ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Nov. 1987, p. 1822–1825
0066-4804/87/111822-04$02.00/0

Vol. 31, No. 11

Cefodizime in Serum and Skin Blister Fluid after Single Intravenous and Intramuscular Doses in Healthy Volunteers

H. C. KORTING,[1]* M. SCHÄFER-KORTING,[2] L. MAASS,[3] N. KLESEL,[4] AND E. MUTSCHLER[2]

Dermatologische Klinik und Poliklinik der Ludwig-Maximilians-Universität, D-8000 Munich,[1] and Pharmakologisches Institut für Naturwissenschaftler der Johann Wolfgang Goethe-Universität,[2] Klinische Forschung, Abteilung für Klinische Pharmakologie,[3] and Pharma-Forschung, Abteilung für Chemotherapie,[4] Hoechst AG, D-6000 Frankfurt, Federal Republic of Germany

Received 20 February 1987/Accepted 12 August 1987

In gonorrhea therapy, cephalosporins are conventionally administered by intramuscular (i.m.) injection, which rather frequently leads to local side effects. To investigate whether the well-tolerated intravenous (i.v.) injection of cephalosporins may be of comparable gonocidal effect, levels of cefodizime, a new broad-spectrum cephalosporin, in serum and tissue fluid (suction blister and cantharides blister fluid) were determined in six healthy men. Single doses of 1 g of cefodizime were injected i.v. and i.m. according to a randomized crossover design. On i.m. injection the drug was completely bioavailable, and the peak concentration in serum was 75 ± 8 μg/ml. The terminal half-life of serum levels was 2.4 h. Cefodizime concentrations in the blister fluids increased for 1.5 to 3 h after the i.v. dose and for at least 3 h on i.m. administration. The concentrations of non-protein-bound cefodizime in blister fluid already exceeded the MIC for 90% of *Neisseria gonorrhoeae* strains 10 min after i.v. injection and 20 to 30 min after the i.m. dose. At 6 h after each dose, active concentrations were still present in serum. The results suggest that cefodizime administered i.v. and i.m. has equivalent high cure rates in uncomplicated gonorrhea. This hypothesis should be tested further by a controlled clinical trial. If equivalent, i.v. administration excels because it is better tolerated locally.

Broad-spectrum cephalosporins proved to be effective drugs in the treatment of uncomplicated gonorrhea (6, 12, 16, 17). In gonorrhea, cephalosporins are administered intramuscularly (i.m.) instead of intravenously (i.v.) as they are in most other infections. However, i.m. injection of β-lactam antibiotics often leads to pain at the injection site (4, 10, 18, 28). Thus, local anesthetics have to be added to the injection solution to increase tolerability (6, 11, 12, 18). Moreover, i.m. injection of antibiotics may result in muscle necrosis and abscess formation (2). Since i.v. injection of cephalosporins has only a low incidence of local side effects and since systemic side effects do not seem to be increased (18), the question arises whether i.v. injection should be preferred in gonorrhea therapy, too.

In advance of an extended clinical study comparing these dosage regimens, it seems rational to determine the pharmacokinetics after single i.v. and i.m. doses in humans and to evaluate the in vitro activity of the obtained concentrations. Because in uncomplicated gonorrhea bacteria are not located in the blood but in other tissues, pharmacokinetic evaluations should include levels in tissue fluids.

This paper presents the pharmacokinetics of cefodizime, a recently developed broad-spectrum cephalosporin highly active against *Neisseria gonorrhoeae* in vitro (14) and in vivo (26) with a rather long half-life in human serum (22). Levels in tissue fluid were measured by both the suction blister fluid (SBF) technique (9, 22) and the cantharides blister fluid (CBF) method (21, 24) for 3 h after drug administration. Recent in vitro experiments showed essentially complete killing of *N. gonorrhoeae* within 2 to 4 h (13). SBF proved to be equivalent to interstitial fluid (27), and it should represent uninflamed tissue fluid. CBF should mimic inflamed tissue fluid (1). Therefore, the blister fluids should be closer to the biophase of antibiotics than serum.

* Corresponding author.

MATERIALS AND METHODS

Subject study. Six male subjects, between the ages of 24 and 31 years and weighing 62.5 to 78.5 kg, who had no hepatic, hematological, or renal disease and no history of allergy to β-lactam antibiotics participated in the study. The study protocol was approved by the local ethics committee, and written informed consent was obtained from each subject. The subjects restrained from using other drugs and alcohol on the days preceding the injections as well as on the days of experiments.

Two single doses of 1 g of cefodizime were injected i.v. (over a period of 3 min) or i.m. to the volunteers according to a randomized crossover design. For i.m. injection the drug was dissolved in a solution containing 1% lidocaine. There were 4 to 7 days between two consecutive doses. At 10:00 p.m. on the days before drug administration, the subjects fixed seven cantharides plasters on their abdomens as described recently (23). The next morning suction blistering was performed first. Using six suction cups with 30 holes (diameter, 8 mm), a negative pressure of −250 mm Hg was raised slowly and maintained for 2.5 h (for details, see references 22 and 23). After blistering was complete, the suction cups were removed and cefodizime was injected. SBF and CBF were collected 10, 20, 30, 45, 90, and 180 min postinjection. If possible, additional CBF was harvested at 6 h. SBF was obtained by pooling the fluid of five blisters. Blood samples were obtained from the cubital vein by individual puncture (on i.v. administration of the other arm) before the injections, as well as 5, 10, 15, 20, 30, and 45 min and 1, 1.5, 2, 3, 4.5, and 6 h thereafter. Blood was allowed to clot, and serum was separated by centrifugation.

In addition, the six volunteers plus two more healthy men received on a separate occasion 1 g of cefodizime i.v. Using two suction cups, 10 blisters were raised before drug administration and also starting immediately after drug injection.

TABLE 1. Pharmacokinetic data of cefodizime derived from levels in serum after 1-g i.v. and i.m. doses to six healthy volunteers

Subject	i.v. dose				i.m. dose					
	V (liters)	CL (ml/min)	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (μg · h/ml)	C_{max} (μg/ml)[a]	T_{max} (h)[a]	$t_{1/2}$ (h)	$AUC_{0-\infty}$ (μg · h/ml)	V (liters)	CL (ml/min)
1	9.8	44.2	2.6	378	104.1	0.25	2.2	391	7.9	42.7
2	10.9	53.7	2.4	311	81.9	1.0	2.5	383	9.4	43.6
3	11.4	46.9	2.8	356	59.7	1.5	3.7	375	14.3	44.5
4	13.3	63.9	2.4	262	59.4	1.5	2.4	305	11.2	54.8
5	8.6	45.5	2.2	367	89.1	1.0	2.5	434	8.4	38.5
6	10.3	54.1	2.2	309	57.1	0.75	6.1	329	26.6	50.8
$\bar{x}$	10.7	51.4	2.4	330	75.2	1.0	3.2	369	13.0	45.8
SEM	0.6	3.0	0.1	18	8.0	0.2	0.6	19	2.9	2.4

[a] C_{max}, Maximum concentration in serum; T_{max}, time to maximum concentration in serum.

At 2.5 h after the injection, all blisters were punctured, and the fluid of the blisters raised simultaneously was pooled. Blood samples were collected before the injection and 2.5 h after. Usually, serum and skin blister fluid were stored at −18°C until analyzed.

Determination of cefodizime concentrations and protein binding in CBF. Levels of cefodizime in serum and skin blister fluid were determined by a bioassay. *Streptococcus pyogenes* A77 was used as the indicator organism (sample volume, 0.1 ml [22]). Samples collected before cefodizime administration were free of antibacterial activity. The method was linear in the range of 1 to 400 mg/liter (serum and urine) and 0.2 to 20 mg/liter (blister fluid). The correlation coefficient was 7.5%. Recent studies comparing the bioassay and a high-pressure liquid chromatographic procedure showed a good correspondence of the results. No metabolites of cefodizime could be detected by high-pressure liquid chromatography.

Solutions for the calibration graphs were made with serum or diluted serum according to the concentration of albumin in SBF and CBF. Cefodizime binding in CBF was calculated from serum protein binding as described previously (15). Serum protein binding was determined by equilibrium dialysis (81%), binding to SBF by ultrafiltration (72%), and calculation (75%) (22).

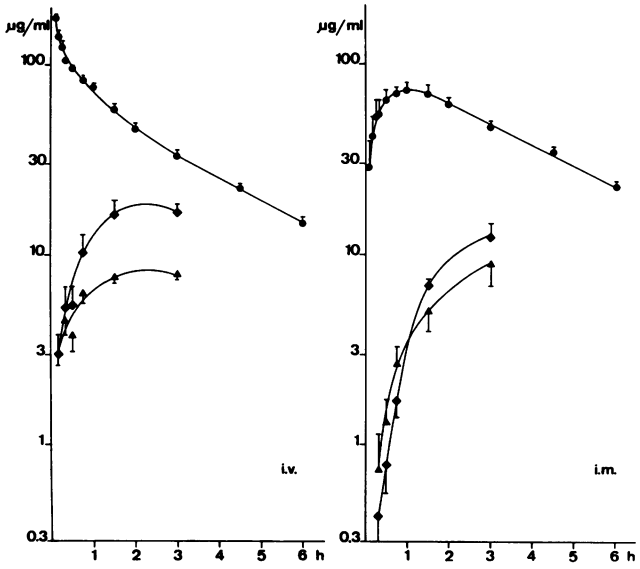

FIG. 1. Cefodizime concentrations in serum (●), SBF (▲), and CBF (◆) after a single i.v. or i.m. administration of 1 g. Mean values (± standard error of the mean [bars]) in six healthy volunteers.

Pharmacokinetic and statistical evaluations. Maximum cefodizime concentrations in serum (i.m. dose) and skin blister fluid and times to peak concentrations were obtained from the measured data. The elimination rate constant (k_{el}) was calculated from the terminal log-linear decline of concentrations in serum. Terminal half-life ($t_{1/2}$) is ln $2/k_{el}$. The areas under the serum and blister fluid level-time curves (AUC_{0-3}) were calculated by the trapezoidal rule. From the levels in serum, $AUC_{0-\infty}$ was estimated by the trapezoidal rule up to 6 h and extrapolated to infinity. The serum clearance (CL) was determined by $D/AUC_{0-\infty}$, and the volume of distribution (V) was determined by CL/k_{el}. Bioavailability (percent) of cefodizime injected i.m. was calculated by [$AUC_{0-\infty}$ (i.m.) × 100]/$AUC_{0-\infty}$ (i.v.).

All data are arithmetic mean values ± standard error of the mean. Statistical evaluations were performed by Student's t test for tied pairs. Significance was determined at $P \leq 0.05$.

RESULTS

Levels in serum. Cefodizime concentrations in serum after the i.v. dose declined biexponentially from 177 ± 10 μg/ml (5 min) to 14.7 ± 1.2 μg/ml at 6 h (Fig. 1.). At 6 h, concentrations of unbound cefodizime in serum were 2.8 μg/ml. The $t_{1/2}$ was 2.4 h. The $AUC_{0-\infty}$ was 330 μg · h/ml. The CL and V were 51.4 ml/min and 10.7 liters, respectively (Table 1). On i.m. administration, maximum concentrations in serum were obtained at 1 h in the mean and amounted to 75 ± 8 μg/ml. The $t_{1/2}$ was 2.7 h. At 1.5 h and thereafter, concentrations in serum after the i.m. dose exceeded those after the i.v. injection. At 6 h, concentrations of total and non-protein-bound cefodizime amounted to 22.8 ± 1.6 and 4.3 μg/ml, respectively. The $AUC_{0-\infty}$ of cefodizime administered i.m. was 369 μg · h/ml; thus, bioavailability was complete. The $t_{1/2}$, CL, and V after the i.m. injection were close to those after the i.v. dose (Table 1).

Levels in skin blister fluid. Total cefodizime concentration in SBF was 3.1 ± 0.4 μg/ml 10 min after i.v. administration. Peak concentrations were observed at 1.5 to 3 h (Fig. 1). At 3 h, levels in SBF amounted to 8.0 ± 0.6 μg/ml; CBF concentrations were 17.0 ± 0.3 μg/ml. However, 10 min after the i.m. injection cefodizime could not be detected in SBF in five of six subjects, and in CBF cefodizime was not detected at all. At 20 min, drug concentrations in either blister fluid were still below the detection limit in two volunteers. Maximum concentrations were obtained at 3 h. At that time, concentrations in SBF amounted to 8.9 ± 2.0 μg/ml, and concentrations in CBF were 16.3 ± 1.7 μg/ml. In the first 45 min, cefodizime concentrations in SBF after the i.v. dose significantly exceeded those after i.m. injection.

Concentrations in CBF were significantly lower for 1.5 h after the i.m. dose than they were after the i.v. dose. For SBF, AUC_{0-3} was 9.6 and 7.3% of the respective serum value after i.v. and i.m. administration of cefodizime. For CBF, the corresponding values were 18.5 and 10.7%, respectively.

Cefodizime binding in CBF is 78.6%. After i.v. injection, concentrations of unbound cefodizime in SBF and CBF were 3.1 ± 0.5 and 3.6 ± 0.9 μg/ml, respectively, at 3 h. They were significantly lower than the respective concentration in serum (6.3 ± 1.1 μg/ml). The same held true on i.m. administration. The concentration of unbound drug in serum was 8.9 ± 1.5 μg/ml, and in SBF and CBF it was 3.4 ± 1.7 and 2.6 ± 1.2 μg/ml, respectively. Therefore at 3 h postinjection, distribution equilibrium between serum and skin blister fluid was not obtained.

Cefodizime concentrations in SBF of blisters raised before and after i.v. injection were 12.1 ± 1.9 and 20.9 ± 1.9 μg/ml, respectively ($P \leq 0.001$), corresponding to 31 and 54%, respectively, of the concentration in serum at 2.5 h.

DISCUSSION

Since infectious diseases were first treated by chemotherapy, it has repeatedly been debated whether sustained low drug concentrations or high peak concentrations which rapidly decline are superior in eradicating infective organisms (5). The former ones are obtained by continuous drug infusion or i.m. injection; the latter ones are obtained by an i.v. bolus injection. The question was up for discussion in gonorrhea therapy, too (7, 8, 19, 25). Traditionally, i.m. application of β-lactam antibiotics is suggested for gonorrhea therapy, although until now there was no definite proof that i.m. administration was superior to i.v. injection. To obtain a rational basis for the selection of the mode of administration, first the effect of the serum concentration profile on the time course of drug levels at the tissue site of infection (biophase) has to be evaluated. The time courses of antibiotic concentrations in tissue fluid in general differ from the corresponding serum level profiles (3). Next, the influence of the drug concentration profile at the biophase on the speed of killing of bacteria has to be determined. In vitro experiments with *N. gonorrhoeae* exposed to continuously changing concentrations of two cephalosporins showed essentially complete killing of bacteria within 2 to 4 h depending on the simulated time course (13). Therefore, the present study focused on the influence of the mode of administration on cefodizime concentrations in tissue fluid within the first 3 h after i.v. and i.m. injection.

Pharmacokinetic parameters of cefodizime derived from levels in serum after the i.v. dose were well in accordance with those determined recently. A minor difference was observed in V (10.7 versus 15.6 liters [22]), possibly resulting from the lower body weight of the volunteers of this study.

The ratio AUC_{0-3} (blister fluid)/AUC_{0-3} (serum) showed that cefodizime penetration is not poorer after the i.v. dose as compared with that after the i.m. injection during the most relevant period of time in gonorrhea therapy. Peak concentrations in the blister fluids were obtained no earlier than 1.5 h after i.v. injection and not before 3 h after the i.m. dose. In addition, at 3 h the concentrations of non-protein-bound cefodizime in serum exceeded those in blister fluid by about twofold. Thus, distribution equilibrium between drug concentrations in serum and blister fluid was not obtained during the entire period of investigation. This holds true for either blister fluid and for both injection regimens.

The concentrations of unbound cefodizime in SBF and CBF were already well above the MIC_{90} (MIC for 90% of strains tested) for *N. gonorrhoeae* (0.21 μg/ml [14]) at 10 min after the i.v. injection and at 20 to 30 min after i.m. administration. At 3 h, the concentrations of unbound drug in both blister fluids exceeded the MIC_{90} at least 12-fold.

Recent investigations showed SBF concentrations effective against *N. gonorrhoeae* to be present 3 to 9 h after a single 1-g i.v. dose. In that study, blisters were raised after cefodizime injection (22). Since suction blisters require at least 2 h for development (9), blistering had to be performed before the injection of cefodizime in the present investigation. To compare the results of both studies, we also had to evaluate the influence of the blistering time (before and after cefodizime administration) on drug concentrations in SBF. At 2.5 h after an i.v. dose, cefodizime levels in SBF of blisters raised after drug administration were 1.7-fold greater than those in the fluid of blisters developed before dosing, and at 3 h the levels were still 1.4-fold higher (12.5 versus 8.9 μg/ml [22]). On the other hand, levels of the lipophilic drug 8-methoxypsoralen in SBF were already independent of the blistering time at 2 h (20). The dependence of cefodizime concentrations in SBF on the time of blistering should result from the rather slow tissue penetration of the hydrophilic drug. A distribution equilibrium between blister fluid and the surrounding tissue fluid thus is obtained later than with lipophilic drugs. Therefore, SBF levels in the present and the previous investigation have to be compared with caution.

In conclusion, the more rapid increase of cefodizime concentrations in skin blister fluid after the i.v. dose suggest this route of administration to be (at least) equally as effective as i.m. administration. In vitro experiments based on the drug level data described here are in accordance (H. C. Korting et al., submitted for publication). Owing to the better tolerability of cephalosporins injected i.v., it seems rational to evaluate this mode of administration of cefodizime and possibly other cephalosporins in uncomplicated gonorrhea.

LITERATURE CITED

1. **Allison, J. H., and F. R. Bettley.** 1958. Investigations into cantharidine blisters raised on apparently normal skin in normal and abnormal subjects. Br. J. Dermatol. **1958**:331–339.
2. **Anonymous.** 1984. Intramuscular or intravenous antibiotics? Lancet **i**:660–662.
3. **Bergan, T.** 1981. Pharmacokinetics of tissue penetration of antibiotics. Rev. Infect. Dis. **3**:45–66.
4. **Cahn, M. M., E. J. Levy, P. Actor, and J. F. Pauls.** 1974. Comparative serum levels and urinary recovery of cefazolin, cephaloridine, and cephalothin in man. J. Clin. Pharmacol. **14**: 61–66.
5. **Eagle, H., R. Fleishman, and M. Levy.** 1985. "Continuous" vs. "discontinuous" therapy with penicillin. The effect of interval between injections on therapeutic efficacy. N. Engl. J. Med. **248**:481–488.
6. **Eichmann, A., G. Weidmann, and L. Havas.** 1981. One-dose treatment of acute uncomplicated gonorrhoea of male patients with ceftriaxone Ro 13-9904, a new parenteral cephalosporin. Chemotherapy (Basel) **27**(Suppl. 1):62–69.
7. **Jaffe, H. W., A. L. Schroeter, G. H. Reynolds, A. A. Zaidi, J. E. Martin, Jr., and J. Thayer.** 1979. Pharmacokinetic determinants of penicillin cure of gonococcal urethritis. Antimicrob. Agents Chemother. **15**:587–591.
8. **Kandhari, K. C., J. S. Pasricha, N. C. Bhargava, A. K. Sharma, O. Singh, P. Sood, and R. A. Bhujwala.** 1975. Penicillin therapy in gonorrhoea: correlation of in vitro resistance of N. gonorrhoeae strains with clinical response to penicillin and its blood levels. Indian J. Med. Res. **63**:818–823.
9. **Kiistala, U.** 1968. Suction blister device for separation of viable dermis from epidermis. J. Invest. Dermatol. **50**:129–137.
10. **Korting, H. C., D. Abeck, and U. Neubert.** 1986. Evaluation of

cefotetan in uncomplicated gonorrhoea. Dermatologica **173:** 237–244.

11. **Korting, H. C., and U. Neubert.** 1984. Susceptibility of Neisseria gonorrhoeae to ceftizoxime in vitro and in vivo. Chemotherapy (Basel) **30:**322–327.
12. **Korting, H. C., and U. Neubert.** 1985. Treatment of gonorrhoea with cefotiam: activity in vitro and clinical results of a 1-gram single-dose regimen. Dermatologica **171:**264–268.
13. **Korting, H. C., H. Niederauer, and M. Ollert.** 1986. Bactericidal activity of cefotiam and ceftizoxime against Neisseria gonorrhoeae in an in vitro model simulating plasma and cantharidal blister fluid levels after the single intramuscular application of one gram. Chemotherapy (Basel) **32:**260–269.
14. **Limbert, M., N. Klesel, G. Seeger, I. Winkler, and E. Schrinner.** 1984. Cefodizime, an aminothiazolylcephalosporin. I. In vitro activity. J. Antibiot. **37:**892–900.
15. **McNamara, P. J., M. Gibaldi, and K. Stoeckel.** 1983. Fraction unbound in interstitial fluid. J. Pharm. Sci. **72:**834–836.
16. **Neubert, U., H. C. Korting, and G. Ruckdeschel.** 1982. Susceptibility of Neisseria gonorrhoeae to cefotaxime: in vitro studies and treatment results. Arch. Dermatol. Res. **274:**321–326.
17. **Rajan, V. S., E. H. Sng, T. Thirumoorthy, and C. L. Goh.** 1982. Ceftriaxone in the treatment of ordinary and penicillinase-producing strains of Neisseria gonorrhoeae. Br. J. Vener. Dis. **58:**314–316.
18. **Richards, D. M., R. C. Heel, R. N. Brogden, T. M. Speight, and G. S. Avery.** 1984. Ceftriaxone: a review of its antibacterial activity, pharmacological properties and therapeutic use. Drugs **27:**469–527.
19. **Sabath, L. D., and J. J. Kivlahan.** 1961. Dosage of penicillin for acute gonorrhoea in males. Am. J. Med. Sci. **240:**663–672.
20. **Schäfer-Korting, M., H. W. Grimm, and E. Mutschler.** 1985. Morphologische, biochemische und pharmakokinetische Untersuchungen an Saugblasen in Abhängigkeit von der Art und dem Zeitpunkt ihrer Entstehung. Arch. Pharm. **318:**711–720.
21. **Schäfer-Korting, M., H. C. Korting, S. Hiemstra, and E. Mutschler.** 1982. Does cantharides blister fluid provide access to the peripheral compartment? Eur. J. Clin. Pharmacol. **23:**327–330.
22. **Schäfer-Korting, M., H. C. Korting, L. Maass, N. Klesel, H.-G. Grigoleit, and E. Mutschler.** 1986. Cefodizime penetration into skin suction blister fluid following a single intravenous dose. Eur. J. Clin. Pharmacol. **30:**295–298.
23. **Schäfer-Korting, M., H. C. Korting, and E. Mutschler.** 1985. Human plasma and skin blister fluid levels of griseofulvin following a single oral dose. Eur. J. Clin. Pharmacol. **29:**109–113.
24. **Simon, C., V. Malerczyk, E. Brahmstaedt, and W. Toeller.** 1973. Cefazolin, ein neues Breitspektrum-Antibiotikum. Dtsch. Med. Wochenschr. **98:**2448–2450.
25. **Staheli, L. T.** 1964. Duration of therapy in management of gonorrhoea. J. Am. Med. Assoc. **90:**118–119.
26. **Stolz, E., S. Santosa, J. C. S. van der Hoek, J. M. Boot, J. H. T. Wagenvoort et al.** 1986. 0.5 and 1 g cefodizime (HR 221) randomized comparative study versus cefotaxime (Claforan) in the treatment of acute uncomplicated urogenital gonococcal infection. 2nd World Congress on Sexually Transmitted Diseases. Imp. M. Vioujas, Paris.
27. **Vermeer, B. J., F. C. Reman, C. M. van Gent.** 1979. The determination of lipids and proteins in suction blister fluid. J. Invest. Dermatol. **73:**303–305.
28. **Yates, R. A., I. D. Cockshott, H. L. Houghton, A. Wardleworth, H. Adam, and R. J. Donelly.** 1983. Pharmacokinetics and tolerance of single intramuscular doses of cefotetan in normal caucasian volunteers. J. Antimicrob. Chemother. **11**(Suppl. A): 207–212.