# Suction-Induced Blister Fluid Penetration of Cefdinir in Healthy Volunteers Following Ascending Oral Doses

MONIQUE RICHER,[1] SYLVIE ALLARD,[1] LUC MANSEAU,[1] FRANÇOIS VALLÉE,[1]
RAPHAEL PAK,[2] AND MARC LeBEL[1]*

*Laboratoire de Pharmacocinétique Clinique, École de Pharmacie, Université Laval, Québec, Québec,
Canada G1K 7P4,[1] and Parke-Davis Pharmaceutical Research, Division of
Warner-Lambert Company, Ann Arbor, Michigan 48105[2]*

The pharmacokinetics and suction-induced blister fluid penetration of cefdinir following single oral administrations of 200, 300, 400, and 600 mg were studied in 16 healthy young male volunteers according to a Latin square design. Plasma, blister, and urine samples were assayed by high-pressure liquid chromatography. We observed a nonlinear relationship ($P = 0.02$) between the dose and the maximum concentration in plasma as well as between the dose and the area under the concentration-time curve (AUC) in plasma ($P < 0.001$), which may be indicative of a limited absorption process. This resulted in a lower AUC value than expected as well as a smaller fraction of cefdinir excreted unchanged at a dose of 600 mg. Renal clearance decreased with increasing doses ($P < 0.006$; analysis of variance with the Latin square design and Games-Howell procedure). Maximal cefdinir concentrations in blister fluid were delayed compared with concentrations in plasma. Blister fluid penetration measured by the ratio of the AUC in blister fluid to the AUC in plasma was extensive (92.4 to 108.4%). Cefdinir concentrations in blister fluid remained equal to or higher than the concentrations in plasma from 6 to 12 h following cefdinir administration. On the basis of the concentrations in blister fluid and the in vitro MIC data, we estimated that cefdinir at 200 to 400 mg administered twice daily would be adequate to treat uncomplicated skin infections caused by *Streptococcus pyogenes*. Seven volunteers experienced episodes of light-to-moderate diarrhea. These adverse events occurred irrespective of dose.

Cefdinir (CI-983), $6R$-[$6\alpha,7\beta(Z)$]-7-[[(2-amino-4-thiazolyl)(hydroxyimino)acetyl]amino]-3-ethenyl-8-oxo-5-thio-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, is a semisynthetic, extended-spectrum cephalosporin antibiotic for oral administration intended for use in the treatment of mild-to-moderate bacterial infections. This compound, comparable in structure and in vitro activity to the oral agent cefixime, offers enhanced activity against methicillin-sensitive *Staphylococcus aureus* and *Staphylococcus epidermidis* as well as effective antimicrobial activity against strains of *Streptococcus* and *Neisseria* spp. and β-lactamase-producing strains of *Haemophilus* and *Moraxella* (3, 5, 11, 12, 15, 17, 20). Its oximino side chain provides excellent stability against the most common plasmid-encoded β-lactamases TEM-1 and TEM-2 (12) but not against extended β-lactamases, such as TEM-3 (15). Pharmacokinetic studies with orally administered cefdinir have shown that at doses ranging between 100 and 800 mg, peak concentrations in plasma were reached at 3 to 4 h after administration, and the half-life was approximately 1.5 h (6, 7). The maximum cefdinir concentration ($C_{max}$) and area under the concentration-time curve (AUC) values increased with increasing doses, but the proportionality of dose to AUC was not observed at doses above 200 mg (6). The extent of binding of cefdinir to plasma proteins has been reported to be 61% (1). The aim of this study was to investigate the extent of cefdinir diffusion into extracellular fluid at increasing doses in young healthy human subjects, by a suction-induced skin blister method.

## MATERIALS AND METHODS

**Subjects and study design.** Sixteen healthy male volunteers between 19 and 30 years of age (mean, $23 \pm 4$ years) provided written informed consent for the study, which was approved by the Ethics Committee, Université Laval, Québec, Canada. The mean ($\pm$ standard deviation [SD]) weight of the subjects was 69.8 $\pm$ 6.2 kg (range, 62.9 to 83.6 kg). The subjects were within 10% of the normal weights for their heights and ages. All subjects were nonsmokers, and each was judged to be healthy on the basis of a medical history, physical examination, chemistry profile, complete blood count, and urinalysis. None had a history of hepatic, renal, cardiovascular, or neoplastic diseases or known allergy to β-lactam antibiotics. No other medication, including iron supplements (19), was allowed at the time of the study. Alcoholic beverages as well as caffeine-containing foods and beverages were withheld 24 h prior to the start of the study, during the study, and until 12 h after the final dose.

In this open single-dose study, treatments were administered to the 16 volunteers according to a standard $4 \times 4$ Latin square design, with each subject receiving the four doses being tested during the study. Four subjects were randomized for each dosing sequence. The subjects received a single dose of either 200, 300, 400, or 600 mg of cefdinir (Parke-Davis Canada, Scarborough, Ontario, Canada) on each of study days 1, 8, 15, and 22. The drug was given orally with 250 ml of drinking water after an overnight fast. Patients were allowed to eat a standardized breakfast 2 h following cefdinir administration.

**Plasma and urine sampling.** Blood samples were drawn from an intravenous catheter in an antecubital vein at 0, 30, and 45 min and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 10, and 12 h after the administration of a dose of cefdinir on the each day of treatment. A diluted heparin solution (33 U/ml) was used to maintain patency of the catheter, and at least 1 ml of blood was discarded before blood was collected. Blood samples were collected in Vacutainer tubes, which contained EDTA as an anticoagulant. Plasma was rapidly separated by centrifugation ($1,000 \times g$, 20 min, 4°C). Plasma samples were stored at −80°C until analyzed. Urine was collected immediately before antibiotic administration and at intervals of 0 to 2, 2 to 4, 4 to 8, and 8 to 12 h after drug administration. Urine volume was recorded for each collection. An aliquot was stored at −80°C until assayed.

**Blister fluid sampling.** Each volunteer had 10 skin blisters produced by suction according to the modified method described by Hellum et al. (8). In brief, a Plexiglas block with 10 bores (diameter, 8 mm) was strapped to the volar area of the forearm after the skin had been swabbed with 70% isopropanol. Controlled suction (−3.6 mm Hg [c. 48 kPa]) was applied until half-spherical blisters had been produced (1.5 to 2 h). Ten uniform dermoepidermal blisters were formed 12 h before the administration of cefdinir on each study day. The blister fluid was sampled by puncture with a minimum-dead-space syringe (Micro-fine III; Becton Dickinson), and 0.10 to 0.25 ml of fluid was aspirated from one blister. Each blister was sampled only once. The harvesting time sequence was 0, 1, 2, 3, 4, 5, 6, 8, and 12 h after the dose on each study day. The samples were stored in polyethylene microtubes at −80°C until assayed.

* Corresponding author. Phone: (418) 656-3158. Fax: (418) 656-2305.
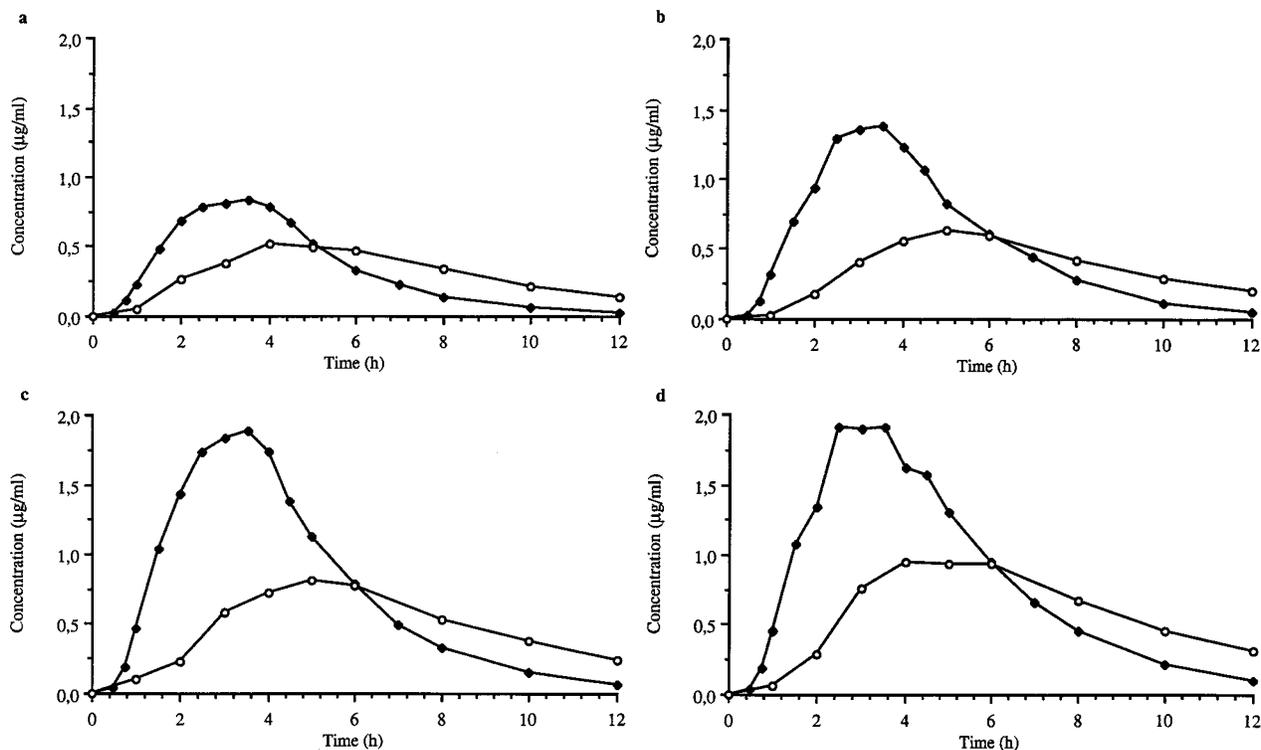
FIG. 1. Mean concentrations of cefdinir in plasma (◆) and blister fluid (○) after single doses of 200 (a), 300 (b), 400 (c), and 600 (d) mg, calculated from the MK-MODEL.

**Sample analysis.** Plasma and urine samples were analyzed for total cefdinir concentration by a reverse-phase, high-pressure liquid chromatography procedure previously described (14) and adapted in our laboratory. Blister fluid samples were analyzed by a similar procedure. The chromatographic system (Shimadzu; Fisher, Montreal, Canada) was equipped with a model LC-600 solvent delivery module, a model SIL-9A automatic sample injector, and a model SPD-6A UV spectrophotometric detector connected to an HP-3394 integrator. Chromatography was performed on 4-μm-diameter Nova-Pak $C_{18}$ columns (Waters Scientific, Mississauga, Ontario, Canada). The mobile phases were composed of 0.015 M dibasic potassium phosphate-acetonitrile (89:11, blister; 88:12, plasma) adjusted to pH 3.3 for blister and 3.1 for plasma, with 85% phosphoric acid. The effluent was monitored by determining the $A_{287}$ with UV light and a flow rate of 1 ml/min. Under these conditions, the retention times were 7.6, 8.2, and 8.5 min for cefdinir in plasma, blister fluid, and urine, respectively. Sample preparation of the plasma, blister fluid, and urine involved incorporation of an internal standard (8-chloro-theophylline). In addition, preparation of the blister fluid and plasma samples involved protein precipitation with acetonitrile and delipidation with methylene chloride. The limits of detection for this method were 0.015, 0.05, and 0.078 μg/ml for cefdinir in plasma, blister fluid, and urine, respectively. Reproducibility measurements for the plasma assay yielded interday variabilities of 2.4% (0.2 μg/ml), 3.5% (1.5 μg/ml), and 5.2% (5 μg/ml). The intraday variability was <3.6% for these cefdinir concentrations in plasma. Reproducibility measurements for the blister fluid assay yielded interday variabilities of 9.5% (0.05 μg/ml), 6.3% (0.2 μg/ml), and 8% (1.5 μg/ml). The intraday variability was <3.6% for these blister fluid cefdinir concentrations. The recoveries of cefdinir in plasma and blister fluid were 80.7% (between 0.25 and 4.0 μg/ml) and 79.7% (between 0.03 and 1.0 μg/ml), respectively. In the standard curve preparation, the concentrations of cefdinir in the samples were mixed in plasma for the plasma and blister fluid curves and in urine for the cefdinir-urine standard curve. Linear regression analysis of all standard curves yielded a result of ≥0.99, indicating the excellent linearity of the assay. The method was selective for those substances analyzed; no endogenous interference was observed on the chromatograms.

**Pharmacokinetic analysis.** The profiles of cefdinir in plasma for each volunteer were fitted to the sum of the exponential equation by using an iterative least-squares modeling program, MK-MODEL (9). This package estimates the initial and final parameters from the concentration-versus-time data for each subject. The individual concentrations ($C$) of cefdinir in plasma after oral administration were best described by equations chosen on the basis of visual inspection and the Schwartz criterion (9). The single variance model is provided by the following equation: $Var(Y) = SD^2 \cdot (V_0 + Y^{PWR})$, where $Var(Y)$ is the predicted variance, $Y$ is the concentration predicted by a pharmacokinetic model, PWR is the power parameter, $V_0$ is the expected variance model when $Y$ is equal to 0 and PWR is not equal to 0, and SD is the standard deviation.

The pharmacokinetic parameters in serum were described by a one- or two-compartment model on the basis of visual inspection and the Schwartz criterion. They were described by a one-compartment model by the following equation:

$$C = \frac{D \cdot F}{V} \cdot \frac{k_a}{k_a - k_{el}} \cdot (e^{-k_{el} \cdot t} - e^{-k_a \cdot t})$$

where $D$ is the dose, $F$ is the bioavailability, $k_{el}$ is the elimination constant, and $K_a$ is the absorption constant. For a two-compartment model, the equation was as follows:

$$C = \frac{D \cdot F \cdot k_a}{V} \cdot \frac{k_{21} - \alpha}{(k_a - \alpha) \cdot (\beta - \alpha)} \cdot e^{-\alpha \cdot t}$$
$$+ \frac{k_{21} - \beta}{(k_a - \beta) \cdot (\alpha - \beta)} \cdot e^{-\beta \cdot t} + \frac{k_{21} - k_a}{(\alpha - k_a) \cdot (\beta - k_a)} \cdot e^{-k_a \cdot t}$$

The AUC from time zero to infinity as well as the area under the moment curve (AUMC) were calculated by logarithmic trapezoidal rule and extrapolation methods from observed points. In turn, the AUC was used to evaluate body clearance (CL/F) as follows: CL/F = dose/AUC. Renal clearance ($CL_R$) was calculated as follows: $CL_R = Ae_{t_1-t_2}/AUC_{t_1-t_2}$, where $Ae_{t_1-t_2}$ is the amount excreted into urine during the time interval $t_1$ to $t_2$.

The nonrenal clearance was estimated by subtracting the renal clearance values from the total clearance value. The apparent volume of distribution was determined from the following equation: $V/F = (dose \cdot AUMC/AUC^2) - [dose/(K_a \cdot AUC)]$, where $K_a$ is the absorption constant for an oral administration. The percentage of the dose excreted unchanged in the urine ($F_u$) was calculated from this ratio: $F_u = (Ae/dose) \cdot 100$. The total clearance, nonrenal clearance, and volume of distribution are expressed as a function of bioavailability ($F$).

The percentage of penetration into blister fluid was calculated by $C_{max(BF)}/C_{max(plasma)}$ and $AUC_{BF}/AUC_{plasma}$, where $C_{max(BF)}$ and $AUC_{BF}$ are the $C_{max}$ in and AUC for blister fluid. Cefdinir concentrations in blister fluid were modeled on a biexponential equation by the same program used for plasma (9).

**Statistical analysis.** Analysis of variance by a Latin square design was used to test for differences among sequences, periods, and dose groups and to determine whether significant linear, quadratic, and cubic relationships existed between the

TABLE 1. Cefdinir pharmacokinetic parameters with increasing doses[a]

| Cefdinir dose (mg) | $C_{max}$ (µg/ml) | $T_{max}$ (h) | $t_{1/2\beta}$ (h) | AUC[b] (µg · h/ml) | CL/F (ml/min/kg) | $CL_R$ (ml/min/kg) | $CL_{NR}/F$ (ml/min/kg) | V/F (liter/kg) | $F_u$ (%)[c] |
|---|---|---|---|---|---|---|---|---|---|
| 200 | 1.00 ± 0.25 | 3.31 ± 0.63 | 1.43 ± 0.23 | 4.08 ± 1.13 | 12.51 ± 2.77 | 2.78 ± 0.87 | 9.73 ± 2.61 | 1.56 ± 0.46 | 23.0 ± 6.8 |
| 300 | 1.55 ± 0.58[d] | 3.20 ± 0.61 | 1.46 ± 0.23 | 6.53 ± 2.73[d] | 13.18 ± 5.07 | 2.14 ± 0.66 | 11.04 ± 4.64 | 1.64 ± 0.63 | 17.7 ± 5.1 |
| 400 | 2.15 ± 1.14[d] | 3.00 ± 0.63 | 1.43 ± 0.31 | 8.83 ± 4.62[d] | 13.90 ± 6.18 | 2.10 ± 0.70[d] | 11.80 ± 5.66 | 1.73 ± 0.98 | 17.3 ± 5.8[d] |
| 600 | 2.35 ± 0.67[d,e] | 3.22 ± 0.88 | 1.50 ± 0.16 | 9.84 ± 3.36[d,e] | 16.50 ± 4.76 | 1.97 ± 0.43[d] | 14.53 ± 4.61[d] | 2.09 ± 0.57 | 12.7 ± 6.2[d] |

[a] Results are expressed as means ± standard deviations. $t_{1/2\beta}$, elimination half-life; CL, total clearance; $CL_R$, renal clearance; $CL_{NR}$, nonrenal clearance; F, bioavailability.
[b] AUC is from time zero to infinity after a single dose.
[c] $F_u$, urinary excretion as unchanged drug as percentage of dose eliminated in 12-h urine sample.
[d] $P < 0.05$ versus 200-mg dose.
[e] $P < 0.05$ versus 300-mg dose.

dose and each parameter (SuperANOVA [analysis of variance]; Abacus Concepts, Inc., Berkeley, Calif.). Multiple comparisons between the four doses of cefdinir and the various pharmacokinetic parameters were done by using the Games-Howell procedure (SuperANOVA). Regression analysis was used to estimate the parameters of these relationships. A P value of <0.05 was considered statistically significant.

## RESULTS

Mean concentrations of cefdinir in both plasma and blister fluid after the administration of the 200-, 300-, 400-, and 600-mg doses are presented in Fig. 1. Peak cefdinir concentrations (mean ± SD) in plasma were 1.00 ± 0.25, 1.55 ± 0.58, 2.15 ± 1.14, and 2.35 ± 0.67 µg/ml at 3.31 ± 0.63, 3.20 ± 0.61, 3.00 ± 0.63, and 3.22 ± 0.88 h for doses of 200, 300, 400, and 600 mg, respectively. No significant difference was observed between the $C_{max}$ at doses of 600 and 400 mg as well as between doses of 400 and 300 mg. Regression analysis revealed a quadratic relationship ($P = 0.02$) between the dose and $C_{max}$. Maximal cefdinir concentrations in blisters were lower than the concentrations in plasma. Significant differences in $C_{max}$ in blisters were observed between doses of 600 and 200 mg, 400 and 200 mg, and 600 and 300 mg. The time to peak drug concentration ($T_{max}$) values in blister fluid were not significantly different with respect to the different doses but were delayed with respect to $T_{max}$ values in plasma. Regression analysis also showed a significant quadratic relationship between the dose and AUC values in plasma ($P < 0.001$), as evidenced by the lack of significant difference between the AUC values observed at doses of 600 and 400 mg as well as between 400 and 300 mg. The dose of cefdinir significantly influenced the AUCs in blister fluid between doses of 600, 400, and 200 mg as well as between 600 and 300 mg.

The pharmacokinetic parameters estimated from the cefdinir concentrations in plasma and blister fluid are listed in

Tables 1 and 2. Drug elimination half-lives in plasma and blister fluid were unchanged with increasing doses. Renal clearance decreased with increasing doses, but this proved significant only between doses of 600, 400, and 200 mg ($P < 0.006$). Nonrenal clearance was significantly higher at 600 mg than at 200 mg.

By using the ratio $C_{max(BF)}/C_{max(plasma)}$, the penetration of cefdinir was estimated at 54.6, 44.8, 44.2, and 47.1% for doses of 200, 300, 400, and 600 mg, respectively. More congruent values were obtained when the $AUC_{BF}/AUC_{plasma}$ ratios (range, 108.4 to 92.4%) were compared. The extent of penetration in blister fluid by using the $AUC_{BF}/AUC_{plasma}$ ratio was statistically different between doses of 600 and 200 mg and of 600 and 300 mg. Concentrations in blister fluid remained equal to or higher than concentrations in plasma from 6 to 12 h following cefdinir administration. Figure 2 depicts these curves in relationship to an arithmetic mean MIC at which 90% of the isolates are inhibited of 0.5 µg/ml for oxacillin-sensitive *S. aureus* (range, 0.03 to 1.0 µg/ml) (3, 5, 10, 13, 15, 17, 20) and an arithmetic mean value for *Streptococcus pyogenes* of 0.04 µg/ml (range, 0.015 to 0.06 µg/ml) (3, 13, 15, 17). Total concentrations in blister fluid remained above the $MIC_{90}$ of *S. pyogenes* for over 12 h at all doses (Fig. 2). The time above the *S. aureus* average MIC ranged from 0.7 to 7.3 h for doses of 200 to 600 mg, respectively (Table 3).

The fraction of dose excreted in urine within 12 h after drug administration was affected by the dose. Renal elimination decreased significantly ($P < 0.001$) with an increasing dose (range, 23.0 to 12.7%) but was significant only between doses of 600 mg and the 200- and 300-mg doses.

Cefdinir was well tolerated by the volunteers. Seven volunteers experienced episodes of light to moderate diarrhea, one

TABLE 2. Pharmacokinetic parameters for cefdinir penetration into blister fluid with increasing doses[a]

| Cefdinir dose (mg) | $C_{max}$ (µg/ml) | $T_{max}$ (h) | $t_{1/2\beta}$ (h) | Penetration (%) $C_{max(BF)}/C_{max(plasma)}$ | Penetration (%) $AUC_{BF}/AUC_{plasma}$[b] |
|---|---|---|---|---|---|
| 200 | 0.54 ± 0.14 | 4.9 ± 1.1 | 3.36 ± 0.43 | 54.6 ± 9.7 | 108.4 ± 16.7 |
| 300 | 0.67 ± 0.25 | 4.9 ± 0.9 | 3.73 ± 0.88 | 44.8 ± 12.3 | 86.3 ± 14.4 |
| 400 | 0.89 ± 0.36[c] | 4.8 ± 1.0 | 3.87 ± 0.90 | 44.2 ± 11.6 | 84.4 ± 10.4[c] |
| 600 | 1.09 ± 0.38[c,d] | 4.8 ± 1.0 | 3.67 ± 0.70 | 47.1 ± 13.7 | 92.4 ± 20.0[c] |

[a] Results are means ± SDs. $t_{1/2\beta}$, elimination half-life.
[b] AUC is from time zero to infinity after a single dose.
[c] $P < 0.05$ versus 200-mg dose.
[d] $P < 0.05$ versus 300-mg dose.



FIG. 2. Mean AUC of cefdinir in blister fluid in volunteers following single oral doses of 200 (●), 300 (○), 400 (·), and 600 (△) mg. $MIC_{90}$, MIC at which 90% of the isolates are inhibited.

TABLE 3. Pharmacodynamic parameters for cefdinir penetration
into blister fluid with increasing doses

| Cefdinir dose (mg) | $AUC_{BF}$ ($\mu g \cdot h/ml$)[b] | Estimated time above $MIC_{90}$ (h)[c] | |
|---|---|---|---|
| | | S. aureus | S. pyogenes |
| 200 | 4.37 ± 1.09 | 0.7 | >12 |
| 300 | 5.54 ± 2.31 | 3.6 | >12 |
| 400 | 7.29 ± 3.30 | 5.7 | >12 |
| 600 | 9.55 ± 3.09 | 7.3 | >12 |

[a] Results are expressed as means ± SDs.
[b] AUC is from time zero to infinity after a single dose.
[c] $MIC_{90}$, MIC at which 90% of the isolates are inhibited.

volunteer complained of abdominal cramping, and one volunteer experienced an episode of light transient headache. The adverse events occurred irrespective of the dose.

## DISCUSSION

The pharmacokinetic parameters of cefdinir found in our study following the administration of single doses ranging from 200 to 600 mg are in agreement with those reported by others (6, 7). We observed nonlinearity in cefdinir peak concentrations and AUC at doses of 600 mg, as reflected by the quadratic relationships between the $C_{max}$, AUC, and cefdinir dose. The same tendency was reported with doses of 800 mg in previous studies (6). However, this quadratic relationship, indicative of a change in bioavailability with respect to increasing doses, does not explain physiologic processes. Since $T_{max}$ occurred on average 3 h after the administration of cefdinir, these results may indicate that breakfast taken 2 h postadministration of cefdinir can affect the absorption process, resulting in a lower AUC value than expected as well as a smaller fraction of drug excreted unchanged in urine at doses exceeding 400 mg. The result of a food effect study was a 24% decrease in the AUC when cefdinir was administered 1 h before a high-fat breakfast (13). Such a decrease in AUC was not found to be clinically significant. In a similar dose proportionality study, the results for subjects who fasted for 4 h postdose demonstrated a quadratic relationship between the cefdinir dose and AUC (6). It follows that the feeding schedule does not appear to affect cefdinir dose proportionality.

Nonrenal clearance was linear with respect to dose. The total clearance and the volume of distribution of cefdinir at the 600-mg dose were higher than expected. These increases were not statistically significant ($P = 0.11$, $CL/F$; $P = 0.15$, $V/F$) with respect to the 200-, 300-, and 400-mg doses. A decreasing bioavailability with increasing doses could explain such a trend. Renal clearance is also significantly decreased at the 600-mg dose of cefdinir. This and a small fraction of drug excreted in the urine may indicate the presence of a rate-limited excretion process, such as active tubular secretion. This has been observed in a previous study (7).

The $C_{max}$ in blister fluid was lower than and delayed compared with concentrations in plasma, but the penetration into blisters was extensive. The mean penetration into blister fluid as determined by AUC ratios ranged from 84 to 108%. Although both the $C_{max}$ and AUC methods were used to estimate the extent of penetration into blister fluid, the AUC ratio is deemed more accurate because multiple datum points are used in its determination (2). The extent of cefdinir penetration, as estimated by AUC ratios, is comparable to penetration achieved with the use of cefpodoxime (104%) (16) but lower

than that achieved with cefixime by using cantharides-impregnated plasters (132.6%) (18).

Experimental data regarding β-lactam antibiotics support the evidence that time above the MIC is best related to outcome (4). In addition, the duration of the time that the concentrations of β-lactam antibiotics in serum exceed the MIC is significant to the outcome of the infection (4). Although these factors appear to be the most important, the postantibiotic effect also contributes to the performance against various organisms. Cefdinir is not an extensively bound drug (61%) and has been reported to have an in vitro postantibiotic effect of 25- to 123-min duration with S. aureus (10).

In comparison, cefdinir offers improved activity of S. pyogenes and better activity against oxacillin-susceptible S. aureus than cefixime (5, 12, 15, 19, 20). Unfortunately, data assessing interstitial fluid penetration and MIC after the administration of oral β-lactam antibiotics are not available. On the basis of available in vitro MIC data, the moderate binding affinity, and the extensive penetration into blister fluid observed in this study, cefdinir at concentrations ranging from 200 to 600 mg administered at 12-h intervals appears adequate for treatment of skin infections caused by S. pyogenes. Despite the lack of correlation of incidences of adverse effects and dosage, the use of lower doses (200 to 400 mg) may have an impact on the incidences of such adverse effects (Fig. 2). If the same considerations and the possibility of a postantibiotic effect are applied to the treatment of skin infections by oxacillin-susceptible S. aureus, dosages of 600 mg every 8 h may be required. These estimations are limited by the use of in vitro MIC data as well as the use of total cefdinir concentrations in blister fluid. In addition, cefdinir penetration into blister fluid may be modified in diseased soft tissue.

In summary, this study showed the possibility of decreased absorption and decreased renal clearance of cefdinir at doses exceeding 400 mg. Cefdinir penetration into blister fluid in healthy volunteers was extensive. This may prove to be advantageous in the treatment of gram-positive skin infections caused by S. pyogenes. Studies with patients with soft tissue infections need to be undertaken.

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