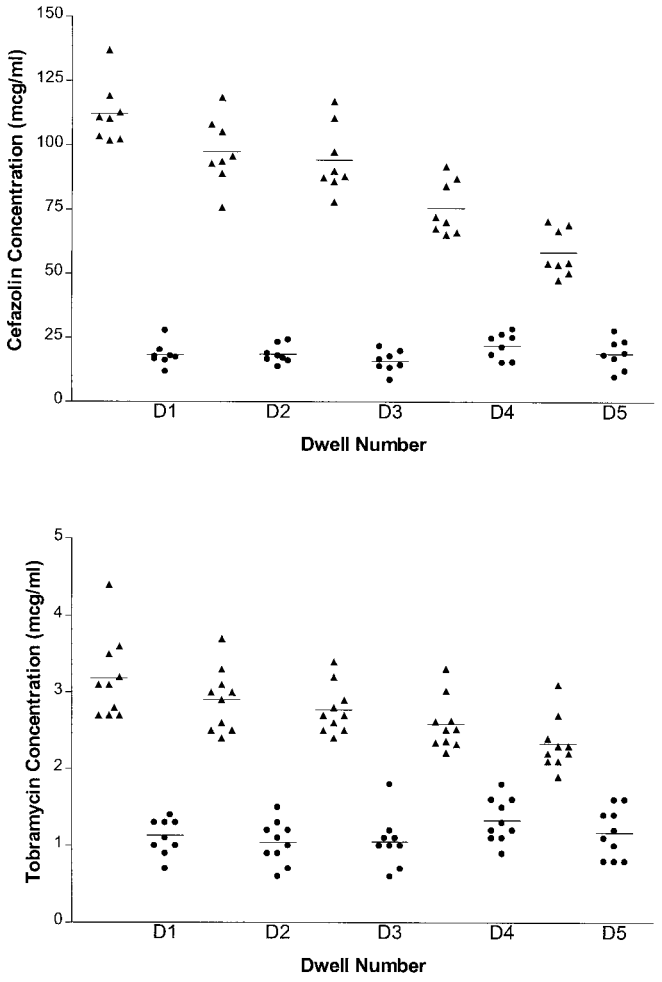

Figure 1. Mean cefazolin and tobramycin serum and dialysate concentrations at end of dwell. ●, dialysate concentration; ▲, serum concentration.

centrations. Model-predicted tobramycin serum concentrations were within an acceptable MIC range during each dwell, regardless of first or second ambulatory dwell administration.

Discussion

The purpose of this study was to characterize the pharmacokinetics of a single intravenous dose of cefazolin and tobramycin in APD patients using three cycler exchanges over 8 h and two ambulatory exchanges occurring over 16 h. The mean serum and dialysate cefazolin concentrations, at the end of the study period after a 15 mg/kg intravenous dose, were about 57.7 and 18.9 mcg/ml, respectively. This would provide adequate coverage for even moderately resistant organisms (14). We have also demonstrated that tobramycin 0.6 mg/kg intravenously yielded adequate serum and dialysate concentrations for susceptible organisms throughout the study period (15).

Although the intermittent regimen of cephalosporins and aminoglycosides has been well studied in CAPD, there are few data for APD systems (8–10,16–19). Extrapolation of our findings observed after intravenous administration to intraperitoneal administration would yield similar pharmacokinetic parameters. However, two significant differences occurred in patients after intraperitoneal administration of cefazolin or tobramycin compared with intravenous administration. First, the initial dialysate concentration in a 70-kg individual would be approximately 500 mcg/ml and 20 mcg/ml for cefazolin and tobramycin in a 2-L exchange, respectively. These concentrations are well above the MIC of even resistant organisms (14–15). This would also enable concentration-dependant killing (tobramycin). Second, intraperitoneal administration would produce lower initial cefazolin and tobramycin serum concentrations. With intraperitoneal administration, approximately 70% of cefazolin dose and approximately 56% tobramycin dose would be absorbed from the antibiotic-containing dwell (8–10). Resulting initial serum concentrations would be approximately 30% (cefazolin) and 44% (tobramycin) less than we observed in our study. The remaining pharmacokinetic parameters (elimination rate constants, half-lives, volumes of distribution, and clearances) should not change.

The Ad Hoc Committee recommends that intraperitoneal antibiotics be allowed to dwell for at least 4 h (4), which would necessitate administration to one of the daytime ambulatory exchanges in an APD patient. As shown in Table 3, model-predicted intraperitoneal cefazolin and tobramycin serum and dialysate concentrations in a 70-kg individual would vary depending on which ambulatory exchange the antibiotics were administered. For example, intraperitoneal cefazolin administration during the second ambulatory exchange would provide adequate serum and dialysate concentrations (8 mcg/ml) for all dwells, whereas intraperitoneal cefazolin administered during the first ambulatory exchange would not. According to our model, it would require 20 mg/kg cefazolin intraperitoneally during the first ambulatory exchange to provide adequate serum and dialysate concentrations throughout.

Model-predicted intraperitoneal tobramycin dosing provided adequate serum concentrations throughout the 24-h period and adequate dialysate concentrations for the antibiotic-containing dwell only. All remaining dwells, on and off the cycler, had inadequate tobramycin end of dwell dialysate concentrations regardless of timing of initial antibiotic-containing dwell. To provide sufficient tobramycin dialysate concentrations ($>$1.0 mcg/ml), the initial intermittent intraperitoneal dose would have to be at least 1.43 mg/kg, if administered during the first ambulatory exchange, or 1.35 mg/kg if administered during the second ambulatory exchange. The overall elimination half-life of tobramycin was about 41 h. It would take approximately 1 wk (4½ half-lives) before tobramycin steady state is achieved, resulting in accumulation. Subsequent daily intraperitoneal tobramycin (0.5 mg/kg), in either the first or second ambulatory exchange, would provide sufficient serum concentrations and dialysate concentrations ($>$1.0 mcg/ml) throughout a 24-h period.

Aminoglycoside-associated otovestibular toxicity becomes a concern in renal failure patients when elevated levels are sustained (20). One study investigated cochlear function in 40 CAPD peritonitis patients who received 1.7 mg/kg tobramycin for the first exchange then 8 mg/L in each exchange thereafter (21). Their results did not demonstrate that tobramycin led to

Table 3. Intraperitoneal cefazolin (15 mg/kg) and tobramycin (0.6 mg/kg) model-predicted serum and dialysate concentrations at end of dwell for first or second ambulatory exchange administration in a 70-kg individual

Dwell	Cefazolin (mcg/ml)		Tobramycin (mcg/ml)	
	Serum	Dialysate	Serum	Dialysate
1st ambulatory[a]	56.2	150.0	1.4	10.0
2nd ambulatory	43.9	13.6	1.3	0.7
Cycler 1	40.3	7.0	1.2	0.4
Cycler 2	37.0	6.4	1.1	0.4
Cycler 3	34.0	5.9	1.0	0.4
2nd ambulatory[a]	56.2	150.0	1.4	10.0
Cycler 1	51.6	8.9	1.3	0.5
Cycler 2	47.4	8.2	1.2	0.4
Cycler 3	43.5	7.5	1.1	0.4
1st ambulatory	34.0	10.5	1.0	0.5

[a] Antibiotics given.

ototoxicity despite obtaining serum concentrations of 4.4 to 4.9 mcg/ml over a mean of 9.5 d. Our tobramycin dosing recommendations would maintain serum concentrations between 2.4 and 3.5 mcg/ml. However, caution is still warranted with prolonged or repeated courses of tobramycin treatment or concurrent use with other potentially ototoxic agents.

The Ad Hoc Committee recommends a 25% increase in antibiotic dose in nonanuric patients (4). Although statistical significance was not found between anuric and nonanuric patients in our study, the correlations between GFR and cefazolin and tobramycin clearance demonstrate the importance of residual renal function on drug elimination. Additionally, our nonstatistical results may be reflective of the low sample size comparisons (7 nonanuric patients *versus* 3 anuric patients) and relatively low residual renal function (GFR = 2 to 3 ml/min per 1.73 m^2). However, patients may begin dialysis at much higher GFR (10 to 15 ml/min per 1.73 m^2) once Dialysis Outcome Quality Initiative guidelines are implemented (13). Cefazolin and tobramycin clearances would be significantly higher in those "early-start" patients. Antibiotic doses will need to be increased appropriately to reflect the higher residual renal function.

During a peritonitis episode, drug pharmacokinetic parameters may be expected to change. With an inflamed peritoneum, more drug would be absorbed from intraperitoneal administration, resulting in higher serum concentrations and providing adequate coverage for more resistant organisms. Conversely, drug elimination from the serum to the dialysate would also increase during drug-free dialysate dwells. This may result in lower than acceptable serum and dialysate concentrations between dosing intervals. Until further investigation of drug pharmacokinetic parameters during peritonitis episodes has been undertaken, caution is warranted when applying our results to peritonitis patients.

We are aware of no other report correlating the effects of peritoneal function (urea Kt/V_{PD}) to cefazolin and tobramycin Cl_{PD}. We found that duration of PD has a significant effect on urea Kt/V_{PD} and drug removal. One might expect that over time the peritoneum becomes less able to transport solutes due to fibrosis and scarring, possibly due to prior episodes of peritonitis. For this reason, the Dialysis Outcome Quality Initiative recommends peritoneal equilibration testing (PET) and creatinine clearance after peritonitis and quarterly to assure that adequate dialysis is being delivered to the patient (13). Our results illustrate that drug removal through the peritoneum may be dependent on individual peritoneal function. The cefazolin and tobramycin absorptive characteristics (*i.e.*, bioavailability) with varying degrees of peritoneal function using PET results would need to be investigated.

In summary, the current cefazolin recommendations (15 mg/kg intraperitoneally) would provide adequate coverage if administered during the second ambulatory exchange in an APD patient with three cycler exchanges occurring over 8 h. Cefazolin (20 mg/kg, intraperitoneally) would be necessary if administered during the first ambulatory exchange. Tobramycin dosing recommendations (0.6 mg/kg intraperitoneally) need to be amended for APD patients with three cycler exchanges occurring over 8 h to 1.5 mg/kg intraperitoneally on day 1, then 0.5 mg/kg intraperitoneally thereafter during either ambulatory exchange. The pharmacokinetics of cefazolin and tobramycin in APD patients prescribed more than three cycler exchanges need further investigation.

Acknowledgment

This study was supported by a grant from Baxter Healthcare Corp.

References

1. Fried LF, Bernardini J, Johnston JR, Piraino B: Peritonitis influences mortality in peritoneal dialysis patients. *J Am Soc Nephrol* 7: 2176–2182, 1996
2. Golper TA, Brier ME, Bunke M, Schreiber MJ, Bartlett BK, Hamilton RW, Strife F, Hamburger RJ: Risk factors for perito-

nitis in long-term peritoneal dialysis: The Network 9 peritonitis and catheter survival studies. *Am J Kidney Dis* 28: 428–436, 1996
3. Gahrmani N, Gorban-Brennan N, Kliger LS, Finkelstein FO: Infection rates in end-stage renal disease patients treated with CCPD and CAPD using the Ultrabag™ system. *Adv Perit Dial* 11: 164–167, 1995
4. Keane WF, Alexander SR, Bailie GR, Boeschoten E, Gokal R, Golper TA, Holmes CJ, Huang C-C, Kawaguchi Y, Piraino B, Riella M, Schaefer F, Vas S: Peritoneal dialysis-related peritonitis treatment recommendations: 1996 update. *Perit Dial Int* 16: 557–573, 1996
5. Lai M-N, Kao M-T, Chen C-C, Cheung S-Y, Chung W-K: Intraperitoneal once-daily dose of cefazolin and gentamicin for treating CAPD peritonitis. *Perit Dial Int* 17: 87–89, 1997
6. Vas S, Bargman J, Oreopoulos DG: Treatment in PD: Patients of peritonitis caused by Gram-positive organisms with single daily dose of antibiotics. *Perit Dial Int* 17: 91–94, 1997
7. Bailie GR, Haqqie SS, Eisele G, Gorman T, Low CL: Effectiveness of once-weekly vancomycin and once-daily gentamicin, intraperitoneally, for CAPD peritonitis. *Perit Dial Int* 15: 269–271, 1995
8. Manley HJ, Bailie GR, Asher RD, Eisele G, Frye RF: Pharmacokinetics of intermittent intraperitoneal cefazolin in continuous ambulatory peritoneal dialysis patients. *Perit Dial Int* 19: 65–70, 1999
9. Low CL, Gopalakrishna K, Lye WC: Pharmacokinetics of once-daily IP cefazolin in CAPD patients. *Perit Dial Int* 19[Suppl 1]: S33, 1999
10. Low CL, Bailie GR, Evans A, Eisele G, Venezia RA: Pharmacokinetics of once-daily IP gentamicin in CAPD patients. *Perit Dial Int* 16: 379–384, 1996
11. United States Renal Data System: *United States Renal Data System 1999 Annual Report*, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Division of Kidney, Urologic, and Hematologic Diseases, Bethesda, MD, 1999
12. Bailie GR, Kane MP: Stability of drug additives to peritoneal dialysate. *Perit Dial Int* 15: 328–335, 1995
13. National Kidney Foundation-Dialysis Outcomes Quality Initiative: Clinical practice guidelines for peritoneal dialysis adequacy. *Am J Kidney Dis* 30[Suppl 2]: S67–S136, 1997
14. Dudley MN: Use of laboratory test in infectious diseases. In: *Pharmacotherapy, a Pathophysiologic Approach*, 3rd Ed., edited by Dipiro JT, Talbert RL, Yee GC, Matzke GR, Wells BG, Posey LM, Norwalk, CT, Appleton & Lange, 1997, pp 1938
15. Nebcin (tobramycin) [package insert]. Indianapolis, IN: Eli Lilly, 1996
16. Grabe DW, Bailie GR, Eisele G, Frye RF: Pharmacokinetics of intermittent intraperitoneal ceftazidime. *Am J Kidney Dis* 33: 111–117, 1999
17. Bunke CM, Aronoff GR, Brier ME, Sloan RS, Luft FC: Cefazolin and cephalexin kinetics in continuous ambulatory peritoneal dialysis. *Clin Pharmacol Ther* 33: 66–72, 1983
18. Kaye D, Wenger N, Agarwal B: Pharmacology of intraperitoneal cefazolin in patients undergoing peritoneal dialysis. *Antimicrob Agents Chemother* 14: 318–321, 1978
19. Morse GD, Apicella MA, Walshe JJ: Absorption of intraperitoneal antibiotics. *Drug Intell Clin Pharm* 22: 58–61, 1988
20. McCormack JP, Jewesson PJ: A critical reevaluation of the "therapeutic range" of aminoglycosides. *Clin Infect Dis* 14: 320–339, 1992
21. Nikolaidis P, Vas S, Lawson V, Kennedy-Vosu L, Bernard A, Abraham G, Izatt S, Khanna S, Bargman JM, Oreopoulos DG: Is intraperitoneal tobramycin ototoxic in CAPD patients? *Perit Dial Int* 11: 156–161, 1991