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Effects of Antacids and Dialysate Dwell Times on Multiple-Dose Pharmacokinetics of Oral Ciprofloxacin in Patients on Continuous Ambulatory Peritoneal Dialysis

THOMAS A. GOLPER,[1]* ALAN I. HARTSTEIN,[2] VIRGINIA H. MORTHLAND,[2] AND J. MARK CHRISTENSEN[3]

Divisions of Nephrology[1] and Infectious Diseases,[2] Oregon Health Sciences University, Portland, Oregon 97201, and College of Pharmacy, Oregon State University, Corvallis, Oregon 97331[3]

Received 9 June 1987/Accepted 10 August 1987

Six stable patients on continuous ambulatory peritoneal dialysis were evaluated for the appearance of ciprofloxacin in their peritoneal dialysate following oral ingestion of 750 mg of the drug every 12 h for four doses. Three subjects participated in this study twice, once while taking and once while abstaining from phosphate-binding aluminum antacids. Subjects tolerated the medication without evidence of toxicity. Food may have delayed or decreased the absorption of ciprofloxacin, whereas antacids definitely decreased the absorption of the drug. Peak concentrations in serum noted in the absence of antacids ranged from 2.9 to 6.4 μg/ml, and peak concentrations in dialysate in the absence of antacids ranged from 1.8 to 4.5 μg/ml. Peak ciprofloxacin concentrations in serum achieved in subjects taking antacids were 14 to 50% of those achieved in subjects without antacids. The peak concentrations in dialysate achieved in subjects on antacids were 8 to 33% of those observed in subjects off antacids. The clearance of ciprofloxacin by continuous ambulatory peritoneal dialysis represented 2% of the total body (systemic) clearance. Simultaneous ratios of concentration in dialysate to concentration in serum (*D/S*) were determined at various durations of dialysate dwelling within the peritoneum. A progressive rise of the *D/S* ratio was noted as dwell time increased. At 4 h *D/S* was 0.57 ± 0.07 ($\bar{x}$ ± standard error of the mean; $n = 9$), and at 8 h it was 0.75 ± 0.04 ($n = 26$). Long-dwell exchanges may be necessary to achieve reasonable concentrations of orally ingested ciprofloxacin in dialysate.

Compared with available quinoline antibiotics (nalidixic acid and norfloxacin) and those in various stages of development, ciprofloxacin is more active in vitro against *Staphylococcus aureus*, coagulase-negative staphylococci, and *Pseudomonas aeruginosa* (17). Because of this activity, ciprofloxacin may prove to be quite useful in treating the infectious complications of chronic peritoneal dialysis. Aluminum-containing antacids, which dialysis patients ingest as phosphate binders, cause malabsorption of ciprofloxacin (L. N. Fleming, T. A. Moreland, W. K. Stewart, and A. C. Scott, Letter, Lancet ii:294, 1986; G. Hoffken, K. Borner, P. D. Glatzel, P. Koepe, and H. Lode, Letter, Eur. J. Clin. Microbiol. 4:345, 1985). In the present study, the multiple-dose kinetics of ciprofloxacin were determined in healthy patients on continuous ambulatory peritoneal dialysis (CAPD) in the presence or absence of aluminum-containing antacids. Toxic accumulation of ciprofloxacin did not occur after four doses. Aluminum-containing antacids impair the absorption of the drug and must be avoided if adequate levels of the drug in serum and dialysate are to be achieved. We have further demonstrated that levels of ciprofloxacin in dialysate may not be adequate during short-dwell exchanges.

MATERIALS AND METHODS

Six stable subjects between the ages of 44 and 74 years on CAPD were enrolled in this study, which was approved by the Committee on Human Research at the Oregon Health Sciences University. Informed consent was obtained, and the subjects were housed at the Clinical Research Center and maintained on their usual diets. Subjects had been on CAPD in stable condition for many months. Several subjects were receiving vancomycin for exit site infections, but no subject was receiving other antibiotics, had exhibited peritonitis for at least 1 month prior to the study period, or had cloudy fluid, dialysate leukocytosis, abdominal pain, or fever at the time of the study. Complete blood counts and chemical profiles were obtained before and after the studies. Medications were continued except for phosphate-binding antacids. Except for predictable abnormalities that accompany end-stage renal disease, subjects demonstrated no other biochemical or hematological abnormalities. Detailed medical histories and physical and visual examinations were performed prior to the study, and visual examinations were repeated after the study period.

The subjects entered the Clinical Research Center on Monday evenings and received 750 mg of ciprofloxacin (Miles Pharmaceuticals, West Haven, Conn.) orally at 0900 and 2100 hours on Tuesday and Wednesday (total of four doses 12 h apart). Breakfast was allowed but had to be completed by 0800 hours. Evening meals were served at 1800 hours. The glucose concentration of the dialysate fluid depended on the unique ultrafiltrative needs of subjects, and subjects used their routine dialysate volumes. Tuesday dialysate exchanges occurred at 0830, 1300, 1700, 2030, and 2400 hours (five exchanges). Wednesday dialysate exchanges occurred at 0830, 1300, 1800, and 2400 hours (four exchanges). Thursday dialysate exchanges occurred at 0830, 1300, and 1700 hours and at bedtime (four exchanges). On Friday, an exchange occurred at 0830 hours; the last samples were obtained, and the subjects were discharged. Blood for determining levels of ciprofloxacin in serum was obtained via an indwelling venous catheter at 0800, 1000, 1030, 1100, 1500, 2100, 2200, 2230, 2300, and 2400 hours on Tuesday; 0900, 1000, 1100, 2100, and 2300 hours on Wednesday; 0900, 1300, and 2100 hours on Thursday; and 0900 hours on Friday. Dialysate was sampled by syringe and needle from

* Corresponding author.

TABLE 1. Peak ciprofloxacin concentrations in serum and dialysate

Subject no. (antacids)[a]	Peak concn (mg/liter) and time of occurrence for:	
	Serum	Dialysate
1 (−)	5.2, 2 h post-dose 4	2.7, 11.5 h post-dose 4
1 (+)	2.6, 1 h post-dose 3	0.88, 3 h post-dose 3 and 11.5 h post-dose 4
2 (−)	5.8, 2 h post-dose 4	4.5, 11.5 h post-dose 4
3 (−)	4.0, 12 h post-dose 4	2.6, 16 h post-dose 4
4 (−)	6.4, 2 h post-dose 4	4.5, 11.5 h post-dose 4
4 (+)	0.90, 6 h post-dose 1	0.36, 11.5 h post-dose 2
5 (−)	2.9, 2 h post-dose 4	1.8, 11.5 h post-dose 4
6 (−)	3.4, 2 h post-dose 4	2.3, 3 h post-dose 4 and 11.5 h post-dose 4
6 (+)	0.96, 2 h post-dose 3	0.64, 8 h post-dose 3

[a] Presence (+) or absence (−) of antacids.

the sampling port of the dialysate bag after a 5-min povidone-iodine preparation. The subject would drain 200 to 300 ml of dialysate into the bag from which the 3-ml sample would be obtained. If an exchange was not at the sampling time, the dialysate remaining in the bag was reinstilled into the subject. This process took less than 7 min. When an exchange was due, a nurse sampled the bag after disconnection. On Tuesday, dialysate was sampled at 0800, 0830, 1000, 1030, 1100, 1200, 1300, 1500, 1700, 2030, 2100, 2200, 2300, and 2400 hours. On Wednesday, dialysate samples were obtained at 0830, 1000, 1100, 1200, 1700, and 2400 hours. On Thursday, dialysate samples were obtained at 0830, 1300, 1700, and 2100 hours. On Friday, a dialysate sample was obtained at 0830 hours.

Subjects utilized Travenol dialysate (Travenol Laboratories, Deerfield, Ill.) for this study period, and subjects routinely using bagless disconnect systems agreed to wear bags for the 3.5 days of the study.

Ciprofloxacin levels in dialysate and serum were determined by microbiological assay (1). Samples were frozen at −70°C until each subject completed the study, and all specimens from each subject were assayed on the same day. Samples from each specimen were assayed in triplicate with standard, large-plate biological assay procedures in Trypticase soy broth (BBL Microbiology Systems, Cockeysville, Md.) seeded with *Klebsiella pneumoniae* ATCC 10031. This test organism is not affected by the presence of vancomycin. Reference standards of ciprofloxacin (Miles Pharmaceuticals) for serum and dialysate were prepared in pooled human serum and in used, drained, postdialysis dialysate, respectively. Random patterns of filling wells were applied to correct for any variations. The incubation period was 18 h at 37°C, after which the zones of inhibition were determined. Means of zone sizes were calculated for each triplicated specimen or standard, and curves of concentration versus zone size were plotted.

Elimination rate constants and biological half-lives were determined by NONLIN, a computer program for nonlinear least-squares fitting of pharmacokinetic data (12). Total body clearance was determined by dividing the total dose given by the area under the curve for drug concentration versus time (7, 14, 18). Total body clearance is expressed as CL/F, where F is the fraction of the dose absorbed. For our purposes we have defined F as 100%, although we know that is not the case (5). F is not utilized in determining half-lives or elimination rate constants.

The clearance of ciprofloxacin by CAPD was determined during the linear decline of drug levels in serum after dose 4 had been clearly absorbed. This strategy was used because the determination of clearance at a steady-state level in serum was not possible with an erratically absorbed drug. The frequency of phlebotomies was not increased in these subjects with chronic anemia or end-stage renal disease. Therefore, clearance was performed 12 to 16 h after the last dose, during a 4-h exchange. Drug levels in serum at 0 and 4 h were obtained (using the mean for calculations), and all of the dialysate was collected. Peritoneal dialysis clearance was determined as the absolute amount of drug removed during the clearance period divided by the mean drug concentration in serum during that period. Surface area was determined by nomogram from height and weight.

RESULTS

Six subjects completed the study. Three of the six agreed to participate twice, once taking and once abstaining from aluminum-containing phosphate-binding antacids. Subjects tolerated four doses of ciprofloxacin without any side effects and especially without nausea. Laboratory biochemical and hematological profiles did not change appreciably, except that the 150-ml blood loss occasionally affected hematocrit. Results of physical and visual examinations were unchanged.

Table 1 shows peak concentrations of ciprofloxacin in serum and dialysate and the timing of their occurrences relative to the dosage schedule. For five of six subjects not ingesting antacids, the peak concentration in serum occurred 2 h after dose 4 and the last dose, while for three subjects receiving antacids, peak concentration in serum occurred at random. In six of nine observations, peak concentration in dialysate occurred at the end of the long-dwell exchange that was sampled 11.5 h after dose 4. Table 2 gives peak concentration of drug in serum and the time of its occurrence after dose 1 only. Four of six patients not taking antacids and two of three patients taking antacids achieved first-dose peak concentrations of drug in serum 6 h later.

For the clearance of ciprofloxacin by CAPD (Table 3), the nine observations were considered equivalent, since antacid effects on absorption would not necessarily affect peritoneal clearances. When clearances were repeated with subjects 1, 4, and 6 on antacids, similar results were obtained for subjects 4 and 6. There is a wide range of clearances in the six subjects, but in all observations, the clearance of ciprofloxacin by CAPD was very low.

Elimination rate constants, half-lives, and systemic (total body) clearances are given in Table 4. Again it should be

TABLE 2. Peak concentration of ciprofloxacin in serum after dose 1

Subject no. (antacids)[a]	Peak concn (mg/ml)	T_{max} (h)[b]
1 (−)	2.4	6
1 (+)	0.90	6
2 (−)	2.7	1.5
3 (−)	1.6	6
4 (−)	2.7	6
4 (+)	0.90	6
5 (−)	2.3	2
6 (−)	2.2	6
6 (+)	0.62	2

[a] Presence (+) or absence (−) of antacids.
[b] T_{max}, Time to maximum concentration of drug in serum after ingestion of drug.

TABLE 3. Clearance of ciprofloxacin by CAPD[a]

Subject no.	Age (yr)	Surface area (m^2)	Antacids[b]	CL (ml/min per 1.73 m^2)[c]
1	57	2.05	−	4.41
1		2.06	+	6.17
2	74	2.12	−	2.90
3	55	1.93	−	4.62
4	68	1.76	−	4.24
4		1.80	+	4.26
5	44	1.65	−	2.84
6	44	1.70	−	4.16
6		1.77	+	3.90
Mean ± SEM				4.16 ± 0.33

[a] Determined from the exchange occurring between 0900 and 1300 hours on Thursday, while levels in serum were declining linearly.
[b] Presence (+) or absence (−) of antacids.
[c] Clearance (CL) of ciprofloxacin by CAPD.

noted that F is assumed to be 100% for calculations for systemic clearance. As the exact value of F for our subjects it not known, the use of 100% at least gives one a reference point. The clearance of ciprofloxacin by CAPD represents about 2% of the total body clearance.

Although the clearance of ciprofloxacin by CAPD is small relative to the total body clearance of ciprofloxacin, the drug did appear in the dialysate at concentrations exceeding the MIC for susceptible bacteria. Simultaneous observations of drug concentrations in serum and dialysate from all subjects (Table 5) show that, except for observations made after 2 h of dialysate dwelling, there is a progressive increase in the ratio of drug concentration in dialysate to drug concentration in serum as the duration of dialysate dwelling in the peritoneum increases. For the long-dwell exchanges (≥8 h), the concentration of ciprofloxacin in dialysate was 75% of that in serum.

DISCUSSION

Ciprofloxacin has excellent in vitro activity against organisms which cause the major infectious complications of CAPD (M. McIntyre, V. Trend, and A. Curran, Letter, Periton. Dialy. Bull. 7:107–108, 1987). Furthermore, ciprofloxacin penetrates into neutrophils (6) and may be useful in treating antibiotic-resistant infections secondary to intraleukocytic sequestration by staphylococci (4). A preliminary report by Kowalsky and associates suggested that ciprofloxacin could be a promising agent in the treatment of CAPD-associated peritonitis (S. F. Kowalsky, R. M. Echols, E. A. Andrews, E. M. McCormick, and R. T. Rasmussen, 6th Natl. Conf. Continuous Ambulatory Peritoneal Dialysis, 1986, p. 203–204). However, pharmacokinetic studies were not performed during that trial.

Pharmacokinetic studies of single-dose orally ingested ciprofloxacin in patients on CAPD were reported by Shalit et al. (16). Their subjects fasted and achieved a mean peak concentration of drug in serum of 3.6 mg/liter 1 to 2 h after ingestion. Our subjects finished breakfast 1 h prior to ingesting a similar dose and achieved a mean peak concentration of drug in serum of 2.3 ± 0.2 mg/liter ($\bar{x}$ ± standard error of the mean for subjects not taking antacids; Table 2), which occurred 1.5 to 6 h after ingestion of the drug. In normal subjects, food has been shown to delay absorption but not to decrease the overall bioavailability of the drug (11). When our subjects were compared with those of Shalit et al. (16), there appeared to be delayed absorption as well as a decrease in bioavailability of the drug.

The ages of the patients studied by Shalit et al. and by us are similar. Ciprofloxacin kinetics are known to be altered in the elderly (3, 9, 10). Subjects 2 and 4 were ≥68 years old, and they demonstrated the highest peak ciprofloxacin concentrations (Tables 1 and 2). Because all our subjects were essentially anephric, these observations suggest that older subjects either absorb the drug better than their younger counterparts do or have a smaller volume of distribution. This issue is important because one-third of the American population on CAPD is elderly (13).

To achieve adequate concentrations of ciprofloxacin in serum and dialysate, infected patients on CAPD will almost certainly have to discontinue the use of aluminum-containing antacids. Fleming et al. (Letter) reported that calcium-containing antacids may cause less malabsorption of ciprofloxacin than does an aluminum-magnesium combination. In addition to observing lower peak concentrations of ciprofloxacin in serum and dialysate with our subjects who ingested antacids, the timing of the peak concentrations was altered, again suggesting effects of the antacids on ciprofloxacin absorption.

In healthy subjects, 30% of the systemic clearance of ciprofloxacin is by the kidney (2, 7). CAPD does not compensate for this. Furthermore, Kowalsky et al. (Letter) noted what may have been ciprofloxacin toxicity symptoms in their patients on CAPD who had been treated for many days with a dose of 1,500 mg/day. Although our subjects tolerated four doses without side effects, the highest concentrations in serum that we observed occurred after the last

TABLE 4. Parameters of ciprofloxacin kinetics

Subject no. (antacids)[a]	k_{el} (h^{-1})[b]	$t_{1/2}$[c] (h)	CL/F (ml/min per 1.73 m^2)[d]
1 (−)	0.0615	11.3	175
1 (+)	0.0614	11.3	564
2	0.0476	14.6	147
3	0.0705	9.8	264
4 (−)	0.0468	14.8	170
4 (+)	0.0787	8.8	1,632
5	0.1334	5.2	437
6 (−)	0.0670	10.4	341
6 (+)	0.0560	12.4	1,202
Mean ± SD (SEM)	0.0692 ± 0.0262	11.0 ± 3.0 (1.0)	256[e] ± 115 (47)

[a] Presence (+) or absence (−) of antacids.
[b] k_{el}, Elimination rate constant.
[c] $t_{1/2}$, Half-life.
[d] CL/F, Total body clearance.
[e] Mean of six observations of subjects without antacids because F is more likely to be constant in that situation.

TABLE 5. Duration of dialysate dwell and ratio of concentrations in dialysate and serum

Dialysate dwell time (h)	No. of observations	Concn in dialysate/concn in serum ($\bar{x}$ ± SEM)
0.5	8	0.103 ± 0.028
1.5	18	0.259 ± 0.027
2.0	8	0.362 ± 0.056
2.5	25	0.263 ± 0.029
3.5	18	0.442 ± 0.046
4.0	9	0.569 ± 0.074
≥8	26	0.755 ± 0.036

dose (Table 1). Had additional doses been prescribed, it is quite possible that concentrations in serum would have continued to rise. Thus, dosing regimens have to be altered for these anephric patients on CAPD.

Although the present study was not specifically designed to rigorously determine the rate of ciprofloxacin appearance in dialysate, enough observations were made to make a meaningful statement. It is clear from the data in Table 5 that dwell times of 4 h or more are required to allow adequate penetration of ciprofloxacin into the dialysate, where adequate means a drug concentration in dialysate of at least 50% of the drug concentration in serum. These observations are consistent with those of Shalit et al. (16). During peritonitis, when ultrafiltration rate decreases, short-dwell exchanges are frequently utilized (15). If ciprofloxacin is used in these situations, the clinician must know that levels in dialysate may be subtherapeutic during short-time dwells.

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LITERATURE CITED

1. **Anhalt, J. P.** 1985. Antimicrobial assays, p. 691–729. *In* J. A. Washington II (ed.), Laboratory procedure in clinical microbiology, 2nd ed. Springer-Verlag, New York.
2. **Aronoff, G. E., C. H. Kenner, R. S. Sloan, and S. T. Pottratz.** 1985. Multiple dose ciprofloxacin kinetics in normal subjects. Clin. Pharmacol. Ther. **36**:384–388.
3. **Ball, A. P., C. Fox, M. E. Ball, R. F. Brown, and J. V. Willis.** 1986. Pharmacokinetics of oral ciprofloxacin, 100 mg single dose, in volunteers and elderly patients. J. Antimicrob. Chemother. **17**:629–635.
4. **Buggy, B. P., D. R. Schaberg, and R. D. Swartz.** 1984. Intraleukocytic sequestration as a cause of persistent Staphylococcus aureus peritonitis in continuous ambulatory peritoneal dialysis. Am. J. Med. **76**:1035–1040.
5. **Drusano, G. L., H. C. Standiford, K. Plaisance, A. Forrest, J. Leslie, and J. Caldwell.** 1986. Absolute oral bioavailability of ciprofloxacin. Antimicrob. Agents Chemother. **30**:444–446.
6. **Easman, C. S. F., and J. P. Crane.** 1985. Uptake of ciprofloxacin by human neutrophils. J. Antimicrob. Chemother. **16**:67–73.
7. **Gasser, T. C., S. C. Ebert, P. H. Graversen, and P. O. Madsen.** 1987. Pharmacokinetic study of ciprofloxacin in patients with impaired renal function. Am. J. Med. **82**(Suppl. 4A):139–141.
8. **Gilbaldi, M., and D. Perrier.** 1982. Pharmacokinetics, 2nd ed., p. 321, 445–449. Marcel Dekker, Inc., New York.
9. **Guay, D. R. P., W. M. Awni, P. K. Peterson, S. Obaid, R. Breitenbucher, and G. R. Matzke.** 1987. Pharmacokinetics of ciprofloxacin in acutely ill and convalescent elderly patients. Am. J. Med. **82**(Suppl. 4A):124–130.
10. **LeBel, M., G. Barbean, M. G. Bergeron, D. Roy, and F. Volle.** 1986. Pharmocokinetics of ciprofloxacin in elderly subjects. Pharmacotherapy **6**:87–91.
11. **Ledergerber, B., J.-D. Bettex, B. Joos, M. Flepp, and R. Lüthy.** 1985. Effect of standard breakfast on drug absorption and multiple-dose pharmacokinetics of ciprofloxacin. Antimicrob. Agents Chemother. **27**:350–352.
12. **Metzler, C. M.** 1973. NONLIN: a computer program for parametric estimation in nonlinear situations. Users manual. The Upjohn Co., Kalamazoo, Mich.
13. **Nolph, K.** 1987. NIH CAPD registry report overview: 7th National Conference on CAPD. Kansas City, Mo.
14. **Riegelman, S., and P. Collier.** 1980. The application of statistical moment theory to the evaluation of *in vivo* dissolution and absorption time. J. Pharmacokinet. Biopharm. **8**:509–534.
15. **Rubin, J., R. Ray, T. Barnes, and J. Bower.** 1981. Peritoneal abnormalities during infectious episodes of continuous ambulatory peritoneal dialysis. Nephron **29**:124–127.
16. **Shalit, I., R. B. Greenwood, M. I. Marks, J. A. Pederson, and D. L. Frederick.** 1986. Pharmacokinetics of single-dose oral ciprofloxacin in patients undergoing chronic ambulatory peritoneal dialysis. Antimicrob. Agents Chemother. **30**:152–156.
17. **Wolfson, J. S., and D. C. Hooper.** 1985. The fluoroquinolones: structures, mechanisms of action and resistance, and spectra of activity in vitro. Antimicrob. Agents Chemother. **28**:581–586.
18. **Yeh, K. C., and K. C. Kwan.** 1978. A comparison of numerical integrating algorithms by trapezoidal, Lagrange, and Spline approximation. J. Pharmacokinet. Biopharm. **6**:79–98.