ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Sept. 1986, p. 485–490
0066-4804/86/090485-06$02.00/0

Vol. 30, No. 3

Pharmacokinetics of Cefixime (CL 284,635; FK 027) in Healthy Subjects and Patients with Renal Insufficiency

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Received 3 March 1986/Accepted 13 June 1986

The pharmacokinetics of the extended-half-life, broad-spectrum oral cephalosporin cefixime (CL 284,635; FK 027) were studied in 7 healthy volunteers and 35 patients with various degrees of renal insufficiency, including patients undergoing continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis. Apparent total body, renal, and apparent nondialysis-nonrenal clearances and protein binding declined and elimination half-life increased with decreasing creatinine clearance. All of these alterations became statistically significant as the creatinine clearance fell below 20 ml/min per 1.73 m^2. Cefixime concentrations in urine exceeded the MICs for most urinary tract pathogens for up to 24 h postdose, even in patients with severe renal insufficiency. CAPD removed an insignificant fraction of cefixime body burden over the 72-h study period (1.57 ± 0.60% [mean ± the standard error of the mean]). Area under the curve data suggested that hemodialysis similarly removed an insignificant fraction of the cefixime body burden. Volume of distribution at steady state was not altered significantly by renal insufficiency. It is recommended that standard doses of cefixime be administered at extended intervals, especially in patients with creatinine clearances less than 20 ml/min per 1.73 m^2. In addition, supplemental doses are not necessary during CAPD and at the end of hemodialysis.

Cefixime (CL 284,635; FK 027) is an oral, extended half-life cephem antibiotic which is active against a broad range of gram-positive and gram-negative microorganisms. These include *Proteus* sp., *Citrobacter freundii*, *Enterobacter aerogenes*, and *Serratia marcescens* (8, 12). Preliminary studies have examined the pharmacokinetics of cefixime in healthy human volunteers. In volunteers receiving a 400-mg oral dose, a mean peak concentration in serum of 3.85 μg/ml was achieved at approximately 4 h postdose; 24-h urinary excretion of the parent compound was 16% of the dose, and the elimination half-life was 3.05 h (2). The free fraction of cefixime was approximately 37% (data on file at Lederle Laboratories, Pearl River, N.Y.). The purposes of this investigation were (i) to define the pharmacokinetics of cefixime in healthy subjects and patients with a wide range of renal insufficiency, (ii) to examine the contribution of peritoneal dialysis and hemodialysis to total body clearance, and (iii) to suggest appropriate dosage regimen modifications for patients with various degrees of renal insufficiency, including those maintained on peritoneal dialysis and hemodialysis.

(This paper was presented in part at the Ninth International Congress of Infectious and Parasitic Diseases, Munich, Federal Republic of Germany, 20 to 26 July 1986.)

MATERIALS AND METHODS

Subjects. Seven healthy subjects and 35 patients with various degrees of renal insufficiency who were otherwise free of clinical illness gave informed written consent to participate in this study. The study was approved by the Faculty Committee on the Use of Human Subjects in Research, University of Manitoba. Complete physical examinations, medical histories, blood chemistry and hematology profiles, and urinalysis results were obtained for all patients before and after participation in the study.

Volunteers were divided into the following seven groups on the basis of measured 24-h creatinine clearances (CL_{CR}) obtained prior to the study day: seven healthy subjects (CL_{CR}, >80 ml/min per 1.73 m^2), seven patients with very mild renal insufficiency (CL_{CR}, 80 to 61 ml/min per 1.73 m^2), eight patients with mild renal insufficiency (CL_{CR}, 60 to 41 ml/min per 1.73 m^2), five patients with moderate renal insufficiency (CL_{CR}, 40 to 21 ml/min per 1.73 m^2), six patients (not maintained on dialysis) with severe renal insufficiency (CL_{CR}, 20 to 5 ml/min per 1.73 m^2), and nine dialysis patients, four of whom were maintained on continuous ambulatory peritoneal dialysis (CAPD) and five of whom were maintained on hemodialysis (HD). The seven groups of patients were comparable in sex distribution, age, weight (total and lean), and height (P was not significant for all comparisons) (Table 1). Lean weight was calculated by the method of Devine (4). As study results did not differ significantly whether total or lean body weight was used, results are presented based on total body weight only.

Dialysis procedures. CAPD patients received a volume of 2,000 ± 50 ml of dialysate containing either 1.5, 2.5, or 4.25% glucose (Dianeal; Baxter Travenol, Malton, Ontario, Canada) instilled intraperitoneally every 6 h through a permanent Tenckhoff peritoneal catheter. No attempt was made to standardize the dialysis regimens with respect to the glucose concentrations used. Glucose concentrations were carefully noted when samples were taken in order to correlate CAPD clearance with glucose concentration.

HD patients were dialyzed for 3 h (one patient), 4 h (two patients), or 5 h (two patients) three times per week. The dialyzers used included GF 120-H or GF 120-M hollow-fiber cartridges with an 8-μm-by-1.2-m^2 cuprophane membrane (Gambro, Lund, Sweden) and PPD 1.3 parallel-plate cartridges with an 11.5 μm-by-1.3-m^2 cuprophane membrane

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TABLE 1. Demographic characteristics of healthy subjects and patients with various degrees of renal insufficiency[a]

Group	No. of subjects	No. of males/no. of females	Age (yr)	Total body wt (kg)	Lean body wt (kg)	Ht (cm)	CL_{CR} (ml/min per 1.73 m^2)
Healthy	7	4/3	42 ± 6	77.3 ± 5.2	66.5 ± 4.1	174 ± 4	111 ± 6
Renal insufficiency							
Very mild	7	4/3	48 ± 8	81.7 ± 5.1	60.4 ± 3.4	169 ± 4	71 ± 2
Mild	8	3/5	61 ± 2	75.1 ± 4.8	58.0 ± 5.1	164 ± 6	51 ± 2
Moderate	5	3/2	60 ± 4	76.0 ± 6.7	61.6 ± 4.4	167 ± 3	28 ± 3
Severe	6	2/4	51 ± 8	66.7 ± 5.6	57.2 ± 3.4	164 ± 5	9.8 ± 1.0
CAPD	4	3/1	47 ± 6	65.3 ± 6.8	62.2 ± 5.2	168 ± 6	3.0 ± 2.2
HD	5	2/3	36 ± 7	68.3 ± 6.3	62.2 ± 4.6	167 ± 4	1.3 ± 0.7

[a] Values are means ± SEM.

(Cobe Laboratories, Lakewood, Colo.). Flow rates were 150 to 250 and 500 ml/min for blood and dialysate, respectively. Ultrafiltration was performed in four of the five patients during dialysis for fluid removal.

Drug administration and fluid sampling. All patients received 400 mg of cefixime by mouth with 120 ml of water after a 12-h overnight fast. HD patients during the on-dialysis study day received the drug 6 h before dialysis, and CAPD patients received the drug just after the first dialysis bag of the day had drained into the peritoneal cavity. Blood samples were obtained via a heparin lock in a forearm vein at 0 (predose), 1, 1.5, 2, 4, 6, 8, 12, 18, and 24 h after dosing in all subjects (except HD patients during the on-dialysis study day). In addition, in patients with renal insufficiency (except the HD group), further blood samples were obtained by venipuncture at 48 and 72 h after dosing. HD patients during the on-dialysis study day had venous blood samples taken at 0 h (predose); 3, 2, and 1 h predialysis; at the start of dialysis; three evenly timed points during dialysis; at the end of dialysis; and 0.5, 1, 2, 6, 12, 18, and 24 h after the end of dialysis. Paired arterial and venous coil blood samples were also collected simultaneously with the three peripheral venous samples taken during dialysis. Blood samples were allowed to clot and then were centrifuged; the sera were saved for analysis. Urine was collected, when possible, predose, and 0 to 2, 2 to 4, 4 to 8, 8 to 12, and 12 to 24 h postdose from all subjects (except HD patients during the on-dialysis study day). In addition, further urine collections during the intervals of 24 to 48 and 48 to 72 h postdose were performed on the patients with renal insufficiency (except the HD group). The urine of HD patients during the on-dialysis study day was collected predose; from administration to commencement of dialysis; during dialysis; and then from 0 to 4, 4 to 8, 8 to 12, and 12 to 24 h after dialysis when possible. Urine collections were quantitated, and samples were saved for analysis. Peritoneal dialysate was collected every 6 h for 72 h after dosing. Dialysate was quantitated, and samples were saved for analysis. All biological samples were stored at −20°C until assayed.

Protein binding. Protein binding in serum samples obtained predose and 4 and 12 h postdose were assessed by equilibrium dialysis. These analyses were performed at Lederle Laboratories. In acrylic dialysis cells, 0.5-ml serum samples were dialyzed across cellulose membranes (Spectra Por 2; Spectrum Medical Industries, McGaw Park, Ill.) against 0.1 mol of pH 7 phosphate buffer per liter for 6 h. After dialysis, 0.25-ml samples were removed and frozen at −20°C until analysis. All samples were analyzed in duplicate. The unbound or free fraction of cefixime in serum was expressed as the ratio of the buffer concentration to that of the drug in serum. As no significant concentration or time dependence was noted, the results within each group were pooled for data analysis.

Analytical methodology. Cefixime concentrations in serum and urine were determined by a high-performance liquid chromatographic method (data on file at Lederle Laboratories). This method was extended to accommodate the analysis of cefixime in dialysate.

Briefly, 100 μl of serum or urine standard or unknown were vortex mixed for 10 s with 100 μl of internal standard solution (10 μg of 7-hydroxycoumarin per ml in 6% trichloroacetic acid). After brief centrifugation, 100 μl of the clear supernatant was injected into the chromatograph. Dialysates were treated in a similar fashion except for different quantities of biological fluid (200 μl) and internal standard solution (50 μl).

The high-performance liquid chromatographic system consisted of a Series 10 pump, an LC-95 variable-wavelength UV-visible wavelength detector, and an R-100A chart recorder (The Perkin-Elmer Corp., Norwalk, Conn.). Two brands of octodecyl reverse-phase analytical column were used: a 5-μm (particle size) Nova-Pak C-18 (150 by 3.9 mm) protected by a Guard-Pak containing μBondapak C-18 (Waters Associates, Inc., Milford, Mass.) for serum analysis and a 5-μm (particle size) Supelcosil C-18 (250 by 4.6 mm) (Supelco, Bellefonte, Pa.) for urine and dialysate analysis. The Supelco column proved superior to the Waters column in separating an interfering peak peculiar to the urine samples from the dialysis patients from the cefixime peak. The mobile phase of 17.5% acetonitrile in 10 mmol phosphate buffer per liter containing 0.2% phosphoric acid (pH 2.1) was pumped at 2.0 ml/min, and the effluent was monitored at 280 (serum) or 313 (urine and dialysate) nm. Although the absorbance of cefixime at 313 nm is decreased compared with that at 280 nm, it was necessary to run the urine and dialysate samples at this longer wavelength to reduce potential interference by endogenous compounds.

Peak height ratios of cefixime to the internal standard and cefixime standard concentrations were used to generate daily linear regression standard curves through the origin. All analyses were performed in duplicate. Day-to-day precision in serum (0.1 to 25 μg/ml), urine (2.0 to 90.0 μg/ml), and dialysate (0.1 to 1.5 μg/ml) specimens was 2.2 to 5.0, 2.0 to 6.3, and 1.0 to 4.8%, respectively. The detection limit in the three biological fluids was 0.05 μg/ml.

Pharmacokinetic analysis. Data were analyzed by model-independent methods (1, 5, 7). The terminal portion of the cefixime concentration in serum versus time data was fitted to a linear regression line by the method of least squares by the equation $\ln C = \ln C_0 + \beta t$, where C is the cefixime concentration in serum at time t, C_0 is the back-extrapolated theoretical cefixime concentration in serum at time zero, and

β is a hybrid elimination rate constant. The elimination half-life ($t_{1/2\beta}$) was calculated from ln 2 divided by β. The peak concentration of cefixime in serum and the time to peak concentration were determined from observed values. The apparent volume of distribution at steady state (V_{SS}/f), apparent total body clearance (TBC/f), renal clearance (RC), peritoneal dialysis clearance (PDC), and apparent nondialysis, nonrenal clearance (NDNRC/f) were calculated by the following equations: V_{SS}/f = (dose)(AUMC)/(AUC)(AUC); TBC/f = dose/AUC; RC or PDC = $(A)(V)/AUC_{t1-t2}$; NDNRC/f = TBC/f − (RC + PDC). Dose is the oral cefixime dose administered; AUMC is the first moment of the total area under the serum concentration versus time curve from time zero to infinity (AUC) obtained by the trapezoidal rule (to the time of the last sample) and extrapolated to infinity by using β; A is the cefixime concentration in urine or peritoneal dialysate; V is the total volume of urine or dialysate; AUC_{t1-t2} is the total AUC during the urine or dialysate collection interval. In addition, the fractional and cumulative amounts of cefixime excreted in urine and peritoneal dialysate were calculated.

Statistical comparison of the study groups was performed with the Kruskal-Wallis and Chi-square tests. Correlations between pharmacokinetic parameters and CL_{CR} were performed by linear correlation-regression techniques (3, 6). Significance was assumed when $P < 0.05$. Data are expressed as means ± the standard errors of the means (SEM).

RESULTS

Clinical. Cefixime was well tolerated by the volunteers. One volunteer experienced transient mild diarrhea commencing 5 h after drug administration, two developed

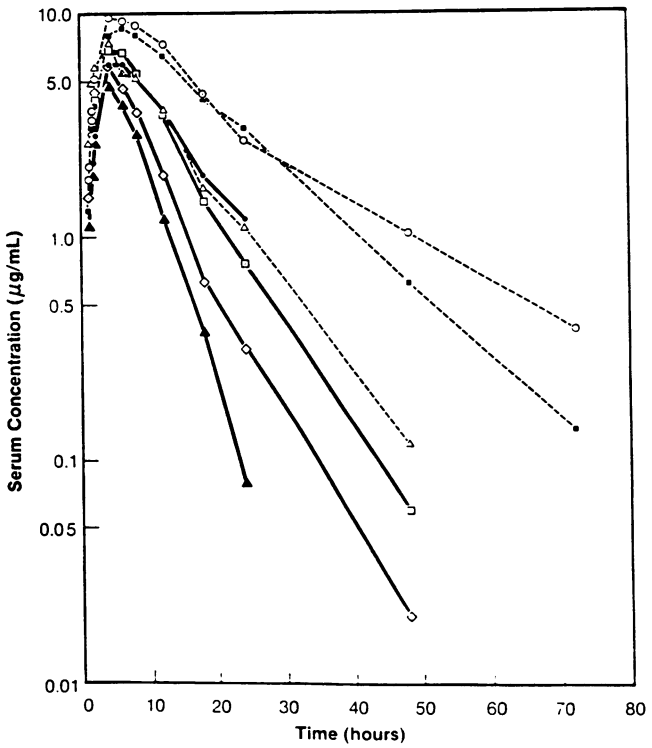

FIG. 1. Mean concentrations (μg/ml) of cefixime in serum of normal subjects (▲); patients with very mild (◈), mild (⊡), moderate (△), or severe (■) renal insufficiency; and patients on CAPD (⊙) or HD (●). SEM bars were omitted for purposes of clarity.

TABLE 2. Concentrations of cefixime in serum at various times after dosing[a,b]

Group	Concn (μg/ml) of cefixime in serum after (h)[c]:											
	1	1.5	2	4	6	8	12	18	24	48	72
Healthy	1.10 ± 0.41	1.87 ± 0.54	2.62 ± 0.64	4.76 ± 0.54	3.90 ± 0.53	2.86 ± 0.24	1.20 ± 0.14	0.38 ± 0.06	0.08 ± 0.03	NA[d]	NA
Renal insufficiency											
Very mild	1.50 ± 0.39	2.69 ± 0.53	4.43 ± 1.03	5.89 ± 0.91	4.58 ± 1.10	3.58 ± 1.02	1.87 ± 0.57	0.63 ± 0.23	0.32 ± 0.15	0.02 ± 0.01	ND[e]
Mild	2.06 ± 0.35	3.34 ± 0.51	4.12 ± 0.53	6.88 ± 0.67	6.73 ± 0.91	5.36 ± 0.84	3.57 ± 0.86	1.45 ± 0.90	0.77 ± 0.18	0.06 ± 0.03	ND
Moderate	2.63 ± 0.91	4.92 ± 1.06	5.75 ± 0.96	7.43 ± 1.55	5.38 ± 1.05	5.12 ± 1.35	3.72 ± 0.58	1.64 ± 0.53	1.12 ± 0.50	0.12 ± 0.08	ND
Severe	1.29 ± 0.29	2.60 ± 0.46	3.91 ± 0.61	8.04 ± 0.86	8.70 ± 1.15	7.95 ± 1.58	6.48 ± 1.36	4.20 ± 0.87	3.10 ± 0.64	0.63 ± 0.10	0.14 ± 0.06
CAPD	1.83 ± 0.49	3.68 ± 0.71	5.12 ± 0.76	9.55 ± 1.17	9.33 ± 1.59	8.89 ± 1.80	7.33 ± 1.91	4.36 ± 1.47	2.69 ± 1.22	1.04 ± 0.69	0.39 ± 0.34
HD	1.09 ± 0.28	2.15 ± 0.48	2.86 ± 0.61	5.95 ± 0.90	6.03 ± 0.85	5.29 ± 0.75	3.71 ± 0.65	1.90 ± 0.36	1.21 ± 0.26	NA	NA

[a] Values are means ± SEM.
[b] In groups in which some samples from patients had concentrations below detection limits (0.05 μg/ml), the concentrations were assumed to be 0 μg/ml for calculation purposes.
[c] Hours after drug administration.
[d] NA, Not applicable.
[e] All samples from patients in the group had nondetectable (ND) cefixime concentrations.

TABLE 3. Pharmacokinetic parameters for cefixime in healthy subjects and patients with various degrees of renal insufficiency[a,b]

Group	C_{max} (μg/ml)	T_{max} (h)	$t_{1/2\beta}$ (h)	AUC (μg/ml per h)	V_{SS}/f (ml/kg)	TBC/f (ml/kg per h)	RC (ml/kg per h)	PDC (ml/kg per h)	NDNRC/f (ml/kg per h)	$f_e(24)$[c]
Healthy	4.92 ± 0.51	4.9 ± 0.6	3.15 ± 0.15	40 ± 3	1,112 ± 187	141 ± 16	21.8 ± 1.7		118 ± 15	16.2 ± 1.3
Renal insufficiency										
Very mild	5.83 ± 0.91	4.0 ± 0.0	4.69 ± 0.73	57 ± 15	930 ± 189	127 ± 33	22.4 ± 6.1		105 ± 29	20.3 ± 3.2
Mild	7.58 ± 0.75	4.5 ± 0.3	7.02 ± 0.92	90 ± 12	699 ± 71	70 ± 11	10.1 ± 2.3		57 ± 11	13.6 ± 1.5
Moderate	7.53 ± 1.53	3.5 ± 0.5	7.16 ± 1.01	100 ± 26	776 ± 215	80 ± 29	3.7 ± 1.0		77 ± 29	5.5 ± 1.5
Severe	9.55 ± 1.28	6.0 ± 0.7	11.46 ± 0.96	188 ± 29	697 ± 156	41 ± 11	2.1 ± 0.3		38 ± 11	4.6 ± 0.9
CAPD	10.15 ± 1.26	5.0 ± 1.0	14.94 ± 2.83	220 ± 70	631 ± 140	42 ± 15	0.5 ± 0.3	0.5 ± 0.1	41 ± 15	0.8 ± 0.6
HD	6.24 ± 0.86	4.8 ± 0.5	8.21 ± 0.71	94 ± 16	984 ± 158	73 ± 13	0.4 ± 0.3		73 ± 13	0.4 ± 0.3

[a] Values are means ± SEM.
[b] The following comparisons demonstrated statistical significance: $t_{1/2\beta}$ (healthy versus severe renal insufficiency and CAPD; very mild versus severe renal insufficiency and CAPD), AUC (healthy versus severe renal insufficiency and CAPD; very mild versus severe renal insufficiency), TBC/f (healthy versus severe renal insufficiency and CAPD), RC (healthy versus severe renal insufficiency, CAPD, and HD; very mild renal insufficiency versus CAPD and HD), NDNRC/f (healthy versus severe renal insufficiency, CAPD), and $f_e(24)$ (healthy versus CAPD and HD; very mild renal insufficiency versus CAPD and HD).
[c] $f_e(24)$, Percentage of dose excreted in urine in 24 h.

eosinophilia, and one developed elevated serum glutamic oxaloacetic transaminase and serum glutamic pyruvic transaminase thought to be possibly drug related. One volunteer each developed elevated partial thromboplastin time and pyuria considered to be remotely drug related. There were no other drug-related adverse clinical or laboratory effects.

Pharmacokinetics. The mean concentrations of cefixime in serum were elevated in patients with renal insufficiency compared with those in healthy volunteers, and the extent of this elevation appeared to be directly related to the increasing degree of renal impairment (Table 2; Fig. 1). The $t_{1/2\beta}$ and peak concentration in serum of cefixime progressively increased and TBC/f, RC, and NDNRC/f progressively decreased as the severity of renal impairment increased (Table 3). V_{SS}/f values were similar across all groups despite the elevation in the free fraction of cefixime in serum as renal function declined (Tables 3 and 4). As expected, the percentage of the dose excreted in urine in 24 h decreased, from 16.2 ± 1.3% in healthy volunteers to 13.6 ± 1.5, 5.5 ± 1.5, and 4.6 ± 0.9% in patients with mild, moderate, and severe renal impairment, respectively (Table 3).

Mean cefixime concentrations in serum were lower in patients undergoing HD compared with those in CAPD patients, despite a lower CL_{CR} in the HD group (Fig. 1). In fact, $t_{1/2\beta}$, AUC, and TBC/f in the HD group were comparable to those in the group with only moderate renal insufficiency (Table 3). The reason for this finding is unknown, although the ability of HD to remove endogenous substances that may affect cefixime distribution, protein binding, and elimination may be involved.

TABLE 4. Free fraction of cefixime in serum of healthy subjects and patients with various degrees of renal insufficiency[a,b]

Group	No. of samples	Free fraction
Healthy	18	0.37 ± 0.03
Renal insufficiency		
Very mild	20	0.39 ± 0.01
Mild	23	0.46 ± 0.03
Moderate	15	0.46 ± 0.02
Severe	17	0.47 ± 0.03
CAPD	12	0.67 ± 0.04
HD	15	0.55 ± 0.04

[a] Values are means ± SEM.
[b] The following comparisons demonstrated statistical significance: healthy versus CAPD, very mild renal insufficiency versus HD and CAPD.

Statistically significant linear correlations were noted with the peak concentration of cefixime in serum, $t_{1/2\beta}$, AUC, TBC/f, RC, NDNRC/f, the percentage of the dose excreted in urine in 24 h, and the free fraction of cefixime in serum versus CL_{CR} (Fig. 2). However, correlation coefficients were generally low (0.417 to 0.766). Statistically nonsignificant correlations were noted with the time to peak concentration versus CL_{CR} and V_{SS}/f versus CL_{CR}.

Methodologic difficulties did not permit calculation of the fraction of the body burden removed or HD clearance, and cefixime was not quantitated in hemodialysate. However, comparison of the AUC from 0 to 24 h postdose on intra- and interdialysis study days revealed no significant difference (89 ± 12 versus 79 ± 13 μg/ml per h, respectively).

PDC was, on average, 1.84 ± 0.85% of TBC/f, and CAPD removed only 1.57 ± 0.60% of cefixime body burden over 72 h. No significant correlation was noted between the glucose concentration in dialysate and PDC, and comparison of the three dialysate concentration groups with regard to PDC by the Kruskal-Wallis test yielded no significant differences.

Concentrations of cefixime in urine are given in Table 5. Concentrations of cefixime in the urine of patients generally fell with increasing severity of renal insufficiency; however, these concentrations still exceeded the MICs for most urinary pathogens until 24 h postdose.

DISCUSSION

This study examined the effects of various degrees of renal impairment on the pharmacokinetics of cefixime. The results of this study must be interpreted with caution as clearance and volume of distribution data were calculated on the basis of an assumed fixed bioavailability. Absolute bioavailability of cefixime in humans is unknown. In addition, the number of subjects in each group was small.

The pharmacokinetic results in our normal volunteers were consistent with those reported previously (2). The reduction in TBC/f and the resulting prolonged $t_{1/2\beta}$ as renal function declined were probably due to reductions in both RC and NDNRC/f, with RC being the major contributor in this regard. Reduced NDNRC/f with declining renal function has been noted with other drugs as well (10).

The progressive elevation in the free fraction of cefixime in serum as renal function declined may be explained by various physiologic changes in uremia including displace-

TABLE 5. Concentrations of cefixime in urine of healthy subjects and patients with various degrees of renal insufficiency[a,b]

Group	Concn (μg/ml) in urine collected between (h):						
	0 and 2	2 and 4	4 and 8	8 and 12	12 and 24	24 and 48	48 and 72
Healthy	31.55 ± 14.05 (<0.05–91.31)	79.56 ± 21.0 (20.61–139.12)	75.75 ± 14.13 (42.56–133.30)	40.52 ± 7.91 (20.45–74.21)	15.70 ± 3.11 (8.00–31.28)	NA[c]	NA
Renal insufficiency							
Very mild	29.88 ± 9.27 (7.90–76.36)	129.90 ± 32.02 (21.00–255.83)	155.57 ± 26.94 (65.67–230.66)	70.19 ± 9.23 (36.45–96.72)	27.32 ± 5.03 (7.20–41.53)	3.54 ± 1.10 (0.73–7.31)	0.63 ± 0.53 (<0.05–3.76)
Mild	35.20 ± 19.08 (7.55–91.60)	64.21 ± 26.79 (10.79–162.30)	97.52 ± 24.92 (58.74–195.40)	80.17 ± 17.69 (42.69–122.30)	24.69 ± 6.56 (15.05–46.04)	3.00 ± 1.23 (0.19–6.17)	0.17 ± 0.14 (<0.05–0.73)
Moderate	8.95 ± 2.59 (3.50–17.72)	18.56 ± 6.18 (6.93–41.64)	21.68 ± 9.20 (1.81–51.00)	16.59 ± 5.94 (2.14–30.72)	7.38 ± 2.39 (1.42–14.89)	1.93 ± 0.80 (<0.05–4.32)	0.43 ± 0.32 (<0.05–1.35)
Severe	2.17 ± 2.10 (<0.05–4.75)	10.57 ± 2.04 (5.56–17.91)	19.12 ± 2.57 (9.12–26.09)	16.85 ± 4.79 (3.91–33.10)	8.61 ± 1.88 (3.50–14.98)	3.67 ± 1.05 (1.44–8.45)	5.48 ± 4.93 (<0.05–30.1)

[a] Values are means ± SEM; values in parentheses are ranges.
[b] In groups in which samples from patients had concentrations below detection limits (0.05 μg/ml), the concentrations were assumed to be 0 μg/ml for calculation purposes.
[c] NA, Not applicable.

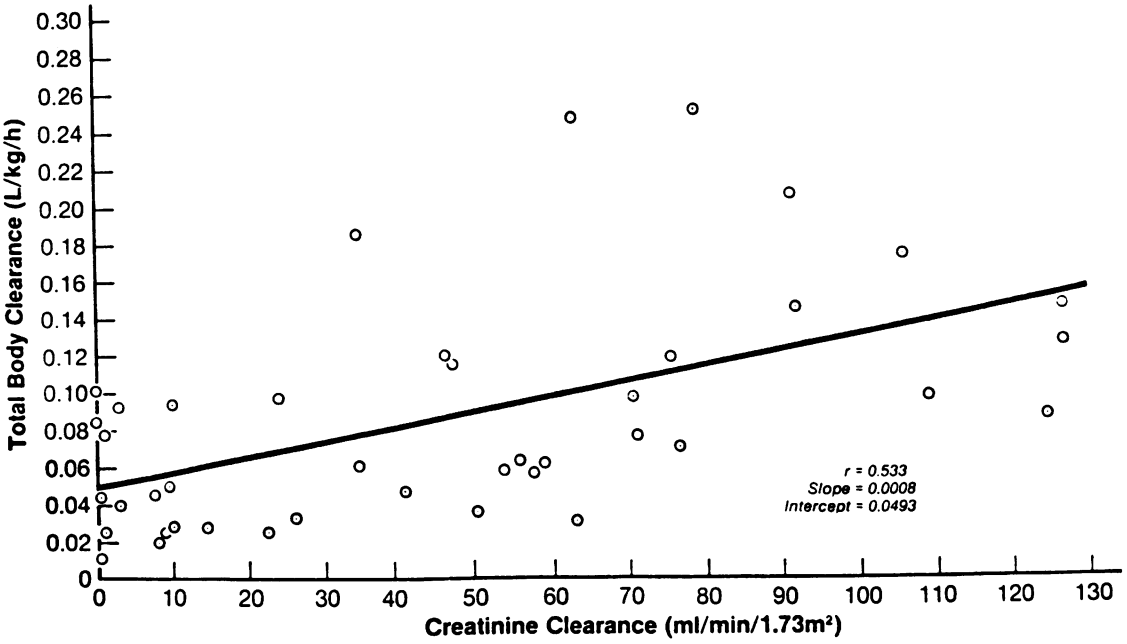

FIG. 2. Correlation between cefixime TBC/*f* and CL_{CR} in normal subjects and patients with various degrees of renal insufficiency.

ment of cefixime from protein binding sites by endogenous binding inhibitors accumulating in renal disease. This has also been noted with other cephem antibiotics (9).

Despite an elevated fraction of free, unbound cefixime in serum of 0.67 ± 0.04 in the CAPD patients, the amount of drug removed by this modality was insignificant. Therefore, supplemental doses of cefixime should not be necessary during CAPD. Although AUC data suggest that the amount of cefixime removed by HD is insignificant despite an elevated free fraction of 0.55 ± 0.04, further studies examining the effect of HD on cefixime pharmacokinetics are warranted. Based on these preliminary data, supplemental doses of cefixime should not be necessary at the end of the HD procedure.

In clinical practice, dosage adjustment of cefixime appears to be unnecessary other than in dialysis and nondialysis patients with severe renal insufficiency (CL_{CR}, <20 ml/min per 1.73 m^2). Using the method of Tozer (11), the most practical approach would appear to be administration of the standard dose at twice the dosing interval recommended for patients with normal renal function. Using these guidelines for dosage adjustment, clinically significant drug accumulation should not occur with multiple-dose cefixime regimens.

ACKNOWLEDGMENTS

We gratefully acknowledge R. D. Faulkner and Z. Look for performing the protein binding studies; K. Smith and J. Lovick for manuscript preparation; and W. Bohaychuk, L. Malo, and I. Ferguson for assistance.

This study was supported in part by a grant-in-aid from Cyanamid Canada, Inc.

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