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Pharmacokinetics and Bacteriological Effect of Ceftazidime in Experimental *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Escherichia coli* Meningitis

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The pharmacokinetics and bacteriological effect of ceftazidime were evaluated in rabbits experimentally infected with *Streptococcus pneumoniae*, *Haemophilus influenzae* type b, and *Escherichia coli* K1. The mean penetration of ceftazidime into cerebrospinal fluid after single-dose or constant-infusion administration ranged from 7.8 to 14.9%. The median cerebrospinal fluid bactericidal titers were 1:64 against *S. pneumoniae* and *H. influenzae* and 1:128 against *E. coli*. The bacterial colony counts in cerebrospinal fluid were reduced by 58% to 100% (−2.3 to −3.9 $\log_{10}$ CFU/ml) in 3 h and by 100% (−3.2 to −5.1 $\log_{10}$ CFU/ml) in 9 h of constant infusion, whereas in untreated infected animals, bacterial counts increased from +1.4 to +2.1 $\log_{10}$ CFU/ml in 9 h. These data on ceftazidime compare favorably with those on penicillin, chloramphenicol, netilmicin, and moxalactam in this experimental meningitis model.

Ceftazidime is a new β-lactam antibiotic that has potential for therapeutic use in bacterial meningitis. The agent has in vitro activity against gram-negative bacilli comparable to that of other new cephalosporin derivatives but is more active against *Pseudomonas aeruginosa* (9, 13). It is also active against β-lactamase-positive and -negative *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and *Neisseria meningitidis* (3, 5), the principal pathogens of meningitis of infancy and early childhood. In addition, this new cephalosporin derivative is not metabolized in vivo (10, 15) and has low protein-binding ability (10), and tubular secretion is unaffected by probenecid (7). These properties are also found with moxalactam (2, 7, 16), which achieves excellent cerebrospinal fluid (CSF) concentrations through inflamed meninges (4, 11, 12).

The present study was designed to determine the pharmacokinetics of ceftazidime in serum and CSF of healthy young rabbits and those with experimental meningitis due to *H. influenzae* type b, *S. pneumoniae*, and *Escherichia coli*. The results of this investigation are compared with those from previous studies in which conventional antibiotic therapy and moxalactam were evaluated in experimental meningitis caused by the same pathogens (8, 11, 12).

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MATERIALS AND METHODS

Test organisms. We used *S. pneumoniae* type 6, *H. influenzae* type b (β-lactamase positive), and *E. coli* K1, obtained from CSF of patients with meningitis. These organisms were grown in Mueller-Hinton broth containing 50 μg of calcium per ml, 25 μg of magnesium per ml, and 1% hemolysed horse blood for *S. pneumoniae*, brain heart infusion broth with Levinthal supplement for *H. influenzae*, and Mueller-Hinton broth for *E. coli*. After centrifugation, each organism was suspended in phosphate-buffered saline (0.01 M PO_4–0.15 M NaCl, pH 7.4) to a concentration of 6 to 8 $\log_{10}$ CFU/ml for inoculation. The minimal bactericidal concentrations of ceftazidime against *S. pneumoniae*, *H. influenza*, and *E. coli* were 0.125, 0.125, and 0.25 μg/ml, respectively.

Rabbit model. New Zealand white male rabbits, weighing 2 to 3 kg each, were prepared by the method described previously (1). At 14 to 16 h after intracisternal inoculation of 6.0×10^5 to 2.5×10^8 CFU of *S. pneumoniae*, 2.4×10^6 to 4.4×10^8 CFU of *H. influenzae*, or 4.8×10^4 to 2.3×10^6 CFU of *E. coli*, the rabbits were lethargic. The cultures of purulent CSF at this time grew from 4.0×10^2 to 1.5×10^5, 2.4×10^2 to 2.3×10^4, and 2.9×10^2 to 5.5×10^5 CFU of *S. pneumoniae*, *H. influenzae*, and *E. coli* per ml, respectively. The mean CSF leukocyte counts were 1,085 (range, 196 to 2,450), 1,297 (range, 175 to 3,800), and 1,314 (range, 500 to 2,400) cells per mm^3 for *S. pneumoniae*-, *H. influenzae*-, and *E. coli*-infected animals, respectively. The mean CSF protein values were 163 (range, 44 to 270), 147 (range, 53 to 390), and 167 (range, 98 to 285) mg/dl for *S. pneumoniae*-, *H. influenzae*-, and *E. coli*-infected rabbits, respectively.

Administration of drugs. Ceftazidime was dissolved in 3 ml of sterile water and diluted in 0.9% NaCl to the

TABLE 1. Pharmacokinetics of ceftazidime after a single intravenous dose in intact rabbits and rabbits with experimental *S. pneumoniae*, *H. influenzae*, and *E. coli* meningitis

Organism	Single dose (mg/kg)	Serum[a]			CSF[a]			% CSF/serum penetration[c]
		C_{max} (μg/ml)[b]	Half-life (h)	AUC (μg · h/ml)	C_{max} (μg/ml)	Half-life (h)	AUC (μg · h/ml)	
S. pneumoniae	25	286	0.61	159	3.16	2.55	12.9	8.1
H. influenzae	25	263	0.76	185	5.35	3.28	27.6	14.9
H. influenzae	50	370	0.75	333	8.31	3.22	40.9	12.3
E. coli	25	236	0.72	165	4.38	3.46	24.2	14.7
None (control)	50	364	0.75	306	2.65	3.53	11.4	3.7

[a] Expressed as mean values.
[b] C_{max}, Mean maximum concentration.
[c] CSF AUC/Serum AUC × 100.

desired concentrations. A single dose of 25 mg of ceftazidime per kg was administered intravenously over a 5-min period to *S. pneumoniae*-, *H. influenzae*-, and *E. coli*-infected animals, and a dose of 50 mg/kg was administered to intact and *H. influenzae*-infected animals. For constant infusion studies over 9 h, a loading dose of 25 mg of ceftazidime per kg was followed by 25 mg/kg per h given in 54 ml of 0.9% NaCl through the femoral vein catheter via a constant infusion pump (model 907 Holton pump; Extracorporeal Specialties, Inc., King of Prussia, Pa.). Light anesthesia was induced by intravenous administration of pentobarbital.

Processing of specimens. Serial blood and CSF samples were collected at 0, 0.25, 0.5, 0.75, 1.0, 2.0, 4.0, and 5.0 h after the single-dose administration of ceftazidime and at 3.0, 6.0, and 9.0 h in the continuous infusion study from an indwelling femoral artery catheter and an intracisternal spinal needle, respectively. Quantification of organisms in CSF was performed by serial 10-fold dilutions of CSF in phosphate-buffered saline (0.01 M PO_4–0.15 M NaCl, pH 7.4); inoculation was performed on 5% sheep blood agar for *S. pneumoniae*, on chocolate agar for *H. influenzae*, and on eosin-methylene blue agar for *E. coli*. Serum and the remainder of the CSF samples were kept at −20°C until antibiotic assays, and bactericidal titers were performed within 3 days.

Antibiotic assay. Concentrations of ceftazidime were determined by an agar-disk diffusion microbioassay (14) with *Morganella morganii* NCTC235 as the test organism. Phosphate buffer (0.04 M, pH 7.0) was used to prepare the dilutions of the antibiotic standard and samples of serum and CSF.

CSF bactericidal titers. CSF bactericidal titers against the test pathogens causing meningitis were determined by a microtiter technique with serial twofold dilutions in Mueller-Hinton broth containing 50 μg of calcium per ml and 25 μg of magnesium per ml plus 1% lysed horse blood for *S. pneumoniae*; in brain heart infusion broth with 1% Supplement C (Difco Laboratories, Detroit, Mich.) for *H. influenzae*; and in Mueller-Hinton broth for *E. coli*. The inoculum was approximately 5×10^5 CFU per ml. The inhibitory titer was defined as the lowest concentration of ceftazidime that inhibited growth after 18 h of incubation at 37°C. The bactericidal titer was defined as that concentration of drug which killed 99.9% of the original inoculum as determined by quantitative subcultures on agar.

Pharmacokinetic determinations. The method of least mean squares was used to obtain a regression line to which ceftazidime concentrations in serum and CSF after single-dose injection were fitted. The half-life in serum and CSF was calculated by dividing $\log_n 2$ by the slope of the line. The areas under the concentration versus time curve in serum and CSF were calculated by successive trapezoidal approximation from

TABLE 2. Bacteriological effect of a single intravenous dose of ceftazidime in experimental meningitis due to *S. pneumoniae*, *H. influenzae*, or *E. coli*

Organism (MBC [μg/ml]) and therapy	Single dose (mg/kg)	$\bar{x}$ Log_{10} CFU/ml in CSF at:		No. (%) of animals with sterile/total CSF culture
		Start of therapy	5 h	
S. pneumoniae (0.125)				
Single injection	25	3.9714	−3.9714	7/7 (100)
No therapy		4.1280	+0.9470	0/5 (0)
H. influenzae (0.125)				
Single injection	25	2.9625	−2.4525	2/4 (50)
Single injection	50	2.6020	−2.1270	2/5 (40)
No therapy		3.5800	+0.8400	0/4 (0)
E. coli (0.25)				
Single injection	25	4.0057	−2.7240	3/7 (43)
No therapy		ND[a]	ND	ND

[a] ND, Not done.

TABLE 3. Concentrations of ceftazidime after continuous intravenous infusion for 9 h in rabbits with experimental *S. pneumoniae*, *H. influenzae*, and *E. coli* meningitis

Organism and time (h) of infusion	No. of animals	Concn (μg/ml) ± SD in:		% Antibiotic in CSF[a]
		Serum	CSF	
S. pneumoniae				
3	6	138 ± 15.6	7.3 ± 1.78	5.3
6	6	138 ± 14.4	11.3 ± 2.27	8.2
9	6	176 ± 15.6	16.6 ± 2.89	9.4
H. influenzae				
3	5	110 ± 22.6	12.7 ± 2.45	11.5
6	5	160 ± 22.3	16.4 ± 2.31	10.3
9	5	195 ± 27.7	20.9 ± 3.54	10.7
E. coli				
3	7	102 ± 4.9	18.0 ± 1.92	17.6
6	7	151 ± 14.6	22.0 ± 2.05	14.6
9	7	201 ± 16.6	26.2 ± 1.98	13.0

[a] The percent penetration of antibiotic in CSF was calculated as (mean CSF concentration/mean serum concentration) × 100.

time 0 to time ∞. The percentage of antibiotic in CSF was defined as: percent antibiotic in CSF = (mean CSF concentration/mean serum concentration) × 100.

RESULTS

Single-dose studies. (i) Pharmacokinetics in serum and CSF. The mean maximum concentrations, half-life values in serum and CSF, and percentages of penetration of drug into CSF, calculated as the ratio of the CSF AUC to serum AUC × 100, are presented in Table 1. Compilation of data for each etiological agent was based on experiments in four to seven animals. Mean maximum concentrations in serum were observed at the completion of the 5-min infusion and at 30 to 45 min after injection for CSF values. The half-life values in CSF were from 4.2- to 4.8-fold longer than those in serum. Penetration was larger (8 to 15%) in animals with meningitis as compared with that (3.7%) in uninfected animals.

(ii) Bacteriological effect. The mean changes in concentration of bacteria in CSF at 5 h after a single injection of ceftazidime are shown in Table 2. Untreated animals had increased colony counts and died within 72 h of inoculation. CSF cultures were sterile in all *S. pneumoniae*-infected animals and in four of nine *H. influenzae*-infected animals.

Constant-infusion administration. (i) Serum and CSF concentrations and CSF bactericidal titers. The mean serum and CSF concentrations of ceftazidime increased over the 9 h of continuous infusion (Table 3). Ceftazidime penetration into CSF increased significantly ($P = 0.049$; Student-Newman-Keuls test) from 5.3 to 9.4% in animals with *S. pneumoniae* meningitis, remained unchanged in animals with *H. influenzae* meningitis, and decreased slightly ($P = 0.14$) in animals with *E. coli* meningitis. The mean penetration values were 7.8, 11.0, and 14.6%, respectively, for the entire 9-h study period. The median CSF bactericidal titers for all values determined at 3, 6, and 9 h were 1:64 (range, 1:16 to 1:128) against *S. pneumoniae* and *H. influenzae* and 1:128 (range, 1:64 to 1:256) against *E. coli*.

(ii) Bacteriological effect. The mean changes in the bacterial colony counts in CSF at 3 and 9 h of continuous infusion therapy are shown in Table 4. The counts declined by 58 to 100% at 3 h, and all CSF cultures were sterile at 9 h of ceftazidime therapy. By contrast, the concentration of bacteria at 9 h increased from 1.4 to 2.1 $\log_{10}$ CFU per ml in untreated animals, and none of the cultures were sterile.

DISCUSSION

The percent penetration of ceftazidime into CSF of 8 to 15% in this meningitis model was similar when calculated by the ratio of CSF AUC to serum AUC in single-dose experiments or by the mean amount of drug in CSF relative to that in serum during 9 h of intravenous infusion. Penetrability into CSF was two- to threefold greater in experimentally infected animals than in healthy animals with uninflamed meninges.

The median bactericidal titers in CSF after ceftazidime administration were 1:64 against *S. pneumoniae* and *H. influenzae* and 1:128 against *E. coli*. These titers are comparable to those seen with penicillin G in experimental pneumococcal meningitis and with moxalactam in experimental *E. coli* meningitis (Table 5). The bactericidal activity of ceftazidime against *H. influenzae* is greater than that of chloramphenicol and less than that of moxalactam or ceftriaxone (8). However, ceftazidime activity in CSF exceeds the amount necessary for a maximal

TABLE 4. Bacteriological effect of a 9-h continuous infusion of ceftazidime in experimental meningitis due to *S. pneumoniae*, *H. influenzae*, and *E. coli*

Organism (MBC [μg/ml]) and therapy	Median CSF bactericidal titer	$\bar{x}$ Log_{10} CFU/ml in CSF at:			No. (%) of animals with sterile/total CSF culture
		Start of therapy	3 h	9 h	
S. pneumoniae (0.125)					
Continuous infusion	1:64	3.2067	−2.3900 (75%)[a]	−3.2067	6/6 (100)
No therapy		4.1280		+2.0620	0/5 (0)
H. influenzae (0.125)					
Continuous infusion	1:64	3.8943	−3.8943 (100%)	−3.8943	5/5 (100)
No therapy		3.5800		+1.3900	0/4 (0)
E. coli (0.25)					
Continuous infusion	1:128	5.0783	−2.9263 (58%)	−5.0783	6/6 (100)
No therapy		4.9600		+1.4800	0/9 (0)

[a] Percentage decline in bacterial count.

TABLE 5. Bacteriological effect of ceftazidime compared with conventionally used antibiotics and with moxalactam in experimental *S. pneumoniae*, *H. influenzae*, and *E. coli* meningitis (8, 11)[a]

Organism and MBC (μg/ml)	Drug (dose [mg/kg per h])	No. of animals studied	Median CSF bactericidal titer	$\bar{x}$ ΔLog_{10} CFU/ml in CSF over 9 h	No. (%) of animals with sterile/total CSF cultures
S. pneumoniae					
0.008	Penicillin G (50)	9	1:64	−4.79	8/9 (89)
2.0	Moxalactam (25)	5	1:4	−1.99	2/5 (40)
0.125	Ceftazidime (25)	6	1:64	−3.21	6/6 (100)
H. influenzae[b]					
2.0	Chloramphenicol (20)	3	1:8	−3.47	3/3 (100)
0.031	Moxalactam (25)	4	1:512	−3.31	4/4 (100)
0.125	Ceftazidime (25)	5	1:64	−3.89	5/5 (100)
E. coli					
1.25	Netilmicin (2)	5	1:2	−2.73	2/5 (40)
0.25	Moxalactam (25)	5	1:64	−4.47	4/5 (80)
0.25	Ceftazidime (25)	6	1:128	−5.08	6/6 (100)

[a] Antibiotics given by continuous intravenous infusion over 9 h.
[b] β-lactamase positive strain.

bacteriological effect in this meningitis model (12).

After 9-h infusions of ceftazidime, CSF cultures were sterile in all animals infected with *S. pneumoniae*, *H. influenzae*, or *E. coli*. This bacteriological effect compares favorably with results obtained with conventional agents or moxalactam in animals experimentally infected with these microorganisms and is superior to results obtained with aminoglycoside therapy in lapin *E. coli* meningitis (Table 5) (8, 11). Additionally, ceftazidime was as effective in reducing the bacterial colony count and in sterilizing CSF cultures at 5 h after a single dose as were penicillin G or ceftriaxone, chloramphenicol or ceftriaxone, and ceftriaxone in experimental *S. pneumoniae*, *H. influenzae*, and *E. coli* meningitis, respectively (8, 12).

We conclude from these data and from other studies conducted in our laboratory (6) that ceftazidime penetrates well into CSF, achieves excellent CSF bactericidal activity, and is effective in reducing CSF bacterial colony counts after single-dose or constant-infusion administration in animals with experimental meningitis. Although these results in animals may not apply directly to humans with meningitis, previous investigations with moxalactam and ceftriaxone are indicative that this meningitis model provides an accurate assessment of the therapeutic potential of an antimicrobial agent (8, 12).

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