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Pharmacokinetics of Ceftizoxime in Subjects with Various Degrees of Renal Function

STEVEN F. KOWALSKY,[1,2]* ROGER M. ECHOLS,[1] ANN R. VENEZIA,[1] AND ELIZABETH A. ANDREWS[1]

Division of Infectious Diseases, Albany Medical College,[1] and Albany College of Pharmacy,[2] Albany, New York 12208

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The pharmacokinetics of ceftizoxime (FK-749) were studied in 20 volunteers with various degrees of renal function. Creatinine clearances ranged from zero to 157 ml/min per 1.73 m^2. One gram of ceftizoxime was administered by a 30-min drip infusion, and blood and urine samples were collected for up to 48 h after drug administration. For volunteers with a creatinine clearance of ≥80 ml/min per 1.73 m^2 (group I), the mean half-life was 1.65 h, whereas for volunteers with a creatinine clearance of <10 ml/min per 1.73 m^2 (group IV), the half-life was 34.7 h. The volume of distribution at steady state (V_{dss}) and the volume of distribution area (V_{darea}) were calculated for each group and ranged from 0.377 to 0.263 and 0.421 to 0.264 liters/kg for groups I and IV, respectively. Total body clearance of ceftizoxime correlated with creatinine clearance ($r = 0.953$), and the mean urinary recovery of unchanged drug in normal volunteers was 72.4%. A 4-h hemodialysis procedure reduced serum ceftizoxime concentrations by approximately 52%; however, serum concentrations at 48 h after drug administration were still >10 μg/ml in dialysis subjects. By using the relationship between total body clearance of ceftizoxime and creatinine clearance, a nomogram was developed to assist in the administration of ceftizoxime to patients with renal dysfunction.

Ceftizoxime is a new injectable semisynthetic cephalosporin with beta-lactamase stability and broad-spectrum antibacterial activity. Since ceftizoxime is primarily dependent on the kidneys for elimination, accumulation of the drug can be anticipated in subjects with decreased renal function. The purpose of this study was to investigate the pharmacokinetics of ceftizoxime in subjects with various degrees of renal function and to establish a dosage regimen for ceftizoxime based on renal function.

MATERIALS AND METHODS

Antibiotic. Ceftizoxime was supplied by Smith Kline & French Laboratories, Philadelphia, Pa., as a dry, sterile powder for reconstitution and intravenous administration.

Human volunteers. Twenty adult male and female volunteers with no known allergies to penicillin or cephalosporin antibiotics were studied after written informed consent was obtained. No volunteer had taken antibiotics for at least 72 h before the time of evaluation. Persistence of long-acting antibiotics was excluded by the absence of bioactivity in the zero-time serum samples. Each subject was selected on the basis of a prestudy 24-h creatinine clearance (C_{cr}) and assigned to one of four study groups (group I, $C_{cr} \geq 80$ ml/min per 1.73 m^2; group II, C_{cr} = 50 to 79 ml/min per 1.73 m^2; group III, C_{cr} = 10 to 49 ml/min per 1.73 m^2; and group IV, $C_{cr} < 10$ ml/min per 1.73 m^2). Subjects in group IV were maintained on 4 h of hemodialysis three times a week. All subjects underwent a prestudy physical examination and laboratory evaluation and had stable renal function before their inclusion in the study. Laboratory tests obtained before and after the study protocol included a complete blood count with differential, platelet count, Coombs test (direct and indirect), SMA-18, 24-h creatinine clearance, urinalysis, and serum pregnancy test.

Procedure. Each subject fasted from midnight until 2 h after drug administration. After base-line serum and urine samples were taken, each subject was placed in the supine position and given 1.0 g of ceftizoxime by drip infusion over 30 min (via IMED infusion pump; IMED, San Diego, Calif.). Ceftizoxime was reconstituted with sterile water and mixed with 50 ml of 0.9% sodium chloride. Samples of whole blood for antibiotic serum level determinations were obtained in all subjects before and at 5, 10, 20, 30, 35, 40, and 45 min and 1, 1.5, 2, 3, 4, 6, 8, 12, 24, 36, and 48 h after the start of the infusion. Subjects in group IV were scheduled for drug administration 24 h before hemodialysis and had additional serum samples collected at 2 and 4 h during hemodialysis and at 1, 2, and 3 h post-hemodialysis. The first 14 serum samples were taken from a 0.2-ml-capacity intermittent infusion set, the first 0.5 to 1.0 ml was discarded, and a 3.0-ml blood sample was collected for analysis. The remaining samples were obtained by separate venipunctures. Blood specimens were collected in sterile, nonheparinized tubes and centri-

fuged, and the serum was pipetted and immediately frozen at −70°C. Urine samples were collected before drug infusion and at intervals of 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, 12 to 18, 18 to 24, and 24 to 48 h thereafter. The total volume was recorded, and a 15-ml portion was frozen at −70°C. The average storage time before sample analysis was approximately 2 months (serum and urine ceftizoxime stability studies conducted in our laboratory have demonstrated no significant difference, by the Wilcoxon signed-rank test of paired differences in medians [2], in drug activity over a 1-year period of storage at −70°C).

Assay technique. Serum and urine samples were thawed and assayed at the same time. *Escherichia coli* ATCC 25922 was grown overnight in brain heart infusion broth (pH 7.4) (BBL Microbiology Systems, Cockeysville, Md.). One milliliter of this overnight culture was added to 1 liter of brain heart infusion agar (pH 7.4) (BBL), and 20 ml was then poured into 100-mm^2 petri plates. Each plate was refrigerated for 2 h, after which time 4-mm wells were cut and filled with 20 μl of sample. All serum standards and patient specimens were diluted in pooled human serum (Flow Laboratories, McLean, Va.), and urine standards and patient specimens were diluted in potassium phosphate buffer (pH 6.0) (standard sensitivity ranged from 25 to 1.52 μg/ml for both serum and urine). Serum or buffer alone did not produce any zone of inhibition. Plates were incubated at 30°C for 18 h, and zones of inhibition were read on a Fischer-Lilly zone reader to the nearest 0.1 mm. Six readings were recorded for each sample. Concentrations of drug were calculated by using a linear semilogarithmic plot with a programable calculator. Interday variation in standard serum and urine assays was 0.0389 and 0.0164, respectively. Intraday variation in reference buffer was 0.0418.

Pharmacokinetic analysis. Serum level results after the 30-min drip infusion of ceftizoxime were described in terms of a linear two-compartment pharmacokinetic model. An iterative least-squares method was used to initially characterize the four parameters in the equation:

$$C = Ae^{-\alpha t} + Be^{-\beta t}$$

This bioexponential equation was further modified (7) to take into consideration the drip infusion method of drug administration and thus minimize the error in describing the pharmacokinetic parameters of ceftizoxime:

$$C_i = \frac{\lambda_i T Y_i}{(e + \lambda_i T - 1)}$$

where λ_i is the appropriate disposition rate constant (α or β), T is the duration of the drip infusion, and Y_i is the appropriate coefficient (R or S) obtained from postinfusion data. The appropriate zero-time intercepts (A or B) were calculated by the method of Gibaldi and Perrier (3). The pharmacokinetic parameters were subsequently calculated by the following equations (6):

$$V_{dss} = D \sum_{i=1}^{n} C_i/\lambda_i^2 \Big/ \left\{ \left(\sum_{i=1}^{n} C_i/\lambda_i \right)^2 \right\}$$

$$V_{darea} = D \Big/ \left(\lambda_1 \sum_{i=1}^{n} C_i/\lambda_i \right)$$

$$C_{ctz} = D \Big/ \sum_{i=1}^{n} C_i/\lambda_i$$

where D is the intravenous dose and C_i and λ_i are the zero-time intercepts and disposition rate constants, respectively. λ_1 is the smallest of the disposition rate constants of the biexponential equation. V_{dss} is the volume of distribution steady state, V_{darea} is the volume of distribution which, when multiplied by plasma concentration in the log-linear phase, is equal to the amount of drug in the body, and C_{ctz} is the total body clearance of drug. The area under the curve (AUC) was calculated by:

$$AUC = \sum_{i=1}^{n} C_i/\lambda_i$$

The average renal clearance of ceftizoxime was calculated from the slope of the line plotting the cumulative amount of drug excreted unchanged in the urine versus the area under the serum concentration-time curve.

The pharmacokinetic parameters described for subjects in group IV were calculated by using serum samples collected during the first 24 h of the study (i.e., before the hemodialysis procedure).

Statistical analysis. Group data and pharmacokinetic parameters were evaluated by one-way analysis of variance (ANOVA) to detect differences among groups I to IV. The relationship between total body clearance of ceftizoxime and creatinine clearance was examined for correlation by the use of an orthogonal regression plot (1).

RESULTS

The intravenous administration of ceftizoxime resulted in no local pain or phlebitis in any of the study subjects. No significant systemic toxicities occurred during or after drug administration, and poststudy laboratory tests were not significantly different from prestudy tests. Table 1 lists mean data for each group. Subjects ranged in health from those in group 1 with no

TABLE 1. Description of study groups[a]

Group	Age	BSA[b]	Ccr[c]
I	32.4 (2.70)	1.81 (0.098)	119 (22.3)
II	54.4 (12.9)	1.92 (0.169)	71.8 (5.97)
III	48.4 (13.8)	1.88 (0.084)	27.2 (9.42)
IV	43.8 (17.1)	1.88 (0.180)	0.480 (0.716)
F ratio	2.64	0.582	217
P value	0.084	0.639	<0.001

[a] All values are means, with standard deviations in parentheses.

[b] BSA, Body surface area in square meters.

[c] Ccr, Creatinine clearance in milliliters per minute per 1.73 m^2.

TABLE 2. Ceftizoxime serum levels

Time (hr)[a]	Ceftizoxime level in serum[b] (μg/ml)			
	Group I	Group II	Group III	Group IV
0.00	59.6 (11.7)	54.9 (17.40)	81.4 (16.5)	68.4 (14.7)
0.08	58.9 (14.7)	52.1 (16.21)	76.7 (11.9)	72.2 (13.0)
0.17	45.2 (3.40)	45.9 (6.96)	72.6 (11.7)	64.3 (5.43)
0.25	40.5 (3.95)	42.0 (6.70)	70.5 (13.2)	63.9 (10.6)
0.50	32.3 (5.12)	36.8 (2.97)	65.6 (10.4)	57.5 (10.6)
1.00	24.3 (3.21)	28.5 (3.78)	58.3 (4.92)	54.9 (7.65)
1.50	18.3 (3.43)	23.4 (4.57)	54.2 (6.10)	53.2 (7.06)
2.50	10.2 (1.84)	17.7 (2.94)	49.9 (6.90)	52.0 (7.91)
3.50	6.8 (1.52)	14.3 (4.14)	43.3 (4.90)	52.1 (7.15)
5.50	3.0 (0.86)	7.3 (2.72)	34.1 (6.83)	48.6 (7.16)
7.50	1.1 (1.02)	4.8 (1.95)	29.5 (7.78)	46.2 (5.70)
11.50		1.9 (1.14)	21.6 (7.00)	42.7 (6.49)
23.50			7.7 (4.82)	34.5 (6.63)
25.50				22.0 (3.07)
27.50				16.6 (1.86)
28.50				16.5 (2.31)
29.50				16.1 (2.63)
30.50				16.7 (2.81)
35.50			3.4 (2.72)	15.3 (2.35)
47.50			1.3 (1.60)	11.6 (3.40)[c]

[a] Time after 30-min drip infusion.
[b] Values are means; standard deviations are shown in parentheses.
[c] Computed from four samples.

underlying diseases (normal healthy adults) to subjects with decreasing renal function and other disease states (e.g., hypertension, diabetes mellitus, gout, peripheral vascular disease, chronic pyelonephritis, glomerulonephritis, etc.). Subjects ranged in age from 26 to 64 years, in body surface area from 1.67 to 2.21 m^2, and in creatinine clearance from 0 to 157 ml/min per 1.73 m^2. There were six females participating in the study protocol, each determined by prestudy pregnancy testing not to be pregnant.

Serum concentrations of ceftizoxime at the conclusion of the drip infusion (peak concentrations) were not significantly different in the four groups, but the rate of excretion varied greatly (Table 2). Subjects in group I exhibited a decline in the concentration of ceftizoxime such that approximately 1 μg/ml was present at 7.5 h after drug administration. In contrast, subjects in group IV (despite a 4-h hemodialysis at 24 h postinfusion) had ceftizoxime serum concentrations greater than 10 μg/ml at 47.5 h. A 4-h hemodialysis procedure resulted in serum concentrations of ceftizoxime 51.9% lower at the end of hemodialysis than concentrations at the beginning of hemodialysis. Table 3 lists the mean pharmacokinetic parameters calculated for each group. Differences among groups I to IV were significant for the zero-time intercept for the beta elimination phase (B), beta elimination rate constant, area under the serum concentration-time curve, volume of distribution at

TABLE 3. Pharmacokinetic parameters for study groups[a]

Group	A (μg/ml)	B (μg/ml)	α (h^{-1})	β (h^{-1})	AUC (μg · h/ml)	V_{dss} (liters/kg)	V_{darea} (liters/kg)	TBC (ml/min/1.73 m^2)	RC (ml/min/1.73 m^2)
I	22.0 (7.56)	29.6 (2.59)	4.05 (4.92)	0.419 (0.052)	84.6 (15.6)	0.377 (0.040)	0.421 (0.042)	193 (33.8)	103 (31.5)
II	18.4 (14.3)	32.2 (6.91)	2.71 (2.89)	0.260 (0.057)	141 (29.8)	0.338 (0.034)	0.369 (0.043)	112 (29.8)	92.7 (59.0)
III	19.3 (11.1)	54.6 (10.9)	2.12 (3.31)	0.085 (0.022)	721 (205)	0.213 (0.026)	0.224 (0.030)	22.6 (6.26)	10.7 (8.03)
IV	15.7 (12.0)	54.5 (6.52)	5.01 (3.10)	0.020 (0.006)	2,859 (945)	0.263 (0.095)	0.264 (0.095)	5.92 (2.08)	0.255 (0.325)
F ratio	0.260	19.231	0.643	99.494	36.33	8.737	12.391	72.612	
P value	>0.05	<0.001	>0.05	<0.001	<0.001	0.001	<0.001	<0.001	

[a] A and B, zero-time intercepts; α and β, alpha and beta disposition rate constants; AUC, area under the serum concentration-time curve; V_{dss}, volume of distribution steady state; V_{darea}, volume of distribution equal to the amount of drug in the body; TBC, total body clearance of drug; RC, renal clearance.

TABLE 4. Ceftizoxime excreted in urine

Collection interval (h)	Ceftizoxime in urine (mg)[a]			
	Group I	Group II	Group III	Group IV
0–2	478 (132)	111 (24.6)[b]	117 (41.4)	1.81 (2.11)[c]
2–4	141 (43.3)	254 (190)	106 (32.9)	9.41[d]
4–6	65.4 (35.7)	76.0 (19.3)[b]	59.5 (3.16)[e]	5.05[d]
6–8	21.8 (8.60)	104 (54.9)	59.5 (10.3)	8.79 (0.191)[c]
8–12	11.2 (7.95)	60.1 (25.8)	78.4 (24.1)	6.01 (4.36)[c]
12–18	5.36 (3.13)	40.7 (25.2)	88.7 (14.2)	11.7 (10.6)[c]
18–24	0.861 (0.462)	15.3 (8.80)	52.0 (17.3)	13.4 (9.60)[b]
24–48	0.10 (0.224)	7.54 (1.68)[c]	106 (75.6)	19.0 (3.68)[c]

[a] Mean (standard deviation).
[b] Computed from three samples.
[c] Computed from two samples.
[d] Computed from one sample.
[e] Computed from four samples.

steady state, volume of distribution area, total body clearance, and renal clearance of ceftizoxime. Volunteers in group IV who were anuric (patients 18 and 19) had an average total body clearance of ceftizoxime of 6.25 ml/min per 1.73 m^2, whereas subjects in group I had an average total body clearance of ceftizoxime of 193 ml/min per 1.73 m^2. Table 4 gives the amount of ceftizoxime excreted in the urine for groups I to IV. Approximately 98% of ceftizoxime is excreted within the first 8 h after drug administration in subjects with normal renal function. It is also apparent from Table 4 that as renal function deteriorates, the amount of drug excreted within the first 8 h decreases such that 81, 51, and 33% were eliminated in groups II, III, and IV, respectively.

Figure 1 shows the relationship between the creatinine clearance (x axis) and the total body clearance of ceftizoxime (y axis). The data were fitted by orthogonal regression to the line $y = -11.95 + 1.792x$. The correlation coefficient was 0.953, and the t test of independence was highly significant ($P < 0.001$).

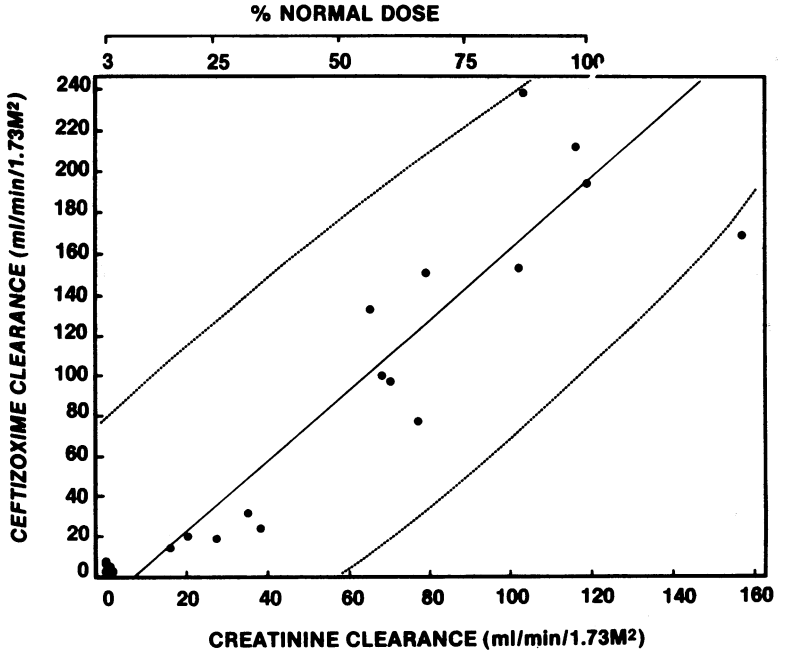

FIG. 1. Ceftizoxime dosage nomogram. Correlation between creatinine clearance (x) and the total body clearance of ceftizoxime (y) in 20 subjects (•) with and without renal insufficiency. $y = -11.95 + 1.742x$. $r^2 = 0.95$ (dotted line refers to the upper and lower 95% confidence limits for the major axis of the ellipse).

DISCUSSION

Ceftizoxime is a broad-spectrum cephalosporin antibiotic which possesses strong antibacterial activity against many gram-negative bacteria. The microbiological characteristics of ceftizoxime suggest that it may have excellent clinical utility in the treatment of infections caused by aerobic and anaerobic gram-negative enteric bacteria; therefore, an understanding of the pharmacokinetic parameters of ceftizoxime will enable the clinician to maximize the microbiological features of the drug and minimize antibiotic complications.

In the present study, the range in the beta elimination half-lives for subjects in groups I to IV was 1.65 to 34.7 h. This is in agreement with observations by other investigators (5; A. D. Blair, E. D. Burgess, D. Parks, and R. E. Cutler, Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 21st, Chicago, Ill., abstr. no. 38, 1981) and comparable to the elimination half-life data report for cefazolin (4). Coupled with the high serum concentrations which are still above the minimum inhibitory concentrations of most susceptible organisms 8 h after drug administration, it would appear that ceftizoxime dosage administration at 8 h intervals would be appropriate in subjects with normal renal function. Urinary concentrations of ceftizoxime observed in this study would suggest that the interval of drug administration could be even longer (e.g., every 12 to 24 h) in normal subjects being treated for urinary tract infections due to susceptible gram-negative organisms.

Analysis of our data shows that the total body clearance of ceftizoxime correlated best with 24-h creatinine clearance results. Such a correlation between drug clearance and creatinine clearance makes it possible to establish a nomogram for adjusting the dose (as a percent of normal) in subjects with renal insufficiency. Functionally anephric patients in our study would theoretically receive approximately 3.0% of the usual 1.0-g intravenous dose at the same interval as subjects with normal renal function. However, in a more practical sense, an alternative would be to change the interval of administration and maintain the normal milligram dose of ceftizoxime. Although not shown on the nomogram, subjects in group II would receive 100% of the normal dose every 12 h, subjects in group III, 100% of the dose every 36 to 48 h, and subjects in group IV would receive the normal dose at some time interval greater than 48 h, depending on the frequency of hemodialysis. Utilization of this nomogram for ceftizoxime administration in subjects with renal insufficiency should provide safe and effective serum concentrations.

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