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Passage of Cefotaxime and Ceftriaxone into Cerebrospinal Fluid of Patients with Uninflamed Meninges

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Cefotaxime and ceftriaxone have proven to be effective in pyogenic infections of the central nervous system. Since in some bacterial central nervous system infections the blood-cerebrospinal fluid (CSF) barrier is either minimally impaired or recovers in the course of the illness, we studied the penetration of both antibiotics in the absence of inflamed meninges. Patients who had undergone external ventriculostomies for noninflammatory occlusive hydrocephalus received either cefotaxime (2 g/30 min) or ceftriaxone (2 g/30 min) to treat extracerebral infections. Serum and CSF were drawn repeatedly after the first dose. With ceftriaxone, they were also drawn after the last dose. The concentrations of cefotaxime, its metabolite desacetylcefotaxime, and ceftriaxone were determined by high-performance liquid chromatography with UV detection. Maximum concentrations of cefotaxime in CSF were reached 0.5 to 8 h (median = 3 h; $n = 6$) after the end of the infusion and ranged from 0.14 to 1.81 mg/liter (median = 0.44 mg/liter; $n = 6$). Maximum levels of ceftriaxone in CSF ranging from 0.18 to 1.04 mg/liter (median = 0.43 mg/liter; $n = 5$) were seen 1 to 16 h (median = 12 h; $n = 5$) after the infusion. The elimination half-life of cefotaxime in CSF was 5.0 to 26.9 h (median = 9.3 h; $n = 5$), and that of ceftriaxone was 15.7 to 18.4 h (median = 16.8 h; $n = 3$). It is concluded that after a single dose of 2 g, maximal concentrations of cefotaxime and ceftriaxone in CSF do not differ substantially. The long elimination half-lives guarantee uniform concentrations in CSF. These concentrations reliably inhibit highly susceptible bacteria but cannot be relied on to inhibit staphylococci and penicillin G-resistant *Streptococcus pneumoniae*.

Because of its morbidity and lethality, bacterial meningitis remains a major medical concern throughout the world. The emergence of bacteria not susceptible to standard antibacterial agents in meningitis of children and immunocompromised adults has stimulated the search for alternative drugs. Broad-spectrum cephalosporins have a broad range of in vitro antibacterial activities, including that against most organisms responsible for purulent meningitis (6, 7, 19), and have been successfully applied as single agents for this indication in children and adults (3, 9, 29, 34, 37). Cefotaxime and ceftriaxone have been recommended by several authors for initial therapy of unidentified purulent meningitis in children and adults (for examples, see references 15 and 41).

In the presence of inflamed meninges, therapeutic concentrations of both cefotaxime and ceftriaxone in cerebrospinal fluid (CSF) have been reported previously (3, 9, 22, 34). However, in encephalitis, in Lyme borreliosis, in some cases of brain abscess and early meningitis, or in the course of meningitis, when the blood-CSF barrier begins to recover, only minor impairment of the blood-CSF barrier may be present (2, 31). Similarly, dexamethasone, recommended recently for adjunctive therapy of bacterial meningitis, rapidly reduced meningeal inflammation (21) and thereby decreased drug penetration into CSF. To ensure successful therapy and to prevent a relapse in these conditions, any antibiotic suggested for the treatment of central nervous system infections should also attain therapeutic concentrations in CSF with uninflamed meninges. The present study was performed in order to evaluate whether cefotaxime and ceftriaxone comply with this demand and to characterize their pharmacokinetics in CSF.

MATERIALS AND METHODS

Thirteen patients who had undergone external ventriculostomies for occlusive hydrocephalus received either cefotaxime ($n = 6$) or ceftriaxone ($n = 7$) to treat extracerebral infections. Patients with inflammatory central nervous system diseases or major impairment of their renal functions (serum creatinine > 0.015 g/liter) were not included. In all cases, cerebrovascular accidents were the underlying diseases. Both groups were similar with respect to age, sex, protein content of CSF, and CSF/serum albumin ratio (33) as measures of blood-CSF barrier impairment. For further details on the patients studied, see Table 1. Comedication varied according to clinical necessity and consisted of catecholamines, sedatives, corticosteroids, antibiotics, diuretics, osmotherapeutic agents, antihypertensive agents, and H_2-receptor blockers.

Two grams of cefotaxime (Claforan; Hoechst AG, Frankfurt/M, Germany) or 2 g of ceftriaxone (Rocephin; Hoffmann-La Roche, Grenzach-Wyhlen, Germany) was infused intravenously within 30 min. Single-dose pharmacokinetics were determined after the first infusion for six patients receiving cefotaxime and six patients receiving ceftriaxone. To obtain a 24-h time course with cefotaxime, the second infusion was administered 24 h after the first dose. Thereafter, therapy was continued with 2 g three times a day or twice a day. For this reason, patients with pneumonia or fever greater than 38.5°C during the 24-h interval before the

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TABLE 1. Characterization of investigated patients[a]

Drug and patient no.	Body wt (kg)	Age/sex	Diseases	CSF protein (mg/liter)	Q_{Alb} (10^3)	Level in CSF of:	
						WBC/mm^3	RBC/mm^3
Cefotaxime							
1	85	65/M	SAH, RTI	770	13.9	1	147
2	70	52/F	SAH, UTI	1,239	6.6	113	10,923
3	75	54/M	ICB, RTI	2,400	27.1	100	65,792
4	90	79/M	ICB, RTI	273	3.6	3	811
5	75	53/M	SAH, RTI	421	4.8	2	424
6	60	76/F	IIN, UTI, RTI	73	1.5	1	20
Ceftriaxone							
7	65	76/F	SAH, RTI	850	15.3	9	2,219
8	75	55/F	SAH, RTI	304	5.7	2	8,533
9	80	63/M	IIN, RTI	99	2.3	0	20
10	80	63/M	ICB, RTI	636	9.0	3	2,389
11	90	49/M	ICB, RTI	264	1.3	4	1,749
12	75	53/M	IIN, RTI	208	5.1	0	40
13	85	60/F	SAH, RTI	334	5.2	8	427

[a] SAH, subarachnoid hemorrhage; ICB, intracerebral bleeding; IIN, infratentorial ischemic infarction; Q_{Alb}, CSF/serum albumin ratio; RTI, respiratory tract infection; UTI, urinary tract infection; WBC, leukocytes; RBC, erythrocytes; M, male; F, female.

initiation of cephalosporin treatment were assigned to receive ceftriaxone, which was administered (2 g) every 24 h. Simultaneous blood and CSF samples were drawn at the end and 5, 15, and 30 min and 1, 2, 4, 6, 8, 10, 12, 14, 16, and 24 h after the termination of the antibiotic infusion. For three patients receiving ceftriaxone, elimination of the drug was studied by drawing three to six serum and CSF samples in 12-h intervals after the last dose. As cefotaxime was metabolized by blood and CSF (ca. 20% decline of cefotaxime within 5 h at 37°C in CSF), samples were cooled in ice water immediately after being drawn. They were then centrifuged at 3,000 × g for 5 min and stored at −70°C for less than 3 months. Six months of storage of cefotaxime-containing CSF at −70°C resulted in a conversion of ca. 5% cefotaxime to desacetylcefotaxime. Ceftriaxone stored at −70°C was stable in serum and CSF for more than 6 months.

The study protocol was approved by the Ethics Committee of the Medical Faculty of the University of Göttingen; informed consent to the participation was obtained from the patient or the nearest relative.

Concentrations in serum and CSF were measured by high-performance liquid chromatography using isocratic systems: separation of deproteinized cefotaxime and ceftriaxone samples (injection volume, 30 μl) was performed at 35°C on C_{18} reverse-phase columns (Spherisorb ODS II, 250 by 4.6 mm) with mobile phases containing phosphate buffer, acetonitrile, and ion-pairing reagents. Cefotaxime was eluted at 10.8 min, and desacetylcefotaxime was eluted at 5.5 min; they were detected by UV absorption at 254 nm. Ceftriaxone was eluted at 4.9 min and was detected with 274-nm UV light. Peak areas of the samples quantitated by using personal computer integrator software (Nelson Analytical, Cupertino, Calif.) were compared with the areas of serum and CSF samples spiked with standard solutions of cefotaxime, desacetylcefotaxime, and ceftriaxone processed identically. A full standard curve was constructed with each batch of samples. Except in patient 12, comedication did not interfere with the assays, as ensured by running control serum and CSF drawn from each patient before starting the antibiotic infusion. The quantification limits of cefotaxime and desacetylcefotaxime were 0.2 and 0.08 mg/liter, respectively, in serum and 0.08 and 0.03 mg/liter, respectively, in CSF. The interday coefficients of variation on replicated determinations in serum were 2.7% at 51.4 mg of cefotaxime per liter, 2.7% at 0.38 mg of cefotaxime per liter, 4.0% at 10.0 mg of desacetylcefotaxime per liter, and 9.5% at 0.15 mg of desacetylcefotaxime per liter (n = 6). The corresponding values in CSF were 2.8% at 5.2 mg of cefotaxime per liter, 6.6% at 0.17 mg of cefotaxime per liter, 8.1% at 1.02 mg of desacetylcefotaxime per liter, and 11.1% at 0.07 mg of desacetylcefotaxime per liter. The quantification limits of ceftriaxone were 0.8 mg/liter in serum and 0.08 mg/liter in CSF. The interday coefficients of variation were 2.0% at 99.7 and 6.8% at 1.55 mg/liter in serum and 3.3% at 16.2 and 6.4% at 0.16 mg/liter in CSF (n = 6).

For noncompartmental and compartmental pharmacokinetic analyses, the programs Excel 2.2 (Microsoft Co., Redmond, Wash.) and Topfit 1.0 (Gödecke-Schering-Thomae, Freiburg-Berlin-Biberach, Germany) were used.

Peak concentrations in serum and CSF (C_{maxS} and C_{maxCSF}, respectively) and time from the end of the infusion to the peak concentrations (T_{maxS} and T_{maxCSF}) were taken directly from the concentration-time curves. Elimination rate constants (k_{el}) were determined by log-linear regression analysis, and half-lives at the rapid elimination phase ($t_{1/2\beta}$) were determined as $\ln 2/k_{el}$. The areas under the concentration-time curves in serum and CSF up to the last measurable drug concentration (AUC_S and AUC_{CSF}, respectively) were estimated by the linear trapezoidal rule. Extrapolation to infinity was done by dividing the last measurable drug concentration (C_l) by k_{el}. For the assessment of the areas under the CSF concentration-time curves from zero to infinity ($AUC_{0-\infty CSF}$) with cefotaxime, C_{lCSF} was divided by k_{elCSF} obtained from the individual patient. Since with ceftriaxone k_{elCSF} was not assessable from patients studied after the first dose, C_{lCSF} was divided by the median value of the individual elimination rate constants estimated after the last dose. The total clearance in serum (CL) was calculated as dose/$AUC_{0-\infty S}$, and the apparent volume of distribution (V) was calculated as dose/$AUC_{0-\infty S} \cdot k_{el}$ (36).

Compartmental analysis was necessary to characterize distribution and elimination of cefotaxime in serum. For this purpose, the weighting function $g(y_i) = 1/y_i$ was employed, and the serum concentration-time curves for all cefotaxime

TABLE 2. Single-dose pharmacokinetics of cefotaxime in serum[a]

Patient no.	C_{max} (mg/liter)	$t_{1/2\alpha}$ (h)	$t_{1/2\beta}$ (h)	$t_{1/2\Gamma}$ (h)	CL (ml/min)	V (liters)	$AUC_{0-\infty}$ (mg · h/liter)	AUC_{α} (%)	AUC_{β} (%)	AUC_{Γ} (%)
1	62.4	0.08	0.50	1.15	474	41.3	70	10.0	56.3	33.7
2	95.1	0.06	0.50	4.15	419	24.1	80	23.8	70.4	5.8
3	127.5	0.05	0.48	1.93	301	29.5	111	24.6	57.6	17.8
4	90.7	0.05	0.66	2.34	212	40.7	157	7.8	27.8	64.4
5	95.8	0.12	0.45	1.34	273	14.7	122	9.2	32.2	58.6
6	111.8	0.15	0.95	2.24	239	42.7	140	21.2	61.3	17.4

[a] $t_{1/2\alpha}$, half-life of the distribution phase; AUC_{α}, AUC_{β}, and AUC_{Γ} relative AUC of the α-, β-, and Γ-phases in percent of $AUC_{0-\infty}$.

TABLE 3. Single-dose pharmacokinetics of cefotaxime in CSF

Patient no.	C_{max} (mg/liter)	T_{max} (h)	$t_{1/2\beta}$ (h)	AUC (mg · h/liter)	$AUC_{0-\infty}$ (mg · h/liter)	$AUC_{0-\infty CSF}/AUC_{0-\infty S}$
1	1.81	0.5	5.0	13.4	15.0	0.21
2	0.56	6	13.3	7.9	11.5	0.14
3	0.54	2	8.8	9.0	13.1	0.12
4	0.34	4	26.9	6.9	16.3	0.10
5	0.27	8	9.3	2.9	3.6	0.03
6	0.14	2				

TABLE 4. Single-dose pharmacokinetics of desacetylcefotaxime in serum and CSF

Site and patient no.	C_{max} (mg/liter)	T_{max} (h)	$t_{1/2\beta}$ (h)	AUC (mg · h/liter)
Serum				
1	5.0	0.08	1.99	21
2	14.5	0.08	1.49	37
3	8.4	0.0	1.56	15
4	8.3	0.0	7.17	75
5	6.0	1.0	2.59	30
6	3.3	0.5	2.73	19
CSF				
1	0.38	8	3.0	4.2
2	0.26	6	7.4	3.1
3	0.13	0.25	14.2	1.7
4	0.09	16		1.7
5	0.06	10	37.4	1.2
6	BQL[a]			

[a] BQL, below quantification limit (desacetylcefotaxime, 0.03 mg/liter).

patients were analyzed by two- and three-compartment models. The Akaike Information Criterion was used for model discrimination.

RESULTS

Maximum concentrations of cefotaxime and ceftriaxone in serum were attained at the end of the drug infusions; levels of desacetylcefotaxime in serum were maximal 0 to 1 h after the end of the infusions (median = 0.08 h).

The distribution and elimination of cefotaxime in serum were adequately described by a three-compartment model: after a short distribution phase, the elimination half-life of the early phase ($t_{1/2\beta S}$) was 0.45 to 0.95 h (median = 0.50 h; n = 6), and that of the late phase ($t_{1/2\Gamma S}$) was 1.15 to 4.15 h (median = 2.09 h; n = 6). The application of a two-compartment model resulted in an inaccurate fitting of the late measured concentrations to the concentration-time curves of the model. With five of the six patients, the Akaike Information Criterion favored the three-compartment model over the two-compartment analysis. The elimination of desacetylcefotaxime and ceftriaxone in serum approximated a single exponential decay; $t_{1/2\beta S}$ of desacetylcefotaxime was 1.49 to 7.17 h (median = 2.29 h; n = 6), and $t_{1/2\beta S}$ of ceftriaxone ranged from 7.5 to 16.5 h (median = 10.2 h; n = 7). The $AUC_{0-\infty S}$, CL, and V of cefotaxime, desacetylcefotaxime, and ceftriaxone are presented in Tables 2 through 6.

Antibiotic concentrations in CSF were maximal after the end of the infusions and indicated slow drug passage into CSF: the respective T_{maxCSF} of cefotaxime, desacetylcefotaxime, and ceftriaxone were 0.5 to 8 h (median = 3 h; n = 6), 0.25 to 16 h (median = 8 h; n = 5), and 1 to 16 h (median = 12 h; n = 5). Elimination rates of cefotaxime, desacetylcefotaxime, and ceftriaxone from CSF were compatible with a first-order elimination (Fig. 1 and 2). The elimination half-life of cefotaxime in CSF ($t_{1/2\beta CSF}$) was estimated as 5.0 to 26.9 h (median = 9.3 h; n = 5), and that of ceftriaxone was estimated as 15.7 to 18.4 h (median = 16.8 h; n = 3). With cefotaxime, $t_{1/2\beta CSF}$ exceeded the corresponding serum parameter by a factor of 10 to 41, and with ceftriaxone $t_{1/2\beta CSF}$ was 1.5 to 2.5 times greater than $t_{1/2\beta S}$ (Tables 2 through 6).

Because of the different shapes of the concentration-time curves, the ratio between corresponding antibiotic concentrations in CSF and serum (C_{CSF}/C_S) was not constant but increased with time. The hysteresis loops of patient 1 (cefotaxime) and patient 7 (ceftriaxone) illustrate this fact (Fig. 3). When the AUC_{CSF} was related to the AUC_S, the AUC_{CSF}/AUC_S ratio ranged from 0.02 to 0.19 (median = 0.08; n = 5) with cefotaxime and from 0.002 to 0.008 (median = 0.003; n = 5) with ceftriaxone. When $AUC_{0-\infty CSF}$ was related to $AUC_{0-\infty S}$, the $AUC_{0-\infty CSF}/AUC_{0-\infty S}$ ratio of cefotaxime was 0.03 to 0.21 (median = 0.12; n = 5) compared with 0.006 to 0.018 (median = 0.007; n = 5) for ceftriaxone.

The AUC_{CSF} of desacetylcefotaxime amounted to 0.18 to 0.41 (median = 0.31; n = 5) of the AUC_{CSF} of cefotaxime. In serum, the AUC desacetylcefotaxime/cefotaxime ratio was almost identical, ranging from 0.14 to 0.48 (median = 0.28; n = 6).

The $AUC_{0-\infty CSF}/AUC_{0-\infty S}$ ratio representing the overall penetration of cefotaxime and ceftriaxone into CSF correlated with parameters used in clinical practice to characterize the condition of the blood-CSF barrier, e.g., the protein content of CSF (for cefotaxime, Spearman's rank correlation coefficient [r_S] = 0.71, $P > 0.05$; for ceftriaxone, r_S = 0.50, $P > 0.05$). The difference in the $AUC_{0-\infty CSF}/AUC_{0-\infty S}$ ratios for the patients receiving ceftriaxone and those for patients receiving cefotaxime was statistically significant ($P < 0.01$, Mann-Whitney U test).

TABLE 5. Single-dose pharmacokinetics of ceftriaxone in serum

Patient no.	C_{max} (mg/liter)	$t_{1/2\beta}$ (h)	CL (ml/min)	V (liters)	$AUC_{0-\infty}$ (mg · h/liter)
7	271.7	10.9	14.3	13.5	2,332
8	247.9	9.9	14.0	12.0	2,373
9	199.3	16.5	13.9	19.8	2,406
10	251.3	10.2	20.2	17.8	1,652
11	259.5	10.2	33.8	29.8	986
12	172.2	7.5	37.2	24.0	896
13		10.6[a]			

[a] Half-life determined after last dose; no determination of C_{max}.

antibiotics achieved concentrations in CSF several times higher than those in the present study (1, 3, 4, 6, 9, 10, 16, 20, 22, 30).

Elimination of both antibiotics in CSF was considerably slower than that in serum. On average, the $t_{1/2\beta CSF}$ of ceftriaxone was slower (median = 16.8 h) than the $t_{1/2\beta CSF}$ of cefotaxime (median = 9.3 h). In one neonate receiving ceftriaxone, the decay in CSF paralleled the plasma concentration-time curve (22). In contrast, previous work (7, 24–27) and the present results indicate that the rate of decline of drug concentrations is slower in CSF than in blood. This is consistent with physiological evidence. A lag of elimination

TABLE 6. Single-dose pharmacokinetics of ceftriaxone in CSF

Patient no.	Result determined after first dose				$AUC_{0-\infty CSF}/AUC_{0-\infty S}$	Result determined after last dose	
	C_{max} (mg/liter)	T_{max} (h)	AUC (mg · h/liter)	$AUC_{0-\infty}$ (mg · h/liter)		C_{12h}[a] (mg/liter)	$t_{1/2\beta}$ (h)
7	1.04	16	18.1	41.3	0.018		
8	0.66	16	12.1	19.5	0.008		
9	0.43	12	8.1	17.3	0.007		
10	0.33	12	4.4	10.5	0.006		
11	0.18	1	2.3	5.8	0.006	0.30	16.8
12	PI[b]					0.53	18.4
13						1.03	15.7

[a] Concentrations 12 h after the end of the last infusion.
[b] PI, peaks could not be quantified for peak interference.

DISCUSSION

The $t_{1/2}$ of ceftriaxone in serum (median = 10.2 h) was slightly higher than that reported before (7, 19, 28). This may be due to the fact that we studied only critically ill patients. In contrast to results of several previous investigations (7, 19), cefotaxime elimination in serum did not approximate a single-exponential decay: $t_{1/2\beta S}$ was shorter and $t_{1/2TS}$ was longer than the $t_{1/2}$ found by others (7, 19). They were close to the early and terminal $t_{1/2}$ estimated by Ings et al. (17) after measuring cefotaxime concentrations in serum by a microbiologic assay. Since the rate of decline slowed at concentrations in serum below 1 mg/liter, $t_{1/2TS}$ is not noticed with less sensitive assays and may be of clinical relevance only with very sensitive pathogens. Similarly, a slow elimination phase has recently been described for penicillin G (11). Desacetylcefotaxime in serum followed a first-order elimination.

Maximum levels in CSF achieved after a single dose (2 g/30 min) of cefotaxime or ceftriaxone did not differ substantially in the present study. In contrast, the $AUC_{0-\infty CSF}/AUC_{0-\infty S}$ ratio was 1 order of magnitude lower with ceftriaxone than with cefotaxime. The main reasons for this behavior probably were the high serum protein binding of ceftriaxone (90 to 95% compared with 40% for cefotaxime) (7, 19) and the higher molecular weight of ceftriaxone (598.5 versus 425.5) (40).

The C_{maxCSF} levels measured by us were considerably smaller than concentrations reported for ceftriaxone in lumbar CSF with uninflamed meninges (5) but were comparable to concentrations reported for cefotaxime in CSF with intact meninges (6, 18) and in Lyme disease (31, 32). C_{max} was attained later with ceftriaxone than with cefotaxime. In fully developed bacterial meningitis in children and adults, both from CSF compared with that from blood originates from the slow CSF turnover and from the even slower drainage of interstitial brain fluid into CSF (8, 35). Similarly, in human brain abscesses the ratio of concentrations of cefotaxime and desacetylcefotaxime in abscesses to those in plasma increased with the time interval between cefotaxime dosing and abscess fluid sampling (39).

Ceftriaxone and cefotaxime have identical antimicrobial spectra. The maximum concentrations of both drugs in CSF achieved in the present study exceeded the MICs for highly susceptible bacteria (*Neisseria meningitidis*, *Haemophilus influenzae*, penicillin G-sensitive *Streptococcus pneumoniae*, *Borrelia burgdorferi*, and some members of the family *Enterobacteriaceae*) approximately 10-fold (7, 13, 14, 19, 32) and therefore should be bactericidal in vivo. However, these levels should not be relied on to inhibit the growth of moderately susceptible bacteria, including relatively or fully penicillin G-resistant *S. pneumoniae* (MIC for 90% of the relatively penicillin G-resistant strains tested, 0.25 mg/liter; MICs for 90% of fully penicillin G-resistant strains tested, 1.0 [ceftriaxone] and 2.0 [cefotaxime] mg/liter) (23) and *Klebsiella*, *Enterobacter*, and *Serratia* spp. (MIC for 90% of strains tested, 0.13 to 0.65 mg/liter) (13). They are inadequate for many strains of *Staphylococcus aureus*, *Staphylococcus epidermidis*, and *Pseudomonas aeruginosa* (MIC for 90% of strains tested, >1 mg/liter) (7, 13, 19). A limited increase of concentrations in CSF can be attained by increasing doses. The low toxicity of both cefotaxime and ceftriaxone permits doubling of the usual daily dose (i.e., 12 g of cefotaxime or 4 g of ceftriaxone per 24 h), and doubling has been recommended for therapy of meningitis (41). *Listeria monocytogenes* and *Streptococcus faecalis*, which are responsible for up to 7% of bacterial meningitis in unselected

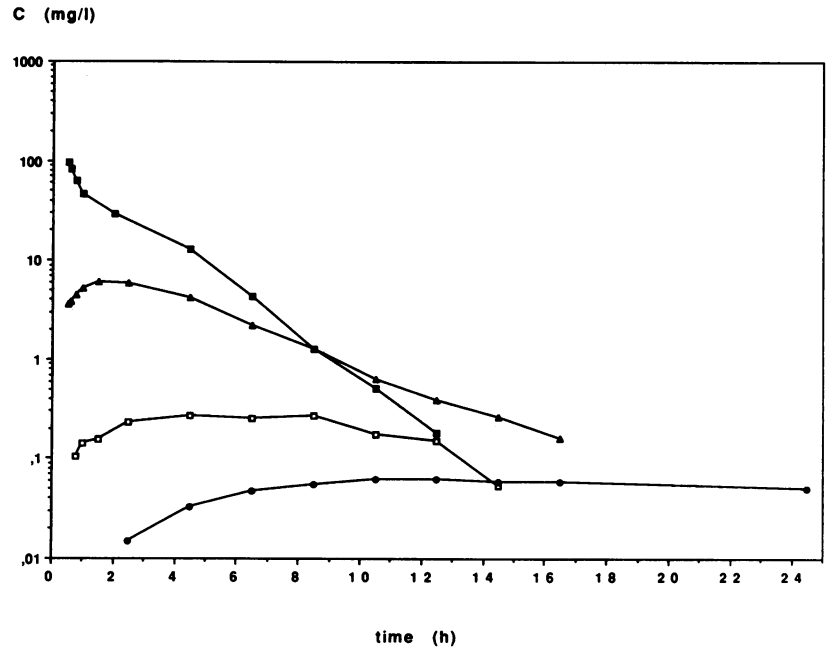

FIG. 1. Semilogarithmic graph of cefotaxime and desacetylcefotaxime concentrations in serum and CSF after the first intravenous infusion of 2 g of cefotaxime within 30 min in patient 5. Closed squares, cefotaxime in serum; closed triangles, desacetylcefotaxime in serum; open squares, cefotaxime in CSF; closed circles, desacetylcefotaxime in CSF.

adults (38, 42), are resistant to newer cephalosporins (6, 7, 19).

Desacetylcefotaxime, the main metabolite of cefotaxime, possesses independent antibacterial activity. It is less active than the parent compound (19). Desacetylcefotaxime and cefotaxime act synergistically in a 1:1 ratio but not in a 0.2:1 ratio (14). In the present study, the desacetylcefotaxime/cefotaxime ratios varied, usually increasing with time after

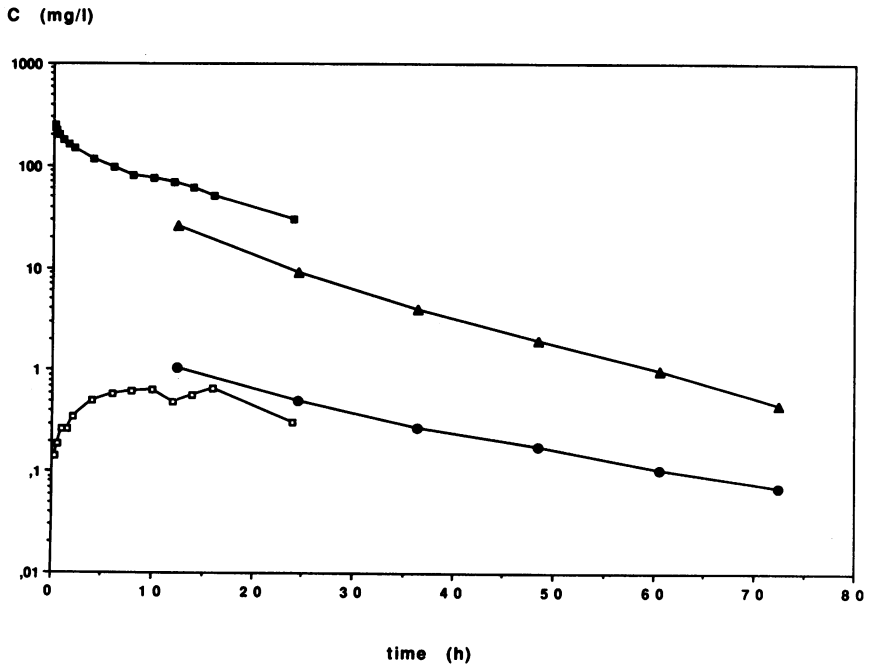

FIG. 2. Semilogarithmic graph of ceftriaxone concentrations in serum and CSF after the first intravenous infusion of 2 g of ceftriaxone within 30 min in patient 8 and after the last infusion of 2 g of ceftriaxone within 30 min in patient 13. Closed squares, ceftriaxone in serum of patient 8; open squares, ceftriaxone in CSF of patient 8; closed triangles, ceftriaxone in serum of patient 13; closed circles, ceftriaxone in CSF of patient 13.

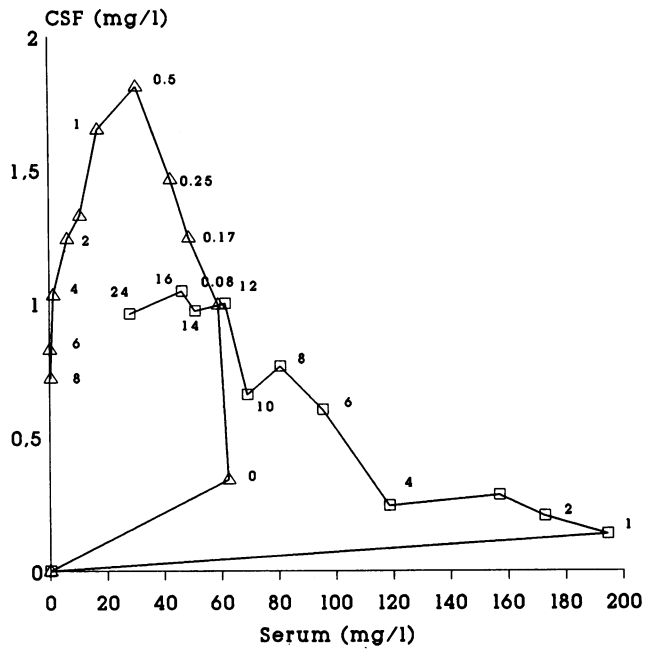

FIG. 3. Hysteresis loop of concentrations of cefotaxime (patient 1 [triangles]) and ceftriaxone (patient 7 [squares]) in CSF versus those in serum after the first 2-g dose. Measurements were taken simultaneously. The numbers near the points represent the intervals between sample withdrawal and termination of the antibiotic infusion.

the end of the infusion. Ratios of the AUC_{CSF} of desacetylcefotaxime and cefotaxime in the individual patients ranged from 0.18 to 0.41. Because of the variability of the ratios, the synergy between cefotaxime and desacetylcefotaxime cannot be counted upon in the clinical routine.

In conclusion, with highly susceptible organisms, both cefotaxime and ceftriaxone achieve therapeutic levels in CSF with inflamed and uninflamed meninges. With moderately susceptible bacteria, the levels in CSF observed in this study after infusion of 2 g of cefotaxime or ceftriaxone were probably subtherapeutic. This may compromise therapy when meningeal inflammation is less pronounced or resolves in the course of the illness. With cefotaxime, maximum concentrations in CSF were attained earlier than with ceftriaxone. Although the long persistence of both ceftriaxone and cefotaxime in CSF would permit long dosage intervals, the rapid elimination of cefotaxime in blood suggests distances between the single infusions of not more than 8 h with meningitis. The lack of a decisive advantage of one drug when they were compared with each other under the conditions studied by us is paralleled by clinical studies of bacterial meningitis and Lyme disease in which they were equally effective (12, 29, 32).

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REFERENCES

1. **Asmar, B. I., M. C. Thirumoorthi, J. A. Buckley, D. M. Kobos, and A. S. Dajani.** 1985. Cefotaxime diffusion into cerebrospinal fluid of children with meningitis. Antimicrob. Agents Chemother. **28**:138–140.
2. **Barling, R. W. A., and J. B. Selkon.** 1978. The penetration of antibiotics into cerebrospinal fluid and brain tissue. J. Antimicrob. Chemother. **4**:203–227.
3. **Belohradsky, B. H., K. Bruch, D. Geiss, D. Kafetzis, W. Margret, and G. Peters.** 1980. Intravenous cefotaxime in children with bacterial meningitis. Lancet **i**:61–63.
4. **Bryan, J. P., H. Rocha, H. R. Da Silva, A. Taveres, M. A. Sande, and W. M. Scheld.** 1985. Comparison of ceftriaxone and ampicillin plus chloramphenicol for the therapy of acute bacterial meningitis. Antimicrob. Agents Chemother. **28**:361–368.
5. **Chandrasekar, P. H., K. V. I. Rolston, B. R. Smith, and J. L. LeFrock.** 1984. Diffusion of ceftriaxone into the cerebrospinal fluid of adults. J. Antimicrob. Chemother. **14**:427–430.
6. **Cherubin, C. E., M. L. Corrado, S. R. Nair, M. E. Gombert, S. Landesman, and G. Humbert.** 1982. Treatment of Gram-negative bacillary meningitis: role of the new cephalosporin antibiotics. Rev. Infect. Dis. **4**(Suppl):S453–S464.
7. **Cherubin, C. E., R. H. K. Eng, R. Norrby, J. Modai, G. Humbert, and G. Overturf.** 1989. Penetration of newer cephalosporins into cerebrospinal fluid. Rev. Infect. Dis. **11**:526–548.
8. **Cserr, H. F., D. N. Cooper, P. K. Suri, and C. S. Patlak.** 1981. Efflux of radiolabeled polyethylene glycols and albumin from rat brain. Am. J. Physiol. **240**:F319–F328.
9. **Dankner, W. M., J. D. Connor, M. Sawyer, R. Straube, and S. A. Spector.** 1988. Treatment of bacterial meningitis with once daily ceftriaxone therapy. J. Antimicrob. Chemother. **21**:637–645.
10. **Del Rio, M., G. H. McCracken, J. Nelson, D. Chrane, and S. Shelton.** 1982. Pharmacokinetics and cerebrospinal fluid bactericidal activity of ceftriaxone in the treatment of pediatric patients with bacterial meningitis. Antimicrob. Agents Chemother. **22**:622–627.
11. **Ebert, S. C., J. Leggett, B. Vogelman, and W. A. Craig.** 1988. Evidence for a slow elimination phase for penicillin G. J. Infect. Dis. **158**:200–202.
12. **Ellmen, J. K., O. V. Renkonen, M. A. Anttila, and H. O. Peltola.** 1991. Antibiotic concentrations in liquor compared to the minimal inhibitory concentrations in pediatric bacterial meningitis. Chemotherapy **37**:1–5.
13. **Emmerson, A. M., P. A. Lamport, D. S. Reeves, M. J. Bywater, H. A. Holt, R. Wise, J. Andrews, and M. J. Hall.** 1985. The in vitro antibacterial activity of ceftriaxone in comparison with nine other antibiotics. Curr. Med. Res. Opin. **9**:480–493.
14. **Friis, H.** 1989. Antibacterial activity of cefotaxime, desacetylcefotaxime, and the combination of the two. Diagn. Microbiol. Infect. Dis. **12**:67–72.
15. **Helwig, H.** 1984. Empfehlungen der Arbeitsgemeinschaft "Meningitis" der Paul-Ehrlich-Gesellschaft für Chemotherapie e.V. zur Diagnostik und Therapie der bakteriellen Meningitis. Z. Antimikrob. Antineoplast. Chemother. **2**:209–213.
16. **Humbert, G., A. Leroy, S. R. Nair, and C. E. Cherubin.** 1984. Concentration of cefotaxime and the desacetyl metabolite in serum and CSF of patients with meningitis. J. Antimicrob. Chemother. **13**:487–494.
17. **Ings, R. M. J., J. P. Filastre, M. Godin, A. LeRoy, and G. Humbert.** 1982. The pharmacokinetics of cefotaxime and its metabolites in subjects with normal and impaired renal function. Rev. Infect. Dis. **4**(Suppl.):S379–S391.
18. **Karimi, A., K. Seeger, D. Stolke, and H. Knothe.** 1980. Cefotaxime concentrations in cerebrospinal fluid. J. Antimicrob. Chemother. **6**(Suppl. A):119–120.
19. **Kucers, A., and N. M. Bennett.** 1987. The use of antibiotics, 4th ed., p. 443–485, 510–524. William Heinemann Medical Books, London.
20. **Latif, R., and A. S. Dajani.** 1983. Ceftriaxone diffusion into cerebrospinal fluid of children with meningitis. Antimicrob. Agents Chemother. **23**:46–48.
21. **Lebel, M. H., B. J. Freji, G. A. Syrogiannopoulos, D. F. Chrane, M. J. Hoyt, S. M. Stewart, B. D. Kennard, K. D. Olsen, and G. H. McCracken.** 1988. Dexamethasone therapy for bacterial meningitis: results of two double-blind, placebo-controlled trials. N. Engl. J. Med. **319**:964–971.
22. **Martin, E., J. R. Koup, U. Paravicini, and K. Stoeckel.** 1984.

Pharmacokinetics of ceftriaxone in neonates and infants with meningitis. J. Pediatr. **105**:475–481.
23. **Marton, A., M. Gulyas, R. Munoz, and A. Tomasz.** 1991. Extremely high incidence of antibiotic resistance in clinical isolates of Streptococcus pneumoniae in Hungary. J. Infect. Dis. **163**:542–548.
24. **Nau, R., T. Dreyhaupt, H. Kolenda, and H. W. Prange.** 1992. Low blood-to-cerebrospinal fluid passage of sorbitol after intravenous infusion. Stroke **23**:1276–1279.
25. **Nau, R., H. W. Prange, J. Martell, S. Sharifi, H. Kolenda, and J. Bircher.** 1990. Penetration of ciprofloxacin into the cerebrospinal fluid of patients with uninflamed meninges. J. Antimicrob. Chemother. **25**:965–973.
26. **Nau, R., H. W. Prange, S. Menck, H. Kolenda, K. Visser, and J. K. Seydel.** 1992. Passage of rifampicin into the cerebrospinal fluid of adults with uninflamed meninges. J. Antimicrob. Chemother. **29**:719–724.
27. **Nau, R., F. J. Prins, H. Kolenda, and H. W. Prange.** 1992. Temporary reversal of serum to cerebrospinal fluid glycerol concentration gradient after intravenous infusion of glycerol. Eur. J. Clin. Pharmacol. **42**:181–185.
28. **Patel, I. H., S. Chen, M. Parsonnett, M. R. Hackman, M. A. Brooks, J. Konikoff, and S. A. Kaplan.** 1981. Pharmacokinetics of ceftriaxone in humans. Antimicrob. Agents Chemother. **20**:634–641.
29. **Peltola, H., M. Anttila, and O.-V. Renkonen.** 1989. Randomized comparison of chloramphenicol, ampicillin, cefotaxime, and ceftriaxone for childhood bacterial meningitis. Lancet **i**:1281–1287.
30. **Peretti, P., L. Sueri, M. Tosi, R. Ciammarughi, G. P. Cadeo, and B. Milanesi.** 1984. Cefotaxime in the cerebrospinal fluid and serum in patients with purulent meningitis. J. Antimicrob. Chemother. **14**(Suppl. B):117–123.
31. **Pfister, H. W., V. Preac-Mursic, B. Wilske, and K. M. Einhäupl.** 1989. Cefotaxime vs penicillin G for acute neurologic manifestations in Lyme borreliosis. Arch. Neurol. **46**:1190–1194.
32. **Pfister, H. W., V. Preac-Mursic, B. Wilske, E. Schielke, F. Sörgel, and K. M. Einhäupl.** 1991. Randomized comparison of ceftriaxone and cefotaxime in Lyme neuroborreliosis. J. Infect. Dis. **163**:311–318.
33. **Reiber, H., and K. Felgenhauer.** 1987. Protein transfer at the blood cerebrospinal fluid barrier and the quantitation of the humoral immune response within the central nervous system. Clin. Chim. Acta **163**:319–328.
34. **Roos, R., W. Margret, H. Trujillo, D. A. Kafetzis, C. J. Papadatos, H. M. van Hattingberg, B. H. Belohradsky, and K. Bruch.** 1980. Multizentrische Studie über Cefotaxim bei Meningitis und Sepsis im Kindesalter. Klinische Ergebnisse, Serum-Pharmakokinetik und Liquorspiegel. Infection **8**:S501–S505.
35. **Rosenberg, G. A., W. T. Kyner, and E. Estrada.** 1980. Bulk flow of brain interstitial fluid under normal and hyperosmolar conditions. Am. J. Physiol. **238**:H42–H48.
36. **Rowland, M., and T. N. Tozer.** 1989. Clinical pharmacokinetics. Concepts and applications, 2nd ed. Lea & Febiger, Philadelphia.
37. **Schaad, U. B., S. Suter, A. Gianella-Borradori, J. Pfenninger, R. Auckenthaler, O. Bernath, J.-J. Cheseaux, and J. Wedgwood.** 1990. A comparison of ceftriaxone and cefuroxime for the treatment of bacterial meningitis in children. N. Engl. J. Med. **322**:141–147.
38. **Schlech, W. F., J. I. Ward, J. D. Band, A. Hightower, D. W. Fraser, and C. V. Broome.** 1985. Bacterial meningitis in the United States, 1978 through 1981: the National Bacterial Meningitis Surveillance study. JAMA **253**:1749–1754.
39. **Sjölin, J., N. Eriksson, P. Arneborn, and O. Cars.** 1991. Penetration of cefotaxime and desacetylcefotaxime into brain abscesses in humans. Antimicrob. Agents Chemother. **35**:2606–2610.
40. **Thea, D., and M. Barza.** 1989. Use of antibacterial agents in infections of the central nervous system. Infect. Dis. Clin. N. Am. **3**:553–570.
41. **Tunkel, A. R., B. Wispelwey, and W. M. Scheld.** 1990. Bacterial meningitis. Recent advances in pathophysiology and treatment. Ann. Intern. Med. **112**:610–623.
42. **Windorfer, A., U. Rohde, and V. Windelboth.** 1990. Meningitiden und Enzephalitiden in Niedersachsen. Niedersächsisches Ärzteblatt **23**:16–20.