Comparative Pharmacology of Cefaclor and Cephalixin

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Two cephalosporin antibiotics, cefaclor and cephalixin, were administered orally to healthy, adult male volunteers for comparison of their pharmacological properties. In doses of 250 mg orally, cefaclor produced a peak serum concentration of 6.01 ± 0.55 (standard deviation [SD]) μg/ml compared with 9.43 ± 2.36 μg/ml for cephalixin (P < 0.01). The half-lives were 0.58 ± 0.07 (SD) h and 0.80 ± 0.12 (SD) h, and elimination constants were 1.22 ± 0.15 and 0.88 ± 0.13 h⁻¹ for cefaclor and cephalixin, respectively (P < 0.001). Neither drug showed accumulation over the dosing period, and both were well tolerated.

Cefaclor, 3-chloro-7-D-(2-phenylglycaminido)-3-cephem-4-carboxylic acid, is a new semisynthetic cephalosporin antibiotic derived from cephalixin. Preliminary reports indicate greater in vitro activity against strains susceptible to the parent compound, with the added advantage of greater bactericidal effect against β-lactamase-producing Haemophilus influenzae (N. J. Bill and J. A. Washington, Prog. Abstr. Intern. Conf. Antimicrob. Agents Chemother. 16th, Chicago, Ill., Abstr. no. 356, 1976; and D. A. Preston, Prog. Abstr. Intern. Conf. Antimicrob. Agents Chemother. 16th, Chicago, Ill., Abstr. no. 342, 1976). In our laboratory, cefaclor was tested against 200 strains of gram-negative bacilli; 78% of the strains were inhibited by <4 μg/ml. The geometric median minimum inhibitory concentrations for cephalixin were 2 to 16 times greater than for cefaclor for the strains tested.

Early clinical trials have indicated that cefaclor is well absorbed and has minimal side effects (H. R. Black, K. S. Israel, G. H. Brier, and J. D. Wolny, Prog. Abstr. Intern. Conf. Antimicrob. Agents Chemother. 16th, Chicago, Ill., Abstr. no. 354, 1976). The present study was designed to compare the absorption, achievable serum concentration, serum half-life, urinary excretion, toxicity, and tolerance of orally administered cefaclor and cephalixin.

MATERIALS AND METHODS

Antibiotics. Cefaclor and cephalixin were supplied by Eli Lilly and Co., Indianapolis, Ind.

Human volunteers. Twenty healthy men with no known allergies to cephalosporin antibiotics participated in the studies after informed written consent was obtained. None were taking any other antimicrobial agents during the investigational period. Their ages ranged between 21 and 32 years of age and their weights ranged between 145 and 220 pounds (ca. 72 to 110 kg). Prestudy physical examinations and laboratory parameters were normal.

Procedure. The subjects were randomly divided into two groups of 10 individuals each. They were assigned to a crossover sequence of the two antibiotic regimens to be taken during two separate dosing periods. Each dosing period was 4 days in duration and separated by 1 week. Group I received 250 mg of cefaclor in capsules orally every 6 h (q6h) during the first period, followed by 250 mg of cephalixin in capsule form orally q6h during the second dosing period. Group II followed a reverse order. All subjects complied with the dosage time schedule.

All subjects fasted for 8 h before each dosing period. After the first dose, a fast of 2 h was maintained before and after each subsequent dose. A control venous blood sample was drawn before the first dose and showed no detectable antibiotic activity in either of the two dosing periods. Venous blood samples for assay of plasma antibiotic concentration were collected at 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 9.0, 24.0, 36.0, 48.0, 60.0, 72.0, 72.5, 72.75, 73.0, 73.5, 74.0, 75.0, 76.0, 78.0, and 90.0 h after the initial dose. Urine samples were collected in 2-h intervals from time 0 to 6 h and from 72 to 78 h. There was a loss of up to 50% activity of cefaclor in serum samples that were left at room temperatures for 3 to 8 h. Therefore, all blood samples were immediately iced, and the serum was separated in a refrigerated centrifuge and either immediately placed in a −70°C freezer or assayed. Using these precautions, a 14.17 ± 1.47 (standard deviation [SD])% loss of activity was found in 16 samples evaluated.

The following tests were performed before and after each dosing period: hemoglobin, hematocrit, leukocyte count and differential, platelet estimation, urinalysis, blood urea nitrogen, glucose, sodium, potassium, chloride, bicarbonate, calcium, phosphorus, alkaline phosphatase, lactic dehydrogenase, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, cholesterol, total bilirubin, total protein, albumin, uric acid, and creatinine. Creatinine clearances were performed.
before and after the first dosing period. Blood pressures and pulses were taken before and after the dosing periods. All subjects were questioned daily during the test periods for possible adverse effects.

Antibiotic assays. The concentrations of cephalexin and cefaclor were determined by an agar well diffusion technique (1). Cephalexin assays were performed with antibiotic medium no. 1 using Sarcina lutea 9341 as the test organism for serum assays and Bacillus subtilis for urine assays. All cefaclor assays were performed with B. subtilis as the test organism on antibiotic medium no. 1. Reference standards were diluted in pooled normal human serum for serum assays. Urine samples were diluted in potassium phosphate buffer with the pH adjusted to 6.0 for cephalexin and to 4.5 for cefaclor. All samples and standards were tested in triplicate.

The plates were incubated at 37°C for 18 h. Zones of inhibition were measured by a Fisher-Lilly zone reader, and antibiotic concentrations were computed by comparing the mean zone of inhibition of each sample with the curve constructed from the zones sizes of the standard dilutions.

Calculated plasma half-life. Plasma concentrations obtained between 0 and 6 h were plotted on semilog graph paper versus time. The half-life was determined from the best-fit line through the points of decline of blood levels (0.75 to 4 h) by using the method of least squares. The elimination constant (Kd) was determined from the formula: Kd = 0.693/ t½.

RESULTS

Cefaclor plasma concentrations usually peaked in 1 h after dosing and steadily declined over the next 4 h, with no cefaclor detectable in the serum at 6 h (Table 1). At 1 h, the mean concentration was 4.98 ± 2.01 (SD) μg/ml (range, 0 to 10 μg/ml) and was comparable to levels achieved on day 4 of therapy: 3.57 ± 1.52 (SD) μg/ml (range, 0 to 6.1 μg/ml). Mean peak serum concentrations were 6.0 ± 1.55 (SD) μg/ml (0- to 6-h interval) and 4.58 ± 1.35 (SD) μg/ml (72- to 78-h interval). Mean concentrations of 0.33 ± 0.53 (SD) μg/ml and 0.20 ± 0.24 (SD) μg/ml were obtained at 4 and 76 h, respectively, showing no accumulation of the antibiotic.

Plasma concentrations of cephalexin were maximal between 0.75 and 1 h (Table 2). At 1 h, the mean concentration obtained was 7.28 ± 2.47 μg/ml, with ranges of 1.35 to 11.0 μg/ml, and this value did not vary at 73 h: 7.28 ± 3.28 μg/ml (range, 1.45 to 13.75 μg/ml). Mean peak serum levels achieved were 9.43 ± 2.37 μg/ml (0- to 6-h interval) and 8.50 ± 2.60 μg/ml (72- to 78-h interval). The levels gradually declined, reaching mean concentrations of 0.68 ± 0.50 μg/ml at 4 h and 1.04 ± 0.67 μg/ml at 76 h. As with cefaclor, at 6 h, levels were zero in almost all subjects. No antibiotic accumulation could be demonstrated over the dosing period. A statistical comparison of peak serum levels for cefaclor (6.0 ± 1.55 μg/ml versus cephalexin, 9.43 ± 2.37 μg/ml) was significant: P value was <0.001 by Student's t test.

Serum half-life was determined for each antibiotic during the 0.75- to 4-h interval, when a linear decline in antibiotic serum concentrations occurred. The mean serum half-life for cefaclor was 0.578 ± 0.074 h, and for cephalexin it was 0.802 ± 0.115 h (P < 0.001, Student's t test). The elimination constant for the same interval was 1.217 ± 0.146 h⁻¹ for cefaclor and 0.881 ± 0.129 h⁻¹ for cephalexin (P < 0.001, Student's t test).

Cefaclor and cephalexin concentrations in urine were determined on 2-h fractions collected during days 1 and 4 of therapy (Table 3). A total of 44.2% of the ingested dose of cefaclor was excreted within 2 h after administration of the drug; 23.6% was excreted from 2 to 4 h, and 23.5% was found in the urine between 4 and 6 h. Over the total 6-h interval, 70.1% of the total oral dose was detected in the urine.

Comparative values for cephalexin were 57.8% excreted from 0 to 2 h, 29.5% excreted from 2 to 4 h, and 8.9% from 4 to 6 h after ingestion of the drug. During the 0- to 6-h interval, 96.3% of the total oral dose was excreted.

Adverse reactions. No changes in pulse or blood pressure were noted during the course of treatment with either drug. All hematological and biochemical tests remained within normal limits except for one transient rise in serum glutamic oxalacetic transaminase while the subject was taking cefaclor. No drug sensitization could be detected. All urinalyses remained normal. Creatinine clearances were within normal limits, except for one determination of 14.8 ml/min obtained on subject no. 20 while he was taking cefaclor. Since simultaneous serum creatinine and blood urea nitrogen were normal and preceding and subsequent (2 weeks later) creatinine clearances were normal, this was believed to be due to laboratory error in the determination of urinary creatinine excretion.

Gastrointestinal tolerance of both antibiotics was, in general, good, with only 6 subjects complaining of transient mild gastrointestinal disturbance: subject 10, 1 liquid stool (cefaclor); subject 4, two episodes of mild nausea 30 min after ingestion of drug (cephalexin); subject 6, transient abdominal discomfort and diaphoresis after the morning dose on day 1 (cefaclor); subject 8, "indigestion" after the morning dose on 2 days (cefaclor); subject 17, mild diarrhea on days 3 and 4 (cefaclor); and subject 20, mild nausea and diarrhea on day 1 (cefaclor). No
### Table 1. Cefaclor plasma concentration of 20 subjects (250 mg q6h)

| Subject no. | Plasma concn (µg/ml) on day 1 at h: | Plasma concn (µg/ml) on day 4 at h: |
|-------------|-----------------------------------|-----------------------------------|
|             | 0.5  | 0.75 | 1.0 | 1.5 | 2.0 | 3.0 | 4.0 | 72.5 | 72.75 | 73.0 | 73.5 | 74.0 | 75.0 | 76.0 |
| 1           | 0    | 0    | 0   | 0.4 | 2.1 | 3.2 | 1.3 | 0    | 0     | 0    | 1.0  | 2.6  | 2.2  | 0.96 |
| 2           | 0    | 1.0  | 10.0| 5.2 | 2.3 | 0.41| <0.3| 2.90 | 3.2   | 2.9  | 2.65 | 1.4  | <0.3 | <0.3 |
| 3           | 1.8  | 1.7  | 3.2 | 2.0 | 0.88| <0.3| <0.3| 3.2  | 3.5   | 3.6  | 2.4  | 1.3  | <0.3 | <0.3 |
| 4           | 0.5  | 1.5  | 4.8 | 3.2 | 1.4 | <0.3| 0   | 0    | 0.36  | 0.48 | 2.1  | 0.72 | 0   | 0   |
| 5           | 3.6  | 6.9  | 4.0 | 2.1 | 1.1 | <0.3| 0   | 0    | 5.7   | 4.2  | 1.1  | 2.2  | 0   | 0   |
| 6           | 2.1  | 5.2  | 4.3 | 2.0 | 2.4 | 0.6 | 0.35| 3.2  | 3.1   | 2.7  | 1.8  | 1.55 | <0.3 | <0.3 |
| 7           | 1.4  | 2.6  | 2.4 | 4.9 | 3.0 | 0.55| <0.3| 2.8  | 3.0   | 2.9  | 2.2  | 2.2  | 0.5  | <0.3 |
| 8           | 3.8  | 6.8  | 4.7 | 1.55| <0.3| <0.3| <0.3| 0.3  | 3.2   | 2.4  | 1.2  | 0.5  | <0.3 | <0.3 |
| 9           | 5.4  | 5.2  | 3.7 | 1.9 | 0.8 | <0.3| 0   | 2.4  | 4.9   | 4.6  | 0.73 | 1.3  | 0   | 0   |
| 10          | 1.9  | 6.2  | 7.2 | 5.2 | 2.1 | 0.66| <0.3| 2.1  | 3.5   | 2.9  | 1.5  | 1.2  | 0.52 | <0.3 |
| 11          | 0.78 | 5.7  | 5.2 | 2.3 | 1.1 | <0.3| 0   | 5.8  | 4.4   | 2.8  | 2.3  | 2.4  | 0   | 0   |
| 12          | 2.3  | 8.0  | 4.9 | 2.7 | 1.3 | <0.3| 0   | 4.4  | 7.4   | 4.1  | 2.3  | 1.2  | 0   | 0   |
| 13          | 0    | 5.4  | 6.4 | 5.5 | 3.1 | 1.0 | <0.3| <0.3 | 0.56  | 2.7  | 3.9  | 1.35 | 0.43 |
| 14          | 3.1  | 7.0  | 5.0 | 1.8 | 1.2 | <0.3| <0.3| 0.3  | 2.3   | 4.3  | 1.4  | <0.3 | <0.3 |
| 15          | 0    | 6.1  | 4.2 | 2.4 | 1.2 | <0.3| 0   | 5.2  | 4.0   | 2.5  | 2.0  | 0.66 | 0   | 0   |
| 16          | 0    | 2.8  | 5.4 | 4.1 | 2.7 | 6.4 | 2.2 | 4.3  | 3.1   | 6.1  | 1.3  | 0.64 | 0   | 0   |
| 17          | 0.34 | 3.1  | 5.0 | 4.8 | 3.1 | 0.58| <0.3| <0.3 | 0.93  | 5.3  | 3.1  | 1.85 | 0.5  | <0.3 |
| 18          | 0    | 0.56 | 6.0 | 4.5 | 2.6 | 0.68| 0   | 1.9  | 4.6   | 3.7  | 1.9  | 0.0  | 0   | 0   |
| 19          | 0    | 5.7  | 4.8 | 3.1 | 2.0 | <0.3| 0   | 5.1  | 6.6   | 4.9  | 0.92 | 1.2  | 0   | 0   |
| 20          | 0.9  | 5.6  | 6.2 | 2.9 | 1.55| 0.4 | <0.3| <0.3 | 3.3   | 4.4  | 2.6  | 1.4  | 0.4  | <0.3 |
| Mean        | 1.34 | 4.21 | 4.98| 3.29| 1.87| 0.87| 0.33| 2.24 | 3.34  | 3.57 | 1.91 | 1.64 | 0.39 | 0.20 |
| ±SD         | ±1.53| ±2.38| ±2.01| ±1.46| ±0.76| ±1.45| ±0.53| ±1.99| ±2.02 | ±1.52| ±0.90| ±0.76| ±0.54| ±0.24 |
| Subject no. | Plasma conc (µg/ml) on day 1 at h: | Plasma conc (µg/ml) on day 4 at h: |
|------------|----------------------------------|----------------------------------|
|            | 0.5  | 0.75 | 1.0 | 1.5 | 2.0 | 3.0 | 4.0 | 72.5 | 72.75 | 73.0 | 73.5 | 74.0 | 75.0 | 76.0 |
| 1          | 5.9  | 9.75 | 7.8 | 4.5 | 2.5 | 1.3 | 0.69 | 2.0  | 1.55  | 1.45 | 2.4  | 3.6  | 3.5  |
| 2          | 1.05 | 12.75| 10.5| 6.25| 3.75| 1.25| 0.48 | 1.56 | 3.3   | 3.0  | 7.75 | 4.2  | 2.4  | 1.18 |
| 3          | 10.0 | 11.0 | 8.5 | 5.25| 3.45| 1.1 | 0.48 | 1.7  | 6.0   | 11.75| 6.25| 4.5  | 1.42 | 0.62 |
| 4          | 4.8  | 7.8  | 6.6 | 4.8 | 2.4 | 1.1 | 0.36 | 10.75| 9.5   | 6.25| 4.05 | 1.6  | 0.7  |
| 5          | 9.0  | 8.4  | 4.1 | 3.0 | 2.4 | 1.18| 0.61 | 1.84 | 7.25  | 9.5  | 4.25| 2.19 | 1.1  | 0.57 |
| 6          | 0    | 12.75| 9.25| 4.6 | 2.61| 1.2 | 0.47 | 1.6  | 5.75  | 6.0  | 4.2  | 1.32 | 0.77 |
| 7          | 0    | 8.4  | 9.25| 4.6 | 6.75| 2.85| 0.78 | 7.5  | 7.75  | 13.75| 6.25| 5.5  | 2.4  | 0.82 |
| 8          | 2.2  | 12.0 | 9.5 | 4.65| 2.94| 1.48| 0.42 | 1.95 | 5.25  | 8.25| 7.25| 5.25| 0.8  | 0.83 |
| 9          | 6.5  | 8.1  | 5.25| 4.5 | 2.32| 1.0 | 0.57 | 4.95 | 7.0   | 7.25| 4.35| 2.55| 1.3  | 0.63 |
| 10         | 0.53 | 12.75| 10.75| 7.5 | 3.75| 1.5 | 0.72 | 0.74 | 9.0   | 11.5 | 8.5 | 4.5  | 0.94 | 0.88 |
| 11         | 0    | 0.96 | 3.6 | 8.0 | 3.4 | 1.5 | 0.8  | 1.1  | 2.9   | 5.7  | 5.5 | 4.2  | 1.35 | 0.78 |
| 12         | 7.75 | 12.5 | 7.65| 5.4 | 2.9 | 1.06| 0.5  | 0.53 | 1.03  | 3.75| 7.25| 5.5  | 2.5  | 1.35 |
| 13         | 0    | 6.25 | 4.8 | 6.75| 3.0 | 1.6 | 1.6  | 2.4  | 1.72  | 2.05| 12.5| 8.4  | 3.50 | 1.9  |
| 14         | 0.42 | 9.0  | 11.0| 6.0 | 3.15| 0.55| <0.4 | 1.8  | 4.9   | 6.0 | 5.5 | 6.0  | 1.66 | 1.48 |
| 15         | 0    | 4.8  | 6.3 | 6.0 | 4.3 | 1.55| 0.66 | 8.5  | 9.0   | 8.4 | 4.6 | 2.58 | 1.5  | 0.87 |
| 16         | 0    | 8.1  | 5.7 | 6.1 | 4.5 | 1.75| 0.92 | 1.45 | 5.5   | 10.5 | 6.5 | 3.75 | 1.5  | 0.64 |
| 17         | 0    | 0.5  | 5.5 | 9.75| 4.5 | 1.86| 0.69 | 1.6  | 7.5   | 7.5 | 6.25| 4.65 | 1.34 | 0.82 |
| 18         | 9.5  | 6.8  | 3.9 | 2.6 | 1.5 | 0.57 | 1.65 | 5.0   | 7.75| 5.75| 3.9  | 2.2  | 1.1  |
| 19         | 3.3  | 6.15 | 5.85| 4.5 | 4.0 | 1.4 | 0.66 | 1.65 | 7.25  | 5.5  | 2.9 | 4.05 | 2.1  | 0.82 |
| 20         | 0    | 0.48 | 1.35| 5.0 | 5.4 | 2.65| 1.25 | 3.15 | 5.5   | 6.5 | 5.25| 2.67 | 0.82 | 0.48 |
| Mean       | 2.73 | 7.43 | 7.28| 5.67| 3.73| 1.52| 0.68 | 3.07 | 5.38  | 7.28| 5.98| 4.31 | 1.67 | 1.04 |
| ±SD        | ±3.54| ±4.59| ±2.47| ±1.53| ±1.26| ±0.64| ±0.30| ±2.91| ±3.01 | ±3.28| ±2.17| ±1.41| ±0.69| ±0.67 |
subject withdrew from the study because of these side effects.

One subject (no. 1) was withdrawn from the study on the last day of ingestion of cefadroxil because he developed aseptic meningitis. He was the index case of a small epidemic of aseptic meningitis involving four related individuals from whom an enterovirus was cultured, all of whom had been in contact with children manifesting an acute upper respiratory infection and skin rash. Recovery was uneventful. The prior ingestion of cefadroxil was not believed to have contributed to his illness.

**DISCUSSION**

Cefadroxil, a new oral cephalosporin, has been compared favorably in vitro with other cephalosporins. This drug is 2 to 16 times more active against *Streptococcus pneumoniae*, staphylococcus, and various species of gram-negative bacilli than cepalexin (N. J. Bill and J. A. Washington, Prog. Abstr. Intersei. Conf. Antimicrob. Agents Chemother. 16th, Chicago, Ill., Abstr. no. 356, 1976). It has demonstrated activity against a number of *Escherichia coli*, klebsiella, and proteus strains that were resistant to cepalexin (W. M. Scheld, O. M. Korzeniowski, and M. A. Sande, submitted for publication). Preliminary data suggests an enhanced activity against *H. influenzae* in contrast to other cephalosporin antibiotics (5). Preston (Prog. Abstr. Intersei. Conf. Antimicrob. Agents Chemother. 16th, Chicago, Ill., Abstr. no. 352, 1976) suggested that cefadroxil may be more effective than ampicillin in the treatment of β-lactamase-producing *H. influenzae* in mice.

Pharmacodynamic studies of cefadroxil in laboratory animals have shown rapid gastrointestinal absorption after oral administration and a relative resistance to metabolic degradation or alteration (2, 3). Studies with [14C]cefadroxil showed resistance to metabolism and unchanged elimination of the biologically active form in rats and mice, comparable to data obtained with cepalexin (4). In dogs, however, cefadroxil is labile to metabolism, with only a 60% bioavailability of intact antibiotic after an oral dose, and only 21.5% urinary excretion of the active fraction in 24 h.

In this study, cefadroxil was compared with cepalexin. Both drugs were rapidly absorbed, showing mean maximal serum levels 0.75 to 1.0 h after ingestion of a 250-mg oral dose. Peak serum concentrations (on days 1 and 4) of cefadroxil were lower than those obtained with cepalexin (6.01 and 4.58 µg/ml versus 9.34 and 8.50 µg/ml) (P < 0.001), as were the mean 4-h levels (0.33 and 0.20 µg/ml for cefadroxil and 0.68 and 1.04 µg/ml for cepalexin). A shorter serum half-life of cefadroxil (0.58 h) as compared with cepalexin (0.80 h) was found (P < 0.001 by Student's t test). No accumulation was seen with either drug, since at 6 h virtually no detectable antibiotic was found in the serum.

The principal route of excretion of both drugs is the urinary tract (2, 3). Black et al. (K. S. Black, K. S. Israel, G. H. Brier, and J. D. Woly, Prog. Abstr. Intersei. Conf. Antimicrob. Agents Chemother. 16th, Chicago, Ill., Abstr. no. 354, 1976) reported that, in humans, 60 to 80% of cefalexin is excreted in the urine. In our study utilizing a biological assay, 70.1% of the active cefalexin (175.5 mg) was excreted by 6 h in contrast to 96.3% (240.8 mg) of cepalexin. Metabolically degraded cefalexin was undetectable by this method, as shown by Sullivan et al., who used both a 14C labeling assay and a bacterial agar diffusion method in their kinetic studies in animals (4). Mean urine concentrations of cefalexin at 2 to 4 h were 428.9 µg/ml, and at 4 to 6 h levels were 50.3 µg/ml, concentrations that should be adequate for the therapy of most urinary tract infections caused by gram-negative enteric bacilli.

Both cephalosporins were well tolerated in a strictly fasting state. Only six subjects com-
plained of mild gastrointestinal disturbance—two were receiving cephalexin and four were receiving cefaclor. No allergic side effects were noted, and all physical and laboratory parameters remained normal.

In conclusion, when compared with its parent compound cephalexin, cefaclor, a new oral cephalosporin, produced one-third lower peak serum levels and was more rapidly excreted. However, a 2 to 16 times greater activity by weight in vitro against many gram-negative organisms, including strains of E. coli, klebsiella, and proteus resistant to cephalexin, suggests its potential usefulness as an alternative to cephalexin in selected bacterial infections.

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