ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Dec. 1982, p. 1061–1063
0066-4804/82/121061-03$02.00/0

Vol. 22, No. 6

Pharmacokinetics of Cefadroxil and Cefaclor During an Eight-Day Dosage Period

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Received 21 June 1982/Accepted 29 September 1982

The concentrations of cefadroxil and cefaclor in serum were studied in eight healthy volunteers receiving 1,000 mg of both substances three times per day for 8 days. Intraindividual comparisons showed an increase in peak serum levels of cefadroxil from days 1 to 8 in seven of eight volunteers. Cefaclor peak concentrations did not rise during the 8 days.

Oral antibiotics are usually administered over a period of 6 to 12 days. Single-dose pharmacokinetics, therefore, will not represent completely the pharmacokinetic properties of antimicrobial agents. The purpose of the present study was to compare the serum concentrations of cefadroxil and cefaclor at various times during an 8-day dosage interval. (These results were presented in part at the 11th International Congress of Chemotherapy and the 19th Interscience Conference on Antimicrobial Agents and Chemotherapy [Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 11th, Boston, Mass., abstr. no. 192, 1979].)

Eight healthy volunteers (four females and four males) with no known allergies to cephalosporin antibiotics participated in the study. None of them had taken any other antimicrobial agent for 4 weeks before and during the 8-day therapy. They ranged in age from 21 to 49 years. Mean body weight was 63.3 kg. Results of pre- and poststudy laboratory tests (renal, hepatic, and hematological function data) were normal.

Cefadroxil monohydrate (lot 15013-E4) in 500-mg capsules (Bristol Laboratories, Paris), and cefaclor monohydrate (YK 4820 GGEX) in 500-mg capsules (Eli Lilly GmbH, Lahn-Giessen, CH.-B.: CT-3397-8A E-420) were administered. Laboratory reference standards of known potency were used for antibiotic assays.

A 1.0-g amount of each antibiotic was given three times daily for 8 days (8:00 a.m., noon, and midnight) in a one-way crossover fashion with a 4-week interval between delivery of the two agents. To determine the absorption rate in the fasting state, capsules were taken on an empty stomach at 8:00 a.m. on days 1, 4, and 8. The fasting state was maintained for 2 additional h. Volunteers were questioned every day about compliance.

Venous blood samples for assay of serum antibiotic concentrations were obtained on days 1 and 8 before a dose and at 0.25, 0.5, 0.75, 1, 1.5, 2, 3, 4, 6, and 8 h thereafter. On day 4, specimens were collected before a dose and at 0.5, 1.5, 4, and 8 h for cefadroxil and before a dose and at 0.5, 1, 1.5, 4, and 6 h for cefaclor. Additional samples were taken every morning at 8:00 (predose), except on day 6, and at 1.5 h (cefadroxil) or 1 h (cefaclor) after the morning dose.

Samples were allowed to clot at 4°C, and serum was then separated in a refrigerated centrifuge. All specimens were assayed on the day of collection except the 8-h samples. Urine samples were collected on days 1 and 8 before dosage and during two 4-h periods thereafter.

Serum concentrations were assayed by the agar well diffusion method (7). Serum assays were performed with nutrient agar (1.5%; Difco 0140-01; Difco Laboratories, Detroit, Mich.) with *Sarcina lutea* ATCC 9341 as the test strain for low concentrations (0.25, 0.5, 4, 6, and 8 h) and *Bacillus subtilis* ATCC 6633 for high serum concentrations (0.75, 1, 1.5, 2, and 3 h). Serum and urine standards in the range of expected concentrations were prepared on the day of assay from pooled antibiotic-free human serum and sodium citrate buffer-hydrochloride (cefadroxil at pH 7.0; cefaclor at pH 4.5), respectively. With this method, the sensitivity limit for both cefadroxil and cefaclor in serum and buffer was 0.3 μg/ml.

The following pharmacokinetic calculations were performed: C_{max}, the peak serum concentration (in micrograms per milliliter); t_{max}, the time (in hours) at which C_{max} was reached; and the area under the serum concentration time curve (AUC) (in micrograms · hour per milliliter). The AUC was estimated by the trapezoidal rule.

For statistical evaluations, the Wilcoxon

TABLE 1. Pharmacokinetic data for cefadroxil and cefaclor on days 1, 4, and 8[a]

Day of treatment and drug	AUC (μg · h/ml)	t_{max} (h)	Serum concentration (μg/ml)			Urinary recovery at 0 to 8 h (% of excreted dose)
			C_{max}	6 h	8 h	
Cefadroxil						
1	93.0 ± 20.7	2.5 ± 0.9	27.5 ± 5.1	5.9 ± 2.5	2.2 ± 1.2	97.3 ± 14.2
4			33.2 ± 7.7		2.2 ± 0.9	
8	100.3 ± 18.6	1.5 ± 0.5	35.5 ± 5.9	5.0 ± 1.5	2.2 ± 0.8	98.2 ± 26.9
Cefaclor						
1	43.3 ± 10.6	1.3 ± 0.5	28.7 ± 5.9	0.4 ± 0.3	<0.3	52.4 ± 16.8
4			31.5 ± 10.2		<0.3	
8	43.1 ± 7.2	1.3 ± 0.5	29.3 ± 6.4	0.4 ± 0.8	<0.3	40.0 ± 26.4

[a] Data are the means ± standard deviations.

matched-pairs signed rank test was used. Probabilities of $2\alpha \leqq 0.05$ were considered significant.

The mean peak serum concentration of cefadroxil was 27.5 ± 5.1 μg/ml and was reached after 2.5 ± 0.9 h. At 6 and 8 h, serum levels were 6.9 ± 2.6 and 2.2 ± 1.2 μg/ml, respectively (Table 1; Fig. 1, upper line). Cefaclor was more rapidly absorbed, with a mean peak serum concentration of 28.7 ± 5.9 μg/ml, reached after 1.3 ± 0.5 h (Table 1; Fig. 1, upper line). After 8 h, the serum concentrations were below the sensitivity of the assay. Significant differences between the two drugs were also observed in the AUCs: 93.0 ± 20.7 versus 43.3 ± 10.6 μg · h/ml for cefadroxil and cefaclor, respectively (Table 1). There were no significant differences in the mean AUCs of days 1 and 8, and intraindividual comparisons did not show any significant differences in AUCs. Urinary recovery data for the first 8 h after administration are shown in Table 1.

During the course of the 8-day treatment,

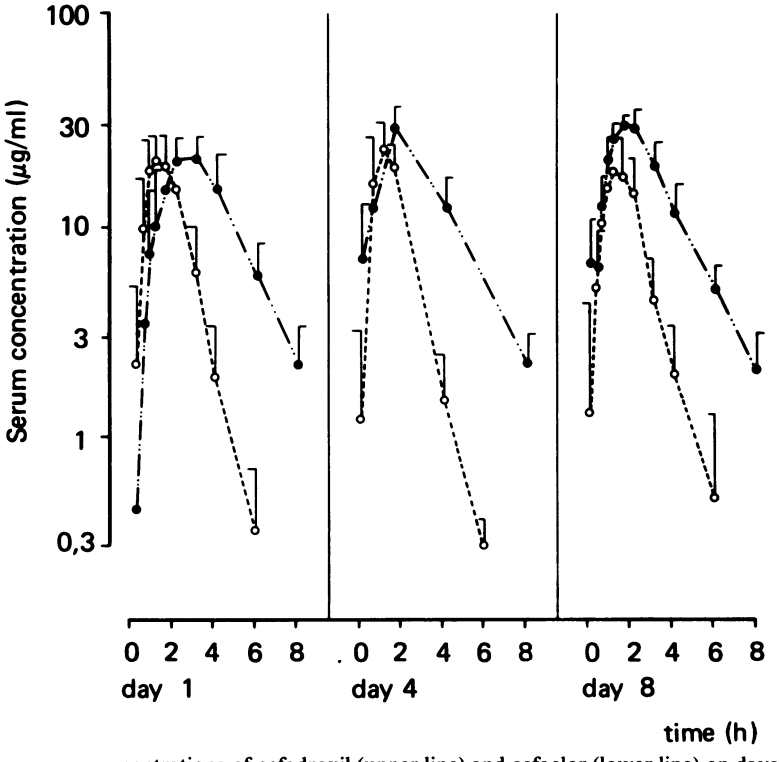

FIG. 1. Mean serum concentrations of cefadroxil (upper line) and cefaclor (lower line) on days 1, 4, and 8 in eight fasting volunteers after administration of 1,000 mg three times a day.

there was an increase in mean peak levels of cefadroxil from 27.1 ± 5.1 μg/ml on day 1 to 35.5 ± 5.9 μg/ml on day 8 (Fig. 1, upper line; Table 1). Intraindividual comparisons showed an increase in peak serum concentrations from day 1 to day 8 in seven of eight volunteers, with a mean value of 8.5 μg/ml (4.8 to 14.5 μg/ml), i.e., approximately 30% of the mean peak serum concentration of day 1. The morning mean trough concentration on day 2 was 3.7 ± 1.0 μg/ml, compared to 6.6 ± 4.2 μg/ml on day 8, whereas the mean 8-h concentration on the first and last day of the study remained at 2.2 μg/ml. Intraindividual comparisons showed an increase in five of eight volunteers; the mean value was 4.5 μg/ml (0.9 to 7.2 μg/ml). In contrast, the mean peak cefaclor concentrations did not increase during the 8-day treatment (Table 1; Fig. 1, lower line). Cefaclor trough concentrations (8 h) could be detected on the morning of day 4 in two volunteers and on the morning of day 8 in three volunteers. During the daytime period, on the other hand, cefaclor concentrations were no longer measurable after 6 h.

A comparison of the serum concentrations recorded during the first dosage interval with cefadroxil yielded good agreement with investigations of other authors in similar studies (2, 4, 5). With regard to repeated doses, Henness et al. (2) did not observe any accumulation of cefadroxil during a 5-day treatment with three different doses (2, 4, and 6 g/day). Another study from the same group (4) described higher and more sustained serum levels of cefadroxil during a 5-day treatment, but no tendency to accumulate in serum. In our study, in comparison, we found an accumulation of cefadroxil in individual peak serum concentrations and in morning trough concentrations (8 h) on days 4 and 8. These data (peak and trough concentrations) were not recorded in the study mentioned above (4). Similarly, our results with cefaclor after a single dose largely agree with previously reported data of other authors (3, 5, 6). Multiple doses yielded results similar to the data of Hodges et al. (3) and Meyers et al. (6), who did not observe any accumulation of cefaclor after repeated doses.

An unexpected finding in our study was the fact that cefaclor serum concentrations measured in the morning of day 8 in three of eight volunteers exceeded the trough levels during days 1, 4, and 8. This can probably be explained by the acidic urine conditions at night. Morning urine pH (7:00 a.m.) was 5.5 ± 0.6 on day 1 and 5.3 ± 0.5 on day 8. In the three volunteers involved, urine pH was 5.0 in the morning of day 8. Acidic urine causes a reduction in the excretion of weak acids by nonionic transcellular diffusion (1).

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