Relative Bioavailability of Three Cefixime Formulations

F. Kees[a], K. G. Naber[b], G. Sigl[b], W. Ungethüm[c], and H. Grobecker[a]

Summary

Three galenic formulations of cefixime (tablet, syrup and dry suspension) containing 200 mg each were compared with respect to their relative bioavailability in twelve healthy volunteers. All three formulations showed reliable absorption. Mean peak plasma concentrations were reached after 3.3—3.5 h, mean terminal half lives were 2.9—3.1 h. 18—24 % of the dose administered were recovered unchanged in the urine. Best bioavailability was obtained with the dry suspension ($AUC_{0-\infty}$ = 25.8 ± 7.0 ug/ml h; C_{max} = 3.4 ± 0.9 µg/ml), followed by the tablet ($AUC_{0-\infty}$ = 20.9 ± 8.1 µg/ml h; C_{max} = 3.0 ± 1.0 µg/ml) and the syrup which is based on triglycerides ($AUC_{0-\infty}$ = 17.8 ± 5.9 µg/ml h; C_{max} = 2.4 ± 0.7 µg/ml). The statistical analysis resulted in bioinequivalence between dry suspension and syrup. It is concluded that best bioavailability of cefixime after oral administration is guaranteed when taken in an "aqueous medium" either as dry suspension or as tablet with "plenty of liquid".

Department of Pharmacology, University of Regensburg[a], Urologic Clinic, Elisabeth-Krankenhaus[b], Straubing, and E. Merck[c], Darmstadt (Fed. Rep. of Germany)

Zusammenfassung

Relative Bioverfügbarkeit von drei galenischen Cefixim-Formulierungen

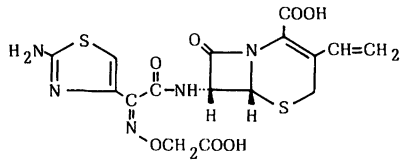
Die relative Bioverfügbarkeit dreier galenischer Formulierungen von Cefixim (Tablette, Fertigsaft und Trockensuspension) mit je 200 mg Wirkstoff wurde bei zwölf freiwilligen Probanden verglichen. Alle Formulierungen zeigten eine zuverlässige Absorption von Cefixim, die mittleren Maximalkonzentrationen wurden im Plasma nach

3.3—3.5 h erreicht. Die mittleren Plasmahalbwertszeiten betrugen 2.9—3.1 h. 18—24 % der Dosis wurden im Urin unverändert wiedergefunden. Die beste Bioverfügbarkeit gewährleistet die Trockensuspension ($AUC_{0-\infty}$ = 25,8 ± 7,0 µg/ml h; C_{max} = 3,4 ± 0,9 µg/ml), gefolgt von der Tablette ($AUC_{0\infty}$ = 20,9 ± 8,1 µg/ml h; C_{max} 3,0 ± 1,0 µg/ml) und dem Fertigsaft, der auf Triglyceriden basiert ($AUC_{0-\infty}$ = 17,8 ± 5,9 µg/ml h; C_{max} = 2,4 ± 0,7 µg/ml). Die statistische Analyse ergab Bioinäquivalenz zwischen Trockensuspension und Fertigsaft. Es wird geschlossen, daß die bestmögliche Bioverfügbarkeit von Cefixim nach oraler Applikation resultiert, wenn der Wirkstoff in einem „wäßrigen Medium" eingenommen wird, entweder als Trockensuspension oder Tablette mit „reichlich Flüssigkeit".

Key words: *Antibacterials · Cefixime, clinical studies, pharmacokinetics · Cephalosporins*

1. Introduction

Cefixime (see structural formula) is an orally absorbed cephalosporin with pharmacodynamic characteristics of the third generation cephalosporins for parenteral use (Bauernfeind 1985). As with other new oral cephalosporins (carboxymethyl and pro-drug cephalosporins, Dürckheimer et al. 1987) the pharmacokinetic behaviour of cefixime is characterized by incomplete bioavailability after oral administration (Faulkner et al. 1987). The aim of the present study was to investigate the influence of three different galenic formulations (tablet, syrup and dry suspension) on the bioavailability of cefixime.



Chemical structure of cefixime

2. Materials and methods

2.1. Drug formulations, reagents and chemicals

Cefixime as tablet (containing 200 mg; batch No. Z 050 0348), syrup and dry suspension (containing 200 mg per 10 ml; batch No. Z 050 0122 and No. Z 050 0362) as well as cefixime standard substance were obtained from E. Merck, Darmstadt (FRG), tetrabutylammonium hydrogensulfate (puriss.) from Fluka, Neu-Ulm (FRG), all other chemicals (analytical or HPLC grade) from E. Merck. Water was purified by a Milli-Q water purification system, Millipore, Eschborn (FRG).

2.2. Clinical part

Twelve volunteers (6 male, 6 female, Table 1) aged 21 to 43 (median 28) years, a body weight of 56 to 89 (median 75) kg, and a height of 159 to 190 (median 174) cm were entered into the study. The study was performed according to the legal aspects of the FR Germany and the revised Declaration of Helsinki. Written informed consent was obtained from each volunteer. The health status of each subject was assessed by routine physical examination and laboratory analysis. Each subject was randomly assigned in a three-way crossover design to receive 200 mg cefixime orally as a tablet, syrup and dry suspension. Dosing periods were separated by one week. The doses were administered with 100 ml of water after an overnight fast and each subject fasted for further 4 h. Thereafter a standard meal was given. Venous blood samples (by Ammonium Heparin Monovette®, Sarstedt, Nümbrecht, FRG) were taken from an arm vein prior to dosing and at 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 8, 10, 12 and 24 h after dosing. Urine was collected prior to, and at 0—2, 2—4, 4—8, 8—12 and 12—24 h intervals after dosing. Aliquots of plasma and urine were stored at —70 °C until assayed.

Table 1: Demographic data of volunteers and sequence of drug administration (A, tablet; B, syrup; C, dry suspension).

No.	Initials	Sex	Age (a)	Weight (kg)	Height (cm)	Sequence
1	H.S.	m	33	73	183	C-A-B
2	C.N.	m	21	89	190	A-B-C
3	K.H.	m	24	80	188	B-C-A
4	F.L.	m	28	88	188	B-C-A
5	H.A.	m	28	85	180	A-B-C
6	W.D.	m	37	81	174	C-A-B
7	G.S.	f	33	62	166	C-A-B
8	A.S.	f	24	57	162	A-B-C
9	G.P.	f	37	64	159	B-C-A
10	K.E.	f	21	68	165	A-B-C
11	P.S.	f	25	56	164	C-A-B
12	B.F.	f	43	76	173	B-C-A
		median	28	75	174	
		min	21	56	159	
		max	43	89	190	

2.3. Drug assay

Concentrations of cefixime were determined by a high-performance liquid chromatographic (HPLC) assay (Kees et al. 1984, 1987). In brief, 200 µl plasma were buffered with 200 µl 50 mmol/l sodium dihydrogen phosphate and deproteinized with 400 µl acetonitrile. The protein was separated by centrifugation and the acetonitrile removed by extraction with dichloro methane. Urine was centrifuged and diluted 1 : 10 with 20 mmol/l sodium phosphate, pH 6.5. 50 µl (urine: 5 µl) of the aqueous layer were injected onto the HPLC column.

The chromatographic system consisted of a pump M6000A, an autosampler WISP 710B, a Novapak® C184 um 100 × 5 mm polyethylene cartridge housed in a compression module RCM 100, a fixed-wavelenght UV detector M440 (280 nm), a data module M730, and a system controller M720 (all from Millipore Waters-Chromatography, Eschborn, FRG). The eluent was a mixture of 800 ml water, 1.38 g sodium dihydrogen phosphate monohydrate, 1.00 g tetrabutylammonium hydrogensulfate, and 220—250 ml acetonitrile (pH 6.6 with 10 N sodium hydroxide). At a flow rate of 1.0 ml/min (back pressure 60 bar) the retention time of cefixime was 4.0—4.8 min (Fig. 1).

The recovery of cefixime from plasma was quantitative (101 ± 2 %, n = 12, concentration 5 µg/ml), standard curves from 0.1 to 5 µg/ml were found to be linear ($r > 0.99990$), the lower limit of quantification in plasma was 0.1 µg/ml, the coefficient of variation for control samples 2.3 and 7.6 % (conc. 2.7 and 0.27 µg/ml). In urine the limit of quantification was 1—2 µg/ml because of higher chromatographic background, especially in morning urine (compare Fig. 1).

2.4. Data analysis

Pharmacokinetic parameters for cefixime were estimated using model-independent methods. The peak plasma concentration (C_{max}) and the time to reach C_{max} (T_{max}) were determined by visual inspection of the plasma concentration versus time data. Values for the elimination rate constant (k_{el}) and terminal half-life ($T_{1/2}$) were estimated by linear regression of the semi-logarithmic plot of the last 4 or 5 plasma concentrations versus time.

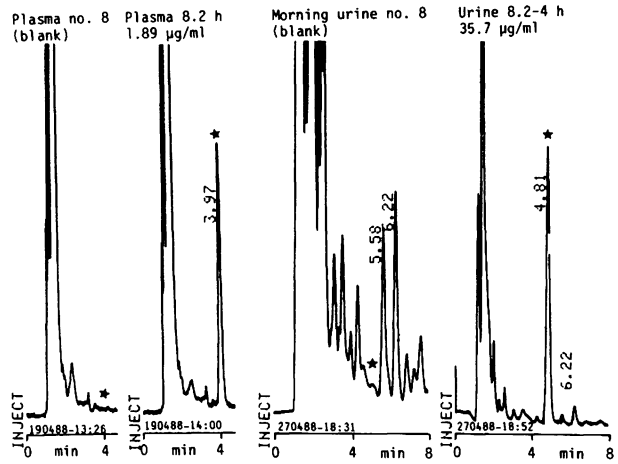


Fig. 1: Chromatograms of plasma and urine of a subject (no. 8) prior to and after oral administration of 200 mg cefixime. The asterisk (*) marks the position of the cefixime peak.

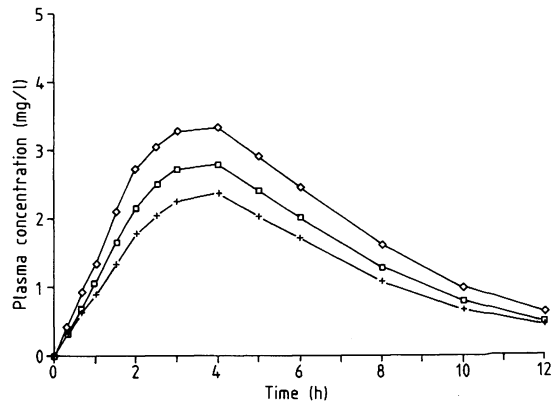


Fig. 2: Mean plasma concentrations (µg/ml) of cefixime in twelve healthy volunteers after oral administration of 200 mg as tablet, syrup and dry suspension; □ = tablet, + = syrup, ◇ = dry suspension.

The area under the plasma concentration-time curve ($AUC_{0-\infty}$) was estimated by the trapezoidal rule and extrapolated to infinity. The extrapolation was performed by dividing the last measurable concentration by the elimination rate constant (k_{el}). Recovery of unchanged cefixime in urine was calculated as percentage of the administered dose.

For statistical analysis of bioavailability of the three oral cefixime formulations a computer program was used (BIO Q, Steinijans and Diletti 1983a, b).

Table 4: Test for bioequivalence between three formulations of cefixime (test/reference; Pitman's permutation tst; abbr.: A, tablet; B, syrup; C, dry suspension.

Test/ref.	$AUC_{0-\infty}$		C_{max}	
	point estimate	95 %-confidence interval	point estimate	95 %-confidence interval
B/A	0.88	0.72—1.08	0.84	0.73—0.98
C/A	1.28	1.12—1.47	1.19	1.04—1.33
C/B	1.46	1.20—1.77	1.40	1.19—1.64

3. Results

The plasma concentrations of cefixime after administration of the three different formulations are compiled in Table 2 (p. 296), the mean values are shown in Fig. 2, the estimated pharmacokinetic parameters in Table 3 (p. 296). Very similar mean values were found for terminal half-life, 2.9 to 3.1 h, and time of peak plasma concentrations, 3.3 to 3.5 h, whereas greater differences were seen in peak plasma concentrations: 2.95 ± 0.99 µg/ml (tablet), 2.43 ± 0.68 µg/ml (syrup) and 3.41 ± 0.92 µg/ml (dry suspension), and AUCs: 20.9 ± 8.1 µg/ml h (tablet), 17.8 ± 5.9 µg/ml h (syrup) and 25.8 ± 7.0 µg/ml h (dry suspension). Mean urinary recovery of unchanged cefixime accounted for 18—24 % (Table 3).

From inspection of mean values the following order of bioavailability of cefixime can be deduced: dry suspension > tablet > syrup. The statistical analysis (paired t-test) revealed significant differences between dry suspension and syrup with respect to AUC ($p < 0.001$) and urinary recovery ($p < 0.05$), and between dry suspension and tablet with respect to AUC ($p < 0.001$). Bioequivalence could not be proved between dry suspension and tablet, whereas bioinequivalence was found between dry suspension and syrup (Table 4) by comparison of the individual ratios of AUC and C_{max}.

Tables 2 and 3 see p. 296.

4. Discussion

A major disadvantage of the newer oral cephalosporins of the carboxymethyl and pro-drug type compared with classical oral cephalosporins of the cephalexin type is incomplete absorption from gastrointestinal tract (Dürckheimer et al. 1987). The absolute bioavailabilities of the active drugs don't exceed 50 %. This was shown for cefixime (Faulkner et al. 1987), cefuroxime axetil (Williams and Harding 1984), cefotiam hexetil (SCE-2174, Couet et al. 1987) and cefetamet pivoxil (Koup et al. 1988). In this study a syrup formulation of cefixime which is based on triglycerides (MCTs) like a commercially available cefaclor syrup was compared with a tablet and dry suspension formulation. It resulted that the syrup showed the lowest bioavailability of cefixime although medium chain glycerides and fatty acids may promote intestinal absorption of β-lactam antibiotics, e.g. cefoxitin (Van Hoogdalem et al. 1989 and references cited). The highest bioavailability showed the dry suspension in which (after combination with water prior to administration) cefixime is partially dissolved. This is in agreement with previous results of Faulkner et al. 1987, who found slightly higher areas under the plasma concentration-time curve after administration of 200 mg cefixime as an aqueous solution with respect to a capsule formulation (average 26 versus 23 mg/l h) which resembles the tablet.

The plasma concentration-time curve could not be fitted by a computer program assuming first-order absorption and elimination processes. Presumably, a better fit would result assuming a zero-order absorption process (c.f. Hespe et al. 1987) because of presumably transmembrane rate-limited absorption of cefixime and other oral β-lactam antibiotics (c.f. Nakashima et al. 1984, Okano et al. 1986, Tsuji et al. 1987). The delayed peak plasma concentrations (3 h) despite fasting administration of the drug and the non-proportionality of bioavailability with increasing doses (Faulkner et al. 1987) would agree with this model. Nevertheless, the percentage of cefixime absorbed was reliable in all three formulations as can be seen from the moderate coefficients of variance of average AUCs (27—39 %) and peak plasma concentrations (27—34 %).

Table 2: Plasma concentrations (µg/ml) of cefixime in healthy volunteers following oral administration of 200 mg as tablet, syrup and dry suspension.

Tablet

Subject	1	2	3	4	5	6	7	8	9	10	11	12	Mean	SD
Time (h)														
0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.06	0.00		
0.33	0.52	0.00	0.39	0.13	0.13	0.30	0.07	0.09	0.37	1.22	0.25	0.35	0.319	0.324
0.67	1.00	0.00	0.91	0.31	0.34	0.66	0.30	0.28	1.16	1.98	0.58	0.84	0.696	0.533
1.00	1.31	0.00	1.26	0.55	0.67	1.07	0.81	0.49	1.79	2.60	1.07	1.22	1.070	0.670
1.50	1.68	0.00	1.75	1.14	1.06	1.88	2.00	1.06	2.73	3.27	1.77	1.68	1.668	0.834
2.00	1.93	0.21	1.94	2.05	1.35	2.14	2.97	1.89	3.33	3.45	2.67	1.92	2.155	0.888
2.50	2.11	0.48	2.14	2.66	1.50	2.29	3.48	2.69	3.55	3.76	2.96	2.33	2.498	0.922
3.00	2.03	0.87	2.21	3.23	1.71	2.59	3.88	3.19	3.66	3.81	3.29	2.30	2.731	0.933
4.00	1.54	1.42	2.09	3.54	1.54	2.44	4.51	3.98	3.64	3.14	3.36	2.46	2.805	1.035
5.00	1.21	1.35	1.57	3.24	1.35	1.86	3.89	3.77	3.28	2.41	2.96	1.94	2.403	0.986
6.00	0.86	1.10	1.31	2.60	1.10	1.71	3.32	3.39	2.64	1.94	2.53	1.68	2.017	0.870
8.00	0.54	0.66	0.80	1.87	0.63	1.09	2.19	2.26	1.66	1.07	1.54	1.03	1.278	0.609
10.00	0.28	0.46	0.46	1.13	0.42	0.67	1.41	1.37	0.91	0.64	0.99	0.63	0.783	0.376
12.00	0.14	0.23	0.26	0.78	0.27	0.44	0.91	0.83	0.53	0.33	0.61	0.29	0.469	0.261
24.00	0.00	0.00	0.00	0.00	0.00	0.00	0.10	0.00	0.00	0.00	0.00	0.00		

Syrup

Subject	1	2	3	4	5	6	7	8	9	10	11	12	Mean	SD
Time (h)														
0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00		
0.33	0.20	0.09	0.47	0.47	0.22	0.23	0.62	0.54	0.32	0.42	0.14	0.14	0.323	1.176
0.67	0.33	0.35	0.80	1.05	0.56	0.62	0.91	0.95	0.62	0.71	0.30	0.33	0.628	0.264
1.00	0.54	0.60	0.91	1.49	0.77	0.77	1.12	1.25	0.86	1.06	0.72	0.56	0.888	0.294
1.50	1.03	0.83	1.45	2.29	1.06	1.49	1.34	1.63	1.20	1.42	1.27	0.95	1.332	0.386
2.00	1.65	1.34	1.44	3.09	1.35	1.71	1.77	2.17	1.75	1.98	1.67	1.50	1.784	0.479
2.50	1.92	1.51	1.57	3.06	1.44	1.86	2.19	2.64	2.13	2.25	1.91	2.07	2.046	0.468
3.00	2.01	1.75	1.49	3.37	1.57	1.75	2.58	2.93	2.34	2.54	2.27	2.49	2.258	0.572
4.00	1.87	1.70	1.39	3.49	1.50	1.80	3.01	3.33	2.39	2.38	2.58	3.07	2.376	0.731
5.00	1.47	1.28	1.07	2.84	1.38	1.40	2.66	3.22	2.10	1.80	2.00	3.03	2.021	0.748
6.00	1.12	1.20	0.80	2.33	1.23	1.08	2.22	2.92	1.78	1.45	1.76	2.59	1.705	0.677
8.00	0.60	0.82	0.46	1.45	0.91	0.66	1.29	2.11	1.25	0.75	0.97	1.54	1.067	0.477
10.00	0.37	0.52	0.26	0.90	0.66	0.39	0.76	1.29	0.76	0.43	0.54	1.00	0.657	0.301
12.00	0.22	0.28	0.19	0.53	0.56	0.31	0.45	0.80	0.51	0.25	0.34	0.70	0.429	0.196
24.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.08	0.00	0.00	0.00	0.00		

Dry suspension

Subject	1	2	3	4	5	6	7	8	9	10	11	12	Mean	SD
Time (h)														
0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00		
0.33	0.26	0.52	0.87	0.85	0.43	0.42	0.62	0.07	0.16	0.70	0.14	0.12	0.431	0.286
0.67	0.70	0.99	1.36	1.49	0.70	0.97	1.36	0.43	0.53	1.71	0.37	0.45	0.923	0.463
1.00	0.97	1.27	1.82	1.93	1.17	1.45	1.97	0.70	0.74	2.48	0.75	0.74	1.334	0.597
1.50	1.67	1.79	2.58	2.72	1.44	2.14	2.74	1.34	1.96	3.80	1.61	1.53	2.111	0.725
2.00	2.14	2.16	2.87	3.20	1.62	2.86	3.24	2.38	3.17	4.48	2.72	1.96	2.733	0.762
2.50	2.72	2.27	2.86	3.57	1.55	2.94	3.47	2.99	3.89	4.70	3.21	2.57	3.061	0.807
3.00	3.20	2.25	2.81	3.87	1.55	3.14	3.62	3.51	4.33	4.78	3.58	2.67	3.275	0.886
4.00	3.28	2.04	2.66	3.97	1.49	3.06	3.67	3.85	4.52	4.48	4.07	2.91	3.333	0.944
5.00	2.85	1.93	2.09	3.54	1.24	2.61	3.19	3.48	3.84	3.68	3.66	2.68	2.899	0.821
6.00	2.24	1.56	1.55	2.92	1.05	2.01	2.96	3.44	3.61	2.83	3.08	2.29	2.460	0.807
8.00	1.39	0.99	1.01	2.07	0.66	1.43	1.69	2.31	2.50	1.56	2.08	1.68	1.614	0.561
10.00	0.80	0.57	0.56	1.25	0.39	0.85	1.20	1.38	1.49	0.81	1.36	1.16	0.986	0.366
12.00	0.42	0.28	0.32	0.77	0.32	0.59	0.76	0.88	0.85	0.45	0.85	0.73	0.602	0.233
24.00	0.00	0.00	0.00	0.00	0.00	0.00	0.00	0.06	0.00	0.00	0.00	0.00		

Table 3: Pharmacokinetic parameters (mean, SD, range) of cefixime in twelve healthy volunteers after oral administration of 200 mg cefixime as tablet, syrup and dry suspension. Abbr.: C_{max}, maximum plasma concentration; T_{max}, time of peak plasma concentration; $T_{1/2}$, terminal plasma half-life; $AUC_{0-\infty}$, area under the plasma concentration-time curve from time zero to infinity; $U_{0-24\,h}$, recovery of unchanged cefixime in urine up to 24 h after dosage.

Parameter	Dimension	Tablet			Syrup			Dry suspension		
		mean	SD	range	mean	SD	range	mean	SD	range
C_{max}	µm/ml	2.95	0.99	1.42– 4.51	2.43	0.68	1.57– 3.49	3.41	0.92	1.62– 4.78
T_{max}	h	3.46	0.58	2.50– 4.00	3.42	0.63	2.50– 4.00	3.33	0.89	2.00– 4.00
$T_{1/2}$	h	2.91	0.43	2.36– 3.97	3.13	0.61	2.44– 4.63	3.01	0.43	2.35– 3.80
$AUC_{0-\infty}$	µg/ml h	20.89	8.08	8.96–33.44	17.83	5.89	10.15–29.28	25.84	6.99	12.50–34.42
$U_{0-24\,h}$	% of dose	22.09	9.82	4.29–40.48	18.38	6.03	6.16–28.51	24.13	8.14	10.48–38.85

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Correspondence: PD Dr. F. Kees, Lehrstuhl für Pharmakologie, Universität Regensburg, Universitätsstr. 31, D-8400 Regensburg (Fed. Rep. of Germany)