Comparative Investigations on the Bioavailability of Cefuroxime Axetil

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Summary

In a three-way cross-over study the bioavailability of cefuroxime was determined in 12 healthy volunteers after oral administration of 250 mg as cefuroxime axetil (Elobact®; CAS 64544-07-6) in a plain aqueous suspension and as tablets from different batches. The tablet formulations showed nearly identical pharmacokinetic parameters and were bioequivalent. The mean maximum serum concentration was 4.7 µg/ml, achieved after 2.1 h. The serum half-live was 1.2—1.4 h, the area under the serum concentration-time curve was 14.3—14.4 µg/ml · h and the urinary recovery of unchanged cefuroxime was 54 %. The bioavailability of cefuroxime after administration of cefuroxime axetil in aqueous suspension was lower, but bio-inequivalence was not demonstrated.

Zusammenfassung

Vergleichende Untersuchungen zur Bioverfügbarkeit von Cefuroximaxetil

In einem Dreifach-cross-over-Versuch wurde bei 12 gesunden Probanden die Bioverfügbarkeit von Cefuroxim nach oraler Einnahme von Cefuroximaxetil-Tabletten (Elobact®; CAS 64544-07-6; Wirkstoffgehalt 250 mg) aus zwei verschiedenen Chargen bestimmt. Als Referenz diente eine wäßrige Suspension von Cefuroximaxetil. Die beiden Tablettenformulierungen ergaben nahezu identische phar-

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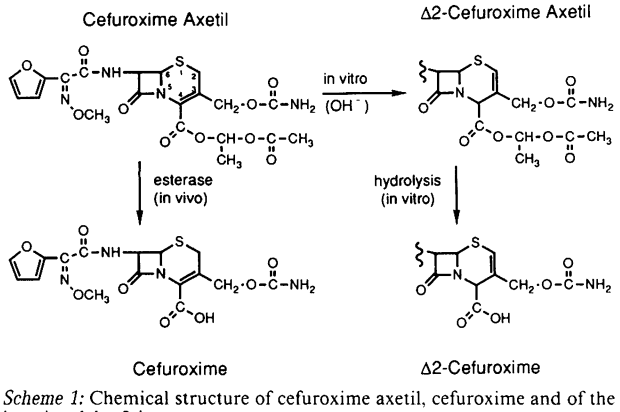
makokinetische Parameter und erwiesen sich als bioäquivalent. Die mittlere maximale Serumkonzentration war 4,7 µg/ml und wurde nach 2,1 h erreicht, die Serumhalbwertszeit 1,2—1,4 h, die Fläche unter der Serumkonzentrations-Zeit-Kurve 14,3—14,4 µg/ml · h und die Wiederfindung von unverändertem Cefuroxim im Urin 54 % der gegebenen Dosis. Die Bioverfügbarkeit von Cefuroxim nach Einnahme von Cefuroximaxetil in wäßriger Suspension war niedriger, doch Bioinäquivalenz wurde nicht gefunden.

Key words: *Antibacterials · CAS 64544-07-6 · Cefuroxime axetil, bioequivalence, clinical studies*

1. Introduction

Cefuroxime axetil (CAS 64544-07-6; see Scheme 1) is the acetoxyethyl-ester of cefuroxime, a second generation cephalosporin for parenteral use, which is β-lactamase stable (O'Callaghan 1979). After oral administration the ester is absorbed from the intestine and during passage through the mucosa it is hydrolysed releasing the active moiety cefuroxime.



Scheme 1: Chemical structure of cefuroxime axetil, cefuroxime and of the inactive delta 2-isomer.

Absorption is enhanced by simultaneous ingestion of food, the absolute bioavailability of cefuroxime axetil on an empty stomach is 30 %, but when administered with food it is up to 60 %. Typical pharmacokinetic parameters after a dose of 250 mg are: peak concentrations in plasma of 4.4 µg/ml found after 2—3 h, AUC of 14.9 µg/ml · h and urinary recovery of 50 % (Williams and Harding 1984, Sommers et al. 1984, Finn et al. 1987).

In the early development of oral formulations of cefuroxime axetil there were reports about varying and sporadically poor bioavailability of the drug (cf. Dürckheimer 1987). This problem was overcome by the development of the RS3-tablet which then was brought into the market. The aim of the present study was to compare the bioavailability of cefuroxime from two batches of such cefuroxime axetil tablets with that from a plain aqueous suspension as reference, in order to determine the relative bioavailability of the tablets and the batch-to-batch variation. In addition, the study should serve as a model for the bioavailability of cefuroxime axetil after single and repeated dosing.

[1] Elobact®; manufacturer: Cascan GmbH & Co. KG, Wiesbaden (Fed. Rep. of Germany).

2. Materials and methods

2.1. Test medications, reagents and chemicals

The test medications and analytical standards (cefuroxime, cefuroxime axetil and d2-cefuroxime axetil) were obtained from Cascan[1]. The test medications were as follows:

A: Cefuroxime axetil, 250 mg amorphous powder, to mix with 10 ml of flavoured aqueous solution, produced April 1988, expiry date April 1990.

B: Cefuroxime axetil, 250 mg tablets, produced December 1987, expiry date December 1989.

C: Cefuroxime axetil, 250 mg tablets, produced January 1987, expiry date December 1988.

Tetrabutylammonium hydrogensulfate (puriss.) was obtained from Fluka, Neu-Ulm (FRG), acetonitrile (HPLC—grade) from Baker, Groß-Gerau (FRG), all other chemicals (analytical grade) were obtained from E. Merck, Darmstadt (FRG). Water was purified by a Milli-Q water purification system (Millipore, Eschborn, FRG).

2.2. Volunteers, drug administration and sampling

Twelve volunteers (6 m, 6 f) aged 20—40 years (median 29 years), with a weight of 48—86 kg (median 68 kg) and height of 154—191 cm (median 174 cm) took part in the study. They were healthy as judged from medical history, physical examination and biochemical tests. The protocol was checked and approved by an ethics committee, and written consent was obtained. The volunteers fasted 12 h prior to each study day and had a standardized breakfast at about 7:00 a.m., consisting of two slices of toast, 50 g jam, 25 g butter and 200 ml fruit tea. 30 min later, 15 min after the end of the breakfast, each volunteer took orally one of the three presentations of 250 mg cefuroxime axetil together with 200 ml water according to a randomized open three-way cross-over schedule. Venous blood was taken through an indwelling venous catheter placed in an arm vein, before dosing and 0.33, 0.67, 1, 1.5, 2, 2.5, 3, 4, 5, 6, 7, 8 and 10 h thereafter. The blood was centrifuged at 4 °C, and the serum separated. Urine was collected before drug administration and up to 24 h thereafter. The specimens were stored frozen at −70 °C until analysis.

2.3. HPLC assay

Plasma and urine were assayed by high-performance liquid chromatography (HPLC) with a modified published procedure (Kees et al. 1990 and references, therein). In brief, 200 µl serum were mixed with 200 µl 0.2 % acetic acid and 400 µl acetonitrile. The precipitated protein was removed by centrifugation, and the acetonitrile was extracted into 2 ml dichloromethane. After centrifugation 50 µl of the aqueous supernatant was injected into the HPLC-column. Urine was centrifuged diluted 1 : 20 with mobile phase (omitting acetonitrile) and 10 µl was injected directly. For separation a Hyperchrome® column (i.d. 250 × 4 mm) was used filled with Nucleosil C18 5 µm obtained from Bischoff, Leonberg (FRG).

The mobile phase was 1000 ml water, 2.5 g tetrabutylammonium hydrogen sulfate, 600 µl acetic acid, 450 ml acetonitrile, pH 4.75 with 10 mol/l sodium hydroxide. The eluent was monitored by a photometric detector set at 275 nm. At a flow rate of 1 ml/min (30 °C) the retention time of cefuroxime was 5.8 min and that of the inactive delta 2-isomer 6.3 min. The retention times of cefuroxime axetil diastereomers were 14.6 and 16.2 min. Recovery

of cefuroxime from serum was quantitative, the limit of quantitation of cefuroxime was 50 ng/ml in serum and 10 µg/ml in urine.

2.4. Pharmacokinetic calculations

The pharmacokinetic parameters were calculated from the plasma concentrations of cefuroxime for each subject. The maximum serum concentration (C_{max}) and the time to reach C_{max} (t_{max}) were determined by visual inspection of the serum concentration versus time data. The elimination constant (k_{el}) and the serum half life ($t_{1/2}$) were calculated by linear regression (log-lin scale) of the concentrations in the elimination phase. The area under the curve (AUC) was calculated by the trapezoidal rule (linear scale). The extrapolation from the last measured point to infinity was obtained by dividing the concentration of the last measured point by the elimination constant. The percentage of the dose administered which was recovered in the urine ($U_{0-24\,h}$) was calculated from the concentration in the 24-h urine collection multiplied by the volume of the urine.

2.5. Statistical evaluation

The following parameters were tested statistically using the Student t-test ($\alpha = 0.05$): $U_{0-24\,h}$, $t_{1/2}$, C_{max}, t_{max}, $AUC_{0-10\,h}$, $AUC_{0-\infty}$. For determination of bioequivalence the individual quotients of C_{max} and $AUC_{0-\infty}$ after administration of the test substances and the reference substance were calculated. The 90 % confidence interval (see Blume and Mutschler, 1989) was calculated using a computer programme (PC-version of BIOQ, Steinijans and Diletti, 1983 a, b, obtained from: Zentrallaboratorium Deutscher Apotheker, Eschborn, FRG).

3. Results

3.1. Pharmacokinetic parameters

The mean serum concentrations are shown in Fig. 1 and the derived pharmacokinetic parameters in Table 1. Very similar pharmacokinetic parameters (mean ± standard deviation) were found for both batches of tablets; the mean serum half life of cefuroxime was 1.36 ± 0.38 h (B) and 1.24 ±0.19 h (C), the maximum serum concentration C_{max} was 4.76 ± 1.20 µg/ml (B) and 4.69 ± 1.58 µg/ml (C) and t_{max} 2.13 ± 0.74 h and 2.13 ± 0.48 h. The $AUC_{0-\infty}$ was 14.4 ± 2.8 (B) and 14.3 ± 3.1 µg/ml · h, and the urinary recovery 53.8 ± 7.8 % and 53.7 ± 6.1 % of the administered dose. In the latter case the urine data of one subject was not included as a portion of the urine was lost. Serum half-life (1.27 ± 0.12 h) and the time to reach maximum serum concentration (2.00 ± 0.43 h) were the same after administration of the aqueous suspension with respect to the tablets, but C_{max} itself (3.85 ± 1.55 µg/ml), $AUC_{0-\infty}$ (12.3 ± 3.8 µg/ml · h) and urinary recovery (42.8 ± 10.1 %) were lower with the aqueous suspension, in the latter case statistically significant.

Bioequivalence was demonstrated for both batches of tablets (Table 2), but not between tablets and aqueous suspension, where appearance of cefuroxime in serum was earlier, although mean bioavailability was lower as measured by AUC and urinary recovery.

3.2. Tolerance

All medications were well tolerated, and not gastrointestinal or allergic side-effects were registered, only headache was reported in two cases 7–8 h after administration. The volunteers were allowed to take a mild analgesic after 10 h. Headache is not a recognized side-effect of orally administered cephalosporins and in this case may have been due to study conditions, i.e. getting up early and avoiding morning-coffee.

4. Discussion

In the present bioavailability study the two batches of cefuroxime axetil tablets appeared bioequivalent. The peak serum concentration of 4.7 µg/ml corresponds to the levels found by other investigators (Williams and Harding 1984, Sommers et al. 1984, Finn et al. 1987) and, after dose correction, they are higher than maximum serum concentrations of other new oral cephalosporins such as cefixime (Kees et al. 1987, 1990; review: Brogden and Campoli-Richards 1989) and cefetamet pivoxyl (review: Stoeckel et al. 1989). Compared with cefotiam hexetil (Couet et al. 1987, Deppermann et al. 1989) the area under the serum concentration-time curve was also higher. In addition, this three-way cross-over study provides a good model for the absorption of cefuroxime axetil after single and repeated dosing, and the results show that cefuroxime axetil is reliably and reproducibly absorbed.

High serum concentration of cefuroxime was achieved more rapidly following administration of the aqueous suspension, compared with the tablet formulations, although maximum serum concentrations and area under the curve were lower. This was surprising since the use of a solution or an aqueous suspension in determination of the relative bioavailability of oral formulations is based on the assumption that it is better absorbed than other formulations (cf. results with older cephalosporins of the cephalexin type, Riess et al. 1982).

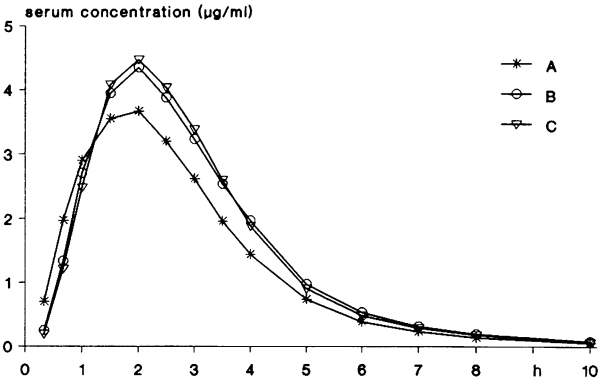


Fig. 1: Mean serum concentration of cefuroxime after oral administration of 250 mg cefuroxime as axetil in 12 healthy volunteers. A = plain aqueous suspension; B = tablet, produced December 1987; C = tablet, produced January 1987.

Table 1: Pharmacokinetic parameters (mean; standard deviation; coefficient of variation) of cefuroxime in 12 healthy volunteers after oral administration of 250 mg cefuroxime as axetil.

Parameter	Dimension	A	B	C
C_{max}	µg/ml	3.85 ± 1.55 (40)	4.76 ± 1.20 (25)	4.69 ± 1.58 (34)
T_{max}	h	2.00 ± 0.43 (22)	2.13 ± 0.74 (35)	2.13 ± 0.48 (23)
$t_{1/2}$	h	1.27 ± 0.12 (09)	1.36 ± 0.38 (28)	1.24 ± 0.19 (15)
$AUC_{0-\infty}$	µg/ml · h	12.4 ± 3.8 (31)	14.4 ± 2.8 (19)	14.3 ± 3.1 (22)
$U_{0-24\,h}$	% of dose	42.8 ± 10.1 (24)	53.8 ± 7.8 (14)	53.7 ± 6.1 (11)[a]

[a] Mean of 11 as in one subject (recovery 9.3 %) part of urine was lost.

Table 2: Test for bioequivalence (test/reference, Wilcoxon test) of three formulations of cefuroxime axetil.

Parameter	B/A		C/A		C/B	
	p.e.	90 %	p.e.	90 %	p.e.	90 %
C_{max}	126.5	112.6–142.9	124.3	112.2–138.6	98.4	89.6–105.4
$AUC_{0-\infty}$	118.5	106.8–131.1	117.7	105.6–128.8	98.9	96.2–101.4

A = plain aqueous suspension; B = tablet, produced December 1987; C = tablet, produced January 1987; abbr.: p.e. = point estimator; 90 % = 90 % confidence interval.

Increased bioavailability following postprandial administration of cefuroxime axetil compared to administration in the fasting state has been demonstrated in previous studies (Sommers et al. 1984, Williams et al. 1984, Finn et al. 1987), and similar results have been obtained with other ester prodrug cephalosporins (Stoeckel et al. 1989, Deppermann et al. 1989). Rapid gastric emptying in the fasting state possibly results in an exessive amount of cephalosporin presented to the upper small intestine, saturating the absorption process (leading presumably to zero-order absorption kinetics, cf. Hespe et al. 1987), thereby having a negative effect on bioavailability. The absolute bioavailability of all newer oral ester prodrug cephalosporins, including the carboxymethyl cephalosporins are below 50—60 % (Dürckheimer et al. 1987) which suggests an absorption mechanism through the mucosa with limited capacity.

It has been postulated that a carrier mediated transport mechanism is involved in the absorption of β-lactam antibiotics (Iseki et al. 1989, and references therein; Muranashi et al. 1987, Okano et al. 1987, Tamai et al. 1987; Tsuji et al. 1987) and that it is similar to that involved in the absorption of dipeptides from the small intestine (Kramer 1987, Kramer et al. 1988). Alternatively absorption may be by passive diffusion, where lipophilicity is the rate limiting factor (Sugawara et al. 1990). This mechanism has been discussed in relation to amoxicillin (Hespe et al. 1987), assumed for cefetamet pivoxyl (Stoeckel et al. 1989), and for cefuroxime axetil is an attractive alternative to the carrier transport theory. The optimal conditions for absorption of ester prodrug cephalosporins are found in the duodenum and the upper part of the small intestine, where pH is in the range of 4 to 6. The water solubility (i.e. low lipophilicity) of ester prodrug cephalosporins is highest at low pH values in the stomach (Stoeckel et al. 1989), and reduces at higher pH. However, increasing the pH above 7 leads to isomerization and inactivation of ester prodrug cephalosporins and/or hydrolysis to the non-absorbable parent cephalosporins (Miyauchi et al. 1989a, b). For cefuroxime axetil in-vitro isomerization to the inactive delta 2-isomer and hydrolysis to delta 2-cefuroxime have been observed (Ayrton 1986), but not to any appreciable degree in-vivo. From the lack of gastrointestinal side effect in this study we assume that active cefuroxime which could impair the natural bacterial flora is not liberated in the gut lumen, and that isomerisation of non-absorbed cefuroxime axetil to delta 2-cefuroxime axetil is the dominating process in the deeper parts of the small intestine.

The urinary recovery rate of 54 % of the administered dose indicates an absolute bioavailability of 60 %: this is lower than that for the older cephalosporins of the cephalexin type which are almost totally absorbed and totally excreted in the urine (review by Riess et al. 1982). On the other hand, urinary recoveries of oral penicillins which are generally considered to have good absorption, e.g. amoxicillin or bacampicillin, are also only about 50 % (cf. Blume and Mutschler 1989), and are less well absorbed when administered after food (Sommers et al. 1984), indicating and absolute bioavailability significantly lower than 100 %.

In conclusion, this study demonstrated the bioequivalence of the two batches of cefuroxime axetil tablets and the reliable absorption of cefuroxime axetil, and that absorption of the aqueous suspension was slightly lower than that of the tablets.

5. References

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