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Pharmacological Evaluation of Cefaclor in Volunteers

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The plasma and urine concentrations of cefaclor were measured after oral administration of single and multiple doses to volunteers. Cefaclor was rapidly absorbed, rapidly excreted in the urine, well tolerated without toxicity, and failed to accumulate in the plasma with chronic dosing.

Cefaclor, 3-chloro-7-D-(2-phenylglycinamido)-3-cephem-4-carboxylic acid, is a new cephalosporin related to cephalexin. Cefaclor is active against staphylococci, streptococci, pneumococci, *Haemophilus influenzae*, and cephalothin-susceptible *Enterobacteriaceae* (1, 4-7; G. J. Couchonnal, J. L. Harms, G. R. Hodges, D. R. Hinthorn, and C. Liu, submitted for publication). Recently, cefaclor was shown to be rapidly absorbed after oral administration (3).

The purpose of the present study was to determine plasma concentrations, urine concentrations, plasma half-life, tolerance, and toxicity of cefaclor after a single dose and multiple doses in a group of healthy human volunteers.

MATERIALS AND METHODS

Antibiotic. Cefaclor was supplied by Eli Lilly & Co., Indianapolis, Ind.

Human volunteers. Six healthy men and four healthy women with no known allergies to cephalosporin or penicillin antibiotics participated in the study after informed written consent was obtained. None of the test subjects was taking any medications prior to or during the cefaclor studies. Their ages ranged from 19 to 55 years, their weights ranged from 50.9 to 82.3 kg, and serum creatinine concentrations ranged from 0.8 to 1.4 mg/dl (normal, 0.3 to 1.5 mg/dl) (Table 1).

Procedure. The subjects received a single 1,000-mg dose of cefaclor orally. Subsequently, each subject received 250 and 500 mg of cefaclor orally, every 6 h for 7 days. At least 3 days elapsed between the dosage regimens.

Samples of venous blood and urine were obtained prior to the single-dose trial. Subsequently, venous blood samples were obtained 0.5, 1, 2, 4, and 6 h after the dose. All urine was collected from 0 to 6 h. For the multiple-dose trials, venous blood samples were collected after administration of the first and last doses of cefaclor, and a urine sample was collected after administration of the initial dose of cefaclor. All venous blood samples were collected in heparinized tubes. Plasma was separated immediately after collection and kept frozen at −70°C until assayed. The urine samples were refrigerated during collection, and volumes were recorded. A sample was filtered and frozen at −70°C at the end of each collection period.

The following tests were performed before and after each dosing period to monitor for toxicity: hemoglobin, hematocrit, leukocyte count and differential, platelet estimation, blood urea nitrogen, creatinine, urinalysis, alkaline phosphatase, serum glutamic oxalacetic transaminase, total bilirubin, lactic dehydrogenase, and glucose. All subjects were questioned daily during the test periods for possible adverse reactions.

Antibiotic assays. The concentrations of cefaclor were determined by using a disk diffusion method (2). All assays were performed with *Sarcina lutea* (ATCC 9341) as the test organism in antibiotic medium no. 1 (Difco, Detroit, Mich.). Reference standards were diluted in pooled normal human serum for the plasma assays. Urine samples and reference standards were diluted in potassium phosphate buffer with the pH adjusted to 4.5. All samples were tested in triplicate. The lowest concentration measured by this assay was 0.62 μg/ml, and the zone diameter observed around a 5-μg/ml cefaclor reference disk was 29.8 ± 0.4 mm (mean ± standard error).

Inoculated plates were incubated at 30 to 32°C for 18 h. Zones of inhibition were measured with a vernier caliper. Antibiotic concentrations were determined by comparing the mean zone of inhibition of each sample with a curve constructed from the mean zones of inhibition of the standard dilutions.

Pharmacokinetic calculations. The half-life was determined from the best-fit line through the points of the decline in plasma concentrations (0.5 to 4 h) by using the method of least squares. The elimination constant (K_d) was determined from the formula: $K_d = 0.693/t_{1/2}$. The pharmacokinetic data (peak observed plasma concentrations, elimination constants, urinary excretion, and area under the cefaclor plasma concentration curves for the 6-h period after a dose [AUC_{0-6}]) for the initial doses were compared by using both analysis of variance for repeated measures and the nonparametric Friedman procedure. The data from the first and last doses were compared by using the paired t test and the Wilcoxon signed rank test.

RESULTS

Cefaclor plasma concentrations after a single dose usually peaked by 1 h after dosing and gradually declined to 4 h, with little or no activity detected at 6 h (Table 2). Mean ± standard error peak observed plasma concentrations were 6.31 ± 1.0, 15.22 ± 2.52, and 25.44 ± 3.9 μg/ml after 250-, 500-, and 1,000-mg doses, respectively. The plasma half-lives ($t_{1/2}$) were 0.49 ± 0.04, 1.0 ± 0.19, and 0.76 ± 0.07 h for the 250-, 500-, and 1,000-mg doses, respectively. Corresponding elimination constants (K_d) were 1.48 ± 0.14, 0.88 ± 0.13, and 0.96 ± 0.08 h^{-1}. The AUC_{0-6} were 10.45 ± 0.93, 29.46 ± 5.62, and 54.0 ± 7.44 μg/ml × h, respectively.

After multiple doses for 7 days, the plasma concentrations of cefaclor peaked by 1 h after dosing and gradually declined to 4 h, with little or no activity detected at 6 h (Table 2). The peak observed plasma concentrations after multiple doses of 250 and 500 mg were 6.4 ± 1.1 and 12.34 ± 2.98 μg/ml, respectively. The $t_{1/2}$ were 0.77 ± 0.13 and 0.75 ± 0.08 h for the 250- and 500-mg multiple doses, respectively. The corresponding elimination constants were 1.12 ± 0.17 and 1.03 ± 0.11 h^{-1}. The AUC_{0-6} were 10.0 ± 1.2 and 26.3 ± 3.5 μg/ml × h, respectively.

The mean ± standard error urine concentrations after single 250-, 500-, and 1,000-mg doses of cefaclor were 273 ± 79, 799 ± 196, and 2,000 ± 525 μg/ml, respectively, during the first 6 h after dosing (Table 3). During that 6-h period, 51 ± 11, 49 ± 4, and 47 ± 7%, respectively, of the administered dose was recovered in the urine.

Analysis of the data revealed that the peak observed concentrations and the AUC_{0-6} increased proportionally to the dose, and the percentage of the administered dose excreted in the urine was not signicantly different among the doses. The elimination constant for the initial 250-mg dose was significantly greater ($P < 0.05$) than for either of the other two doses. However,

TABLE 1. *Characteristics of the volunteers receiving cefaclor*

Volunteer	Age (yr)	Sex	Ht (cm)	Wt (kg)	Serum creatinine (mg/dl)
1	19	M	172.5	59.1	1.4
2	25	M	167.5	82.3	1.2
3	27	M	180.0	79.1	1.2
4	24	M	172.5	70.4	1.4
5	34	M	178.8	80.4	1.3
6	55	M	167.5	72.7	1.0
7	23	F	162.5	58.6	1.0
8	23	F	165.0	72.7	0.8
9	37	F	167.5	63.6	1.1
10	27	F	162.5	50.9	1.0

TABLE 2. *Cefaclor plasma concentration of 10 subjects*

No. of doses	Dose (mg)	Plasma concn (μg/ml) at h: 0	0.5	1.0	2.0	4.0	6.0	$t_{1/2}$ (h)	K_d (h^{-1})	AUC_{0-6} (μg/ml × h)
1	250	0[a]	4.38	6.31	1.94	0.20	0	0.49	1.48	10.45
			±1.32[b]	±0.95	±0.47	±0.18		±0.04	±0.14	±0.93
1	500	0	8.22	15.22	6.99	1.83	0	1.0	0.88	29.46
			±2.66	±2.39	±1.49	±0.90		±0.19	±0.13	±5.62
1	1,000	0	8.82	25.44	12.74	1.94	0	0.76	0.96	54.0
			±2.85	±3.70	±4.50	±0.28		±0.07	±0.08	±7.44
28	250[c]	—[d]	4.86	6.4	2.02	0.07	0	0.77	1.12	10.0
			±1.50	±1.03	±0.26	±0.08		±0.13	±0.17	±1.2
28	500	—	4.8	12.34	7.2	1.52	0.28	0.75	1.03	26.3
			±2.07	±2.83	±1.04	±0.71	±0.21	±0.08	±0.11	±3.5

[a] 0 = <0.62 μg/ml.
[b] Mean ± standard error.
[c] Samples available from only nine subjects.
[d] Zero hour not done; this would have been a 6-h sample for previous dose.

TABLE 3. *Urinary excretion of cefaclor during the 6-h interval after a single dose*

Dose (mg)	No. of subjects[a]	Urinary concn (μg/ml ± SE)[b]	Urine recovery (mg ± SE)	Urine recovery of administered dose (% ± SE)
250	7	273 ± 79	128 ± 27	51 ± 11
500	8	799 ± 196	244 ± 21	49 ± 4
1,000	9	2,000 ± 525	468 ± 65	47 ± 7

[a] Complete collections not available for testing from all 10 subjects.
[b] SE, Standard error.

the elimination constants after multiple 250- and 500-mg doses were not significantly different. Neither the peak concentrations nor the elimination constants for the initial and last doses of the 250- and 500-mg multidose trials were significantly different. The results of the parametric and the nonparametric testing procedures were similar.

No clinical or laboratory adverse or toxic reactions were observed during the single- or multiple-dose trials.

DISCUSSION

Cefaclor is more active than the parent compound, cephalexin, against streptococci, pneumococci, *H. influenzae*, and cephalothin-susceptible *Enterobacteriaceae* (1, 4–7). In the present pharmacological evaluation in healthy human volunteers, the results suggest that cefaclor is rapidly absorbed and excreted in the urine after oral administration. Cefaclor was well tolerated, and no toxicity was observed in the volunteers studied. The relative bioavailability was similar among the various doses, and no accumulation was observed after 1 week of chronic dosing. The elimination constants for the initial 500- and 1,000-mg doses and after multiple 250- and 500-mg doses were similar. The reason(s) for the significantly different elimination constant after the initial 250-mg dose is not apparent. The peak observed plasma concentrations and half-lives after single and multiple 250-mg doses in our study are similar to those previously reported (3). However, the 6-h urinary excretion in our subjects was about 50%, which was less than the 70% previously reported (3). The reason(s) for the different urinary excretion in these two studies is not apparent. Possible explanations for these differences include actual differences between the two groups of volunteers or variations in the assays for biological activity.

When compared to its parent compound, cephalexin, cefaclor produces one-third lower peak serum concentrations and is more rapidly excreted (3). However, because of its increased antibacterial activity by weight against a variety of organisms and its high urine concentrations, cefaclor may be efficacious in treating selected bacterial infections.

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