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Pharmacology of Ceftizoxime Compared with That of Cefamandole

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The pharmacokinetics of ceftizoxime, a new β-lactam antibiotic, were studied in normal, male volunteers and compared with the pharmacokinetics of cefamandole. After administration of 500 mg intramuscularly, ceftizoxime produced a peak level of 13.7 ± 1 μg/ml, compared with 13.2 ± 1.6 μg/ml for cefamandole. At 4 h, the serum level of ceftizoxime was 4.8 μg/ml, and that of cefamandole was 1.9 μg/ml. At 8 h, ceftizoxime was still detected at 0.73 μg/ml, whereas cefamandole was not. The half-life of ceftizoxime after intramuscular administration was 1.7 h, compared with 1 h for cefamandole. Serum levels of ceftizoxime and cefamandole after 1 g infused over 30 min were 84 and 88 μg/ml, respectively. At 5 h cefamandole was not detectable, whereas ceftizoxime had a serum level of 4.5 μg/ml and, at 7 h, 2.1 μg/ml. The half-life of ceftizoxime was 1.9 h, compared with 0.78 h for cefamandole. Urinary recovery of ceftizoxime after intramuscular and intravenous administration was 70 and 80%, respectively, compared with 78 and 73% for cefamandole.

Ceftizoxime is a new cephalosporin which has in vitro antibacterial activities similar to those of cefotaxime, moxalactam, and cefoperazone (4, 9). The minimal inhibitory concentrations of ceftizoxime for most *Enterobacteriaceae* are less than 1 μg/ml; for some *Pseudomonas aeruginosa* and *Bacteroides fragilis* isolates, minimal inhibitory concentrations are less than 25 μg/ml (4, 9). With these activities, ceftizoxime has promise for therapy in infections due to organisms resistant to older cephalosporins and to aminoglycosides. This led us to the current study, in which pharmacokinetic parameters and tolerance of ceftizoxime after intravenous (i.v.) and intramuscular (i.m.) administration to normal volunteers are compared with the same features of cefamandole, a widely used cephalosporin which ceftizoxime would seem likely to replace.

MATERIALS AND METHODS

Ceftizoxime was supplied by Fujisawa Pharmaceutical Corp. via Smith Kline & French Laboratories, and cefamandole was purchased from Lilly Research Laboratories.

Eight male volunteers between the ages of 25 and 43 were the subjects of the study. Informed, written consent in accordance with federal guidelines was obtained from each individual. The mean weight of the subjects was 72.7 kg (range, 52 to 96 kg). The mean age was 29 years (range, 25 to 43 years), and the mean body surface area was 1.9 m^2 (range, 1.66 to 1.98 m^2). All subjects were judged healthy on the basis of history, physical examination, electrocardiogram, chemistry profile (SMAC, Technicon), complete blood count, and urinalysis. Subjects with known allergy to penicillins or cephalosporins were excluded. No subjects had received an antimicrobial agent in the prior 2 weeks.

Each of eight subjects received either 500 mg of ceftizoxime or cefamandole on the initial day of the study, followed by the alternate drug 1 week later. Drug assignment was by random numbers. Blood samples of 5 ml were obtained at 0, 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 h after the injection. Urine samples were collected immediately before injection and at 0 to 2, 2 to 4, 4 to 8, and 8 to 24 h postinjection. Blood samples were allowed to clot at room temperature and centrifuged within 30 min of being drawn. Each serum and urine sample was divided into equal portions, immediately frozen, and stored at −20°C until assay. Ceftizoxime in urine, serum, and phosphate buffer was stable at −20°C at concentrations of 10 and 100 μg/ml for 90 days.

The same eight subjects received 1,000 mg of ceftizoxime or cefamandole in a volume of 30 ml infused i.v. through a small-bore needle over 30 min at a rate of 1 ml/min, followed by the alternate drug 1 week later. Blood samples were drawn before infusion and at 0.25, 0.5, 0.75, 1, 1.25, 1.5, 2, 2.25, 3, 3.5, and 6.5 h after the start of the infusion. Urine samples were collected as previously mentioned, and blood and urine were processed as in the i.m. study.

Assays. Ceftizoxime and cefamandole were assayed by the agar well diffusion technique, using antibiotic medium no. 2 (Difco Laboratories) as previously described (3, 4). Antibiotic standards for assay of serum samples were prepared in pooled normal human serum from the subjects who had been shown to lack anti-

bacterial activity against the assay organisms. Urine samples were diluted in 0.5 M potassium phosphate buffer, pH 7. The serum assay organisms were *Escherichia coli* 3989 (from our collection) for ceftizoxime and *Staphylococcus aureus* ATCC 3472 for cefamandole. Urine samples of ceftizoxime were assayed with *Bacillus subtilis*, using a paper disk diffusion technique which could detect 2 μg/ml. Serum and urine samples were assayed in quadruplicate, and five standards were used on each plate. Concentrations of drug were calculated by using a linear semilogarithmic plot with use of a computer.

The assay for ceftizoxime could detect 0.3 μg/ml, and the assay was linear from 0.3 to 80 μg/ml. The assay for cefamandole could detect 0.4 μg/ml. Samples which gave results outside the linear part of the curve were diluted in normal serum from the volunteers. Samples were thawed only once, since duplicates of all samples were kept. Both ceftizoxime and cefamandole are stable under the conditions of assay (information from Fujisawa Pharmaceutical Corp. and Eli Lilly & Co.). Furthermore, samples were prepared at the time of injection and infusion and stored in similar manner as samples from the subjects to detect decay. No decay was detected.

Pharmacokinetic and statistical methods. The semilogarithmic plot of the serum concentrations of both agents when plotted as time after i.v. infusion conformed to a biexponential curve with an initial distribution and subsequent elimination phase. Thus, two-compartment kinetics were used to define the i.v. data (5). Regression lines were determined by the method of least squares, using a computer. The basic equation was $C = A_e^{-\alpha t} + B_e^{-\beta t}$, with volume of distribution expressed as

$$V_d = \frac{\text{dose}}{\beta\left(\frac{A}{\alpha} + \frac{B}{\beta}\right)}$$

and the rate constants expressed as

$$k_{10} = \frac{\alpha\beta}{k_{21}},\ k_{21} = \frac{A\beta + B\alpha}{A + B},\ \text{and}$$

$$k_{12} = \alpha + \beta - k_{21} - k_{10}$$

The area under the curve (AUC) was determined by Simpson's rule (2). Serum clearance was expressed in milliliters per minute per 1.73 m^2, using the relationship

$$C = \frac{\text{dose}}{\text{AUC}} \times 60 \times \frac{1.73}{\text{BSA}}$$

where the dose is in micrograms and BSA is the body surface area. The effect of infusion was considered (6).

A one-compartment open model was used to calculate the parameters after i.m. injection (5). Least-squares analysis was done with a computer.

RESULTS

Intramuscular study. Table 1 gives the mean serum concentrations after i.m. administration of 500 mg of ceftizoxime and cefaman-

TABLE 1. *Serum levels of ceftizoxime and cefamandole after i.m. and i.v. administration*

Compound	Route	Dose (g)	Serum concn (μg/ml) at given time (h)[a]												
			0.25	0.5	0.75	1	1.25	1.5	1.75	2	2.5	3	4	5	6	7	8
Ceftizoxime	i.m.	0.5	8.9 ± 1.7	13.3 ± 1.9	13.6 ± 1.4	13.7 ± 1		12.4 ± 0.6		9.2 ± 0.7		6.5 ± 0.3	4.8 ± 0.3		1.8 ± 0.2		0.73 ± 0.1
Cefamandole	i.m.	0.5	6.6 ± 2.3	10.2 ± 2.4	13.2 ± 1.6	12.8 ± 2.3		8.1 ± 1.6		5.8 ± 0.8		3.4 ± 1.2	1.5 ± 0.5		NA		NA
Ceftizoxime	i.v.	1[b]		86.4 ± 12.5[c]	57.1 ± 5.4	41.2 ± 5.6	32.3 ± 3.3	28.4 ± 3.1	22.6 ± 1.9	16.4 ± 2	12.5 ± 1.5	10 ± 1.4	6.4 ± 0.8	4.5 ± 0.5		2.1 ± 0.1	
Cefamandole	i.v.	1[b]		87.7 ± 5.8[c]	52.5 ± 2.6	30.1 ± 2.5	20.4 ± 2.4	16 ± 1.8	11.2 ± 1.2	8.8 ± 1.1	5.9 ± 0.8	3.8 ± 0.6	1.9 ± 0.1	NA		NA	

[a] Mean ± standard error of the mean. NA, Not assayed.
[b] Infusion over 0.5 h.
[c] End of infusion.

dole. The mean peak serum concentration after 500 mg of ceftizoxime was 13.7 ± 1 μg/ml, reached at 60 min. A peak level could occur as early as 30 min in some individuals and as late as 90 min in others. The peak serum level after i.m. injection of cefamandole was 13.2 ± 1.6 μg/ml, which occurred at 45 min, but as with ceftizoxime, peak levels for individuals occurred between 30 and 60 min after injection. After 4 h the mean serum level of cefamandole was only 1.5 ± 0.17 μg/ml, and levels were not detectable at 8 h (Fig. 1). In contrast, the mean serum level of ceftizoxime at 4 h was 4.8 ± 0.3 μg/ml, and the mean serum level at 8 h was 0.73 ± 0.1 μg/ml. The AUC for the period zero to infinity for ceftizoxime was 55.3 μg·h/ml, whereas it was 35.1 μg·h/ml for cefamandole.

The mean half-life of ceftizoxime after i.m. administration was 1.7 ± 0.1 h, whereas the half-life of cefamandole was 1 ± 0.1 h. The elimination rate constant, K_e, was 0.41 for ceftizoxime and 0.68 for cefamandole. The apparent volumes of distribution for the two agents were similar (Table 2). Serum clearance of ceftizoxime was 141 ml/min, compared with 226 ml/min for cefamandole.

Approximately 24% of the dose was excreted in the first 2 h, with 67% excreted in 8 h and a total recovery of 70% (range, 58 to 87%) (Fig. 1). Urine concentrations ranged from 700 to 3,200 μg/ml in the first 4 h and from 8 to 130 μg/ml from 8 to 24 h. Concentration obviously depended on the volume of urine. The urinary recoveries of ceftizoxime and cefamandole were similar (Table 2, Fig. 1). Renal clearance of ceftizoxime was 98 ml/min, compared with 187 ml/min for cefamandole.

Intravenous study. Figure 1 shows the mean serum levels after infusion of 1,000 mg of ceftizoxime and cefamandole and the pharmacokinetic parameters. The mean peak serum concentration occurred at the end of the 30-min infusion and was 84 ± 12 μg/ml. At 2.5 h after the start of the infusion, the mean serum level of ceftizoxime was 10 ± 1.3 μg/ml; at 4.5 h it was 4.5 ± 0.5 μg/ml, and at 6.5 h it was 2.1 ± 0.1 μg/ml. Although the mean peak serum concentration of cefamandole was 87.7 ± 5.8 μg/ml at the end of the infusion, the serum level at 2.5 h was 3.8 ± 0.6 μg/ml; the drug was not detectable at 5 h. With both agents, minor intersubject variations in serum levels did not correlate with the differences in body sizes nor with the minor differences in creatinine clearance in these normal individuals. The mean half-life of ceftizoxime was 1.9 ± 0.2 h, and that of cefamandole 0.78 ± 0.1 h. The apparent volume of distribution

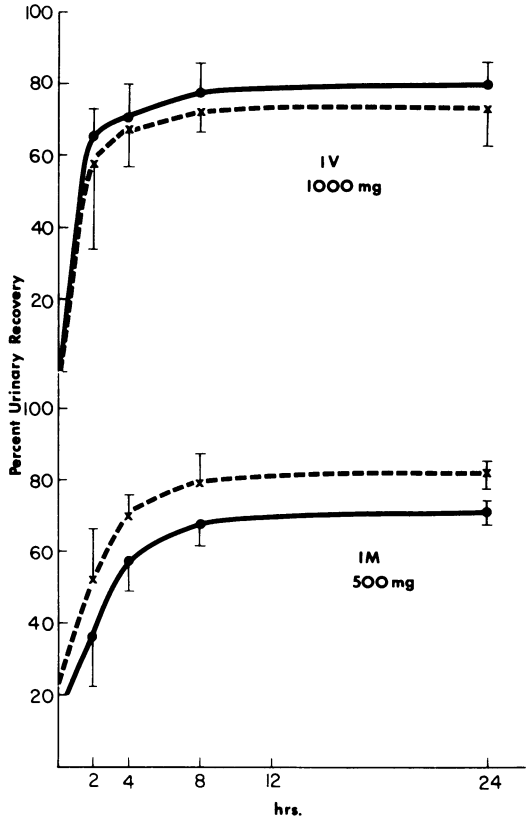

FIG. 1. *Cumulative urinary recovery of ceftizoxime (●) and cefamandole (×) after i.v. administration of 1,000 mg over 30 min and i.m. administration of 500 mg.*

TABLE 2. *Pharmacokinetic parameters of ceftizoxime and cefamandole*[a]

Drug	Route	Dose (mg)	Peak level (μg/ml)	Level at 4 h (μg/ml)	Time to peak (min)	$t_{1/2\beta}$ (h)	V_d (liters/1.73 m^3)	Serum clearance (ml/min per 1.73 m^3)	Renal clearance (ml/min per 1.73 m^3)	AUC (μg·h/ml)	Urinary recovery (%)
Ceftizoxime	i.m.	500	13.7 ± 1	4.8 ± 0.3	54 ± 8	1.7 ± 0.1	23.1 ± 1.8	141 ± 7	98 ± 5	55.3	70
Cefamandole	i.m.	500	12.8 ± 2.3	1.5 ± 0.2	54 ± 11	1 ± 0.1	23.2 ± 4.3	226 ± 26	187 ± 34	35.1	78
Ceftizoxime	i.v.	1,000	84.4 ± 12[b]	6.4 ± 0.8		1.9 ± 0.1	27.9 ± 3.9	161 ± 15	113 ± 17	88.1	80
Cefamandole	i.v.	1,000	87.7 ± 6	1.9 ± 0.1		0.78 ± 0.1	19.2 ± 1.9	276 ± 14	222 ± 10	51.4	73

[a] Each value is mean ± standard error.
[b] Level at end of 30-min infusion.

was 27.9 ± 3.9 liters/1.73 m^2 for ceftizoxime, compared with 19.2 ± 1.9 liters/1.73 m^2 for cefamandole.

The urinary recovery of ceftizoxime ranged from 61 to 92%, with a mean urinary recovery of 81% of the administered dose (Fig. 1). The majority of urinary excretion occurred in the first 2 h after injection. The range of urinary concentration was largely due to variations in the volume of urine produced. However, levels of at least 100 μg/ml were present for the first 8 h after injection. The renal clearance was 112 ml/min per 1.73 m^2. This compared with the mean renal clearance of 222 ml/min found for cefamandole.

Tolerance. Ceftizoxime as a single injection was as well tolerated by both the i.m. and the i.v. routes as was cefamandole. There was minimal discomfort in the i.m. study, and phlebitis was not encountered with a single i.v. infusion.

DISCUSSION

Ceftizoxime, like several of the new cephalosporins such as cefotaxime and moxalactam, inhibits such diverse organisms as *Streptococcus pneumoniae, Haemophilus influenzae, Neisseria gonorrhoeae, S. pyogenes, E. coli, Klebsiella pneumoniae, Enterobacter* species, and *Proteus* species at concentrations below 1 μg/ml; the majority (90%) are inhibited at concentrations below 0.2 μg/ml (4, 9). This pharmacokinetic study shows that an i.m. dose of 500 mg of ceftizoxime provides serum and urine levels that would readily inhibit most important gram-positive species and most of the *Enterobacteriaceae*. The half-life of ceftizoxime is appreciably longer than that of cephalosporins such as cephalothin, cephapirin, cefoxitin (10), and cefamandole (7).

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