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Comparison of Cefprozil and Cefaclor Pharmacokinetics and Tissue Penetration

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The pharmacokinetics and tissue penetration, as judged by skin blister fluid, of cefprozil and cefaclor were examined in 12 healthy male volunteers. Doses of 250 and 500 mg of each drug were given to fasting subjects in a crossover fashion. Serially obtained plasma, skin blister fluid, and urine samples were analyzed for cefprozil or cefaclor by validated high-pressure liquid chromatographic methods. After oral administration of 250 and 500 mg of cefprozil, mean concentrations in plasma rose to peak levels (C_{max}) of 6.1 and 11.2 μg/ml, respectively, and those of cefaclor were 10.6 and 17.3 μg/ml, respectively. The elimination half-life of cefprozil (1.3 h) was significantly longer than that of cefaclor (0.6 h), and as a result, the area under the curve for cefprozil was about two times greater than that for cefaclor. Both cephalosporins were primarily excreted unchanged in urine. The mean skin blister C_{max} values were 3.0 and 5.8 μg/ml for cefprozil and 3.6 and 6.5 μg/ml for cefaclor after the 250- and 500-mg oral doses, respectively. The mean C_{max} values in skin blister fluid for both cephalosporins were comparable and were significantly lower than the corresponding C_{max} values in plasma. However, the levels of cefprozil and cefaclor in skin blister fluid declined more slowly than they did in plasma. The skin blister fluid half-life estimates for cefprozil were significantly longer than they were for cefaclor. Parallel to the observation in plasma, the mean skin blister fluid areas under the curve for cefprozil were significantly higher than they were for cefaclor. The plasma and skin blister fluid pharmacokinetic analyses suggest that the exposure of humans to cefprozil is significantly greater than that to cefaclor at the same dose.

Cefprozil is a new cephalosporin antibiotic that is under development as an oral anti-infective agent for humans. In vitro, the compound is more active than cefaclor and cephalexin against streptococci, staphylococci, *Listeria monocytogenes*, and *Haemophilus influenzae* (5, 8, 16). Members of the family *Enterobacteriaceae* are equally susceptible overall to cefprozil and cefaclor but are less susceptible to cephalexin (5, 8, 16). Cefprozil displays remarkably good activity against *Clostridium difficile*, a causative agent of antibiotic-associated pseudomembranous colitis (4). The oral therapeutic efficacy of cefprozil in the systemically infected mouse model is congruent with its activity in vitro (16). Cefprozil is more active than cefaclor and cephalexin against infections caused by streptococci and penicillinase-producing staphylococci. Against infections caused by gram-negative organisms, cefprozil is more effective than cephalexin and is comparable to cefaclor in its effectiveness (5).

Pharmacokinetic studies conducted in humans indicate that cefprozil is well absorbed by the gastrointestinal tract (1–3). Cefprozil appears to have a significantly longer half-life ($t_{1/2}$) than cefaclor (2, 3). As a result, cefprozil is expected to have higher and more sustained concentrations in plasma than cefaclor in the postdistribution phase.

While information concerning the concentration of a drug in plasma is of great importance in studying its absorption and excretion, it may be of less value in ascertaining the actual concentration of an antibacterial substance at a site of infection. In antimicrobial chemotherapy, it is very important to understand the tissue penetration of the antibiotics. The majority of animal models (6, 9, 12, 20) developed to study the tissue penetration of antibiotics are not applicable to humans or require surgical intervention (26). The suction blister technique provides a relatively safe alternative and eliminates the use of toxic substances to produce extravascular fluid compartments. Except for a slight leukotaxis, the suction blister procedure elicits no inflammatory reactions, provokes no bleeding, and leaves the basement membrane intact with minimal tissue breakdown (15). The suction blister technique produces blisters that contain fluid reservoirs that communicate with the intravascular fluid through a noninflamed barrier such that an immediate representation of the levels of antibiotics in tissues may be assumed. The suction blister model has been extensively used for studying the tissue penetration of antibiotics (11, 21–23).

The present study was designed to determine concentrations in plasma and skin blister fluid and urinary excretion of cefprozil and a reference cephalosporin, cefaclor, after administration of 250- and 500-mg single oral doses.

MATERIALS AND METHODS

Antibiotics. Cefprozil capsules (lot no. 20738) were supplied by the Pharmaceutical Product Development Department, Bristol-Myers Squibb Co. Cefaclor (Distaclor; lot no. 64044AE) was purchased commercially.

Subjects. A total of 12 male subjects participated in the study after signing an informed consent form. The volunteers had a mean ± standard deviation age of 24.4 ± 4.4 years (range, 18 to 31 years), a mean body weight of 66 ± 9 kg (range, 52 to 77 kg) and an average height of 174 ± 4 cm (range, 168 to 180 cm). The subject exclusion criteria in-

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cluded the presence of drug allergies or intolerance and a history of alcohol or drug abuse. Subjects with renal or hepatic impairment were also excluded from the study. Use of any medications within 2 weeks and use of alcohol within 24 h of induction into the study were not permitted. Use of any drug, including alcohol and caffeine, was forbidden during the course of the study.

Study design. The study was an open, four-way crossover design balanced for treatment and sequence in an order determined from the rows of a 4 by 4 Latin square. Each subject was given a single oral dose of 250 mg of cefprozil (treatment 1), 500 mg of cefprozil (treatment 3), 250 mg of cefaclor (treatment 2), or 500 mg of cefaclor (treatment 4). The subject received each treatment with a 7-day interval between doses. Blood, skin blister fluid, and urine samples were collected at intervals after each dose.

Preparation of skin blisters. Skin blisters were raised by suction by a previously described procedure (22). At approximately 8 to 10 h prior to dosing in each leg of the study, the subject's back was divided (figuratively) into quadrants bounded proximally by the scapulae and distally by the waist. The quadrants were designated as upper left (A), upper right (B), lower left (C), and lower right (D). For each dosing session, two sets of blisters (eight per set) were raised in a given quadrant (quadrant A for session 1, quadrant B for session 2, etc.). A minimum of 12 blisters were raised per subject per treatment to ensure adequate collection of samples. For the production of suction-induced skin blisters, a perspex block (10 by 5 by 2 cm) with eight cups (1.2-cm diameter by 1.5-cm depth) was symmetrically bored in position, and the eight cups were joined to each other with a common outlet. This device was connected to a vacuum pump via thick-walled (diameter, 0.2 cm) rubber tubing. The device was placed over the skin, with a rubber O ring providing an airtight seal between each cup and the skin surface. The vacuum pump was turned on, and a continuous evacuation at 200 to 280 mm Hg (2.7×10^4 to 3.7×10^4 Pa) was maintained for 2 h. In order to obtain at least 12 good blisters, two suction blister devices were used per treatment.

Drug administration. The subjects fasted from about 10 p.m. of the day before dosing until 4 h after dosing. Upon rising on the study day, each subject emptied his bladder, and approximately 1 h prior to drug administration, each subject drank approximately 360 ml of water. The subjects were dosed with either 250 or 500 mg of cefprozil or cefaclor with 300 ml of water.

Collection of samples for pharmacokinetic analysis. (i) Blood. Serial blood samples (ca. 7 ml) were collected in heparinized tubes immediately before dosing (predose) and at 15, 30, and 45 min and 1, 1.5, 2, 3, 4, 5, 6, 7, and 9 h after drug administration. The actual times and dates of collection of each sample were recorded on the case report forms.

The blood samples were kept in an ice bucket and were centrifuged within 30 min of collection. Plasma was separated, and samples were then flash-frozen in a solid CO_2-methanol bath and stored at or below −20°C, with appropriate quality-control (QC) samples prepared prior to the start of the study.

(ii) Skin blister fluid. Skin blister fluid samples were drawn immediately prior to dosing (predose) and at 30 and 45 min and 1, 1.5, 2, 3, 4, 5, 6, 7, and 9 h after drug administration.

The skin blisters were punctured with a sterile 21-gauge needle, and the fluid was collected in a micropipette. The maximum amount of fluid available from the blister was collected. Immediately after collection, each blister fluid sample was transferred to a capped plastic conical tube with a volume of 1 ml. Each tube containing a blister fluid sample was flash frozen and stored at or below −20°C with appropriate QC samples. Because of the limited availability of skin blister fluid, the QC samples were prepared in plasma.

(iii) Urine. Total urine output was collected just prior to dosing (predose) and over intervals of 0 to 2, 2 to 4, 4 to 6, 6 to 8, and 8 to 10 h after dosing. To ensure adequate urine flow, subjects drank 100 ml of water at 4 and 6 h after dosing.

At the end of each urine collection interval, total urine volumes and pHs were measured and recorded on the appropriate case report forms. For the subjects who received cefprozil, exactly 5 ml of the urine sample was transferred to a screw-cap tube containing 5.0 ml of 0.01 M sodium acetate (pH 3.57) buffer. For cefaclor samples, a 9-ml portion of the urine sample was transferred to a screw-cap tube containing 1 ml of 1.0 M citrate buffer (pH 2.0). Each urine sample tube was gently shaken to ensure thorough mixing, flash-frozen, and stored at or below −20°C.

Assays. Plasma, skin blister fluid, and urine samples from the study subjects and stored QC samples were assayed for cefprozil or cefaclor by using validated high-pressure liquid chromatographic assays (3, 18). Because of the limited supplies of blister fluid, the skin blister fluid assays were performed by using the plasma standards and the procedure for the plasma assays. The validity of this approach was based on the lack of interference from the drug-free skin blister fluid sample at the retention times for the cephalosporin and the internal standard as well as constancy of the slopes of the plasma and skin blister fluid standard curves. The accuracy and precision of the QC samples, which were prepared in skin blister fluid and assayed by using the standard curve prepared from the plasma samples, were also assessed. It was determined that the levels of cefprozil and cefaclor in skin blister fluid could be determined accurately and precisely by using standards prepared in plasma.

Pharmacokinetic analysis. The following noncompartmental pharmacokinetic parameters were calculated by using standard techniques (13, 19): maximum concentration in plasma (C_{max}), time to C_{max} (T_{max}), area under the drug-concentration-versus-time curve from 0 h to infinity ($AUC_{0-\infty}$), $t_{1/2}$, mean residence time (MRT), renal clearance (CL_R), and percentage of dose excreted in the urine ($\%X_u$). Terminal elimination rate constants (β) were estimated for all plasma-level-versus-time profiles by performing standard unweighted linear least-squares regression analysis of the linear segment of the log concentration-versus-time data. The elimination $t_{1/2}$ was estimated by dividing 0.693 by β. The AUC from time zero to time m, the portion prior to the log-linear phase, was calculated by using the linear trapezoidal rule method, and the AUC from time m to the last measurable time point n was calculated by using the log trapezoidal rule method and was extrapolated to infinity (13).

Statistical analyses. The plasma and skin blister fluid pharmacokinetic parameters were evaluated to compare sample matrices (plasma and skin blister fluid), drugs (cefprozil and cefaclor), and dose levels (250 and 500 mg) within each drug. Statistical analyses of the plasma, skin blister fluid, and urine parameters were carried out in the context of a split-plot analysis of variance model. The Bonferroni procedure was used for making multiple comparisons among the four groups of study subjects. The proportionality of the two drugs was assessed by evaluating $AUC_{0-\infty}$ and C_{max} normalized to a 250-mg dose. A rank transformation was applied to the urine concentration data to reduce the skewness in the distribution. An estimate of post hoc power of the

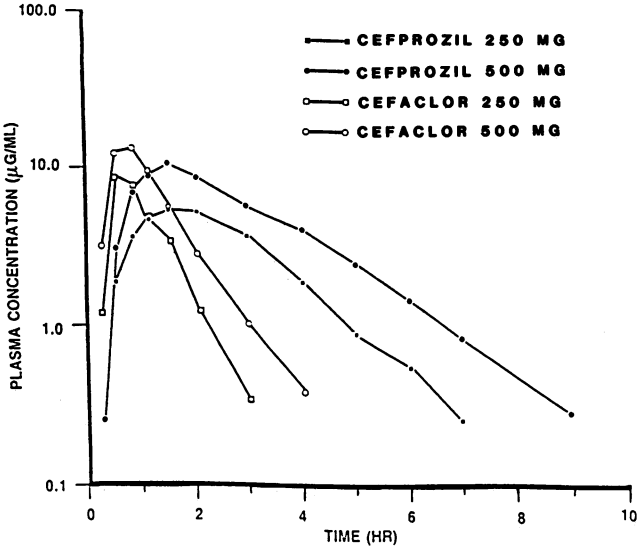

FIG. 1. Mean concentration-versus-time profiles of cefprozil and cefaclor in plasma.

analysis of variance model was calculated for each parameter by a procedure discussed previously (28).

The ratios of concentrations in skin blister fluid to those in plasma were compared between drugs at each dose level. Ratios were formed from $AUC_{0-\infty}$ and C_{max}. Analyses were carried out in the context of the split-plot analysis of variance model. Comparisons were made at the 5% significance level.

RESULTS

The profiles of the mean drug concentrations in plasma and skin blister fluid versus time for each drug are shown in Fig. 1 and 2, respectively. The mean pharmacokinetic parameters for cefprozil and cefaclor in plasma and skin blister fluid are presented in Tables 1 and 2, respectively. The

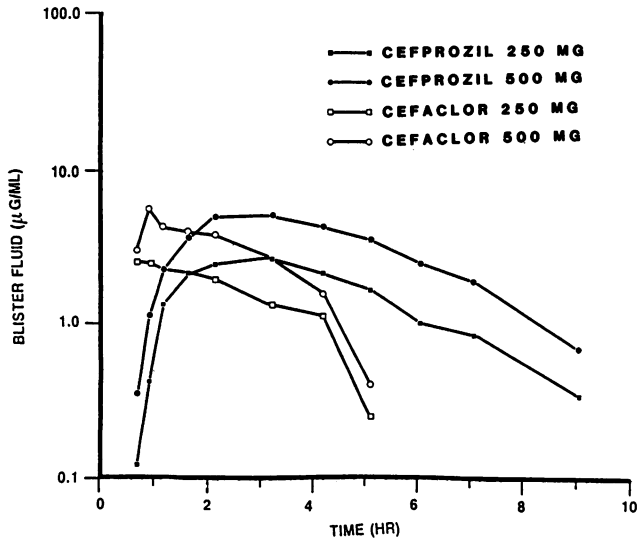

FIG. 2. Mean concentration-versus-time profiles of cefprozil and cefaclor in skin blister fluid.

TABLE 1. Pharmacokinetic parameters and statistical comparisons for cefprozil and cefaclor in plasma[a]

Drug (dose)	C_{max} (μg/ml)	T_{max} (h)	$t_{1/2}$ (h)	MRT (h)	$AUC_{0-\infty}$ (μg h/ml)	CL_R (ml/min)	X_u (%)
Cefprozil (250 mg)	6.1 ± 1.1	1.5 ± 0.6	1.4 ± 0.3	2.6 ± 0.4	16.1 ± 2.1	182 ± 34.5	69.2 ± 6.9
Cefaclor (250 mg)	10.6 ± 2.4	0.5 ± 0.0	0.5 ± 0.2	1.0 ± 0.1	8.7 ± 1.4	315 ± 109	66.5 ± 21.3
Cefprozil (500 mg)	11.2 ± 2.1	1.4 ± 0.5	1.3 ± 0.2	2.7 ± 0.3	32.0 ± 3.8	161 ± 37.7	62.1 ± 14.3
Cefaclor (500 mg)	17.3 ± 3.6	0.7 ± 0.2	0.6 ± 0.1	1.2 ± 0.2	17.5 ± 2.1	382 ± 83.1	78.9 ± 11.7
Statistical comparisons[b]	A < C	A = C (NS)	A = C (NS)	A = C (NS)	C > A	A = C (NS)	A = C (NS)
	B < D	B = D (NS)	B = D (NS)	B = D (NS)	D > B	B = D (NS)	B = D (NS)
	A < B	A > B	A > B	A > B	A > B	B > A	A = B (NS)
	C < D	C > D	C > D	C > D	C > D	D > C	D > C

[a] Values are means ± standard deviations and are after oral administration of drugs at 250- and 500-ng doses.
[b] Cefprozil (A, 250 mg; C, 500 mg) and cefaclor (B, 250 mg; D, 500 mg) were compared for statistical significance (NS, not significant). Each comparison was made at the $\alpha = 0.5/4 = 0.0125$ significance level.

TABLE 2. Pharmacokinetic parameters and statistical comparisons for cefprozil and cefaclor in skin blister fluid[a]

Drug (dose)	C_{max} (μg/ml)	T_{max} (h)	$t_{1/2}$ (h)	MRT (h)	$AUC_{0-\infty}$ (μg · h/ml)
Cefprozil (250 mg)	3.0 ± 0.4	2.4 ± 0.6	2.4 ± 1.0	5.0 ± 0.9	13.4 ± 2.5
Cefaclor (250 mg)	3.6 ± 1.2	1.1 ± 0.4	1.5 ± 0.3	2.6 ± 0.5	7.7 ± 1.1
Cefprozil (500 mg)	5.8 ± 1.1	2.5 ± 0.8	2.2 ± 0.6	4.8 ± 0.8	27.3 ± 3.9
Cefaclor (500 mg)	6.5 ± 3.0	1.0 ± 0.4	1.4 ± 0.4	2.7 ± 0.4	14.4 ± 3.7
Statistical comparisons[b]	A < C	A = C (NS)	A = C (NS)	A = C (NS)	A > C
	B < D	B = D (NS)	B = D (NS)	B = D (NS)	B > D
	A = B (NS)	A < B	A > B	A > B	A > B
	C = D (NS)	C < D	C > D	C > D	C > D

[a] Values are means ± standard deviations and are after oral administration of drugs at 250- and 500-mg doses.
[b] Cefprozil (A, 250 mg; C, 500 mg) and cefaclor (B, 250 mg; D, 500 mg) were compared for statistical significance (NS, not significant). Each comparison was made at the $\alpha = 0.05/4 = 0.0125$ significance level.

pharmacokinetic parameters are reported along with a summary of statistical analyses which were sufficiently sensitive (power, ≥80%) to discern at least a 20% difference between drugs and dose levels within each day. The observed mean C_{max} values of cefprozil in plasma were 6.1 and 11.2 μg/ml for doses of 250 and 500 mg, respectively, while mean C_{max} values of cefaclor in plasma were 10.6 and 17.3 μg/ml, respectively. The C_{max} values were significantly higher for cefaclor than they were for cefprozil at both the 250- and 500-mg dose levels. No deviations from dose proportionality were apparent, as mean normalized dose levels within each drug were not statistically different.

The mean C_{max} values in skin blister fluid were 3.0 and 5.8 μg/ml for cefprozil and 3.6 and 6.50 μg/ml for cefaclor after administration of the 250- and 500-mg oral doses, respectively. Peak concentrations in skin blister fluid were significantly lower than those in the plasma for each drug and dose level. In contrast to the plasma C_{max} data, no differences in peak levels in skin blister fluid were observed between drugs at each dose level. The mean dose-normalized C_{max} levels in skin blister fluid were not significantly different between the two doses of each drug. The T_{max} values ranged from 1.0 to 5.0 h for cefprozil and from 0.5 to 2.0 h for cefaclor and were statistically comparable between doses within each drug but were significantly longer for cefprozil than for cefaclor. Peak levels were reached in the skin blister fluid significantly faster after the administration of cefaclor (T_{max}, 1.2 h) than after the administration of cefprozil (T_{max}, 2.7 h). The time to reach T_{max} did not differ significantly between doses within each drug.

The mean elimination $t_{1/2}$ for cefprozil (1.30 h) in plasma was significantly longer than that for cefaclor (0.60 h) at each dose level. The $t_{1/2}$ values for cefprozil and cefaclor were comparable within doses of each drug. The levels of cefprozil and cefaclor in skin blister fluid declined more slowly than they did in plasma. As a result, the $t_{1/2}$ values for cefaclor (0.62 to 3.4 hours) and cefprozil (1.33 to 4.52 h) in skin blister fluid were significantly longer than those obtained in plasma. The mean skin blister fluid $t_{1/2}$ values for cefprozil were significantly longer than those for cefaclor. The average MRT for cefprozil (2.76 h) was significantly longer than that for cefaclor (1.2 h).

The mean AUC after administration of cefprozil were significantly higher than those after administration of cefaclor at each dose level. No deviation from dose proportionality was observed, as the mean dose-normalized values between doses and within each drug were not significantly different.

Parallel to the observations in plasma, the mean skin blister fluid AUC after the administration of cefprozil were significantly higher than those after the administration of cefaclor. No apparent deviation from dose proportionality was observed for either drug. The mean dose-normalized AUC were comparable between dose levels within each drug. The mean AUCs for skin blister fluid were slightly but significantly lower than the AUCs for plasma after administration of the cefprozil (250 and 500 mg) and cefaclor (500 mg) doses. The mean AUC for skin blister fluid and plasma were comparable after administration of the 250-mg cefaclor dose.

The pharmacokinetics of cefprozil and cefaclor in plasma were compared with those in skin blister fluid within each drug and dose level. Comparisons of these parameters between drugs was carried out by forming ratios of the skin blister to plasma parameters (Table 3). The ratios of the AUCs, which reflect the relative bioavailabilities in skin blister fluid, were not significantly different between drugs at each dose level. However, the C_{max} ratios were significantly higher after administration of cefprozil than after that of cefaclor.

Urinary excretion was a major route of elimination of both cefprozil and cefaclor. Cefprozil excretion proceeded more slowly and for a more prolonged period than cefaclor excretion did. Initially (0 to 2 h) the cefaclor concentrations in urine were significantly higher than the cefprozil concentrations. The concentrations of both cephalosporins in urine at 0 to 2 h exceeded the MIC for 50% of susceptible organisms tested (MIC_{50}s) manyfold. Two hours after dosing, the cefprozil concentrations in urine were consistently higher than those of cefaclor (Table 4).

The mean cumulative urinary excretion of the two cephalosporins ranged from 61.7 to 78.5%. The mean CL_R values

TABLE 3. Comparison of mean ratio of skin blister fluid/plasma pharmacokinetic parameters between cefprozil and cefaclor[a]

Drug (dose)	Ratio (%)[b]	
	C_{max}	$AUC_{0-\infty}$
Cefprozil (250 mg)	50.3 ± 3.8	83.2 ± 13.5
Cefaclor (250 mg)	36.0 ± 16.3	89.0 ± 16.1
Cefprozil (500 mg)	51.7 ± 7.8	85.1 ± 7.5
Cefaclor (500 mg)	37.8 ± 15.1	82.7 ± 19.1
Statistical comparison[b]	C250 < B250	NS
	C500 < B500	NS

[a] Values are means ± standard deviations.
[b] Cefprozil (B) and cefaclor (C) were compared for statistical significance (numbers indicate drug dose, in milligrams; NS, not significant.

TABLE 4. Mean concentration of orally administered cefprozil and cefaclor in urine

Urine collection interval (h)	Dose (mg)	Mean ± SD drug concn (μg/ml)		Statistical comparison[a]
		Cefprozil	Cefaclor	
0–2	250	256 ± 150	482 ± 327	C > B
	500	372 ± 261	1,174 ± 831	C > B
2–4	250	370 ± 319	73 ± 57	B > C
	500	645 ± 340	321 ± 413	B > C
4–6	250	194 ± 96	15 ± 11	B > C
	500	349 ± 161	65 ± 87	B > C
6–8	250	50 ± 36	1.8 ± 4.1	B > C
	500	75 ± 40	8.4 ± 8.2	B > C
8–10	250	15 ± 12	0.0 ± 0.0	NA
	500	27 ± 19	5.9 ± 18.3	NA

[a] Cefprozil (B) and cefaclor (C) were compared for statistical significance (NA, not analyzed).

for cefaclor were approximately twofold higher than those for cefprozil. These values ranged from 161 to 182 ml/min for cefprozil and from 315 to 382 ml/min for cefaclor.

DISCUSSION

Several studies have defined the pharmacokinetics of cefprozil and cefaclor in human volunteers (1–3, 14, 17, 24, 27). However, they are usually limited to one drug, one dose level, or both. Comparisons between the two cephalosporins were difficult since these studies were not carried out in the same subjects or institutions. The present study was designed to evaluate the pharmacokinetics in plasma and penetration into skin blister fluid of these compounds in a way which permitted intraindividual comparisons.

The pharmacokinetic parameters used for assessing orally administered drugs were C_{max}, T_{max}, $t_{1/2}$, MRT, AUC, and $\%X_u$. With these parameters as criteria, with the exception of C_{max}, cefprozil showed the most favorable pharmacokinetics in our investigations. The values for $t_{1/2}$, MRT, and AUC of cefprozil were about twofold greater than those of cefaclor. The MRT and AUC data suggest that the level of exposure of humans to cefprozil is significantly greater than that to cefaclor. Single-dose C_{max} and AUC data suggested that the pharmacokinetics of cefprozil and cefaclor are linear in the 250- to 500-mg dose range. The values of the pharmacokinetic parameters for cefprozil and cefaclor in this study were in good agreement with those presented in previous reports (1–3, 14, 17, 24, 27).

In the clinical application of an antibiotic, it is important to investigate the drug levels in various tissues and body fluids and to elucidate the relationship between drug concentrations in plasma and tissues or body fluids. The entry of cefprozil and cefaclor into the suction blister was delayed, as determined by a comparison with the levels of drugs in plasma. As a result, the peak drug concentrations in skin blister fluid were significantly lower than the corresponding C_{max} values in plasma. The MRT and AUC values for cefprozil in skin blister fluid were about two times greater than those for cefaclor. The bioavailability of each drug in blister fluid, relative to that in plasma, was calculated from the ratio of skin blister fluid AUC to plasma AUC. Although the relative bioavailabilities in skin blister fluid were comparable for both cephalosporins, the exposure of cefprozil to blister fluid, as judged by the AUC estimates, was significantly greater than that of cefaclor.

Total urinary recovery of cefprozil (61.2 to 69.2% of the dose) was consistent with previously obtained values (1–3). The urinary excretion of cefaclor (66.5 to 78.9% of the dose), on the other hand, was higher than most previously reported values (14, 17, 24, 27). Acidification, flash-freezing, and storage of cefaclor-containing urine samples at −70°C appear to be the most plausible explanations for the stabilization of cefaclor and the increased urinary recovery found in the present study. The average CL_R values for cefprozil and cefaclor were 171 and 347 ml/min, respectively. Since these values are substantially greater than the average glomerular filtration rate of 120 ml/min, a significant portion of both cephalosporins must be cleared by tubular secretion in the kidneys. Probenecid prolongs the $t_{1/2}$ of cefaclor (24) by blocking tubular secretion. The effect of probenecid on the $t_{1/2}$ of cefprozil is not known.

In human serum, cefprozil and cefaclor are 45 and 47% protein bound, respectively (16, 25). The fraction of the concentration that exists as free drug is expected to be virtually the same for each of the two cephalosporins. Therefore, data derived from the total drug concentrations in body fluids are appropriate for comparisons of the pharmacokinetics of cefprozil and cefaclor.

With beta-lactam antibiotics, the pharmacodynamic vari-

TABLE 5. Duration over which cefprozil and cefaclor levels in plasma and skin blister fluid exceeded the literature values for the MIC_{50}s for important common pathogens

Organism	MIC_{50} (μg/ml)[a]		Time (h) over which MIC_{50} was exeeded in[a]:							
			Plasma				Blister fluid			
			250-mg dose		500-mg dose		250-mg dose		500-mg dose	
	B	C	B	C	B	C	B	C	B	C
Streptococcus pyogenes[b]	0.016	0.063	>7	>3	>9	>4	>9	>5	>9	>5
Streptococcus pneumoniae[b]	0.125	0.5	>7	3	>9	4	>9	4.5	>9	4.5
Staphylococcus aureus[b]	2.0	8.0	4	<1	5.5	1	2.5	0	6.5	0
Haemophilus influenzae[c]										
Penicillinase nonproducing	1.0	1.0	5	2.5	6.5	3	5	3	8	4
Penicillinase producing	2.0	2.0	4	1.5	5.5	2.5	2.5	1.5	6.5	6.5
Moraxella catarrhalis[b]	4.0	8.0	3	<1	4	1	0	0	2.5	0

[a] B, Cefprozil; C, cefaclor.
[b] Data have been published previously (16).
[c] Data on file (Bristol-Myers Squibb Co.).

able that may correlate with clinical efficacy is the duration over which concentrations in plasma and various tissues remain above the MIC_{50} (7). The drug-concentration-versus-time profiles, which are presented in Fig. 1 (plasma) and 2 (skin blister fluid), were compared with the MIC_{50}s for *Streptococcus pyogenes* (16), *Streptococcus pneumoniae* (16), *Staphylococcus aureas* (16), β-lactamase-negative and β-lactamase-positive strains of *H. influenzae* (data on file, Bristol-Myers Squibb Co.), and *Moraxella catarrhalis* (16). Both in plasma and skin blister fluid, the duration over which the drug concentration remained above the MIC_{50} of cefprozil exceeded that of cefaclor at the same dose (Table 5). The sole exception to this was in skin blister fluid, in which neither drug had concentrations above the MIC_{50} for *M. catarrhalis* at the 250-mg dose. Since cefaclor is not very stable at neutral pH or in biological fluids (10), its lack of stability may be responsible for its accelerated disappearance from skin blister fluid and plasma. Concentrations of the two cephalosporins in urine greatly exceeded the MIC for 90% of most susceptible urinary tracer pathogens tested (MIC_{90}) during the first 6 h after dosing. During the subsequent urine collection periods (6 to 10 h), cefprozil levels remained above the MIC_{90} for the most susceptible urinary tract pathogens tested, whereas those of cefaclor were not detectable in most subjects. If the therapeutic concept is maintained that concentrations of a beta-lactam antibiotic in plasma and tissues should exceed the MICs for the offending pathogens over a period which approximates the entire dosing interval, then cefprozil appears to be suitable for twice-daily administration, whereas cefaclor should probably be administered three or even four times a day.

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