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Pharmacokinetics of Ceftazidime in Normal and Uremic Subjects

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The pharmacokinetics of ceftazidime, administered as a single intravenous dose of 15 mg/kg given in a bolus injection over 3 min, were investigated in 5 normal subjects and in 19 uremic patients. The subjects studied were divided into five groups according to values for endogenous creatinine clearance (CL_{CR}): group I, five subjects with CL_{CR} > 80 ml/min; group II, five patients with CL_{CR} = 30 to 80 ml/min; group III, six patients with CL_{CR} = 10 to 30 ml/min; group IV, four patients with CL_{CR} = 2 to 10 ml/min; and group V, four anuric patients on hemodialysis. A two-compartment open model was used to calculate the pharmacokinetic parameters. In normal subjects, the mean apparent elimination half-life was 1.57 ± 0.13 h. The central distribution volume and the apparent volume of distribution were 0.127 ± 0.023 and 0.230 ± 0.015 liter/kg, respectively. Of the injected dose, 83.6 ± 3.6% was eliminated in the urine as parent drug within 24 h. The terminal half-life increased with impairment of renal function to about 25 h in severely uremic patients. Impairment of function did not significantly modify the half-life at α phase, central distribution volume, or apparent distribution volume. A 6- to 8-h hemodialysis procedure reduced concentrations of ceftazidime in plasma by approximately 88%, and the elimination half-life was 2.8 ± 0.2 h. There was no evidence of accumulation of ceftazidime in four patients with severe and chronic impairment of function who received doses of 0.5 to 1.0 g every 24 h for 10 days.

In normal subjects, the pharmacokinetics of ceftazidime are characterized by lack of metabolism, low degree of protein binding (17%), and renal elimination by glomerular filtration (5, 13). The present study was undertaken to compare the pharmacokinetics of ceftazidime in subjects with normal renal function and renal functions that were impaired to various degrees.

MATERIALS AND METHODS

Single-dose study. Subjects. Twenty-four subjects with no known sensitivity to β-lactam antibiotics participated in the study after providing informed written consent. Of the 24, 5 had normal renal function, and 19 had various degrees of impaired renal function, 4 being on hemodialysis. The five normal subjects, with no evidence of hepatic or hematological disease, ranged in age from 22 to 31 years (mean, 27 ± 3 years) and in weight from 64 to 78 kg (mean, 71 ± 6 kg). The 19 patients with chronically impaired renal function ranged from 26 to 74 years in age and from 41 to 83 kg in weight. The 24 subjects in this study were divided into five groups on the basis of endogenous creatinine clearance (CL_{CR}) (2): group I, five normal subjects (CL_{CR} > 80 ml/min); group II, five patients with mildly impaired renal function (CL_{CR} = 30 to 80 ml/min); group III, six patients with moderately impaired renal function (CL_{CR} = 10 to 30 ml/min); group IV, four patients with severely impaired renal function (CL_{CR} = 2 to 10 ml/min); and group V, four hemodialysis patients. The effect of hemodialysis on the concentrations of ceftazidime in plasma was determined in patients of group V.

Ceftazidime administration and sampling. All subjects were given, after an overnight fast, a single intravenous (i.v.) dose of 15 mg of ceftazidime per kg over a period of 3 min. Blood samples were drawn at 0, 3, 5, 10, 15, 20, 30, 45, and 60 min and 1.5, 2, 3, 4, 6, 8, and 12 h after i.v. injection from all subjects, with additional samples at 24 and 34 h in group III and 48 h in groups IV and V. Urine samples were collected at 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, and 12 to 24 h from subjects in group I. From uremic patients, they were collected at 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 34, and 34 to 48 h. Patients on hemodialysis received a dose of 15 mg of ceftazidime per kg at the beginning of the dialysis session. Hemodialysis was performed with Travenol coil dialyzers (0.90 to 1.10 m^2); the blood flow rate was 300 ml/min, and the dialysate flow rate was 500 ml/min. Venous blood samples were taken at 0.3 (end of injection), 30, and 60 min and each hour thereafter up to the end of the dialysis session, which lasted 6 to 8 h.

Multiple-dose study. Four patients with chronic renal impairment (CL_{CR} < 15 ml/min) were treated for 10 days with 500 or 1,000 mg of ceftazidime i.v. every 24 h. Blood samples were taken before and at 5, 10, 15, 20, 30, 45, and 60 min and 1.5, 2, 3, 4, 6, 8, 12, and 24 h after the first and the last doses of ceftazidime. Additional daily blood samples were drawn before and at 1 and 8 h after injection.

Assay technique. Ceftazidime concentrations in plasma and urine were assayed by high-pressure liquid chromatography as described by Ayrton (1). Perchloric acid (0.8 M) containing the internal standard, cefalexin, was added to 0.5 ml of a standard or unknown plasma sample; this preparation was mixed for 5 min and centrifuged for 10 min at 2,000 × *g* and 4°C. A 20-μl sample of the supernatant was injected onto a 5-μm Hypersil ODS high-pressure liquid chromatography column and eluted at a flow rate of 1.5 ml/min with 0.05 M ammonium dihydrogenophosphate (pH 4) containing 8.4% methanol. The eluate was monitored for UV absorption at a wavelength of 257 nm. Calibration solutions were prepared by adding known amounts of ceftazidime standard to drug-free plasma or blank urine. A computing integrator determined the regression between the peak-height ceftazidime-to-cefalexin ratio and the concentrations of ceftazidime. This regression was found to be linear from 0 to 500 μg/ml, with a mean slope standard deviation of 2%.

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TABLE 1. Pharmacokinetic data on subjects with normal and impaired renal functions after a single i.v. dose of 15 mg of ceftazidime per kg

Subject	CL_{CR} (ml/min)	Peak concn at 3 min (μg/ml)	Area under the curve (μg · h/ml)	Half life (h)		Vol of distribution (liters/kg)		Urine elimination at 24 h (%)	Clearance (ml/min per 1.73 m^2)	
				Distribution	Elimination	V_1	Steady state		Total body	Renal
Group I										
1	141.4	103.00	114.17	0.20	1.53	0.132	0.245	81.9	137.5	111.9
2	138.5	149.00	138.79	0.12	1.54	0.088	0.209	83.1	118.5	96.7
3	131.2	100.00	141.17	0.28	1.68	0.151	0.226	88.9	118.8	100.3
4	115.6	110.00	132.36	0.29	1.70	0.128	0.224	84.8	118.1	87.6
5	110.1	100.00	108.57	0.15	1.38	0.136	0.244	79.3	157.2	122.8
Mean ± SD	127.4 ± 13.9	112.40 ± 20.86	127.01 ± 14.77	0.21 ± 0.08	1.57 ± 0.13	0.127 ± 0.023	0.230 ± 0.015	83.6 ± 3.6	130.0 ± 17.3	103.9 ± 13.7
Group II										
6	72.5	184.00	321.25	0.10	3.01	0.088	0.194	50.8	55.2	24.1
7	71.5	102.00	256.60	0.12	3.30	0.119	0.265	64.4	70.0	48.4
8	69.2	215.00	309.17	0.10	3.31	0.063	0.214		50.6	45.2
9	39.0	72.00	363.80	0.13	4.52	0.202	0.267	59.5	46.8	25.3
10	39.0		321.39	0.52	4.58	0.225	0.296	50.9	52.0	31.2
Mean ± SD	58.2 ± 17.6	143.25 ± 67.30	314.44 ± 38.42	0.19 ± 0.18	3.74 ± 0.75	0.139 ± 0.071	0.247 ± 0.042	56.4 ± 6.7	54.9 ± 9.0	34.8 ± 11.3
Group III										
11	27.0		683.97	0.37	7.13	0.120	0.216	68.5	23.4	18.5
12	25.0	149.00	999.61	0.49	9.50	0.109	0.196	47.9	18.7	11.0
13	22.5	119.00	749.22	0.18	9.70	0.127	0.276	40.4	23.0	11.5
14	21.3		735.79	0.42	10.29	0.137	0.289	43.4	22.6	11.9
15	17.5		674.51	0.34	9.43	0.203	0.295	35.5	23.7	10.1
16	13.8		792.81	0.21	9.43	0.140	0.251	31.2	19.1	6.9
Mean ± SD	21.2 ± 4.9	134.00	772.65 ± 119.43	0.34 ± 0.12	9.25 ± 1.09	0.139 ± 0.033	0.254 ± 0.041	44.5 ± 13.1	21.8 ± 2.2	11.7 ± 3.8
Group IV										
17	12.0	133.30	1,321.59	0.33	13.08	0.081	0.145	33.1	23.8	12.3
18	11.0	41.20	1,151.99	0.27	18.41	0.186	0.293	30.8	15.5	4.6
19	6.2	213.00	1,468.74	0.28	15.33	0.111	0.285	26.5	16.2	6.2
20	2.0	61.70	688.85	0.17	14.50	0.241	0.469	19.2	5.9	2.9
Mean ± SD	6.7 ± 5.0	112.28 ± 77.87	1,157.99 ± 338.36	0.26 ± 0.08	15.33 ± 2.25	0.155 ± 0.072	0.298 ± 0.133	27.4 ± 6.1	15.4 ± 7.3	6.5 ± 4.0
Group V										
21	Anuric	83.00	2,195.33	0.13	27.69	0.157	0.272		7.5	
22	Anuric	124.00	2,736.48	0.25	25.94	0.136	0.202		5.9	
23	Anuric	88.00	1,789.15	0.37	19.23	0.177	0.231		7.3	
24	Anuric		2,529.97	0.03	28.21	0.123	0.237		6.6	
Mean ± SD		98.33 ± 22.37	2,312.73 ± 414.20	0.20 ± 0.15	25.27 ± 4.14	0.148 ± 0.024	0.236 ± 0.029		6.8 ± 0.7	

Pharmacokinetic analysis. The data on levels of ceftazidime in plasma were analyzed by the two-compartment open model (3), and the decline in concentration in plasma was fitted by a Hewlett Packard HP-85 computer program by nonlinear regression analysis (10). The concentrations of ceftazidime in plasma (C_P) were described by the sum of two exponentials: $C_P = (A \cdot e^{-\alpha t}) + (B \cdot e^{-\beta t})$ where A, α, B, and β are hybrid constants and t is the time. The following pharmacokinetic parameters were calculated from the usual equations (3): plasma distribution half-life, $t_{1/2\alpha} = \ln 2/\alpha$; apparent elimination half-life, $t_{1/2\beta} = \ln 2/\beta$; volume of distribution in the central compartment, V_1 = dose/$(A + B)$; apparent volume of distribution at steady state, $V_{ss} = [(k_{12} + k_{21})/k_{21}]\ V_1$ where k_{12} and k_{21} are the intercompartmental transfer rate constants; area under the plasma concentration-time curve, AUC = $(A/\alpha) + (B/\beta)$; total body clearance, CL_{TB} = dose/AUC; and renal clearance, $CL_R = [U(t_1 - t_2)]/(\int_{t_2}^{t_1} C \cdot dt)$ where U is the amount of drug excreted in urine during the time interval $t_1 - t_2$ and $\int_{t_2}^{t_1} C \cdot dt$ is the area under the curve during the same time interval.

Statistical analysis. Results in the text and Table 1 are presented as means ± standard deviations. Statistical comparisons of the pharmacokinetic data in subjects with normal and impaired renal function were performed by one-way analysis of variance, with $P < 0.05$ taken as the threshold of probability.

RESULTS

Subjects with normal renal function. Results are summarized in Table 1. After i.v. bolus injection of a single dose of 15 mg/kg, the mean peak level of ceftazidime in plasma at 3 min was 112.40 ± 20.86 μg/ml. The mean distribution half-life was 0.21 ± 0.08 h, and the apparent elimination half-life averaged 1.57 ± 0.13 h. V_1 and the apparent volume of distribution at steady state were 8.30 ± 1.64 liters/1.73 m^2 (i.e., 0.127 ± 0.023 liter/kg) and 14.99 ± 1.17 liters/1.73 m^2 (i.e., 0.230 ± 0.015 liter/kg), respectively. The total body clearance averaged 130.0 ± 17.3 ml/min per 1.73 m^2, and the mean renal clearance was 103.9 ± 13.7 ml/min per 1.73 m^2; the fractional clearance (renal clearance/CL_{CR}) was 0.83 ± 0.17. Of the total dose, 83.6 ± 3.6% was recovered as parent drug in 24-h urine samples.

Patients with chronically impaired renal function. As renal function decreased, the apparent elimination half-life of ceftazidime increased to 3.74 ± 0.75, 9.25 ± 1.09, 15.33 ± 2.25, and 25.27 ± 4.14 h in patients in groups II, III, IV, and V, respectively (Table 1, Fig. 1). The peak concentration in plasma and the distribution half-life were not significantly different in subjects with normal and impaired renal functions ($F_{5\%} = 0.42$, $F_{5\%} = 1.23$). V_1 and the apparent volume of distribution were not statistically modified by renal impairment ($F_{5\%} = 0.21$, $F_{5\%} = 0.81$). Urinary elimination of ceftazidime was inversely related to the degree of impairment of renal function since 83.6% of the dose was recovered unchanged in 24 h in normal subjects and 27.4% was recovered in patients with severe renal insufficiency (group IV). Total body clearance decreased from 130.0 ± 17.3 ml/min per 1.73 m^2 in subjects in group I to 6.8 ± 0.7 ml/min per 1.73 m^2 in patients in group V. Renal clearance fell from 103.9 ± 13.7 ml/min per 1.73 m^2 in normal subjects to 6.5 ± 4.0 ml/min per 1.73 m^2 in patients in group IV (Table 1). During hemodialysis, concentrations of ceftazidime in plasma rapidly decreased, and the elimination half-life was 2.8 ± 0.2 h. In patients with chronically impaired renal function, the increase in the elimination half-life was particularly pronounced as soon as CL_{CR} fell below 20 ml/min (Fig. 2).

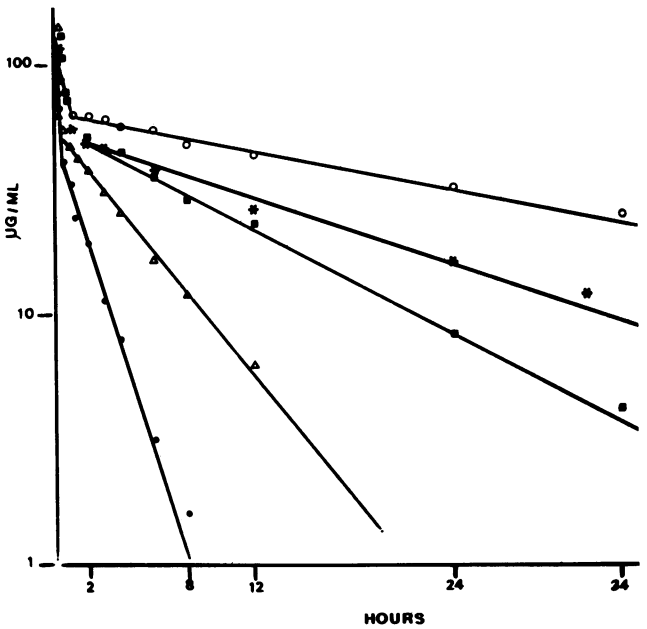

FIG. 1. Mean of ceftazidime in plasma concentrations versus time after i.v. injection of 15 mg of ceftazidime per kg in subjects with normal and impaired renal functions. Mean half-lives (± standard deviation) were as follows (in hours): group I (●), 1.57 ± 0.13; group II (△), 3.74 ± 0.75; group III (■), 9.25 ± 1.09; group IV (*), 15.33 ± 2.25; group V (○), 25.27 ± 4.14.

Multiple-dose study. The pharmacokinetic data for ceftazidime were compared at the beginning and the end of treatment, using the Student t test for paired differences. After the first and the last injection of ceftazidime, the mean concentrations in plasma at 5 min were 75.58 ± 38.87 and 86.73 ± 27.82 μg/ml, respectively ($P < 0.20$). Comparing the first and last doses, the areas under the serum concentration-time curve were not statistically different ($P < 0.20$), and the apparent elimination half-life did not significantly increase (12.61 ± 6.90 and 11.43 ± 5.53 h, $P < 0.50$). The slight increase in the trough levels of ceftazidime in plasma was not significant ($P < 0.10$). With the regimen used in this study, there was no marked tendency towards accumulation of the antibiotic.

DISCUSSION

In subjects with normal renal function, ceftazidime pharmacokinetic data were similar to those reported by other authors (5–8, 11–13). The apparent elimination half-life ranged from 1.3 to 1.8 h; the apparent volume of distribution was from 15 to 18 liters; 85 ± 10% of the dose was recovered unchanged in urine samples after 24 h. Lüthy et al. (8) found that the kinetics of ceftazidime were not significantly affected by administration of probenecid. No metabolites of ceftazidime could be detected in serum or urine (7, 13). The bioavailability of ceftazidime was almost complete (12).

Pharmacokinetic data in the present study are in good agreement with those reported by other authors (4, 9; K. Alestig, R. Andersson, L. Olaison, and B. Tallfors, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 22nd, Miami Beach, Fla., abstr. no. 802, 1982; A. B. Straughn, M. C. Meyer, S. Acchiardo, J. Chubb, and T. J. Comstock,

22nd ICAAC, abstr. no. 801). Renal insufficiency did not significantly modify the apparent volume of distribution (4). The total body clearance and the renal clearance decreased in relation to the degree of impairment of renal function. The fractional clearance was essentially unchanged in normal and uremic subjects, from 0.65 to 0.80. In patients with end-stage renal dysfunction, the elimination half-life of ceftazidime was from 20 to 30 h, and the dialysis clearance was 27 to 50 ml/min (Straughn et al., 22nd ICAAC, abstr. no. 801). By using the linear least-squares regression method, a relationship was found between the apparent elimination rate constant and endogenous CL_{CR} (4). In the present study, the equation of this relation was $\beta = 0.004\ CL_{CR} + 0.004$ (Fig. 3) ($n = 20$, $r = 0.985$, $P < 0.001$). The relationship between the total body clearance of ceftazidime and endogenous CL_{CR} could be expressed by the equation $CL_{TB} = 1.15\ CL_{CR} + 10.6$ ($n = 20$, $r = 0.991$, $P < 0.001$). From this relation, the nonrenal clearance of ceftazidime could be calculated at about 10 ml/min.

Ceftazidime is eliminated predominantly by the kidneys, and the elimination half-life increases considerably with decreasing glomerular filtration rate. Therefore, the dosage of ceftazidime should be adjusted according to the degree of renal impairment. In normal subjects, the concentrations of ceftazidime in plasma after a 1-g dose exceeded the concentrations required to inhibit 90% of *Enterobacteriaceae* for 8 h and 90% of *Pseudomonas aeruginosa* strains for 6 h. Therefore, a schedule of 1 g every 8 h should provide plasma levels adequate for treatment of infections with these organisms. For patients with chronically impaired renal function, dosing intervals should be lengthened to avoid accumulation of ceftazidime. The terminal half-life can be evaluated by using the relation $\beta = 0.004\ CL_{CR} + 0.004$ between the apparent elimination rate constant and endogenous CL_{CR} (Fig. 3). The same standard dose as in normal subjects may be used, but the dosing frequency should be reduced according to the CL_{CR} and the MICs of the drug for the responsible organisms: 12 to 24 h in patients with CL_{CR} from 30 to 80 ml/min,

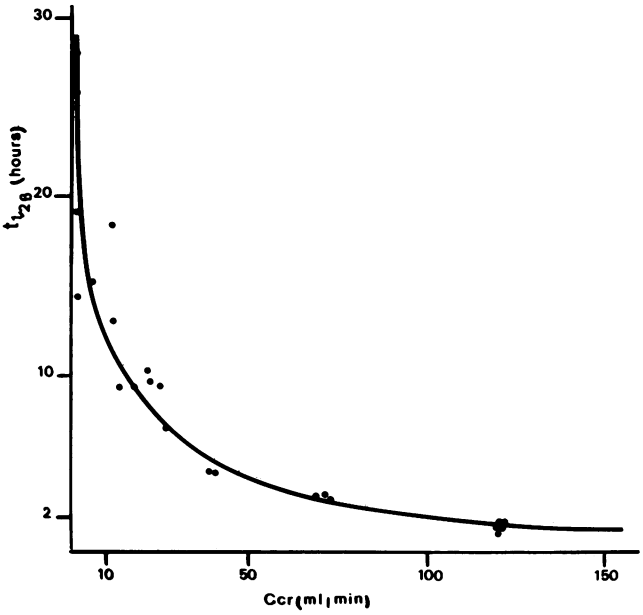

FIG. 2. Relationship between apparent elimination half-life of ceftazidime and endogenous CL_{CR}.

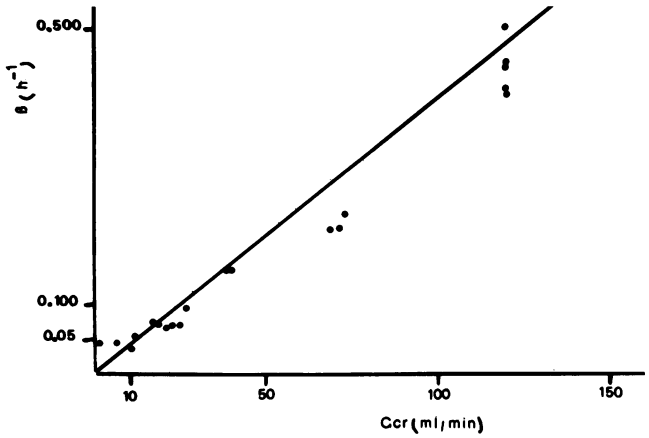

FIG. 3. Relationship between apparent elimination rate constant of ceftazidime (β) and endogenous CL_{CR}. $\beta = 0.004\ CL_{CR} + 0.004$; $n = 20$; $r = 0.985$; $P < 0.001$.

24 to 36 h in patients with CL_{CR} from 10 to 30 ml/min, and 36 to 48 h in patients with CL_{CR} lower than 10 ml/min. Patients on hemodialysis should be given an additional dose at the end of dialysis since the half-life of ceftazidime during hemodialysis was reduced from 25.3 to 2.8 h.

Ceftazidime is an effective and well-tolerated antibiotic, as shown in multiple-dose studies (7–9). No severe side effects and no nephrotoxic potential of this antibiotic were noted. Norby et al. (9) demonstrated that ceftazidime did not affect the proximal tubular function of the patients; they found only a slight decrease in the glomerular filtration rate in 14 patients treated with a ceftazidime dose of 1 g every 8 h for 4 to 9 days. Using dosage schedules previously described, no accumulation of the antibiotic could be observed in four uremic patients during a 10-day study period. The dosages of ceftazidime should be monitored by determinations of renal function and concentrations of antibiotic achieved in serum, particularly in patients with severe renal impairment.

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