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Bioequivalency of solid oral dosage forms of cefixime *

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Summary

A study was performed in 24 healthy subjects to determine whether tablet and capsule formulations of cefixime (CL 284,635; FK027), a new oral cephalosporin, given as a single 400 mg dose, were bioequivalent to one another and to a reference oral solution. Mean values of C_{max} in serum were 3.87, 3.39, and 3.82 μg/ml after tablet, capsule and solution doses, respectively. Comparison (ANOVA) of the pharmacokinetic parameters showed significantly ($P < 0.05$) lower $AUC_{0\rightarrow\infty}$ and C_{max} values for the capsule than for the tablet; however, the mean differences were less than 16%. All pharmacokinetic parameters for the tablet, except for a significantly larger MRT_{ni} and t_{max}, were comparable to those for the solution. The bioavailability of cefixime based on $AUC_{0\rightarrow\infty}$ and 24-h urinary recovery data from the tablet dosage form was slightly better (mean differences 14–16%) than from the capsule and virtually identical to that after the oral solution. The statistical power of the study was greater than 90% to detect a difference in $AUC_{0\rightarrow\infty}$ values of 20%. Overall, based on $AUC_{0\rightarrow\infty}$ comparisons, the results show that the tablet, capsule and oral reference solution are bioequivalent to one another.

Introduction

Cefixime (CL 284,635; FK027) is a new orally active third-generation cephalosporin with a broad spectrum of antibacterial activity (Brittain et al., 1985). Cefixime has been shown to be resistant to β-lactamase hydrolysis and to have a longer elimination half-life ($t_{1/2}$) and larger dose-adjusted area under the serum concentration time curve (AUC) relative to other currently available oral penicillins and cephalosporins (Silver et al., 1977; Meyers et al., 1969; Pfeffer et al., 1977). In the course of the development of oral formulations of cefixime, a pilot screening study showed that the concentration–time course profile of the drug was similar after prototype tablets and capsule and solution formulations (Faulkner et al., 1985). The purpose of this study was to determine the bioequivalence of a newly developed tablet intended for marketing, relative to a capsule formulation used in many of the pharmacokinetic and Phase II/III clinical studies and to a reference oral solution.

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Materials and Methods

Subjects

After physical examination and biochemical tests, 24 healthy male subjects ranging in age from 19 to 39 (mean 26) years and weighing 61–86 (mean 71) kg took part in the study. Written informed consent was obtained from the subjects and the study was approved by the Research Review and Ethics Committee of the Institute of Clinical Pharmacology, Piscataway, NJ.

Study design

Each subject was randomly assigned in a 3-way randomized cross-over design to receive a single oral 400-mg dose of cefixime as tablet, capsule (2×200 mg) and oral reference solution formulations (Table 1). Each dose was administered with 250 ml water with 72-h intervals between dosings. All subjects fasted from 22.00 h the night prior to until 4 h after each morning dose on days 1, 4 and 7 of the study. Subjects were confined to a clinical research facility (Institute of Clinical Pharmacology, Piscataway, NJ) for the duration of the 9-day study. Blood samples (6 ml each) were obtained by venipuncture or an indwelling heparin lock in a forearm vein prior to dosing (0 h) and at 0.5, 1, 2, 3, 4, 5, 6, 8, 12, 16 and 24 h after each dose. Following clot formation, serum was harvested by centrifugation and stored at $-15\,^{\circ}C$ or lower until analyzed. Urine specimens were collected by natural voiding over the 2-h period prior to dosing (-2 to 0 h) and at 0–6 , 6–12, 12–24 and 24–48 h intervals after each dose. For each collection, total urine volume and pH were recorded and an aliquot was stored at $-15\,^{\circ}C$ or lower until analyzed.

Drug analysis

Concentrations of cefixime in serum and urine

TABLE 1

Randomization schedule and pertinent demographic data

Subject	Randomization schedule	Age (yr)	Race	Weight (kg)	Height (cm)
1	Tab/Cap/Soln	20	Black	74.8	178
2	Cap/Tab/Soln	22	Caucasian	74.4	170
3	Tab/Soln/Cap	29	Black	70.8	163
4	Cap/Soln/Tab	38	Caucasian	73.0	175
5	Soln/Tab/Cap	23	Caucasian	67.1	170
6	Soln/Cap/Tab	32	Black	73.9	170
7	Tab/Cap/Soln	39	Caucasian	63.5	175
8	Tab/Soln/Cap	22	Caucasian	64.9	183
9	Soln/Cap/Tab	23	Caucasian	76.7	178
10	Soln/Tab/Cap	28	Black	63.0	160
11	Cap/Tab/Soln	19	Caucasian	66.2	178
12	Cap/Soln/Tab	30	Black	86.2	180
13	Soln/Cap/Tab	24	Black	74.8	175
14	Tab/Soln/Cap	21	Black	68.0	173
15	Soln/Tab/Cap	20	Black	61.2	168
16	Cap/Soln/Tab	22	Black	77.6	173
17	Cap/Tab/Soln	30	Caucasian	60.8	173
18	Tab/Cap/Soln	25	Caucasian	66.2	173
19	Soln/Cap/Tab	21	Caucasian	65.8	178
20	Cap/Soln/Tab	21	Black	84.4	183
21	Cap/Tab/Soln	27	Caucasian	73.3	178
22	Tab/Cap/Soln	22	Caucasian	72.1	180
23	Soln/Tab/Cap	21	Caucasian	73.3	180
24	Tab/Soln/Cap	34	Black	73.7	175
Mean ± S.D.		25.5 ± 5.8		71.1 ± 6.6	175 ± 6

Six study groups with 4 subjects each.

were determined using a reverse-phase high performance liquid chromatographic (HPLC) method (Falkowski et al., 1987). Samples were analyzed in duplicate. The sensitivity limits of the assay were 0.05 μg/ml and 5.0 μg/ml for serum and urine, respectively.

Data analysis

Pharmacokinetic parameters for cefixime were estimated using model-independent methods (Gibaldi, 1984; Gibaldi and Perrier, 1982; Riegelman and Collier, 1980). The peak serum concentration (C_{max}) and time to C_{max} (t_{max}) were determined from visual inspection of the serum concentration–time data. The zero- and first-moment area under the serum concentration–time curves (AUC and $AUMC$, respectively) were estimated by the linear trapezoidal method in the ascending portion and by the log e trapezoidal method in the descending portions of the serum concentration–time profiles utilizing classical extrapolation methods (Gibaldi, 1984; Gibaldi and Perrier, 1982; Riegelman and Collier, 1980). The elimination rate constant (K) was estimated by least-squares regression analysis of the terminal portion of the log e serum concentration–time profile. The elimination half-life ($t_{1/2}$) was estimated from the ratio of $0.693/K$. The 48-h urinary recovery ($Ae_{0\to 48}$) was also expressed as the percentage of the dose (f_e). Renal clearance (CL_r) was estimated from the quotient $Ae_{0\to 24}/AUC_{0\to 24}$.

The bioavailability of cefixime from the two solid dosage forms relative (F_{rel}) to the oral reference solution was estimated from the ratios of $AUC_{0\to\infty}$ and 48-h urinary recovery ($Ae_{0\to 48}$) data.

The serum and urinary excretion pharmacokinetic parameters estimated after the 3 oral dosage forms were statistically compared using analysis of variance (ANOVA; GLM) with treatment, period and subject as factors in the linear model (SAS; SAS Institute Inc., Cary, NC). Where significant ($P < 0.05$) treatment effects were observed, a least significant difference t-test examined the difference between each pair of dosages (Tukey, 1953).

Results

Mean serum concentrations of cefixime after each dosage form are provided in Table 2 and graphically presented in Fig. 1. The mean pharmacokinetic parameters and statistical results are summarized in Table 3. At the early time points, the solution yielded comparable serum concentrations to the tablet and somewhat higher serum concentrations than after the capsule. At later time points, serum concentrations were very similar after all 3 formulations.

Mean C_{max} values were 3.87, 3.39 and 3.82 μg/ml after the tablet, capsule and solution, respectively; differences that were not significant ($P > 0.05$). t_{max} values were reached by about 4 h after the tablet and capsule; significantly ($P < 0.01$) longer than after the solution (3.1 h). Mean $AUC_{0\to\infty}$ values were 27.6, 23.9 and 27.1 μg · h/ml for the tablet, capsule and solution formulations, respectively; differences which were not significant ($P > 0.05$). The mean $t_{1/2}$ of 2.9–3.0 h was comparable after all 3 doses. The MRT_{ni} of cefixime after the tablet and capsule formulations were significantly ($P < 0.01$) longer ($\sim \frac{1}{2}$ h) than the solution dose.

Mean cumulative recovery of cefixime in 48-h urine collections ($Ae_{0\to 48}$) are summarized in Table 3. Except for one occasion (subject no. 1, solution), no detectable concentrations of cefixime

TABLE 2

Mean (± S.D.) serum concentrations (μg/ml) of cefixime in 24 male subjects given 400 mg cefixime in tablet, capsule (2×200 g), and oral (reference) solution formulations

Time (h)	Tablet	Capsule	Solution
0	0	0	0
0.5	0.24±0.18	0.16±0.32	0.73±0.39
1	1.12±0.43	0.81±0.85	1.86±0.62
2	2.64±1.06	1.93±1.12	3.35±0.70
3	3.35±1.13	2.72±0.99	3.67±0.78
4	3.69±1.27	3.18±0.92	3.56±0.78
5	3.49±1.38	3.16±0.95	3.14±0.85
6	2.82±1.12	2.58±0.83	2.47±0.82
8	1.79±0.75	1.64±0.55	1.51±0.59
12	0.66±0.29	0.60±0.22	0.57±0.34
16	0.25±0.12	0.24±0.11	0.23±0.17
24	0.04±0.05	0.03±0.04	0.04±0.08

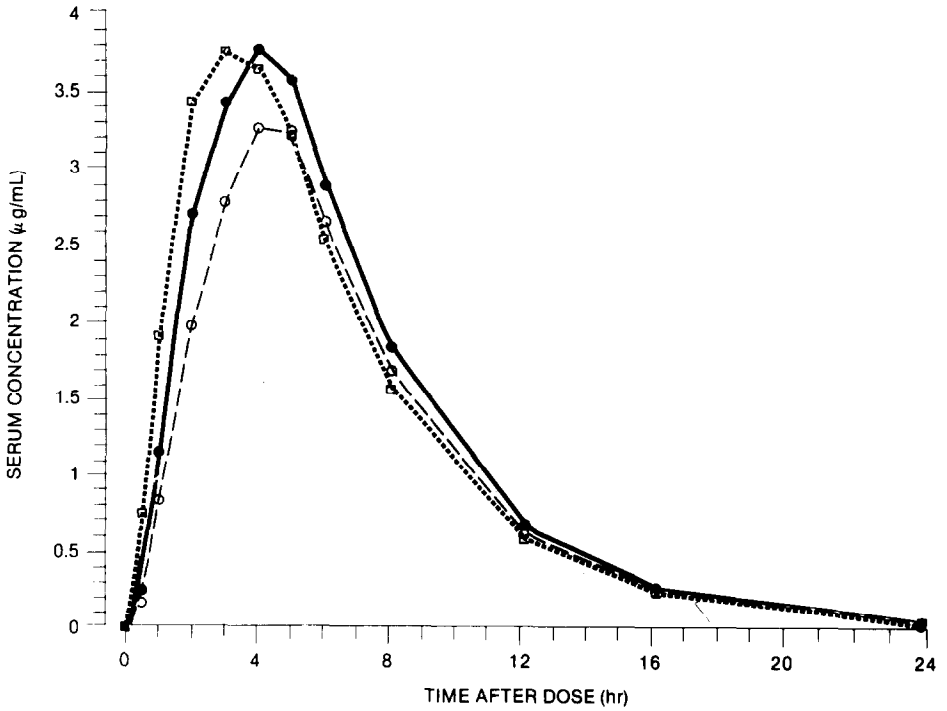

Fig. 1. Mean serum concentration profiles for cefixime after single 400 mg oral doses in tablet (●), capsule (○) and solution (□) formulations.

TABLE 3

Mean (± S.D.) pharmacokinetic parameters of cefixime in 24 healthy male subjects receiving 400 mg cefixime as tablet, capsule and oral reference solution formulations

	Tablet ($n = 23$)	Capsule ($n = 23$)	Solution ($n = 22$)	ANOVA level of significance [a]
C_{max} (μg/ml)	3.87 ± 1.34 [b]	3.39 ± 1.08	3.82 ± 0.78	> 0.05
t_{max} (h)	4.0 ± 0.71 [c]	4.2 ± 0.80 [d]	3.1 ± 1.02	< 0.01
$AUC_{0\rightarrow 24}$ (μg · h/ml)	27.3 ± 9.21 [b]	23.7 ± 7.12 [d]	26.8 ± 7.72	< 0.05
$AUC_{0\rightarrow\infty}$ (μg · h/ml)	27.6 ± 9.31 [b]	23.9 ± 7.22 [d]	27.1 ± 8.12	< 0.05
$t_{1/2}$ (h)	2.9 ± 0.44	3.0 ± 0.46	3.0 ± 0.69	> 0.05
MRT_{ni} (h)	6.5 ± 0.85 [b]	6.8 ± 0.81	6.0 ± 0.98	< 0.01
$Ae_{0\rightarrow 48}$ (mg)	40.4 ± 18.4 [b]	32.0 ± 15.5	37.4 ± 18.5	< 0.05
f_e (%)	10.1 ± 4.6 [b]	8.0 ± 3.9	9.4 ± 4.6	< 0.05
CL_r (ml/min)	24 ± 9	22 ± 8	23 ± 7	> 0.05
MDT (h)	0.5 ± 0.6	1.0 ± 0.8	–	0.05
F_{rel} [b] ($AUC_{0\rightarrow\infty}$) %	99	90	100	–
($Ae_{0\rightarrow 48}$) %	96	82	100	–

[a] Comparison of all 3 formulations.
[b] Comparison of tablet vs capsule was statistically significant ($P < 0.05$).
[c] Comparison of tablet vs solution was statistically significant ($P < 0.05$).
[d] Comparison of capsule vs solution was statistically significant ($P < 0.05$).

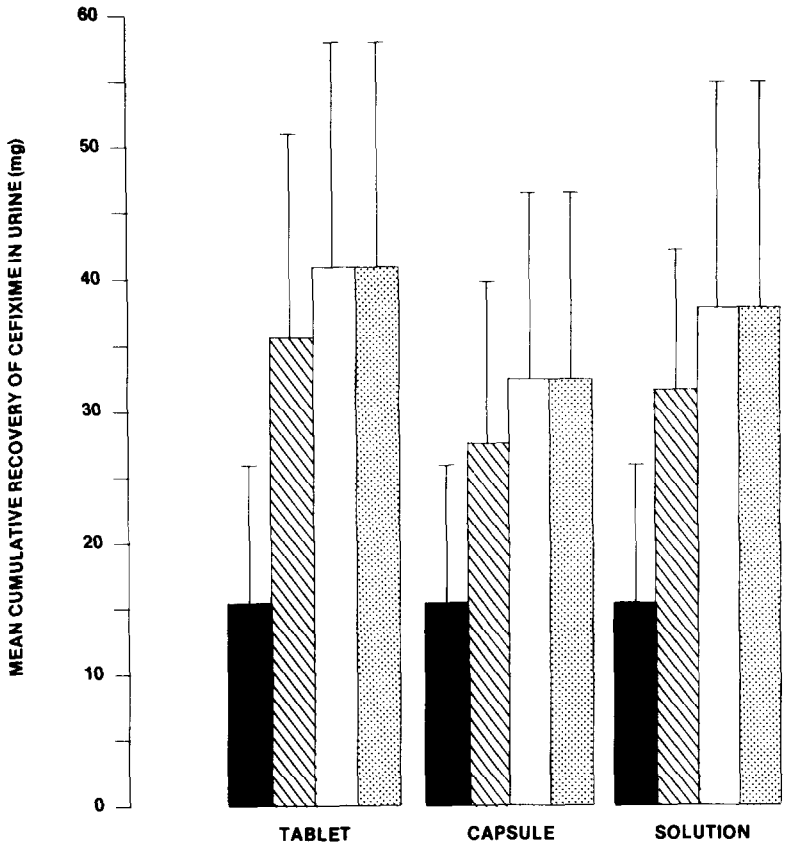

Fig. 2. Mean cumulative urine recovery of cefixime (■) 0 → 6 h, (▨) 0 → 12 h, (□) 0 → 24 h and (▤) 0 → 48 h (S.D. bars are included) after each 400 mg dose.

were obtained in any of the 24–48-h urine collection samples. Recovery of unchanged drug expressed as a percentage of the administered dose (f_e), was somewhat less ($P < 0.05$) for the capsule (8.0%) when compared with tablet (10.1%) and solution (9.4%) doses. The mean renal clearance (CL_r) of cefixime (~ 23 ml/min) was similar ($P > 0.5$) after each of the 3 formulations of the drug.

Discussion

A previous bioequivalency study demonstrated comparable bioavailability of cefixime from two different tablet and a capsule formulations (Faulkner et al., 1985). Based on these results, a tablet intended for marketing was formulated. This tablet was shown in the present study to be bioequivalent to the capsule formulation of the drug and to a reference solution.

The statistical power of the study was greater than 90% to detect a difference in $AUC_{0\rightarrow\infty}$ values of 20%. Although comparisons of the pharmacokinetic parameters for cefixime after the 3 treatments yielded some statistically significant differences, the magnitude of the mean differences in C_{max} and $AUC_{0\rightarrow\infty}$ between the tablet and capsule dosage forms were less than 16% and are not expected to be clinically significant. For each solid dosage form, the bioavailability of cefixime relative to the reference solution averaged 99% for the tablet and 90% for the capsule. Based on the

ratios of $Ae_{00\rightarrow 48}$ values, the respective mean values were 96 and 82%.

Comparison of the mean dissolution time data for the two solid dosage forms showed a somewhat faster release rate of cefixime from the tablet formulation. Relative to the solution, the mean release time (MDT) for the tablet and capsule formulations were somewhat different ($P < 0.05$); on average about 0.5 and 1.0 h, respectively.

At equivalent doses, the intersubject variabilities (CV%) in C_{max} (about 14%) and $AUC_{0\rightarrow\infty}$ (range 31–34%) for the two solid dosages were comparable to that for the solution (10 and 31%, respectively).

The urinary recovery of cefixime from the 3 formulations is listed in Table 3. For both solid dosage forms, the 48-h recovery was comparable ($P > 0.05$) to that following the solution, with the recovery following the tablet somewhat greater ($P > 0.05$) than that for the capsule. However, evaluation of the fractional collections showed comparable amounts recovered within each collection interval for the 3 formulations (Fig. 2). More than 80% of the excreted drug was recovered in the urine within 12 h after dosing for all 3 formulations.

The serum concentrations and pharmacokinetic parameters obtained from the capsule formulation in this study are consistent with previous reports (Britain et al., 1985; Faulkner et al., 1985).

For all 3 formulations, serum concentrations of drug were maintained above the reported MIC_{90}'s (about 0.2 μg/ml) for most common Gram-negative bacteria (Kamimura et al., 1984) for at least 16 h after the single oral dose. In summary, both tablet and the capsule formulations of cefixime are bioequivalent to one another and to the reference oral solution formulation of the drug.

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