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Skin tissue fluid levels of cefotiam in healthy man following oral cefotiam hexetil

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Summary. Cefotiam hexetil is a pro-drug of cefotiam available for oral administration. To evaluate cefotiam concentrations at the active site in skin and soft-tissue infections, drug levels in skin suction blister fluid (SBF), cantharides blister fluid (CBF) and serum were determined. Six healthy subjects received oral cefotiam 400 mg as cefotiam hexetil. On an other day 200 mg was injected intravenously.

Following the oral dose, the bioavailability of cefotiam was 45.5%, and the maximum concentration in serum of 2.6 mg·l^{-1} was obtained at 2.1 h. Peak concentrations in both types of blister fluid (0.9 mg·l^{-1}) were significantly lower than after the iv dose (SBF 1.4 mg·l^{-1}, CBF 1.5 mg·l^{-1}), and the peak levels occurred later (3.3 versus 1.5 h in CBF). Despite the delay, the extent of penetration was about 100% following either mode of administration (SBF, iv dose 112%, oral dose 117%). The cefotiam level in skin blister fluids declined significantly more slowly than the serum level. Following the oral dose, the mean terminal half life was serum 0.8 h, SBF 2.6 h and CBF 4.6 h.

Cefotiam concentrations in the blister fluids were close to the MIC_{90} of *Staphylococcus aureus, S. epidermis* and *H. influenzae* and exceeded the MIC_{90} of Streptococci, *E. coli* and *Proteus mirabilis.*

Thus, the oral administration of cefotiam 400 mg t. i. d. should be curative in the majority of bacterial infections of the skin and soft-tissues.

Key words: Cefotiam, skin tissue fluid; pharmacokinetics, concentration in the skin

Second generation cephalosporins, such as cefotiam, are highly active against common gram-negative aerobic organisms [1]. And, in contrast to many third generation cephalosporins, cefotiam also inhibits gram-positive cocci [2]. The broad spectrum of second generation cephalosporins makes them candidates for the treatment of skin and soft-tissue infections in which mixed bacterial colonization may occur [3]. Moreover, the severity of such diseases may require instantaneous treatment before the microorganism has been cultured.

The need for repeated parenteral administration has restricted the use of new cephalosporins in out-patients [4], so cephalosporin esters suitable for oral administration (such as cefotiam hexetil or cefuroxime axetil) [5–7] have been developed. During absorption, the ester is hydrolysed and the active agent is released [5, 8]. In a first clinical study, cefotiam hexetil 300–600 mg/day was effective in 87% patients suffering from bacterial infection of the skin (Kumazawa J, 1987 unpublished data). Cure rates exceeding 90% were reported with cefuroxime axetil [6] and cefaclor [6, 9, 10] 0.5–2.0 g/day.

To study cefotiam concentrations at the site of bacterial infections in skin and soft-tissue infections following cefotiam hexetil (SCE2174), skin blister fluid [11, 12] and serum levels have been determined in healthy volunteers. The drug levels following a single oral dose have been compared to those after an intravenous injection.

Material and methods

Subjects

Six healthy subjects (5 male, 1 female, aged 23–35 y, weight 60–90 kg, height 173–200 cm) participated in the experiments after giving written informed consent to it. The subjects refrained from taking other drugs, alcohol and caffeine.

Protocol

The study followed a randomized, cross-over design. During the preceding night of cefotiam and cefotiam hexetil administration food intake was not allowed. The subjects received one oral dose of 400 mg cefotiam as cefotiam hexetil (2 tablets of 200 mg) and one iv injection (200 mg) of cefotiam dihydrochloride (Spizef®; injection period 3 min; end of infusion was taken as 0 time point). Both preparations were supplied by Takeda Pharma, Stolberg, FRG. The drugs were administered together with breakfast. The washout period between the administrations was 7 days. Blood samples to provide serum were taken before drug administration, and after 5, 10, 20, 30, and 45 min as well as 1, 1.5, 2, 2.5, 3, 4, 5, 6, and 8 h. Suction blister

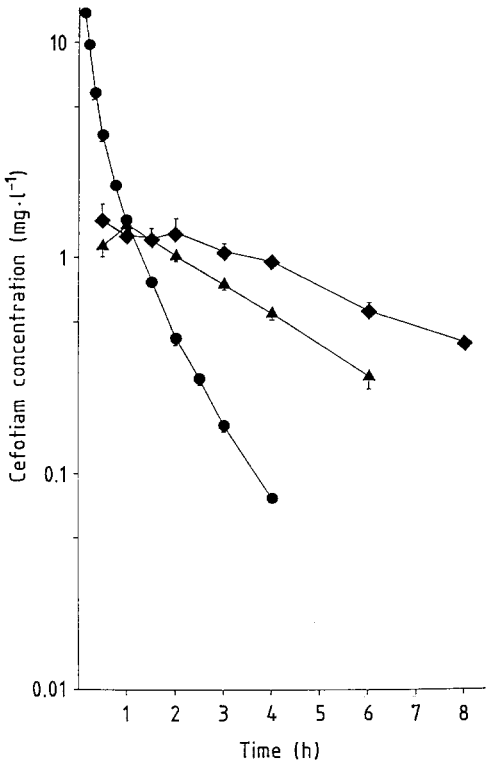

Fig. 1. Cefotiam concentrations in serum (●), SBF (▲) and CBF (◆) following a single intravenous dose of 200 mg cefotiam in six healthy volunteers. Mean (SEM)

fluid (SBF) and cantharides blister fluid (CBF) were obtained at 0.5, 1, 2, 3, 4, and 6 h, and CBF at 1.5 and 8 h, too. The induction of cantharides and suction blisters started 13 and 3 h before dosing. Details of the blistering procedures are given elsewhere [13, 14]. Serum and blister fluid samples were stored at −20 °C until analyzed.

Drug assay

Cefotiam was determined in serum, SBF and CBF by HPLC (F. Kees et al., in preparation). In brief, serum and blister fluids were deproteinized with acetonitrile, which was removed by extraction with dichloromethane. 50 µl of the aqueous phase (kept frozen until injected) were directly chromatographed using reversed-phase HPLC. The eluate was monitored at 254 nm. Linear results were obtained in the range cefotiam 0.1 to 10 µg/ml; the relative standard deviation was 3 to 7%. The method also allowed determination of the isomeric d3-cefotiam (detection limit 0.01–0.02 mg/l).

Serum standards for the calibration graphs were prepared using blank human serum. Blister fluid standards were made in phosphate buffer pH 7.0.

Protein binding

Cefotiam binding in SBF and CBF was calculated as described by McNamara et al. [15], based upon serum binding of 40% [16] and the albumin concentration in serum and skin blister fluids previously determined [13].

Pharmacokinetic calculations

Maximum cefotiam concentrations (C_{max}) in serum, SBF and CBF, and the times to those maximum concentrations (t_{max}), were obtained from the measured data. The elimination rate constant (k) was calculated from the terminal loglinear decline in concentration in the appropriate fluids. The areas under the cefotiam concentration-time curves (AUC), serum clearance (Cl), the volume of distribution (V_z) and bioavailability of cefotiam following cefotiam hexetil were calculated.

Drug penetration into the skin blister fluids (Pen) was obtained as the area ratio blister fluid/serum based upon free drug levels.

Statistical evaluation

The data are expressed as the arithmetic mean (SEM). They were evaluated statistically using the Wilcoxon test for tied pairs. $P \leq 0.05$ was considered as significant.

Results

Intravenous dose

Mean serum and blister fluid concentrations of cefotiam are depicted in Fig. 1. The maximum concentration in serum was 16.2 $mg \cdot l^{-1}$ and the cefotiam level had declined to 0.078 (0.004) $mg \cdot l^{-1}$ at 4 h. The mean terminal half life of the serum level was 0.8 h (Table 1). Plasma clearance amounted to 31.8 (1.8) $l \cdot h^{-1}$ and the volume of distribution was 0.35 (0.002) $l \cdot kg^{-1}$.

The maximum concentrations of 1.4 $mg \cdot l^{-1}$ in SBF and 1.5 $mg \cdot l^{-1}$ in CBF were obtained after 1.0 and 1.5 h, respectively. Thereafter, the blister fluid levels exceeded the serum concentration. The mean concentration in the blister fluids declined to SBF 0.28 (0.03) and CBF 0.56 (0.03) $mg \cdot l^{-1}$ at 6 h and the mean terminal half lives were 2.3 h in SBF and 3.5 h in CBF, thus significantly exceeding the serum half life. The fraction unbound of cefotiam was 0.775 in SBF and 0.635 in CBF. Thus, cefotiam penetration into SBF and CBF amounted to 112 and 151%, respectively.

The serum concentration of d3-cefotiam was below the detection limit in four subjects and was up to 0.061 $mg \cdot l^{-1}$ in the others. In all volunteers, d3-cefotiam in CBF was always below the detection limit. In SBF minor concentrations of the metabolite were found in four volunteers (≤ 0.045 $mg \cdot l^{-1}$).

Oral dose

The mean cefotiam levels are shown in Fig. 2. The peak serum level of 2.6 $mg \cdot l^{-1}$ occurred after 2.1 h. At 4 and 6 h cefotiam concentrations were 0.59 (0.15) and 0.11 (0.03) $mg \cdot l^{-1}$, respectively.

The bioavailability of cefotiam following oral ingestion of cefotiam hexetil was 45%. The terminal half life was 0.8 h (Table 1). In SBF the mean peak concentration of 0.9 $mg \cdot l^{-1}$ was obtained at 3.5 h, and the corresponding values in CBF were 0.9 $mg \cdot l^{-1}$ and 3.3 h. The maximum concentrations in the blister fluids were significantly lower and the time to the peak concentrations were significantly prolonged as compared to the iv dose. At 6 h the cefotiam concentration in SBF was 0.47 (0.05) $mg \cdot l^{-1}$, thus significantly exceeding the drug level following the iv dose. CBF concentrations were 0.52 (0.05) and 0.30 (0.06) $mg \cdot l^{-1}$ at 6 and 8 h. The terminal half lives in SBF

Table 1. Pharmacokinetics of cefotiam following single oral and iv doses of 400 and 200 mg; respectively ($n = 6$; $\bar{x}$ (SEM))

Parameter	Serum		SBF		CBF	
	iv	oral	iv	oral	iv	oral
t_{max}[h]	0.083[a]	2.1 (0.3)	1.0	3.5 (0.6)[b]	1.5 (0.2)	3.3 (0.3)[b]
C_{max}[mg/l]	16.2 (8)[a]	2.6 (0.3)	1.4 (0.9)	0.9 (0.1)[b]	1.5 (0.1)	0.9 (0.1)
$t_{1/2}$ [h]	0.8 (0.06)	0.8 (0.08)	2.3 (0.3)[c]	2.6 (0.5)[c]	3.5 (0.4)[c]	4.6 (0.8)[c]
AUC [mg·l^{-1}h]	6.4 (0.3)	5.8 (0.5)	5.5 (0.2)	5.3 (1.1)	9.0 (0.3)	6.3 (0.9)
Pen [%]			112 (3)	117 (11)	151 (8)	114 (11)

[a] first sampling time 5 min after administration; [b] $P \leq 0.05$ versus iv administration; [c] $P \leq 0.05$ versus serum

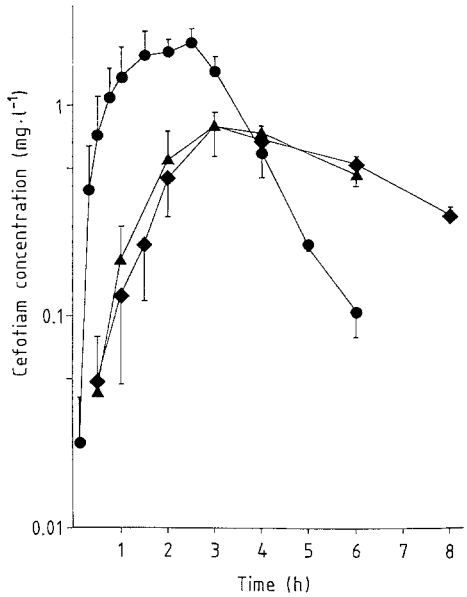

Fig. 2. Cefotiam concentrations in serum (●), SBF (▲) and CBF (◆). Six healthy volunteers received a single oral dose of 400 mg cefotiam as cefotiam hexetil. Mean (SEM)

(2.6 h) and CBF (4.6 h) was in accordance with the corresponding values following the intravenous injection. Cefotiam penetration into SBF and CBF was 117 and 114%, respectively.

d3-Cefotiam was detected in serum samples from five subjects. The peak level (0.019 to 0.097 mg·l^{-1}) was found after 1 to 1.5 h. In four subjects d3-cefotiam was detectable in CBF (0.010 to 0.045 mg·l^{-1}), and in SBF the maximum d3-cefotiam level (0.051 to 0.099 mg·l^{-1}) was observed 2 to 4 h after the dose of cefotiam. At 6 h the SBF level of d3-cefotiam was 0.045 (0.023) mg·l^{-1}.

Discussion

In a previous study serum and skin blister fluid levels of cefotiam were evaluated following a single intramuscular dose of 1 g. Drug penetration into the blister fluid was about 100%. SBF and CBF levels were well above the MIC of *Neisseria gonorrhoeae,* suggesting the suitability of a 1 g single-dose regimen of cefotiam for gonorrhoea [17, 18], as subsequently proven in a clinical trial [19]. In the present study, the SBF and CBF levels of cefotiam were lower than following i. m. administration [17], even after correction for the dose administered.

Following the iv dose, cefotiam concentrations in serum and the derived pharmacokinetic parameters were in accordance with those reported by Brisson et al [20], if corrected for the 200 mg dose.

The isomer d3-cefotiam was found in very low concentrations following the iv injection, but after cefotiam hexetil p.o. higher d3-cefotiam concentrations were observed in serum and blister fluids. This suggests isomerization of cefotiam during drug absorption. Isomerization has also been observed in homogenates of small intestine, liver and in plasma from mice [5]. d3-Cefotiam is devoid of antibacterial activity [21].

Following cefotiam hexetil, the bioavailability of cefotiam was 45%, and its terminal half life was 0.8 h. The concentrations of d3-cefotiam, cefotiam bioavailability and terminal half life are close to the data reported by Couet et al. [1987, unpublished data]. The bioavailability of cefotiam is close to that of cefuroxime administered as cefuroxime axetil (52%) [22] but is less than that of cefaclor availability ($\geq 65\%$) [23].

Levels in CBF have been evaluated following cefuroxime 1 g im. The terminal half life in CBF (1.6 h) was consistent with the serum half life, and the maximum level in CBF was 12.6 mg/l [12], which is close to the peak cefotiam level following 1 g im [17]. With cefotiam, however, the drug level in SBF and CBF declined more slowly than the serum concentration (Table 1). Such behaviour is frequently observed with drugs of high hydrophilicity and very rapid elimination [18]. Thus, cefotiam concentrations in both blister fluids exceeded the serum concentrations from about 4 h after the oral dose, and even 1 to 1.5 h after following the iv dose (Figs. 1, 2). Therefore, active concentrations will persist in the skin and probably also in soft tissues for a longer period of time than in serum.

No essential difference between cefotiam concentrations in SBF and CBF were observed. Following an oral dose, the penetration of cefotiam into SBF and CBF amounted to 117% and 114%, respectively, which means that tissue penetration was close to the 100% expected, if the free drug were homogeneously distributed between plasma and tissue fluid [18]. The inflammatory reaction of the tissues obtained by the induction of cantharides blisters, but not by suction blistering [13, 18], did not have a major influence on tissue penetration by cefotiam.

Cefotiam only binds to a minor extent to serum proteins (serum 40%; SBF 22.5%). Therefore, MIC values are virtually not affected by the addition of serum to the incubation medium [24], and drug levels in blister fluids may be compared to in vitro activity without the need to

correct for protein binding. Following 400 mg p.o. and 200 mg i.v., the peak concentrations of cefotiam in the blister fluids were close to the MIC_{90} values of *Staphylococcus aureus, S. epidermidis* and *H. influenzae* [2, 25, 26], and they exceeded the MIC_{90} values of *Streptococcus pyogenes, S. pneumoniae, E. coli* and *Proteus mirabilis* [2]. These organisms are frequently isolated from skin infections [3]. It appears that the doses used in the investigation of cefotiam hexetil in skin infections (100–200 mg t.i.d.) were low, and increasing the dose should result in a higher cure rate, as described for cefuroxime axetil and cefaclor [6, 9, 10].

In conclusion, the present results suggest that cefotiam hexetil 400 mg t.i.d. p.o. should be curative in the majority of skin and soft-tissue infections. Nevertheless, in severe cases, as well as in instances of treatment failure, increasing the daily dose would be advisable.

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