ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, June 1990, p. 1094–1099
0066-4804/90/061094-06$02.00/0

Vol. 34, No. 6

Pharmacokinetics of Cefpodoxime in Plasma and Skin Blister Fluid following Oral Dosing of Cefpodoxime Proxetil

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Received 22 November 1989/Accepted 26 March 1990

The single-dose and steady-state pharmacokinetics of cefpodoxime were assessed in plasma and skin blister fluid (SBF) after oral dosing of 200 mg ($n = 8$) and 400 mg ($n = 8$) of cefpodoxime proxetil (doses are expressed as cefpodoxime equivalents) in healthy subjects in an open-label, parallel-design study. Skin blisters were formed by air suction on the midvolar forearm by a previously validated method. After single-dose administration, serial plasma and SBF samples were collected over 24 h for measurement of cefpodoxime by microbiological assays. After a 1-week washout, subjects received the same doses of antibiotic every 12 h for 5 days, with plasma and SBF sampling on day 5. After 200 mg of cefpodoxime proxetil, average peak concentrations (C_{max}) in plasma and SBF were 2.18 ± 0.52 and 1.55 ± 0.59 μg/ml, respectively, after a single dose and 2.33 ± 0.74 and 1.56 ± 0.55 μg/ml, respectively, at steady state. After 400 mg of cefpodoxime proxetil, C_{max} in plasma and SBF averaged 4.16 ± 1.04 and 2.94 ± 0.71 μg/ml, respectively, following a single dose and 4.10 ± 0.95 and 2.84 ± 0.88 μg/ml, respectively, at steady state. C_{max} occurred 1.1 to 1.6 h later in SBF than in plasma. There was no accumulation of cefpodoxime in plasma or SBF when dosing was done every 12 h. Cefpodoxime blister fluid penetration was estimated to be 67 to 101%, consistent with the relatively low serum protein binding of the drug. Cefpodoxime levels exceeding the MIC for 90% of many skin pathogens, such as *Streptococcus* species (<1 μg/ml) or *Staphylococcus* species (2 to 4 μg/ml), were achieved in plasma and SBF following the 200- and/or 400-mg dosing regimens.

Cefpodoxime proxetil is a broad-spectrum oral cephalosporin (19, 20, 35). Cefpodoxime proxetil is a prodrug which is thought to be deesterified to its active metabolite (cefpodoxime) by intestinal wall esterases (19, 20, 35). The drug acts by binding to penicillin-binding proteins and affects bacterial wall synthesis (19, 35). In vitro tests have revealed low MICs against bacteria such as *Streptococcus* species or *Haemophilus influenzae* (19, 35). Cefpodoxime proxetil has been studied for the treatment of skin and soft tissue infections caused by gram-positive organisms, especially *Staphylococcus* and *Streptococcus* species, in Japan and has been shown to be effective (17, 24, 25). Information on tissue penetration would be useful in interpreting these clinical findings.

The assessment of antibiotic concentrations in skin blister fluid (SBF) (skin blisters formed by air suction) is a commonly used experimental model to predict antibiotic levels in tissues (4, 38). This method has been used to assess tissue penetration of several penicillins (29, 30, 37), cephalosporins (2, 5, 9, 21–23, 28, 31, 36, 39, 40), tobramycin (1), and aztreonam (41). The present study used this SBF model to assess the penetration of cefpodoxime into SBF after single and multiple oral doses of cefpodoxime proxetil.

MATERIALS AND METHODS

Subjects. Sixteen healthy volunteers (10 males and 6 females) aged 18 to 35 years (mean, 27 years) and with an average weight of 72.3 kg (range, 55.9 to 97.7 kg) successfully completed all aspects of the study. Subjects were enrolled in the study following a complete physical exam, medical history, electrocardiogram, blood studies and urinalysis, and written informed consent. The protocol was approved by the Bronson Methodist Hospital (Kalamazoo, Mich.) Human Use Committee, and the study was conducted at the Upjohn Research Clinics (Kalamazoo, Mich.).

Study design. Eight subjects were randomly assigned to each of the following treatment groups: (i) a single 200-mg dose of cefpodoxime proxetil followed by 200 mg every 12 h for five consecutive days and (ii) a single 400-mg dose of cefpodoxime proxetil followed 7 days later by 400 mg every 12 h for five consecutive days. A 1-week washout separated the single-dose and multiple-dose portions of the study. Treatments were administered orally as one or two 200-mg cefpodoxime proxetil tablets (lot 25,178; The Upjohn Co., Kalamazoo, Mich.); the dose is expressed as free-acid (cefpodoxime) equivalents.

A bacampicillin treatment group consisting of eight healthy volunteers (six males and two females) aged 18 to 34 years and with a mean weight of 73.5 kg was included in this study for procedural validation of the SBF method. A single 800-mg oral dose of bacampicillin (given as two 400-mg bacampicillin tablets; Spectrobid; lot 68027; containing 280 mg of ampicillin per tablet; Roerig, New York, N.Y.) followed 7 days later by 800 mg every 12 h for five consecutive days was administered to this group. Results from this experiment were consistent with those of previous reports (6, 29, 30, 32), in particular, the study by Schreiner et al. in which skin blisters were also produced by suction, thus validating the method used to produce blisters in this study.

Sample collection. Serial blood and SBF samples were obtained for the determination of cefpodoxime levels. Blood samples were collected in 5-ml lavender-top tubes (freeze-dried EDTA anticoagulant; Becton Dickinson and Co., Rutherford, N.J.) from individual venipunctures at the following times: 0 (prior to dosing), 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 10, 12, 16, 20, and 24 h following the single-dose regimen and the final dose of the multiple-dose regimen. Plasma was harvested from each sample, frozen on dry ice, and stored at −70°C until assayed.

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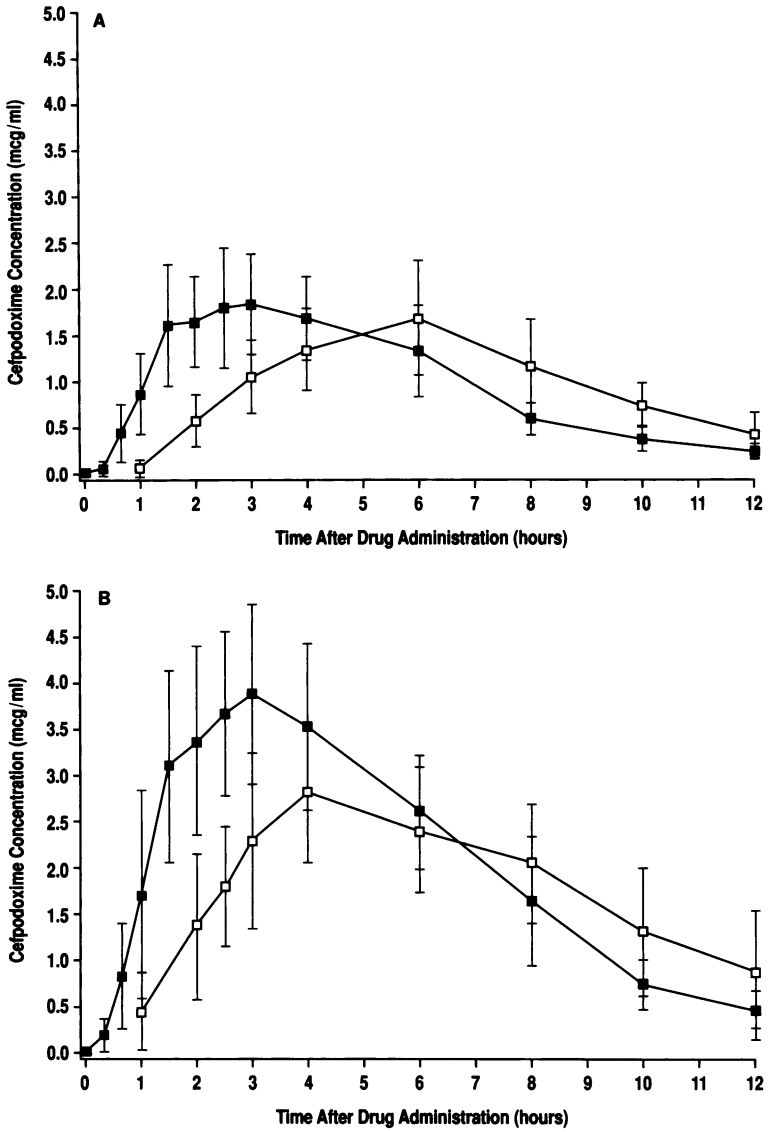

FIG. 1. Cefpodoxime concentrations (mean ± standard deviation) in plasma (■) and SBF (□) after single-dose administration of 200 mg (A) and 400 mg (B).

Eight skin blisters were produced within 2 h of dosing in each volunteer by a previously described suction method (4, 38). Briefly, a Perspex block containing eight holes (diameter, 8 mm) was strapped to the left midvolar forearm after the skin had been cleaned with 70% alcohol and allowed to equilibrate to room temperature (25°C). Controlled suction (250 mm Hg [ca. 33.3 kPa]) was applied until uniform blisters were formed within 2 h. Fifty to 200 μl of blister fluid was aspirated with a 27-gauge 0.5-in. (1.27-cm) needle with a syringe (Becton Dickinson and Co., Rutherford, N.J.) at 1, 2, 3, 4, 6, 8, 10, and 12 h following drug administration (single-dose regimen and the last dose of the multiple-dose regimen). Samples were stored in ultracentrifugation tubes (Sarstedt, Newton, N.C.) at −70°C until assayed for cefpodoxime concentrations.

Bioanalytical assays. Concentrations of cefpodoxime in plasma and SBF were determined by a microbiological assay developed and validated by the Upjohn Clinical Research Laboratories. Quantitation of cefpodoxime was based on the diffusion of 30-μl samples from 6-mm wells into antibiotic medium 1 (Difco Laboratories, Detroit, Mich.) seeded with 0.15% (vol/vol) *Providencia rettgeri* UC-12186 (CDC 4334-69; provided by Bronson Methodist Hospital). Zones of inhibition were measured and read against the standard curve. Validation of the assay included linearity, pH effect, recovery, precision, and stability. The cefpodoxime assay was shown to be linear over the cefpodoxime concentration range of 0.04 to 1.28 μg/ml.

Plasma samples were diluted with pooled plasma, whereas SBF was diluted with phosphate-buffered saline as necessary, to obtain a linear standard curve. Over the pH range of 4 to 8, sample pH was found to have no effect on the sensitivity of the assay or cefpodoxime recovery. The assay showed a mean recovery of 94%, with a maximum within-day precision (coefficient of variation) of 3.9% and a between-day coefficient of variation of 8.0%. Cefpodoxime was stable in plasma and buffer over a 12-week period at −30°C.

Pharmacokinetic analysis. Pharmacokinetic analysis of plasma and SBF concentration-time data was performed by noncompartmental methods (15). Terminal elimination rate

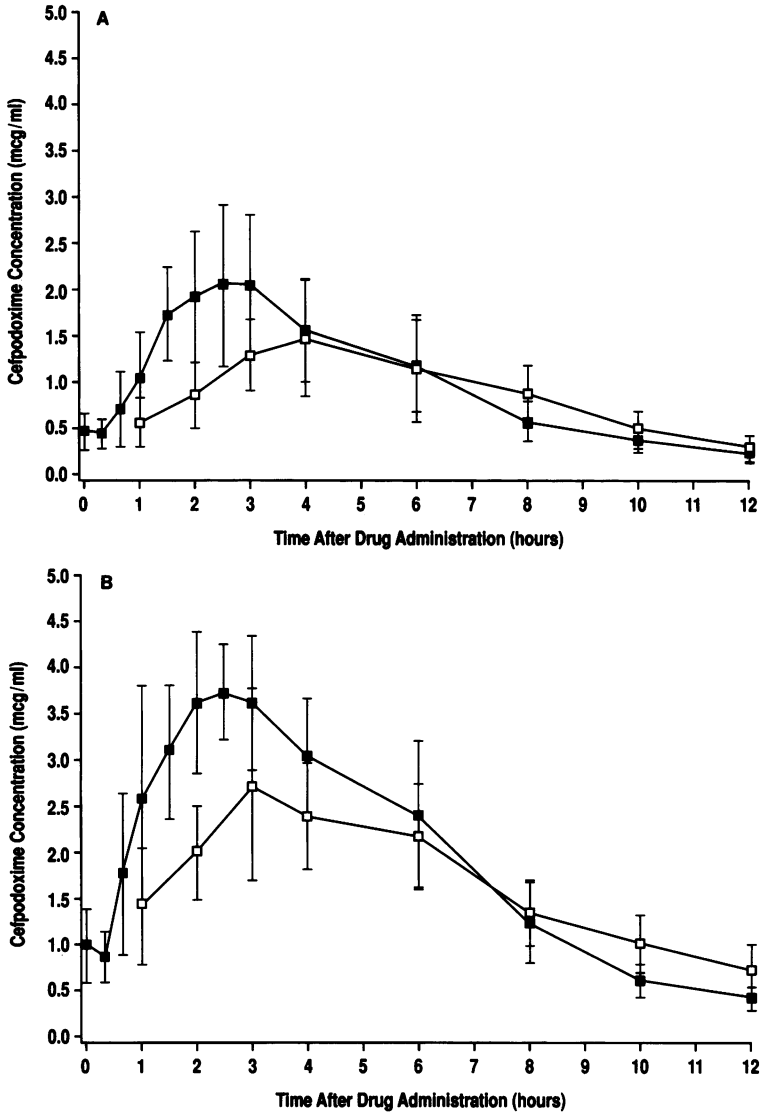

FIG. 2. Cefpodoxime concentrations (mean ± standard deviation) in plasma (■) and SBF (□) at steady state (day 5) for doses of 200 mg (A) and 400 mg (B).

constants were estimated by least-squares regression of plasma concentration-time datum points lying in the terminal log-linear region of the curves with RSTRIP (11). The elimination half-life was calculated as 0.693 divided by the terminal elimination rate constant. Areas under the plasma and SBF concentration-time curves (AUC) were determined with the trapezoidal rule. AUC from time zero to infinity ($AUC_{0-\infty}$) following single-dose administration was estimated by adding AUC_{0-T}, where T was the time of the last detectable sample concentration or 12 h (last sampling time) for the SBF data, to $AUC_{T-\infty}$, obtained by extrapolation with the terminal elimination rate constant. AUC at steady state for the 96- to 108-h interval (AUC_{ss}) was calculated for the last dose of the multiple-dose regimen with the trapezoidal approximation. Steady-state conditions in plasma were assumed on the basis of the results of previous multiple-dose studies (data on file; The Upjohn Co.). Apparent systemic clearance was estimated as the dose divided by the AUC, where AUC is $AUC_{0-\infty}$ for single-dose data and AUC_{ss} for steady-state data. Penetration of drug into SBF was estimated as $C_{max_{sbf}}/C_{max_p}$ ratios for both single-dose and multiple-dose data and AUC_{sbf}/AUC_p ratios for single-dose data, where sbf and p are notations for SBF and plasma, respectively, and C_{max} is the peak concentration. SBF/plasma concentration ratios (C_{sbf}/C_p) at analogous sampling times were also calculated for all treatments and dosing regimens. Drug accumulation after multiple dosing was estimated as the ratio of AUC_{ss} to AUC_{0-12} (single-dose data) in plasma (7).

Statistical analysis. A paired t test procedure was used to determine the statistical significance of pharmacokinetic parameter differences between plasma and SBF and between analogous single- and multiple-dose data within treatment groups. Comparisons between treatment groups were performed with analysis of variance for comparisons of means of two independent samples. All analyses were conducted with SAS (Cary, N.C.) version 5.

RESULTS

Mean cefpodoxime concentrations in both plasma and SBF after single-dose administration and at steady state are

TABLE 1. Mean (standard deviation) pharmacokinetic parameters after single and multiple doses of cefpodoxime proxetil

Dose (mg)	Fluid	AUC ($\mu g \cdot h/ml$)[a,b]	C_{max} ($\mu g/ml$)[c]	Time to C_{max} (h)[c]	Half-life (h)[d]	Apparent systemic clearance (ml/min)[b]
200						
Single	Plasma	11.8 (2.7)	2.18 (0.52)	3.1 (1.4)	2.7	275 (57)
	SBF		1.55 (0.59)	4.7 (1.3)	3.0	
Steady state	Plasma	11.8 (3.8)	2.33 (0.74)	2.3 (0.6)	2.6	309 (101)
	SBF		1.56 (0.55)	3.5 (0.8)	2.3	
400						
Single	Plasma	25.0 (6.3)	4.16 (1.04)	2.9 (0.8)	2.6	264 (76)
	SBF		2.94 (0.71)	4.3 (1.6)	2.7	
Steady state	Plasma	24.0 (5.9)	4.20 (0.95)	2.4 (0.8)	2.7	296 (90)
	SBF		2.84 (0.88)	3.5 (1.2)	3.2	

[a] $AUC_{0-\infty}$ for single dose and AUC_{ss} for steady state.
[b] SBF parameters could not be accurately estimated because of missing samples in several subjects.
[c] $P < 0.05$, SBF versus plasma, after single- and multiple-dose administration.
[d] Harmonic mean.

presented in Fig. 1 and 2. Following both single and multiple doses, cefpodoxime levels in SBF were generally lower than those in plasma for the first 6 h after dosing and exceeded levels in plasma thereafter. Peak levels of cefpodoxime in SBF were delayed as compared with peak levels in plasma. Selected mean pharmacokinetic parameters following single-dose administration and at steady state are listed in Table 1. Individual subject AUC_{sbf} could not be accurately estimated because of missing cefpodoxime concentrations in SBF of several subjects in whom less than eight blisters were formed during the suction procedure. After both 200- and 400-mg doses, peak cefpodoxime concentrations in plasma were significantly higher than those in SBF following a single dose or at steady state.

Assessment of the potential accumulation of cefpodoxime in either plasma or SBF following multiple dosing was performed by a comparison of single-dose and steady-state pharmacokinetic parameters and C_{sbf}/C_p ratios. Plasma pharmacokinetic parameters following single-dose and multiple-dose administration were not significantly different for either the 200- or the 400-mg dose. Accumulation ratios in plasma following the 200- and 400-mg doses were estimated to be 1.01 ± 0.248 and 0.976 ± 0.193, respectively. These values are in close agreement with the theoretical accumulation value of 1.05; that is, essentially no accumulation of cefpodoxime is expected with a twice-daily multiple-dosing regimen.

Cefpodoxime SBF single-dose and steady-state pharmacokinetic parameters (C_{max}, time to C_{max}, and terminal elimination rate constant) were consistent with the analogous data for plasma in that there were no statistically significant differences between the single- and multiple-dose data at either dose level. Average C_{sbf}/C_p ratio-versus-time profiles were similar after single- and multiple-dose administration. With the exception of the 1-h and 10-h time points following 200-mg cefpodoxime doses, there were no significant ($P > 0.05$) differences between single-dose and steady-state C_{sbf}/C_p ratios.

Penetration of cefpodoxime in SBF was estimated to be $72.3\% \pm 16.0\%$ and $71.2\% \pm 9.1\%$ following 200- and 400-mg doses, respectively, determined with $C_{max_{sbf}}/C_{max_p}$ ratios from single-dose data. Estimates from multiple-dose data were similar ($67.0\% \pm 6.1\%$ and $67.3\% \pm 11.2\%$, respectively). AUC_{sbf}/AUC_p ratios were calculated from average concentration-time data as opposed to averaging individual subject data, since AUC_{sbf} could not be accurately estimated for all subjects, as discussed previously. These values were 101 and 89.6%, respectively, following 200- and 400-mg single doses. Single-dose C_{max} and AUC ratios and steady-state C_{max} ratios did not vary significantly with dose ($P > 0.05$), indicating similar cefpodoxime interstitial fluid penetration at the two dose levels.

DISCUSSION

Cefpodoxime pharmacokinetic parameters in plasma for this trial were in good agreement with the results of previous studies (18a). There were no significant differences in dose-corrected and dose-independent cefpodoxime pharmacokinetic parameters between the 200- and 400-mg cefpodoxime proxetil treatments after a single dose or at steady state, suggesting linear pharmacokinetics. In addition, pharmacokinetic parameters within each cefpodoxime treatment group were unaltered following multiple-dose administration as compared with single-dose administration. This finding, along with the observed mean accumulation ratio of approximately 1, indicates that cefpodoxime does not accumulate when 200- or 400-mg doses are given every 12 h.

Cefpodoxime SBF penetration was estimated to be >67%, and drug levels in SBF equivalent to or greater than those in plasma could be achieved with either dosing regimen. The levels of cefpodoxime in plasma and SBF (in part) should exceed the MIC for 90% of many skin pathogens, especially *Streptococcus* species (MIC for 90%, < 1 μg/ml) and some *Staphylococcus* species (MIC for 90%, 2 to 4 μg/ml) (19, 35).

The extent of SBF penetration by cefpodoxime (67 to 101%) is consistent with the relatively low serum protein binding of the drug (40%) (20). Protein binding is one of the primary factors affecting extravascular interstitial passage of antibiotics (3, 8, 12, 14, 18, 34, 42). In a comparative study of the interstitial passage of four cephalosporins in humans, it was shown that the compound with the highest protein-binding capacity had a lower penetration and slower rate of penetration than the other cephalosporins examined by a skin blister technique (13). However, good diffusibility into interstitial fluid was reported for ceftriaxone, which is 83 to 96% protein bound; a persistent high concentration gradient provided by its long serum half-life resulted in higher skin

fluid levels than would have been expected based on protein binding alone (33). Thus, other factors, such as lipophilicity, local pH, and binding to cellular components, must also be considered in evaluating drug penetration into tissues (3, 10, 16). In this study, the extent of SBF penetration achieved by cefpodoxime was consistent with its low protein binding, suggesting that the amount of free drug in plasma was the driving force for passage into SBF.

The results of this investigation demonstrated high blister fluid penetration of cefpodoxime following oral administration of cefpodoxime proxetil. The extent of penetration observed was similar to values reported for cefuroxime and cefotaxime, which are comparably bound to serum protein (33%) (13). Although these data are suggestive of good tissue penetration for cefpodoxime, levels of drug in inflammatory tissues could differ because of higher protein concentrations found in inflammatory exudates as compared with noninflammatory blister fluid (16, 26, 27). Thus, additional work may be needed to validate this experimental model in infectious foci induced by different types of microorganisms during drug treatment.

ACKNOWLEDGMENTS

We thank the staff of the Upjohn Research Clinics-Bronson Clinical Investigation Unit/Jasper for their expert technical assistance and Barbara Burton for preparation of the manuscript.

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