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Antimicrobial Therapy of Experimental Meningitis Caused by *Streptococcus pneumoniae* Strains with Different Susceptibilities to Penicillin

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The pharmacokinetics and bacteriological efficacies of penicillin G, ceftriaxone, vancomycin, and imipenem were determined in rabbits with experimental meningitis caused by *Streptococcus pneumoniae* strains with different penicillin susceptibilities. Drug dosages were adjusted to attain peak concentrations in serum that were similar to those observed in infants and children. In animals infected with a penicillin-susceptible (MBC, 0.008 μg/ml) pneumococcus, penicillin G and ceftriaxone reduced the number of organisms in cerebrospinal fluid (CSF) by ≥4.14 $\log_{10}$ CFU/ml after single doses and after 9-h continuous infusions. A single large dose (50 mg/kg) of penicillin G was comparatively ineffective (−2.15 $\log_{10}$ CFU/ml) against a relatively penicillin-resistant (MBC, 0.5 μg/ml) strain, whereas ceftriaxone therapy resulted in a 3.66- and 4.77-$\log_{10}$ CFU/ml reduction after single doses and 9-h continuous infusions, respectively. In animals in which meningitis was caused by a penicillin-resistant (MBC, 8.0 μg/ml) pneumococcus, a single dose of penicillin (50 or 150 mg/kg) or of ceftriaxone failed to lower the number of organisms in CSF. Vancomycin and imipenem reduced the counts in CSF by at least 2.19 and 4.10 $\log_{10}$ CFU/ml after single doses and 9-h infusions, respectively. In all experiments, a bactericidal titer of ≥1:8 in CSF was necessary to achieve a maximal bacteriological effect.

In recent years, strains of *Streptococcus pneumoniae* that are relatively resistant and resistant to penicillin have caused meningitis in infants and children (1, 3, 8, 9, 11, 16–18). Relatively resistant *S. pneumoniae* strains have MICs of 0.1 to 1.0 μg of penicillin per ml and a prevalence rate of 3 to 16% (1, 2, 9). We recently reported that, of *S. pneumoniae* strains obtained from cultures of infants and children at Children's Medical Center, Dallas, Tex., in a 17-month period from 1981 to 1983, 8% were relatively penicillin resistant (9). In this report, two infants with meningitis caused by these strains failed to respond to conventional doses of penicillin (250,000 U/kg per day); one infant was successfully treated with chloramphenicol, but the second required vancomycin for cure because the strain was also resistant to chloramphenicol. Others have also used chloramphenicol alone or with penicillin for therapy of meningitis caused by relatively resistant *S. pneumoniae* strains (1, 11, 16, 17).

Meningitis caused by penicillin-resistant *S. pneumoniae* (MIC, >1 μg/ml) was reported in three South African infants in 1977 (3) and in an infant from Denver, Colo., in 1981 (18). Only the latter infant survived; however, the responses to ampicillin, choramphenicol, and rifampin therapy was delayed. The penicillin-resistant strains have generally shown cross-resistance to most other beta-lactam antibiotics and to chloramphenicol.

In the present investigation, the experimental rabbit meningitis model was used to assess the pharmacokinetics and bacteriological efficacy of ceftriaxone against a relatively penicillin-resistant pneumococcal strain and of ceftriaxone, vancomycin, and imipenem against a penicillin-resistant pneumococcal strain. Ceftriaxone was chosen because of its documented efficacy and safety in the therapy of non-neonatal meningitis caused by *Haemophilus influenzae*, *Neisseria meningitidis*, and penicillin-susceptible strains of *S. pneumoniae* (5, 7, 23). Because ceftriaxone might someday replace conventional ampicillin and chloramphenicol therapy for initial, empirical treatment of meningitis, it is important to know whether it is effective against these increasingly prevalent, relatively penicillin-resistant strains of *S. pneumoniae*. Although penicillin-resistant pneumococcal strains are still rarely encountered in the United States, in vitro susceptibility data (10, 24) and results from one study in experimental animals (4) suggest that vancomycin or imipenem might be effective for the therapy of meningitis.

MATERIALS AND METHODS

Susceptibility studies. The MICs and MBCs of the study drugs were determined for the three test strains of *S. pneumoniae* by the standard tube dilution technique, in which an inoculum of 5×10^5 CFU and Mueller-Hinton broth supplemented with 1% horse blood, 0.25 ml of $MgCl_2$, and 0.5 ml of $CaCl_2$ is used. The MIC was defined as the lowest concentration of drug that was required to inhibit visible growth; the MBC was defined as the lowest concentration of drug that killed ≥99.9% of the original inoculum, as determined by quantitative subcultures on blood agar of each tube containing no visible growth.

Test organisms. Three strains of *S. pneumoniae* with different susceptibilities to penicillin G were used. A penicillin-susceptible strain (MIC and MBC, 0.008 μg/ml) and a relatively penicillin resistant strain (MIC, 0.25 μg/ml; MBC, 0.5 μg/ml) were obtained from cerebrospinal fluid (CSF) cultures of two infants with meningitis. The penicillin-resistant strain (MIC, 4.0 μg/ml; MBC, 8.0 μg/ml; kindly provided by Joel Ward, Harbor View Medical Center, University of California, Los Angeles) was obtained from a South African infant with meningitis. The organisms were maintained on sealed blood agar slants and grown overnight in Mueller-Hinton broth supplemented with 1% lysed horse blood, 0.25

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TABLE 1. Concentrations of antibiotics in serum and CSF of animals experimentally infected with a multiply resistant strain of *S. pneumoniae*

Drug	Dose (mg/kg)	Body fluid	Mean ± SD concn (μg/ml) at following intervals (h) during 5-h expt[a]: 0.25	0.5	1	2	4	5	AUC[b] (μg · h/ml)	CSF AUC/serum AUC
Penicillin G	50	Serum	28 ± 6	11.5 ± 7	1.5 ± 1.0	0.3 ± 0.2	0.07 ± 0.3	0.03 ± 0.2	17	0.06
		CSF	0.5 ± 0.4	0.3 ± 0.2	0.2 ± 0.1	0.04 ± 0.03	ND[c]	ND	0.98	
Penicillin G	150	Serum	307 ± 73	83 ± 122	29 ± 4.1	5.2 ± 1.0	0.7 ± 0.1	0.4 ± 0.2	135	0.02
		CSF	2.2 ± 0.2	1.6 ± 0.2	0.6 ± 0.05	0.2 ± 0.02	0.05 ± 0.00	0.03 ± 0.00	2.1	
Ceftriaxone	25	Serum	124 ± 15	88 ± 3.2	75 ± 3.8	46 ± 8.3	29 ± 5.2	21 ± 6.7	366	0.08
		CSF	1.0 ± 0.1	1.7 ± 0.4	2.6 ± 1.4	3.1 ± 0.1	2.9 ± 0.3	2.4 ± 0.5	29	
Imipenem	25	Serum	32 ± 7.8	14 ± 3.1	4.9 ± 3.0	1.3 ± 1.4	0.16 ± 0.2	0.05 ± 0.1	41	0.13
		CSF	1.5 ± 0.3	1.3 ± 0.4	1.9 ± 1.0	1.1 ± 0.6	0.5 ± 0.2	0.32 ± 0.1	5.5	
Vancomycin	15	Serum	48 ± 8	35 ± 6	20 ± 3	11 ± 2.4	3.7 ± 0.9	2.4 ± 1.0	112	—
		CSF	ND	ND	1.5[d]	1.7 ± 0.4	1.5 ± 0.4	1.3 ± 0.4	—[e]	

[a] Times shown are hours after a single intravenous infusion given over a 5-min period.
[b] AUC, Area under the curve.
[c] ND, Not detected.
[d] One concentration was detected in specimens from five animals.
[e] —, Not calculated.

ml of $MgCl_2$, and 0.5 ml of $CaCl_2$ before each experiment. An inoculum of 1×10^5 to 4×10^7 CFU was inoculated intracisternally.

Rabbit model. New Zealand white male rabbits, weighing 2 to 3 kg each, were prepared by the method of Dacey and Sande (6) and Scheld et al. (21). Antibiotics were administered intravenously at 14 to 18 h after intracisternal inoculation of *S. pneumoniae*. At this time the animals were lethargic and febrile, and cultures of purulent CSF grew 3.73 to 5.57 $\log_{10}$ CFU/ml. The CSF leukocyte counts were 120 to 3,820/m^3 (mean, 828/m^3), and the protein concentrations were 62 to 480 mg/dl (mean, 136 mg/dl). All animals were sacrificed by an overdose of pentobarbital after completion of the experiments.

Administration of drugs. The antibiotics were dissolved in sterile water to the desired concentration. The dose of each drug was chosen to produce concentrations in serum at 0.25 or 0.5 h after the dose that were in the desired therapeutic range for infants and children (i.e., penicillin, 20 to 30 μg/ml; ceftriaxone, 120 μg/ml; imipenem, 25 to 30 μg/ml; vancomycin, 30 μg/ml). The following single doses were administered intravenously over 5 min: 50 or 150 mg of penicillin G per kg, 25 mg of ceftriaxone per kg, 25 mg of imipenem per kg, and 15 mg of vancomycin per kg. For constant-infusion experiments, in which the drugs were administered intravenously over 9 h, doses identical to those indicated above were given as a loading dose and hourly in 54 ml of 0.9% NaCl solution via a constant-infusion pump.

Processing of specimens. Serial blood and CSF samples were collected before and at 0.25, 0.5, 1, 2, 4, and 5 h after a single dose of drug and before and at 3, 6, and 9 h of the constant infusion of drug from an indwelling femoral artery catheter and an intracisternal spinal needle, respectively. Quantitation of organisms in CSF was performed within 5 to 10 min of extraction by serial 10-fold dilutions of CSF in phosphate-buffered saline (0.01 M PO_4–0.15 M NaCl, pH 7.4); specimens were inoculated on 5% sheep blood agar. Serum and CSF samples were stored at −70°C until antibiotic assays were performed and bactericidal titers were determined, within 48 h. Specimens were held for no longer than 30 to 45 min at room temperature during the pre- and post-storage periods.

Antibiotic assays. Concentrations of antibiotic were measured by an agar disk diffusion microbioassay method with *Sarcina lutea* ATCC 9341 for penicillin G and vancomycin, *Escherichia coli* RO1346 for ceftriaxone, and *Bacillus subtilis* MB3Z and SDR (Glaxo) for imipenem. Serum and CSF from untreated healthy and infected rabbits did not inhibit the assay organisms. Standards and serum samples were diluted in 100% normal rabbit serum, whereas standards and CSF samples were diluted in phosphate buffer (pH 6.0). The intraassay variability was ≤5% (coefficient of variation) and the interassay variability was ≤10% for the five antibiotics.

Titers in CSF and serum. Bacteriostatic and bactericidal titers in CSF against each strain causing meningitis were determined by a microtiter technique (12), in which serial twofold dilutions of serum or CSF in Todd-Hewitt broth and an inoculum of approximately 5×10^5 CFU/ml were used. The bacteriostatic and bactericidal titers were defined by criteria identical to those used for determining the MIC and MBC, respectively.

Pharmacokinetic determinations. The method of least mean squares was used to obtain a regression line to which antibiotic concentrations in serum and CSF after single-dose injection were fit. The area under the concentration versus time curve in serum and CSF were calculated by successive trapezoidal approximation from time 0 to time ∞.

RESULTS

Pharmacokinetic studies. (i) Single-dose experiments. Compilation of pharmacokinetic data for each drug was derived from studies in four to six animals. The highest mean concentrations in serum were observed at 0.25 h after infusion (Table 1). The highest mean concentrations in CSF occurred at 0.25 h after the dose for penicillin G, 2 h for ceftriaxone and vancomycin, and 1 h for imipenem. The maximum concentrations in CSF were 1.1 and 2.4 μg of penicillin per ml after 50- and 150-mg/kg doses, respectively; 4.7 μg of ceftriaxone per ml; 1.9 μg of imipenem per ml; and 2.0 μg of vancomycin per ml. Vancomycin was not detected in CSF at 0.25 and 0.5 h after the dose and was detected in only one of five samples at 1 h. It was not possible, therefore, to calculate an area under the curve for van-

TABLE 2. Concentrations of antibiotics in serum and CSF of rabbits experimentally infected with a relatively penicillin-resistant or a multiply resistant strain of *S. pneumoniae*

Drug	No. of animals	Dose (mg/kg per h)	Mean ± SD concn (μg/ml) in[a]:		CSF concn/ serum concn
			Serum	CSF	
Ceftriaxone	4	25	147 ± 17	5.4 ± 1.8	0.04
Vancomycin	4	15	82 ± 15	8.3 ± 2.4	0.10
Imipenem	4	25	36 ± 10	5.5 ± 2.0	0.15

[a] Continuous infusion for 9 h.

comycin in CSF. The penetration of antibiotics into CSF, defined as (area under the curve in CSF/area under the curve in serum) × 100, was 6 and 2% for penicillin given in doses of 50 and 150 mg/kg, respectively; 8% for ceftriaxone; and 13% for imipenem.

(ii) Constant-infusion experiments. The concentrations of ceftriaxone, vancomycin, and imipenem in serum and CSF were measured during 9-h constant-infusion experiments (Table 2). With the exception of ceftriaxone, the mean concentrations in CSF during the infusions were higher than the maximum concentrations observed for vancomycin and imipenem after a single dose. The penetration of drugs in CSF, defined as (concentration in CSF/concentration in serum) × 100, was 4% for ceftriaxone, 10% for vancomycin, and 15% for imipenem.

Bacteriological effect. (i) Meningitis caused by penicillin-susceptible *S. pneumoniae*. In single-dose experiments, a dose of 50 mg of penicillin G per kg produced peak bactericidal titers of 1:16 in CSF and a reduction in the number of bacteria in CSF of 4.14 $\log_{10}$ CFU/ml (Table 3). Two of five animals had sterile CSF cultures at 5 h after the dose. A single dose of ceftriaxone produced a peak bactericidal titer of 1:256 in CSF and a reduction in the number of *S. pneumoniae* of 4.46 $\log_{10}$ CFU/ml at 5 h after the dose. At this time, four of five animals had sterile CSF cultures. In contrast, the $\log_{10}$ CFU of *S. pneumoniae* per milliliter increased by 1.51 in the CSF of seven untreated animals. When these two antibiotics were given by constant infusion over 9 h, the median bactericidal titers in CSF were 1 dilution higher than peak values after a single dose, and the bacteriological results were similar.

(ii) Meningitis caused by a relatively penicillin-resistant *S. pneumoniae* strain. A larger dose of penicillin G (150 mg/kg) was given as a single dose to animals infected with a relatively penicillin-resistant (MBC, 0.5 μg/ml) strain of *S. pneumoniae* (Table 3). The peak bactericidal titer in CSF was 1:4, and the numbers of organisms in CSF were reduced by only 2.15 $\log_{10}$ CFU/ml. CSF from one of four animals was sterile at 5 h. Ceftriaxone (MBC, 0.5 μg/ml) produced a similar bactericidal titer in CSF and reduced the number of bacteria in CSF by 3.66 $\log_{10}$ CFU/ml. Two of five animals had sterile cultures at 5 h. In five untreated animals, the colony count in CSF increased by 1.8 $\log_{10}$ CFU/ml.

After a 9-h constant infusion, ceftriaxone decreased the numbers of organisms in CSF by 4.77 $\log_{10}$ CFU/ml, and cultures were sterile in all four animals. The median bactericidal titer in CSF was 1:8 against this relatively resistant strain. In five untreated animals, the colony count increased by 1.86 $\log_{10}$ CFU/ml after 9 h, and none of five animals had sterile CSF cultures.

(iii) Meningitis caused by a penicillin-resistant *S. pneumoniae* strain (MBC, 8.0 μg/ml). In single-dose experiments both a conventional and a large dose of penicillin G were ineffective and failed to produce detectable bactericidal activity in CSF (Table 4). The numbers of organisms in CSF increased by 1.2 to 1.5 $\log_{10}$ CFU/ml, an effect similar to that observed in five untreated animals. A single dose of ceftriaxone (MBC, 2.0 μg/ml) produced a peak bactericidal titer of only 1:2, and the initial numbers of organisms in CSF (5.47 $\log_{10}$ CFU/ml) were unchanged at 5 h. By contrast, vancomycin (MBC, 0.5 μg/ml) and imipenem (MBC, 0.5 μg/ml)

TABLE 3. Bacteriological effect of penicillin and ceftriaxone in experimental meningitis caused by penicillin-susceptible or a relatively resistant strain of *S. pneumoniae*

Treatment and drug (MBC [μg/ml])	Dose (mg/kg[a] or mg/kg per h[b])	Peak[a] or median[b] bactericidal titer in CSF	$\log_{10}$ CFU/ml in CSF		No. of animals with sterile CSF cultures/ total at 5[a] or 9[b] h
			Mean no. at start of therapy	ΔNo. at 5[a] or 9[b] h	
Single dose					
Penicillin G (0.008)[c]	50	1:16	5.57	−4.14	2/5
Penicillin G (0.5)[d]	150	1:4	4.20	−2.15	1/4
Ceftriaxone (0.008)[c]	25	1:256	4.83	−4.46	4/5
Ceftriaxone (0.5)[d]	25	1:4	4.30	−3.66	2/5
None[c]			4.60	+1.51	0/7
None[d]			4.12	+1.18	0/5
Continuous infusion					
Penicillin (0.008)[c]	50	1:32	5.25	−4.85	7/8
Ceftriaxone (0.008)[c]	25	1:512	4.89	−4.89	8/8
Ceftriaxone (0.5)[d]	25	1:8	4.77	−4.77	4/4
None			4.12	+1.86	0/5

[a] Single-dose experiments.
[b] Nine-hour continuous-infusion experiments.
[c] Penicillin-susceptible strain.
[d] Relatively penicillin-resistant strain.

TABLE 4. Bacteriological effect of a single dose or a 9-h continuous infusion of antibiotics in experimental meningitis caused by a penicillin-resistant strain of *S. pneumoniae*

Treatment and drug (MBC [μg/ml])	Dose (mg/kg[a] or mg/kg per h[b])	Peak[a] or median[b] bactericidal titer in CSF	Log_{10} CFU/ml in CSF		No. of animals with sterile CSF cultures/ total at 5[a] or 9[b] h
			Mean no. at start of therapy	ΔNo. at 5[a] or 9[b] h	
Single dose					
Penicillin G (8.0)	50	0	3.80	+1.55	0/4
Penicillin G (8.0)	150	0	3.73	+1.23	0/3
Ceftriaxone (2.0)	25	1:2	5.47	−0.09	0/4
Vancomycin (0.5)	15	1:2	3.80	−2.19	1/5
Imipenem (0.5)	24	1:4	4.37	−2.42	1/4
None			4.87	+2.18	0/5
Continuous infusion					
Vancomycin (0.5)	15	1:8	4.10	−4.10	4/4
Imipenem (0.5)	25	1:8	4.21	−4.21	4/4
None			4.87	+2.74	0/5

[a] Single-dose experiments.
[b] Nine-hour continuous-infusion experiments.

reduced the numbers of *S. pneumoniae* by 2.19 and 2.42 log_{10} CFU/ml, respectively. Cultures of CSF from one of five animals treated with vancomycin and one of four animals treated with imipenem were sterile at 5 h.

Because penicillin G and ceftriaxone were ineffective in the single-dose experiments, only vancomycin and imipenem were evaluated in constant-infusion experiments in animals infected with the penicillin-resistant pneumococcal strain. Median bactericidal titers of 1:8 were achieved in CSF with both drugs. In all animals treated with vancomycin or imipenem, the bacterial counts in CSF were reduced by >4 log_{10} CFU/ml and all CSF cultures were sterile.

DISCUSSION

The rabbit model of meningitis has been useful to investigators as a means to predict in humans penetration of antimicrobial agents through inflamed meninges and bactericidal titers against common meningeal pathogens that are achieved in CSF with these agents (13). Although bacteriological results from these in vivo studies do not necessarily correlate with clinical efficacy in humans with meningitis, the model has become an essential early step in the process of evaluating investigational antibiotics or of determining alternative therapeutic regimes for meningitis caused by organisms that have developed resistance to conventionally used drugs. Caution must be used in directly applying data from this model to clinical situations.

In the present study, a relatively penicillin-resistant strain and a penicillin-resistant strain of *S. pneumoniae* were used to produce meningitis in rabbits, and ceftriaxone and imipenem, two investigational agents, and vancomycin, an agent not yet approved for the therapy of pneumococcal meningitis, were evaluated. Penicillin G and ceftriaxone were comparably effective in rabbits infected with a penicillin-susceptible strain. In contrast, penicillin in large doses (150 mg/kg) was comparatively ineffective against the relatively resistant strain and failed against the resistant pneumococcal strain. A 9-h continuous infusion of ceftriaxone sterilized CSF cultures of four animals with meningitis caused by the relatively resistant strain, whereas a single dose of ceftriaxone failed to reduce the bacterial count in CSF of animals with meningitis caused by the penicillin-resistant strain. Both vancomycin and imipenem produced excellent bacteriological results against the penicillin-resistant pneumococcus.

The concentrations achieved in the sera of these animals approximated the therapeutic concentrations in infants and children and were similar to those previously reported for this model by our laboratory (15, 19) and others (4, 11, 21). After the large dose of penicillin, the 0.25-h serum specimens contained concentrations that were approximately 10-fold greater than those found in children after conventional doses; the mean concentration at the end of the 150-mg/kg infusion exceeded 800 μg/ml. Even so, the bacteriological effect after these large doses was poor in animals infected with a relatively resistant or resistant strain of *S. pneumoniae*.

The concentrations of penicillin and ceftriaxone found in CSF of infected animals were 2 to 6% of those found in serum; this degree of penetration for both drugs was similar to values reported by others for this model (21, 22). As shown previously by us (19), imipenem penetrates well through inflamed meninges. Beam (4) showed the penetration of vancomycin after 8-h infusions to be approximately 15 and 18% in experimental pneumococcal meningitis after doses of 8 and 20 mg/kg, respectively. In our continuous-infusion experiments, the penetration of vancomycin was 10%. After single doses, however, vancomycin was undetected in CSF at 0.25 and 0.5 h after the dose and was detected in only one of four samples at 1 h.

Bactericidal titers in CSF usually correlate well with bacteriological outcome in experimental meningitis and in humans with meningitis. Sande (20) and McCracken (14) have previously shown that a minimum bactericidal titer of 1:8 to 1:10 in CSF is required for an optimal bacteriological and clinical result. Titers exceeding these values have not correlated with a superior effect (7). In this study, a titer of ≤1:4 in CSF was associated with smaller reductions in numbers of *S. pneumoniae* in CSF compared with results obtained with titers of ≥1:8. With the exception of one of eight animals treated with penicillin for meningitis caused by the susceptible strain, bacteriological cure was consistently achieved after 9-h continuous infusions in all animals with titers of ≥1:8 in CSF, regardless of the antibiotic or strain of pneumococcus used.

The results of these studies of experimental *S. pneumoniae* meningitis must be considered incomplete, because not all of the therapeutic regimens were tested in single-dose and continuous-infusion experiments for each pneumococcal

strain. For example, in animals with meningitis caused by a relatively penicillin-resistant strain, the bacteriological effect of penicillin was not evaluated after continuous intravenous infusion. We made this decision because penicillin was only modestly effective after a single dose in this model and because clinical experience indicates that penicillin is usually ineffective in patients with meningitis caused by relatively resistant *S. pneumoniae* (1, 9, 16). Similarly, we did not assess penicillin or ceftriaxone after continuous intravenous infusion in animals infected with the penicillin-resistant pneumococcus. These two antibiotics were ineffective after single doses in this model, and penicillin is totally ineffective clinically in patients with meningitis caused by these strains (3, 18). However, it is possible that, had they been evaluated after 9-h continuous infusions, these drugs would have been bacteriologically effective in our meningitis model. Conclusions from our investigation should be considered tentative until additional studies have been conducted. We believe ceftriaxone should be considered for the therapy of meningitis caused by relatively penicillin-resistant *S. pneumoniae*, but further experience with the animal model under controlled clinical conditions are required before recommendations can be made. Vancomycin or imipenem might prove effective for the therapy of meningitis caused by penicillin-resistant strains. Because clinical experience will be difficult to obtain, additional studies in animals are required.

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