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Clinical Pharmacology of Ceftriaxone in Patients with Neoplastic Disease

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Pharmacological studies of ceftriaxone, a new semisynthetic cephalosporin, were conducted in 35 cancer patients. This antibiotic was administered in a variety of doses and schedules with no observed toxicity. Intramuscular administration of 500 mg of ceftriaxone to seven patients produced mean peak serum concentrations of 32.9 μg/ml 2.0 h after administration. The terminal serum half-life was 10.9 h. Intravenous infusion of 500 mg of ceftriaxone over 5 min to the same group of seven patients produced a mean peak concentration of the drug in serum of 83 μg/ml at the end of administration which decreased to 16.8 μg/ml at 8 h. A dose of 1 g of ceftriaxone given in identical fashion to the same group of seven patients produced mean peak concentrations in serum of 130 μg/ml at the end of administration and 17.3 μg/ml at 12 h. The mean percentages of drug recovered in urine 12 h after single intravenous doses of 500 mg and 1 g were 30 and 20%, respectively. A 1-g dose of ceftriaxone was administered every 8 h to 10 patients, and a 2-g dose was administered every 12 hours to 9 patients. Drug concentrations in serum were measured for each patient after drug administration on day 1, day 3 or 4, and day 7 or 8. The 1-g dose produced an observed mean peak concentration of 154 μg/ml and a mean terminal-phase half-life of 5.6 h on day 3 or 4. The 2-g dose produced a mean peak concentration in serum of 262 μg/ml and a terminal-phase serum half-life of 6.3 h on day 3 or 4. Continuous infusion studies were performed in nine neutropenic patients for up to 8 days by using a loading dose of 1 g over 30 min, followed by 2 g every 8 h. Mean concentrations in serum were maintained at about 135 μg/ml during the infusion period.

Ceftriaxone is a new semisynthetic cephalosporin which has a broad spectrum of activity in vitro (4). Ceftriaxone was found to be more active in vitro against *Enterobacteriaceae* than any commercially available cephalosporin. Also, its activity against most gram-negative bacteria was greater than those of some of the other new broad-spectrum cephalosporins (1, 7). The in vitro activity of ceftriaxone against gram-positive aerobic and anaerobic organisms compares favorably with those of other cephalosporins (10). Animal pharmacokinetic studies indicate that biliary excretion is a significant excretory pathway for this drug (5). Preliminary data from studies in humans have shown minimal toxicity. Because of its long half-life, stability against β-lactamases, and broad spectrum of activity, ceftriaxone is of clinical interest. The pharmacokinetics of ceftriaxone have been studied in normal adults, infants, and patients with impaired renal function (8, 9, 12). In this study, we report that pharmacokinetic properties of ceftriaxone in a group of 35 patients with neoplastic disease who were hospitalized for either the treatment of their primary disease or its complications.

MATERIALS AND METHODS

Studies were conducted in 35 patients (23 males and 12 females). Body surface area in these patients ranged from 1.15 to 2.30 m^2 (median, 1.7 m^2). With few exceptions, patients had normal renal and hepatic function, defined as a serum creatinine level of less than 1.3 mg/dl, serum glutamic oxalacetic transaminase of less than 50 U/dl, and serum bilirubin of less than 1.0 mg/dl. All but one patient had normal serum creatinine levels. The exception was a 60-year-old male with preleukemia who entered the study with an initial serum creatinine level of 1.6 mg/dl which decreased to 1.2 mg/dl by day 2 and remained within normal limits thereafter. Since the concentrations of drug in the serum of this patient were similar to those of the other patients, his studies have been included.

Eight patients had elevated baseline serum glutamic oxalacetic transaminase measurements ranging between 71 and 129 U/dl which declined during drug administration. Only one of these patients had an elevated bilirubin level (1.5 mg/dl) which returned to normal on day 4 of the study. None of these patients showed drug concentrations in serum that were substantially different from those with normal liver function tests, and therefore the data were included. The median age of these patients was 41 years (range, 17 to 70 years), and all were hospitalized for cancer chemotherapy; however, they were not receiving therapy during the period covered by these pharmacology studies.

Single-dose crossover studies of ceftriaxone were performed in seven volunteer patients. Each patient received an intramuscular (i.m.) dose of 500 mg reconstituted with 1.0% lidocaine hydrochloride solution to minimize discomfort. They subsequently received intravenous (i.v.) doses of 500 mg and 1 g. The i.v. doses were given in 50 ml of 5% dextrose over a period of 5 min. Patients were randomly assigned to the three different sequences of drug administration. A minimum of 2 days lapsed between each treatment scheduled in the same patient. Blood samples were collected at 0, 5, and 30 min and 1, 2, 4, 6, and 8 h after the 500-mg doses; a 12-h sample was also collected after the 1-g dose. Urine samples were collected before drug administration and consecutively for 12 h after each dose (0 to 3, 3 to 6, and 6 to 12 h).

A total of 32 multiple-dose studies of ceftriaxone were conducted in 28 other patients, most of whom were in a protected environment and volunteered to accept substitution of ceftriaxone temporarily for other prophylactic antibiotic regimens (2). Six patients received ceftriaxone therapeutically, four for presumed and two for proven infections. Nine patients received 2 g of ceftriaxone i.v. in 50 ml of 5% dextrose over a period of 5 min every 12 h for 7 or 8 days. Another group of 10 patients received 1 g of ceftriaxone i.v. in 15 ml of 5% dextrose over a period of 5 min every 8 h for 7 or 8 days. Pharmacological studies in both groups of patients were conducted on day 1, day 3 or 4, and day 7 or 8 of administration. Blood samples were collected at 0, 5, and 30 min and 1, 2, 4, 6, and 8 h after drug administration. An additional specimen was collected 12 h after drug administration for the group of patients receiving the drug every 12 h. Nine neutropenic patients received a 1-g loading dose of ceftriaxone in 50 ml of 5% dextrose solution over 30 min, followed immediately thereafter by 2 g of ceftriaxone in 200 ml given as a continuous infusion every 8 h by means of an infusion pump. Blood specimens were collected at 0, 15, and 30 min and 1, 2, 4, and 6 h after the first loading dose and twice daily thereafter (at 10 a.m. and 2 p.m.) for 8 days.

Assays were performed in the laboratories of the Department of Pharmacokinetics and Biopharmaceutics, Hofmann-LaRoche, Inc., Nutley, N.J. Ceftriaxone was assayed in an acetonitrile protein-free serum filtrate by reverse-phase ion-pair high-pressure liquid chromatography with UV detection at 280 nm. The same assay was applied to acetonitrile dilutions of urine. Ro 5-2922 (the *N*-1-ethyl analog of *N*-desmethyl diazepam) and Ro 5-9973 (prazepam) were used as internal standards for the analyses of serum and urine, respectively. Serum samples were prepared by mixing 0.25 ml of serum and 0.75 ml of distilled water in a borosilicate tube to which 2.0 ml of an acetonitrile solution of Ro 5-2922 (50 μg/ml) was added and shaken on a reciprocating shaker for 10 min, followed by centrifugation at 2,500 rpm for 10 min at 10°C, and transferring 2.0 ml of the supernatant liquid to an autosampler vial. Urine samples were prepared by combining 0.25 ml of urine with 2.0 ml of an acetonitrile solution containing 30 μg of Ro 5-9973 per ml into an autosampler vial.

The high-pressure liquid chromatographic analyses were performed by automatic injection of 50-μl samples onto a column (30 cm by 4.6 mm [inner diameter]) of 10-μ Chromegabond C-18. The solvent system for the serum analyses was prepared by dissolving 3 g of hexadecyltrimethylammonium bromide in 600 ml of acetonitrile, adding 10 ml of a 1.0 M phosphate buffer (pH 7.0), and diluting to 1 liter with water. The solvent system for the urine analyses was prepared by dissolving 3.5 g of tetraoctylammonium bromide in 400 ml of acetonitrile, adding 12 ml of the 1.0 M phosphate buffer (pH 7.0), and diluting to 1 liter with water. In addition to the samples from patients, analyses were performed on 0.25-ml specimens of controlled serum and urine and six 0.25-ml specimens of the same controlled fluid to which known quantities of ceftriaxone had been added. Sufficient distilled water was added to these calibration standards to adjust the total volume to 1 ml before adding 2 ml of the acetonitrile solution (containing the appropriate internal standard). The assays are validated in the ranges of 2 to 400 and 6 to 167 μg/ml for plasma and urine, respectively. The standards were used to establish a linear least-squares regression calibration curve for the quantitation of ceftriaxone, using the peak height ratio of this drug versus the analogs. In all cases, the intra-assay correlation coefficient (r^2) was 0.998 or higher. The mean coefficients of variation for the serum assay calibration (four injections at six different concentrations) and the urine assay calibration (four injections at five different concentrations) were 4.3 and 3.6%, respectively.

A set of external standards prepared in the same manner as that used for the calibration standards were also assayed. These samples were used to standardize the chromatographic system and to calculate percent recovery. The recovery of ceftriaxone in both assays was approximately 100%.

All pharmacokinetic calculations were made after correcting for the time of drug administration. The mean drug concentrations in serum for the i.v. treatment schedules were best fit to the biexponential equation $C_s = Ae^{-\alpha t} + Be^{-\alpha t}$ by a nonlinear least-squares calculator program, using the method of residuals (11). This equation implies a one-compartment open model. Similarly, the serum concentrations for the i.m. schedule were fit to the biexponential equation $C_s = Be^{-K_{el}t} - Ae^{-K_a t}$, which implies a single-compartment open model with an initial absorption phase. The mean and standard error of the mean were calculated for each point for all treatment schedules, and 95% confidence limits were taken as twice the standard error of the mean (6). The area under the concentration-time curve (AUC), which is a measure of the total exposure of the drug, was determined from the following equations: $AUC = [(A/\alpha) + (B/\beta)]$ for i.v. administration and $AUC = [(B/K_{el}) - (A/K_a)]$ for i.m. administrations (11). Serum concentrations at

zero time were determined by the sum of A + B. Volume of distribution (V_d) values of the drug were calculated according to the following formula: V_d = [(Dose)/(AUC × β)] (11).

RESULTS

The mean concentrations of ceftriaxone in serum during the single-dose crossover studies with seven patients are shown in Table 1. The i.m. administration of 500 mg of ceftriaxone resulted in a mean peak drug concentration in serum of 32.9 μg/ml 2 h after drug administration and decreased to 25.4 μg/ml at 6 h. The mean terminal-phase serum half-life was estimated to be approximately 10.9 h. After the i.v. administration of 500 mg of ceftriaxone over a 5-min period, the mean peak drug concentration in serum was 83 μg/ml at the end of the infusion. This concentration declined to 25.4 μg/ml at 4 h and 16.8 μg/ml at 8 h. The i.v. administration of 1 g of ceftriaxone over a 5-min period produced a mean peak drug concentration in serum of 130 μg/ml at the end of the infusion. This concentration decreased to 28.7 μg/ml at 6 h and 17.3 μg/ml at 12 h. The V_d and AUC values increased with higher i.v. dose, from 11.6 to 14.8 liters and from 380 to 561 μg · h/ml, respectively (see Table 3).

The mean concentrations of ceftriaxone in the sera of 10 patients who received 1 g of the drug i.v. over a 5-min period every 8 h and those of 9 patients who received 2 g of the drug i.v. over 5 min every 12 h for 7 or 8 days are shown in Table 2. Mean peak concentrations in serum for the 1-g dose were 118.7 (day 1), 154, and 145 μg/ml on days 1, 3 to 4, and 7 to 8, respectively, with a clearance half-life range of 5.6 to 6.6 h (Table 3). For the 2-g regimen, the mean peak concentrations in serum were 253.5, 262.2, and 262.8 μg/ml on days 1, 3 to 4, and 7 to 8, respectively,

TABLE 1. Mean concentrations of ceftriaxone in serum in a single crossover study with seven patients

Dose and route	Time (h)	Mean ± SEM concn (μg/ml) in serum
500 mg i.m.	0	0
	0.17	17.0 ± 3.9
	0.5	28.0 ± 4.7
	1.0	31.9 ± 3.9
	2.0	32.9 ± 4.3
	4.0	28.3 ± 3.7
	6.0	25.5 ± 4.3
500 mg i.v.	0	0
	0.17	83.0 ± 5.9
	0.5	54.4 ± 7.7
	1.0	44.7 ± 5.0
	2.0	33.5 ± 2.6
	4.0	25.4 ± 5.0
	6.0	20.9 ± 4.6
	8.0	16.8 ± 4.9
1 g i.v.	0	0
	0.17	130.2 ± 9.8
	0.5	79.3 ± 5.0
	1.0	65.7 ± 6.5
	2.0	52.2 ± 4.0
	4.0	38.5 ± 1.7
	6.0	28.7 ± 4.3
	8.0	22.3 ± 3.2
	12.0	17.3 ± 3.5

TABLE 2. Mean ceftriaxone concentrations in serum after multiple doses

Dose (g)[a]	Time (h)	Mean ± SEM concn (μg/ml) on day:		
		1	3 or 4	7 or 8
1	0	0	51.6 ± 4.0	57.6 ± 6.4
	0.25	118.7 ± 13.9	154.1 ± 12.0	145.3 ± 10.2
	0.5	78.9 ± 5.1	115.7 ± 9.0	120.3 ± 6.6
	1.0	69.3 ± 5.0	108.7 ± 7.9	116.8 ± 6.8
	2.0	57.5 ± 3.9	93.8 ± 6.9	94.7 ± 8.1
	4.0	46.0 ± 2.6	72.7 ± 5.3	82.8 ± 7.5
	6.0	38.6 ± 1.8	58.1 ± 5.0	64.6 ± 5.2
	8.0	32.4 ± 1.2	45.1 ± 4.1	54.3 ± 5.6
2	0.25	253.5 ± 20.0	262.2 ± 17.4	262.8 ± 13.7
	0.5	171.1 ± 6.6	229.3 ± 10.3	208.8 ± 13.8
	1.0	156.2 ± 7.6	183.3 ± 10.8	181.0 ± 12.5
	2.0	125.6 ± 5.1	160.7 ± 8.0	152.1 ± 5.4
	4.0	94.3 ± 4.7	131.1 ± 6.4	116.1 ± 5.7
	6.0	79.1 ± 4.6	103.6 ± 7.8	91.1 ± 3.0
	8.0	62.3 ± 2.9	82.1 ± 3.1	75.8 ± 1.3
	12.0	48.2 ± 2.9	55.1 ± 4.8	51.2 ± 2.4

[a] Ceftriaxone was given i.v. in a dose of 1 g over a 5-min period every 8 h to 10 patients and in a dose of 2 g over a 5-min period every 12 h to 9 patients.

TABLE 3. Mean pharmacokinetic data of ceftriaxone studies

Dose (g)	Schedule	$t_{1/2\beta}$ (h)[a]	C_s^0 (μg/ml)[b]	V_d (liters)	AUC (μg · h/ml)
0.5	Single i.m. dose	10.9			572
0.5	Single i.v. dose	6.1	79	11.6	380
1.0	Single i.v. dose	5.7	130	14.8	561
1.0	Multiple i.v. doses (day 1)	6.6	119	13.6	701
1.0	Multiple i.v. doses (day 3 or 4)	5.6	154	8.3	973
1.0	Multiple i.v. doses (day 7 or 8)	6.6	145	8.1	1,173
2.0	Multiple i.v. doses (day 1)	6.6	254	12.7	1,496
2.0	Multiple i.v. doses (day 3 or 4)	6.3	262	9.7	1,878
2.0	Multiple i.v. doses	6.5	259	10.8	1,719

[a] $t_{1/2\beta}$, Beta (elimination) phase half-life.
[b] C_s^0, Concentration in serum calculated for zero time.

with terminal-phase serum half-lives ranging from 6.3 to 6.6 h. The V_d values decreased from the initial dose to day 3, but less change was observed thereafter (Table 3). The initial 1.0-g dose gave a value of 13.6 liters which decreased to 8.3 liters on day 3 and 8.1 liters on day 7. The initial dose of 2.0 g gave a value of 12.7 liters and decreased to 9.7 liters on day 3 but increased to 10.8 liters on day 7. The AUC values for multiple doses generally increased with later infusions of the same dose and with higher doses. The initial 1.0-g dose gave a value of 701 μg · h/ml and increased to 973 μg · h/ml on day 3 and 1,173 μg · h/ml on day 7. The increase in the AUC value on day 3 or 4 showed evidence of drug accumulation, as compared with day 1, when 1 g of ceftriaxone was given every 8 h. This increase is presumably due to the nonlinear behavior of the system which is affected by drug accumulation in the eliminating organs. There was a less substantial increase on day 7 or 8 of the infusion study. When 2 g of ceftriaxone was given every 12 h for the same length of time, the drug accumulation was less significant.

Continuous infusion studies were conducted in nine patients. A loading dose of 1 g of ceftriaxone administered over 30 min was followed immediately thereafter by 2 g every 8 h by continuous infusion. The mean drug concentration in serum was 100 μg/ml at the end of the loading dose and remained above that concentration during the initial 6-h infusion. Mean concentrations of drug in serum at 10 a.m., during day 2 through day 8 of the study, varied between 117 and 151 μg/ml (Fig. 1). Variations in the drug concentrations in serum for any given patient on different days of the study were not significant.

Data on the urinary excretion of ceftriaxone are shown in Table 4. A mean of 29% of a single dose of 500 mg i.m. was recovered in the urine by 12 h. Corresponding values were 30.6% for a single 500-mg i.v. dose and 20.4% after a single 1-g i.v. dose. Drug concentrations in urine between 6 and 12 h after drug administration ranged from 29 to 400 μg/ml for a single 500-mg i.m. dose, 28 to 730 μg/ml for a single 500-mg i.v. dose, and 54 to 1,110 μg/ml for a single 1-g i.v. dose.

Six patients received ceftriaxone therapeutically for proven or presumed infections. Only two patients had documented infections. A patient who had pneumonia of unknown etiology failed to respond to 2 g of ceftriaxone i.v. every 12 h. A patient with perineal cellulitis from which no organisms were recovered failed to respond to 1 g of ceftriaxone i.v. every 8 h. Four neutropenic patients with fever but no identified source of infection received ceftriaxone i.v. by continuous infusion. The temperature in all four

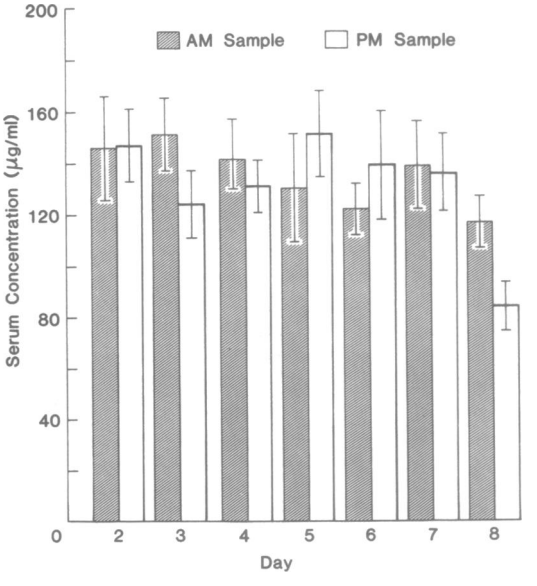

FIG. 1. Mean morning and afternoon concentrations of ceftriaxone in serum obtained with continuous i.v. infusion of 2 g every 8 h after a 1-g loading dose. Vertical bars indicate standard errors of the means.

TABLE 4. Urinary excretion of ceftriaxone

Dose and route[a]	Collection time (h)	Urinary excretion		Mean (range) urinary concn (μg/ml)
		Mean total (mg)	% Dose (mean)	
500 mg i.m.	0–3	39.5	7.9	137.3 (59–388)
	3–6	45.1	9.0	277.5 (8–648)
	6–12	60.4	12.1	187.8 (29–400)
500 mg i.v.	0–3	34.2	6.8	393.0 (104–955)
	3–6	67.6	13.5	286.8 (77–478)
	6–12	51.1	10.2	217.6 (28–730)
1 g i.v.	0–3	88.3	8.8	882.6 (71–1710)
	3–6	38.9	3.9	252.3 (96–475)
	6–12	76.7	7.7	429.8 (54–1110)

[a] Given as single doses.

patients rapidly returned to normal. No toxicities were observed, and the drug was well tolerated by all patients.

DISCUSSION

Ceftriaxone is a new semisynthetic cephalosporin which is highly active in vitro against many gram-negative bacilli. Its stability to β-lactamases is superior to those of most cephalosporins, and it has an exceptionally long biological half-life in comparison with those of most other cephalosporins.

Single-dose pharmacokinetic studies of ceftriaxone have been conducted in normal volunteers (B. Scully and H. C. Neu, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 21st, Chicago, Ill., abstr. no. 805, 1981). Scully and Neu administered doses of 500 mg and 1 g i.v., which produced peak concentrations in serum of 85 and 156 μg/ml, respectively. We conducted single-dose crossover studies with doses of 500 mg i.m. and i.v. and 1 g i.v.

The mean peak drug concentration in serum at 2.0 h after a dose of 500 mg i.m. was only 32.9 μg/ml. The reasons for the lower concentrations in serum after the i.m. administration, as compared with those obtained in the prior study, are not clear. Possible causes are variable absorption of ceftriaxone by the i.m. route or differences in assay specificity. Single-dose i.v. studies of 500 mg i.v. and 1 g i.v. in the same group of patients produced concentrations comparable to those obtained by other (8).

Multiple-dose studies conducted with either 1 g of ceftriaxone every 8 h or 2 g every 12 h produced serum levels substantially higher than those required to inhibit 90% of most gram-negative clinical isolates, except for *Pseudomonas aeruginosa* (4). Although there was evidence of drug accumulation occurring with the schedule consisting of 1 g every 8 h, no evidence of toxicity was observed.

In patients with impaired host defense mechanisms, maintenance of concentrations above the minimal inhibitory concentration may be important because of the propensity of gram-negative organisms to resume proliferation quickly once serum concentrations fall below this level (3). From our data, it appears that a schedule of ceftriaxone consisting of 2 g every 8 h by continuous i.v. infusion maintains serum levels of more than 100 μg/ml. Actually, lower doses may be adequate for this purpose.

Our urinary excretion studies also confirm the findings of others which show that a substantial amount of the drug is eliminated by mechanisms other than the kidneys. Urinary excretion ranged between 20.4 and 30.6% of an administered ceftriaxone dose during a 12-h period after a single i.m. or i.v. dose. Biliary excretion is a significant excretory pathway of ceftriaxone, as shown in pharmacokinetic studies with baboons (5). In this respect, ceftriaxone resembles other cephalosporins, such as cefamandole and moxalactam, which are excreted via the bile.

The serum terminal-phase half-life of ceftriaxone in this study (Table 3) is shorter than those of earlier reports (average of 7 to 8 h) but substantially longer than those reported for cephalothin (0.6 h), cefoxitin (0.8 h), cefamandole (0.9 h), cefazolin (1.9 h), and moxalactam (2 to 3.2 h). The extended terminal-phase half-life of ceftriaxone may be related to the fact that only 7 to 9% of the drug is recovered in the urine during the first 3 h after i.v. administration, as compared with 68 and 66% for cephalothin and cefamandole. The prolongation in biological half-life may be due to an increased V_d or decreased clearance.

Because of its exceptional in vitro susceptibility against most gram-negative bacteria and long

elimination half-life, this novel semisynthetic cephalosporin shows great promise. On the basis of our study, 1 or 2 g of ceftriaxone every 8 to 12 h seems to be adequate for the parenteral therapy of most bacterial infections due to susceptible organisms.

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