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Therapeutic Studies of Cefepime (BMY 28142) in Murine Meningitis and Pharmacokinetics in Neonatal Rats

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Cefepime (BMY 28142) was compared with ceftazidime, cefotaxime, and moxalactam for efficacy in treating experimental meningitis in mice and neonatal rats. Mice were infected intracranially with *Streptococcus pneumoniae*, *S. agalactiae*, *Staphylococcus aureus*, *Escherichia coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* and treated intramuscularly. Five- to eight-day-old neonatal rats were injected intracisternally with *Haemophilus influenzae*, *S. pneumoniae*, and *S. agalactiae* and treated intraperitoneally. Cefepime was found to be the most active compound against induced meningitis in mice infected with *S. agalactiae*. Cefepime was as active as cefotaxime against *Staphylococcus aureus* meningitis, slightly more active than cefotaxime against *S. pneumoniae* and *E. coli*, and as active as ceftazidime against *K. pneumoniae* and *P. aeruginosa* meningitis. Cefepime was found to be the most active compound against *S. pneumoniae* and *S. agalactiae* meningitis in neonatal rats. Against *H. influenzae*, cefepime was as active as moxalactam and cefotaxime. Ceftazidime was the least active compound. The pharmacokinetics of cefepime in neonatal rats were similar to those of ceftazidime. Both compounds penetrated well into cerebrospinal fluid and brain tissues of uninfected neonatal rats. Relative concentrations were twice as high as those of cefotaxime and moxalactam.

Cefepime (BMY 28142) is a new aminothiazolyl methoximinocephalosporin whose antibacterial spectrum (1, 6, 8, 16, 18, 20) has been established. Therapeutic efficacy in systemically infected mice (8, 12), effectiveness in treating meningitis caused by *Streptococcus pneumoniae* in rabbits (19), and *S. agalactiae* and *Escherichia coli* infections in newborn rats (9) have also been studied. This report compares the efficacies of cefepime, ceftazidime, cefotaxime, and moxalactam in experimental bacterial meningitis. Infections were established intracranially in mice, using *S. pneumoniae*, *S. agalactiae*, *Staphylococcus aureus*, *E. coli*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa*. In neonatal rats, *S. pneumoniae*, *S. agalactiae*, and *Haemophilus influenzae* were introduced intracisternally.

MATERIALS AND METHODS

Antibiotics. Cefepime sulfate salt was prepared at Bristol-Myers Co., Syracuse, N.Y. Ceftazidime pentahydrate, cefotaxime sodium, and moxalactam disodium were provided by Glaxo Group Research Ltd., Greenford, United Kingdom; Hoechst-Roussel Pharmaceuticals Inc., Somerville, N.J.; and Lilly Research Laboratories, Indianapolis, Ind., respectively.

Bacteria. Strains were selected for virulence in mice or neonatal rats after intracranial injection of appropriate numbers of bacteria (see below). Most of the strains were clinical isolates obtained from hospitals; two (*S. agalactiae* A21995 and *S. pneumoniae* A22884) were from the American Type Culture Collection (ATCC 12927 and 10813, respectively). *Staphylococcus aureus* A9537 is the Smith strain, which does not produce penicillinase, and *E. coli* A15119 is the Juhl strain. *H. influenzae* A21518 is ampicillin resistant and produces penicillinase. The organisms were maintained as described previously (8).

Activity in vitro. Growth-inhibitory activity was determined on solid medium by the serial twofold dilution technique. Mueller-Hinton medium (BBL Microbiology Systems, Cockeysville, Md.) was used for *Staphylococcus aureus*, *E. coli*, *K. pneumoniae*, and *P. aeruginosa*. The same medium supplemented with 4% defibrinated sheep blood was used for streptococci. *H. influenzae* susceptibility was determined on GC medium base (BBL) supplemented with 1% hemoglobin (BBL) and 1% IsoVitaleX (BBL). Preparation of inocula, inoculation, and MIC determinations were as described previously (8).

Preparation of challenge. *K. pneumoniae* was grown overnight, without shaking, in Mueller-Hinton broth (BBL). The culture was diluted with brain heart infusion broth (Scott Laboratories, Inc., Fiskeville, R.I.). Nonfastidious organisms requiring a large challenge (*Staphylococcus aureus*, *E. coli*, and *P. aeruginosa*) were grown overnight, with shaking, in Mueller-Hinton broth. Cells were harvested by centrifugation at 2,500 × *g* for 15 min, washed with saline, and suspended to the desired density in brain heart infusion broth. Streptococci were grown overnight in a candle jar in Mueller-Hinton broth supplemented with 1% defibrinated sheep blood. The culture was diluted to the appropriate cell density with brain heart infusion broth. The challenge of *H. influenzae* was prepared from a culture growing for 4 to 5 h, with shaking, in brain heart infusion broth containing supplement C (Difco Laboratories, Detroit, Mich.). Challenge sizes for all inocula were confirmed by plating.

Dosing solutions. Cephalosporins were dissolved in saline at serial fourfold dilutions. Concentrations were adjusted for potency.

Treatment of experimental meningitis in mice. For establishing meningitis, male Swiss-Webster mice weighing 20 g were used. Cultures were grown for 18 to 24 h and diluted in broth to give the desired number of CFUs for infection. Actual CFUs in the challenge inoculum were determined by viable count. Animals were infected by injecting 50 μl of the appropriately diluted bacterial suspension through the right orbital surface of the zygomatic bone (posterior corner of the right eye). A 27-gauge needle was introduced just beneath

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TABLE 1. Activity in vitro of cefepime, ceftazidime, cefotaxime, and moxalactam

Organism	Inoculum (CFU)	MIC (μg/ml)			
		Cefepime	Ceftazidime	Cefotaxime	Moxalactam
S. pneumoniae A9585	2×10^6	0.032	0.5	0.016	1
S. pneumoniae A22884	2×10^6	0.032	0.5	0.016	1
S. agalactiae A21995	2×10^6	0.13	0.25	0.32	4
Staphylococcus aureus A9537	2×10^6	4	16	4	8
E. coli A15119	2×10^5	0.032	0.25	0.063	0.13
K. pneumoniae A15130	2×10^5	0.063	0.5	0.13	0.25
P. aeruginosa A22328	2×10^5	2	2	16	16
H. influenzae A21518	1×10^6	0.032	0.063	0.004	0.032

the zygomatic bone and directed toward the right side of the skull into the brain to about 3 mm. This infection procedure has been described previously (21). At appropriate challenge levels, all bacterial strains used in the study were 100% lethal to mice in 1 to 4 days after intracranial infection. The bacterial strain injected can be recovered (cultured) from brain tissues of infected mice as early as 0.5 h after infection and also from infected dying and recently dead animals. Unpublished histopathology results for organisms other than *S. pneumoniae* were similar to those published for *S. pneumoniae* (21). Animals were treated intramuscularly with 0.2 ml of drug solution in accordance with the schedule given in Table 2. In each experiment, five mice were used per dose level for each drug. Four dose levels were used for each drug tested. Two experiments were performed for each drug and for each bacterial infection. Control animals, which received no treatment, died in 1 to 4 days. The dose, in milligrams per kilogram, required to protect half of the animals from death for 7 days (PD_{50}) was estimated by means of a log probit plot (14). The PD_{50}s and 95% confidence limits were calculated from the results of at least two separate experiments by the Spearman-Karber method (5).

Treatment of experimental meningitis in newborn rats. Five- to eight-day-old Sprague-Dawley rats were injected in the cisterna magna with 30 μl of a bacterial suspension. The challenge varied with the organism (see Table 3). A 1-ml tuberculin syringe fitted with a 30-gauge needle (Becton Dickinson & Co., Rutherford, N.J.) was used for inoculation. The needle was sheathed with Intramedic polyethylene tubing (Clay-Adams, Inc., New York, N.Y.), leaving a 2.5-mm-long segment at the tip uncovered. This device facilitated targeting of the challenge by controlling penetration. The needle was introduced at a 45° angle to the animal's neck. After withdrawal of the needle, pressure was applied to the area of the cisterna magna with the thumb of the hand holding the animal, to prevent leakage. All bacterial strains used in the study were 100% lethal to neonatal rats in 1 to 4 days. Bacterial strains infected could be recovered (cultured) from non-blood-contaminated cerebrospinal fluid (CSF) and brain tissues (cold saline flushed and with moisture removed) of infected neonatal rats as early as 0.5 h after infection as well as from dead animals. Animals were treated intraperitoneally, 3 h after infection, with 0.1 ml of antibiotic solution. A litter of 8 to 12 infants was used per dose level. Each litter was housed individually with a dam. One litter was left untreated; these animals died in 1 to 4 days. One litter was injected with sterile medium as a procedural control. PD_{50}s were calculated as described above.

Pharmacokinetics in newborn rats. Five- to 8-day-old Sprague-Dawley rats were given a dose of 40 mg of antibiotic per kg intraperitoneally in 0.1-ml volume. Litters of 8 to 12 infants were used. Each litter was housed individually with a dam. Samples of blood, CSF, and brain were obtained 0.5, 1, 2, 3, 4, 5, and 6 h after administration of the compound. Four rats were used per time interval. The animals were asphyxiated in an atmosphere of CO_2 generated by dry ice. Blood was sampled by cardiac puncture; CSF was sampled by cisternal tap. Before tapping CSF and removing the brain, neonatal rats were exsanguinated by heart puncture. Tapped CSF was examined for contamination with blood prior to use. Only uncontaminated CSF was used. After removal, the brain was rinsed in cold saline, excess moisture was removed, and the brain was weighed. Then 1 ml of saline-ethanol (1:1) extracting solution was added and the brain was homogenized with a Polytron homogenizer (model PT 10-35; Brinkmann Instruments, Inc., Westbury, N.Y.), followed by centrifugation at 22,500 × *g* for 15 min at 4°C. The supernatant was removed for assay. Antibiotic concentration in blood, CSF, and brain extract was determined by agar disk diffusion test as described previously (8) except that the assay organisms were *E. coli* A9624 (for cefepime), *Proteus vulgaris* A9539 (for ceftazidime), *Morganella morganii* A9695 (for cefotaxime), and *Providencia rettgeri* A15167-2 (for moxalactam). Antibiotics for the standard curves were in the same solutions as the unknowns: heparinized rat blood, normal saline (substituted for CSF), and brain extract solution. Sampling sizes for the standard curves were the same as for the unknowns. The sensitivity of the assay was 0.6 to 1.2 μg/ml.

The pharmacokinetics of cefepime and cefotaxime in neonatal rats infected with 5×10^2 CFU of *S. pneumoniae* A22884 were determined in a similar manner. The strain used to assay cefotaxime is not susceptible to the desacetyl

TABLE 2. Parenteral therapeutic efficacy in mice infected intracranially (meningitis)[a]

Organism	Challenge (CFU)	PD_{50} per treatment (mg/kg)[b]			
		Cefepime	Ceftazidime	Cefotaxime	Moxalactam
S. pneumoniae A 9585	5×10^4	1.0 (0.7–1.5)	11.9 (7.1–20.0)	2.9 (1.5–5.6)	151.6 (79.4–289.8)
S. agalactiae A21995	2.5×10^6	4.3 (2.3–7.8)	17.8 (9.1–34.7)	15.4 (8.7–27.2)	>200
Staphylococcus aureus A 9537	4×10^8	7.2 (4.5–11.4)	50 (31.5–79.4)	7.2 (4.5–11.4)	66 (36.5–119.3)
E. coli A15119	5×10^8	4.8 (2.1–11.0)	30.9 (19.3–49.7)	18.9 (9.6–37.3)	20.3 (15.4–26.8)
K. pneumoniae A15130	1×10^4	1.3 (0.7–2.2)	3.6 (1.7–7.4)	11.7 (6.9–19.6)	14.3 (6.4–32.1)
P. aeruginosa A22328	1×10^7	33 (21.0–51.8)	21.7 (12.2–38.7)	ND[c]	75.8 (46.8–122.8)

[a] Animals infected with *S. pneumoniae*, *Staphylococcus aureus*, and *E. coli* were treated 1 and 3.5 h after infection; those infected with *S. agalactiae* and *P. aeruginosa* were treated 1, 3, and 6 h after infection; and those infected with *K. pneumoniae* were treated 3 and 6 h after infection.
[b] Values in parentheses are 95% confidence limits (low limit–high limit).
[c] ND, Not determined.

TABLE 3. Parenteral therapeutic efficacy in neonatal rats infected intracisternally (meningitis)[a]

Organism	Challenge (CFU)	PD_{50} (mg/kg)[b]			
		Cefepime	Ceftazidime	Cefotaxime	Moxalactam
S. pneumoniae A22884	1×10^3	0.2 (0.15–0.22)	2.6 (2.2–3.1)	0.4 (0.3–0.6)	47.4 (34.5–65.2)
S. agalactiae A21995	3×10^3	0.4 (0.3–0.6)	2.8 (2.3–3.6)	3.5 (1.9–6.3)	>200
H. influenzae A21518	1×10^7	0.9 (0.6–1.2)	4.1 (2.6–6.5)	0.4 (0.2–0.5)	1.0 (0.6–1.6)

[a] Animals were treated 3 h after infection.
[b] Values in parentheses are 95% confidence limits (low limit–high limit).

metabolite; hence, values reflect the concentration of cefotaxime alone. Drug concentrations in blood, CSF, and brain tissue beyond the peak value were fitted to a regression line by the method of least mean squares. The half-lives ($t_{1/2}$) in blood, CSF, and brain tissue were determined by dividing *ln* 2 by the slope of the line. The area under the drug concentration curve (AUC) for blood, CSF, or brain tissue was obtained by successive trapezoidal approximation from $t = 0$ to 6 h.

The percent drug penetration into CSF or brain was calculated as the ratio of the AUC of CSF or brain to AUC of blood multiplied by 100.

RESULTS

Activity in vitro. The growth-inhibitory activities of cefepime, ceftazidime, cefotaxime, and moxalactam for the infecting strains (Table 1) were typical of each species (8). Streptococci were more susceptible to cefotaxime and cefepime and least susceptible to moxalactam. Cefepime and cefotaxime were more active than moxalactam and ceftazidime against *Staphylococcus aureus*. All four were very active against *E. coli*, *K. pneumoniae*, and *H. influenzae*. Against *P. aeruginosa*, cefepime and ceftazidime were eightfold more active than cefotaxime and moxalactam.

Treatment of meningitis in mice. Cefepime was more effective than the other cephalosporins in treating meningitis caused by *S. agalactiae* (Table 2). Cefepime and cefotaxime were more effective than moxalactam and ceftazidime against *S. pneumoniae* and *Staphylococcus aureus*. Cefepime was more active than ceftazidime and moxalactam against *E. coli*. Against infections with *K. pneumoniae* and *P. aeruginosa*, cefepime and ceftazidime were comparable in efficacy and more effective than the other cephalosporins.

Treatment of meningitis in neonatal rats. Meningitis caused by *S. pneumoniae* or *S. agalactiae* was most effectively treated with cefepime (Table 3). Cefotaxime and ceftazidime were also effective, but moxalactam had little or no detectable activity against these infections. The low PD_{50} of cefotaxime for animals infected with *H. influenzae* probably reflects the exquisite in vitro susceptibility of this organism to the antibiotic (Table 1), but could also reflect the unmeasured contribution of the desacetyl metabolite. Cefotaxime was marginally more active than cefepime and moxalactam against *H. influenzae*. Ceftazidime required a dose 10 times higher than that of cefotaxime to prevent death in half of the animals.

Pharmacokinetics in newborn rats. Figure 1 and Table 4 show the pharmacokinetic parameters of cefepime, ceftazidime, cefotaxime, and moxalactam in blood, CSF, and brain over a 6-h period after intraperitoneal administration of 40 mg/kg to neonatal rats.

Cefepime reached a peak concentration in blood of 43 μg/ml about 1 h after administration. Its half-life was 1 h. Peak concentrations of cefepime in the CSF and brain tissue occurred 2 to 3 h after administration, with levels of 9.5 μg/ml and 2.2 μg/g, respectively. Concentrations in CSF at 5 and 6 h were higher than those in blood. The clearance of cefepime from CSF and brain was slower ($t_{1/2}$ = 3.5 and 4.5 h) than that in blood. The penetration percentages of cefepime into CSF and brain of uninfected neonatal rats were 36 and 8%, respectively.

The pharmacokinetic parameters of ceftazidime in blood, CSF, and brain resembled those of cefepime.

The values given for cefotaxime are those of cefotaxime itself since our assay organism did not detect the desacetyl metabolite. The pharmacokinetic parameters of cefotaxime resemble those of cefepime in the blood of neonatal rats. The peak concentration of cefotaxime in CSF, 4.5 μg/ml, was only half that of cefepime. The antibiotic was not detectable in CSF at 5 and 6 h or in brain tissue throughout the observation period. The percent penetration of cefotaxime into CSF of noninfected animals was 13%.

Moxalactam had a peak concentration of 60 μg/ml in blood. Its half-life of 1.1 h was similar to those of the other three compounds. The AUC of moxalactam is larger (142 μg · h/ml) than those of cefepime (116 μg · h/ml) ceftazidime (130 μg · h/ml), and cefotaxime (94 μg · h/ml). The peak concentration of moxalactam in CSF was half that of cefepime. In contrast to cefepime, the concentration of moxalactam in CSF 5 and 6 h after administration was lower than that in blood. Although not shown, moxalactam concentration in the brain tissue peaked at about 1 to 2 h, with a level of 1.0 μg/g, and was not measurable after 2 h.

TABLE 4. Pharmacokinetic parameters of cefepime, ceftazidime, cefotaxime, and moxalactam in neonatal rats[a]

Compound	Tissue	Mean C_{max} (μg/ml or μg/g)[b]	$t_{1/2}$ (h)	Mean AUC_{0-6} (μg · h/ml)[b]	Penetration (%)
Cefepime	Blood	43 (8.7)	1.0	116 (14.6)	100
	CSF	9.5 (1.8)	3.3	42 (5.9)	36
	Brain	2.2 (0.6)	4.5	9 (1.8)	8
Ceftazidime	Blood	56 (21.4)	1.0	130 (32)	100
	CSF	9.0 (2.9)	3.5	39 (8.3)	30
	Brain	1.9 (0.9)	3.8	8 (2.8)	6
Cefotaxime	Blood	47 (22)	1.0	94 (13.6)	100
	CSF	4.5 (0.8)	1.7	12 (1.9)	13
	Brain	ND[c]	ND	ND	ND
Moxalactam	Blood	60 (6.6)	1.1	142 (14.4)	100
	CSF	4.8 (0.6)	3.3	21 (1.0)	15
	Brain	1.0 (0.2)	ND	1.5 (0.7)	1.1

[a] After intraperitoneal administration of a dose of 40 mg/kg to 5- to 8-day-old rats.
[b] C_{max}, Peak concentrations. Values in parentheses are standard deviations.
[c] ND, Not detectable or not determinable.

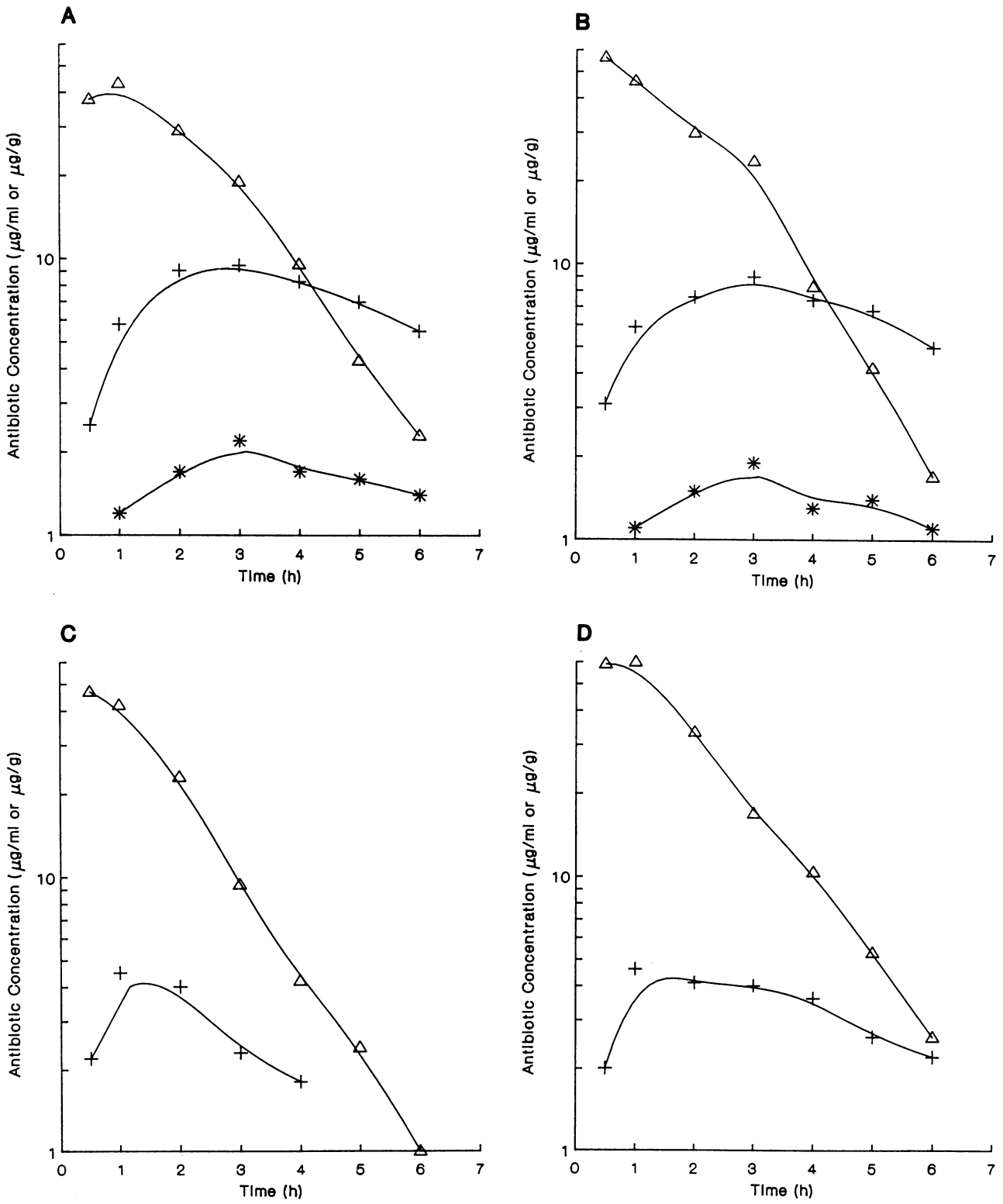

FIG. 1. Levels of cefepime (A), ceftazidime (B), cefotaxime (C), and moxalactam (D) in blood (△), CSF (+), and brain (*) following a single intraperitoneal injection of 40 mg/kg in normal neonatal rats.

Table 5 shows the assessment of the penetration of cefepime and cefotaxime from blood into CSF and brain tissue of noninfected and infected neonatal rats. As shown here, the pharmacokinetic parameters of cefepime and cefotaxime in the blood of noninfected and infected neonatal rats were similar. However, the AUC and penetration of cefepime into CSF of infected animals were larger (62 μg · h/ml and 56%, respectively) than those of noninfected

TABLE 5. Penetration of cefepime and cefotaxime into the CSF of noninfected[a] and infected[b] neonatal rats after intraperitoneal administration of 40 mg/kg

Compound	Neonatal rats	Blood[c]		CSF[c]		Penetration (%)
		C_{max} (μg/ml)	AUC_{0-6} (μg · h/ml)	C_{max} (μg/ml)	AUC_{0-6} (μg · h/ml)	
Cefepime	Noninfected	43 (8.7)	118 (14.6)	9.5 (1.8)	42 (5.9)	36
	Infected	37 (7.4)	110 (9.3)	13.9 (1.4)	62 (4.1)	56
Cefotaxime	Noninfected	47 (11.3)	94 (13.6)	4.5 (1.9)	12 (1.9)	13
	Infected	42 (8.6)	89 (9.2)	6.4 (2.2)	20 (4.4)	23

[a] Noninfected 5- to 8-day-old rats.
[b] 5- to 8-day-old rats infected with *S. penumoniae* A22884 by infecting 5×10^2 CFU into the cisterna magna 3 h before antibiotic administration.
[c] All values are means. See footnote *b*, Table 4.

animals (42 μg · h/ml and 36%, respectively). This is also the case for cefotaxime. The AUC and penetration of cefotaxime into CSF of infected animals were larger, 20 μg · h/ml and 23%, respectively, compared with 12 μg · h/ml and 13% in noninfected animals.

DISCUSSION

Bacterial meningitis is a life-threatening disease caused by numerous agents. The important bacterial agents for all age groups are *H. influenzae*, *Neisseria meningitidis*, and *S. pneumoniae*. *E. coli* and *S. agalactiae* (group B streptococcus) are also important meningitis agents in neonates. The activity of cefepime has been evaluated in a pneumococcal meningitis model in rabbits (19) and in a newborn rat model, using *E. coli* and group B streptococcus (9). In the latter study, organisms were introduced subcutaneously (10); other methods for establishing meningitis with *H. influenzae*, *S. pneumoniae*, and *S. agalactiae* in a neonatal rat model use intraperitoneal injection (2, 4, 17).

Intranasal instillation has been done with *H. influenzae* (15). These challenge techniques in newborn rats require frequent monitoring for the presence of bacteria in CSF and blood, and mortality rates are variable. The procedure for establishing bacterial meningitis by intracisternal injection in neonatal rats we describe is simple and reproducible, and mortality is always 100%. Monitoring the presence of bacteria in blood and CSF is not necessary. The technique is also suitable for establishing meningitis with other pathogens for in vivo screening of antibiotic efficacy.

The level of cefepime in CSF of neonatal rats was 15% that in serum (9). Penetration of cefepime into CSF was 36% (uninfected) and 56% (infected) when calculated from the ratio of the AUCs of cefepime in blood and CSF. Ceftazidime also penetrated well, 30%, in our study; a value of 22.8%, unaffected by infection with *H. influenzae*, was reported previously (11). Moxalactam and cefotaxime penetration of 15 and 13% was comparable to previously reported values of 10% (3) and 16.2% (10), respectively.

In rabbits, the level of cefepime in CSF was approximately 20% that in serum (19). However, the bactericidal activity of cefepime against *S. pneumoniae* in the CSF of infected rabbits was comparable to that of cefotaxime, which penetrates the CSF of rabbits with meningitis only moderately (3.5%). In our study, cefepime was only marginally more active than cefotaxime against *S. pneumoniae*. However, the levels of the desacetyl metabolite of cefotaxime were not measured in either study. The active desacetyl metabolite penetrates well into CSF (7), which probably accounts for the relatively good activity of cefotaxime despite inferior pharmacokinetics of the parent compound. Both cefotaxime and cefepime were more active than ceftazidime or moxalactam against *S. pneumoniae* in these murine models.

Ceftazidime and moxalactam have been efficacious against *H. influenzae* in previous studies (3, 11, 13). Cefepime, cefotaxime, and moxalactam were all comparable to each other and more efficacious than ceftazidime against the ampicillin-resistant *H. influenzae* used in our study.

Against *S. agalactiae*, cefepime was at least three- and sevenfold more active than cefotaxime and ceftazidime in mouse and neonatal rat models, respectively. Moxalactam was inactive (PD_{50}, >200 mg/kg).

As expected, cefepime and cefotaxime exhibited similar activity against *Staphylococcus aureus*. They were also more active than cefotaxime and moxalactam against *P. aeruginosa* and *K. pneumoniae*.

Cefepime and cefotaxime were reported to be similar in activity against *E. coli* in a single-dose (50 mg/kg) study done in newborn rats (9). In our study, the PD_{50} for the *E. coli* strain used was at least fourfold lower for cefepime than for cefotaxime, but the 95% confidence limits overlapped slightly.

Based on the CSF penetration properties of cefepime and its performance in these meningitis models, cefepime should be evaluated further in meningitis in humans.

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