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Pharmacokinetics of Cefonicid, a New Broad-Spectrum Cephalosporin

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This study determined the pharmacokinetic disposition of cefonicid. A single dose of 7.5 mg/kg of body weight was administered to five healthy volunteers as a 5-min intravenous infusion. Multiple plasma and urine samples were collected for 48 h. Peak plasma concentrations ranged from 95 to 156 μg/ml and fell slowly (mean plasma half-life, 4.4 ± 0.8 h), so that levels after 12 h were in the range of 6 to 12 μg/ml. Urinary concentrations were high but variable and ranged from 100 to 1,000 μg/ml for the first 12 h after the dose and averaged 84 μg/ml between 12 and 24 h. Plasma and renal clearances were 0.32 ± 0.06 and 0.29 ± 0.05 ml/min per kg, respectively. An average of 88 ± 6% of the dose was excreted unchanged in the urine over 48 h. The mean steady-state volume of distribution was found to be 0.11 ± 0.01 liters/kg.

More than 90% of strains of *Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis*, indole-positive *Proteus* spp., and *Enterobacter* spp. are inhibited by 12.5 μg or less of cefonicid per ml (1, 6). This range of activity is at least partly explained by the relative resistance of cefonicid to hydrolysis by various beta-lactamases elicited by gram-negative organisms (6). Most strains of *Serratia marcescens* are resistant, as are all strains of *Pseudomonas aeruginosa* (4). Cefonicid is less active than cefamandole or the older cephalosporins against gram-positive cocci. However, nearly all strains of *Staphylococcus aureus* are inhibited by ≤6.25 μg/ml. In animal experiments, cefonicid appears to have a longer elimination half-life as compared with cefamandole or cefazolin (1). This was recently confirmed in humans (7), in whom a half-life of approximately 3.5 h was noted after intravenous or intramuscular administration. This feature and the in vitro activity of the compound make cefonicid a potentially very useful antibacterial agent. Thus, the purpose of this study was to determine the pharmacokinetic disposition of cefonicid after a single intravenous dose in healthy volunteers.

MATERIALS AND METHODS

Experimental procedure. Five healthy adult male volunteers participated in the study. Informed consent was obtained from each subject, and the guidelines for human experimentation of the U.S. Department of Health and Human Services and of our institution were followed in the conduct of this clinical research. A panel of laboratory tests consisting of a complete blood count, measurement of the concentration of sodium, potassium, chloride, bicarbonate, calcium, phosphate, and creatinine in serum and urea N in blood, liver function tests, urinalysis, creatinine clearance, direct Coombs test, and a complete medical history and physical examination were carried out before and after drug administration. The subjects ranged in age from 26 to 34 years and in weight from 79 to 88 kg. Creatinine clearance in the subjects averaged (± standard deviation) 117.2 ± 8.5 ml/min. Cefonicid (1,000-mg vials) was reconstituted with 2.5 ml of sterile water for injection, so that each milliliter of solution contained 330 mg of cefonicid. The appropriate amount of cefonicid solution was then further diluted to 50 ml with 5% dextrose solution (USP) immediately before infusion. A dose of 7.5 mg/kg of body weight was infused over a 5-min period with a constant-rate Harvard infusion pump. Blood samples (5 ml) were collected in heparinized tubes before the dose was administered and at 5, 10, 20, 30, 45, 60, 75, 90, 120, 150, 180, 210, 240, 300, 360, 480, 720, and 1,440 min after. Additional blood samples were taken at 36 and 48 h after the dose. Samples were immediately placed in ice and centrifuged, and the plasma was harvested for assay. Urine specimens were collected at 30, 60, 90, 120, 150, 180, 240, 300, 360, 480, 720, and 1,440 min. Urine was collected and pooled during two additional 12-h intervals ending at 36 and 48 h. All samples were frozen at −20°C until assayed, usually within 2 weeks of the study day.

Analytical Methods. (i) Microbiological assay. Samples of plasma and urine were assayed by an agar diffusion method, with *Bacillus subtilis* used as the test organism. Blank filter paper disks (6.35-mm) were loaded with suitably diluted samples, placed onto seeded agar, and incubated overnight at 35°C. The diameters of the zone of inhibition were plotted against

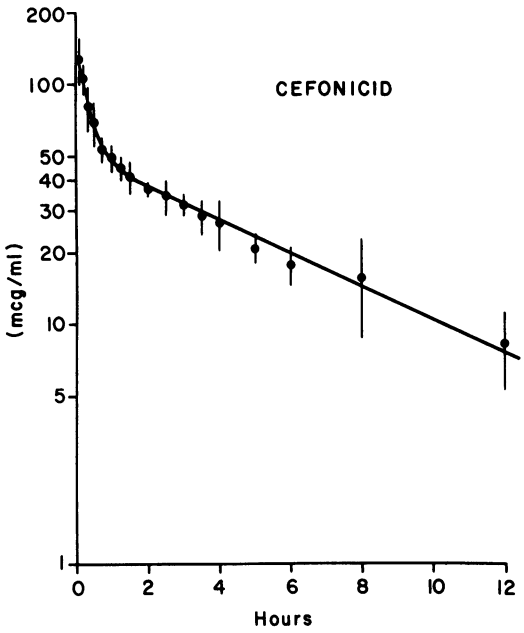

FIG. 1. Semilogarithmic plot of mean (± standard deviation [vertical bars]) cefonicid plasma concentrations versus time for all five subjects.

the log of concentration to make a standard curve. The linear range of the standard curves was 0.4 to 100 μg/ml. The diluent for plasma samples was normal human serum. The urine samples were diluted in phosphate buffer at pH 6. The assays were performed in triplicate for each sample, and variability was less than 10%. No active metabolites of cefonicid have been found that could interfere with the bioassay. Some samples were also analyzed by specific high-performance liquid chromatography, and good correlation was obtained.

The cefonicid (lot no. 79260; Smith Kline & French Laboratories, Philadelphia, Pa.) used for this study was found to have a purity of 822 μg/mg. Reconstituted vials of cefonicid were found to contain 108.25% of the stated amount. Therefore, the doses administered and the measured concentrations were adjusted to correct for these differences.

(ii) Pharmacokinetic analysis. Compartment-independent methods were used for the determination of pharmacokinetic parameters. After graphic analysis of the cefonicid plasma level-time curves on a semilogarithmic plot, a log-linear, least-squares fit of the terminal linear portion of the curve was used for determination of the slope or terminal disposition rate constant, λ. The half-life was then calculated by dividing λ into the natural logarithm of 2. The volume of distribution at steady state (V_{ss}) was calculated by the compartment-independent equation of Benet and Galeazzi (3), V_{ss} = (dose [AUMC])/AUC^2, where AUC is the area under the plasma concentration-time curve and AUMC is the area under the first moment of the plasma concentration-time curve. The areas were calculated by the trapezoidal rule and determined from time zero to infinity. As this equation is appropriate only for an intravenous bolus dose, the correction for infusion was made by subtracting (t/2)·(dose/AUC) from the values of V_{ss} obtained, where t is the infusion time. The volume of distribution for the elimination phase was calculated by the equation V = dose/AUC(λ). Total plasma clearance was determined by the equation Cl_p = dose/AUC. Renal clearance was calculated by two methods, Cl_{r1} = FE·Cl_p and Cl_{r2} = (AE[t_2/t_1])/(AUC[t_2/t_1]), where FE is the fraction of the dose excreted unchanged in the urine and AE is the amount of drug excreted in the time interval t_1 to t_2. Ten time interval measurements in each subject were used to calculate the mean renal clearance over 48 h.

RESULTS

Figure 1 shows a plot of mean plasma concentrations versus time for all five subjects. Peak plasma concentrations achieved immediately after a 7.5-mg/kg dose ranged from 95 to 156 μg/ml. Concentrations fell biexponentially, and by 6 h values in excess of 16 μg/ml were measured. At 12 h the mean plasma concentration was 8.2 μg/ml. Levels at 24 h were consistently lower than 2.5 μg/ml in all subjects.

The elimination phase half-life averaged 4.4 h and ranged from 3.7 to 5.8 h (Table 1). This agreed well with the mean half-life of 4.9 h determined from the urine excretion rate. Plasma clearance averaged 27.1 ml/min (0.32 ml/min per kg). The renal clearance of the drug accounted for approximately 90% of the total plasma clearance. The average renal clearance was 24.5 ml/min (0.29 ml/min per kg). The volume of distribution calculated from the elimination phase of cefonicid averaged 10.4 liters (0.12 liters/kg). The steady-state volume of distribution was slightly less, 9.3 liters (0.11 liters/kg).

TABLE 1. Pharmacokinetic parameters of cefonicid

Volunteer no.	Wt (kg)	Cl_p (ml/min)	Cl_r[a] (ml/min)	$t_{1/2}$ (h)	V (liters)	V_{ss} (liters)	FE (%)
1	84	30.2	26.4	4.3	11.4	10.7	83
2	79	28.7	23.3	3.7	9.1	8.7	81
3	83	29.4	27.8	4.5	11.3	10.3	95
4	88	19.3	16.6	5.8	9.7	8.8	85
5	88	27.9	25.7	3.9	9.4	8.2	94
Mean ± SD		27.1 ± 4.5	24.0 ± 4.4	4.4 ± 0.8	10.4 ± 1.2	9.3 ± 1.1	88 ± 6

[a] Calculated from FE × Cl_p.

TABLE 2. Urinary excretion of cefonicid[a]

Time (min)	Concn (μg/ml)	Amt excreted (mg)	Cumulative dose excreted (%)
30	1,017 (62)	88.9 (46.1)	12.8 (7.1)
60	506 (266)	63.8 (18.2)	22 (9.5)
90	195 (150)	40.7 (4.1)	27.9 (9.4)
120	162 (112)	37.4 (2.7)	33.3 (9.2)
150	181 (99)	31.2 (10.5)	37.8 (9.0)
180	113 (55)	27.4 (4.2)	44.3 (8.0)
240	362 (344)	45.2 (5.3)	47.5 (10.0)
300	496 (498)	51.8 (16.5)	55 (9.4)
360	549 (391)	36.0 (5.7)	60.1 (9.5)
480	375 (314)	58.2 (20.6)	68.6 (9.1)
720	149 (74)	51.9 (15.5)	76.2 (6.6)
1,440	84 (41)	58.2 (21.3)	84.6 (6.1)
2,160	17 (10)	16.6 (7.4)	87 (5.8)
2,880	6.5 (4.3)	6.9 (4.9)	87.7 (6.4)

[a] The standard deviation is given in parentheses.

The average amount of cefonicid excreted unchanged in the urine was 88% of the administered dose. Urinary concentrations of cefonicid varied, but averaged higher than 100 μg/ml for 12 h after the dose (Table 2). The mean level from 12 to 24 h after the dose was 84 μg/ml. The cumulative percentage of the dose excreted over 48 h is also given in Table 2. Regression analysis revealed that 50% of the dose was excreted in 4.2 h. This agreed well with the half-life calculated from plasma concentrations (4.4 h) and the half-life from the urinary excretion rate plot (4.9 h).

No adverse effects or abnormal laboratory tests were noted in any of the volunteers studied.

DISCUSSION

Our data showed that after a single 7.5-mg/kg intravenous dose of cefonicid, concentrations above 12.5 μg/ml were sustained for 6 to 8 h. Levels in excess of 8 μg/ml were maintained for 12 h after the dose. These concentrations equal or exceed the minimal inhibitory concentration for most of the cefonicid-susceptible gram-negative bacilli and *Staphylococcus aureus* (1, 4, 6). Extrapolation of the plasma concentration-time curve indicated that a level of 1 μg/ml would still be present in serum 24 h after the dose. This level exceeds the minimal inhibitory concentration for gonococci, meningococci, and *Haemophilus influenzae* (1). Urine concentrations of cefonicid exceeded the minimal inhibitory concentrations of all of the susceptible urinary pathogens for as long as 36 h.

The dose used in this study was 7.5 mg/kg, or approximately 500 mg for a 70-kg person. Peak plasma concentrations in excess of 100 μg/ml were achieved immediately after a 5-min infusion. These values are slightly higher than those reported for cefazolin, which reaches peak concentrations of 80 μg/ml after a 500-mg dose. Doses of cefamandole of 1,000 mg are required to achieve peak plasma concentrations approaching 80 μg/ml (2).

The pharmacokinetic characteristics of cefazolin and cefamandole have been reported previously (2, 5). Cefazolin is the only currently available cephalosporin with a half-life (1.8 h) approaching that of cefonicid. The antibacterial activity of cefamandole is similar to that of cefonicid, but its elimination half-life is less than 1 h. Kirby and Regamey (5) found that the serum clearance of cefazolin is approximately the same as the renal clearance, 0.91 ml/min per kg (assuming 70 kg for 1.73 m^2 body surface area). The steady-state volume of distribution was calculated to be 0.14 liters/kg. Aziz et al. (2) determined that the plasma and renal clearances of cefamandole are also approximately the same, 2.8 versus 2.7 ml/min per kg, respectively. The steady-state volume of distribution was 0.16 liters/kg in this study. The plasma and renal clearances of cefonicid are markedly lower than either of these agents, and the volume of distribution is somewhat smaller.

The renal clearance of cefonicid averaged only 21% of creatinine clearance in these subjects. The available data for cefazolin and cefamandole indicate that renal clearance is approximately 50 and 160%, respectively, of creatinine clearance (2, 5). Thus, both cefonicid and cefazolin undergo net tubular reabsorption in the kidney, and cefamandole undergoes net tubular secretion. The protein binding of cefonicid has been reported to be 98% in human serum (1). Thus, a small fraction of renal elimination is achieved via glomerular filtration.

In conclusion, the pharmacokinetics of cefonicid are significantly different from those of currently available cephalosporins with similar antibacterial spectra. The low renal clearance of the compound and its small volume of distribution provide high, prolonged plasma concentrations. These features and its enhanced in vitro activity against many aerobic gram-negative bacilli make cefonicid an antimicrobial agent of potential value in the management of selected infectious diseases. Conceivably, systemic infections may be adequately treated with doses of cefonicid given every 12 h. Urinary concentrations are high for prolonged periods of time, and thus urinary tract infections could be effectively managed with a single daily dose.

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