Effect of Dexamethasone on Therapy of Experimental Penicillin- and Cephalosporin-Resistant Pneumococcal Meningitis

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Treatment of pneumococcal meningitis has become problematic because of the emergence of penicillin- and cephalosporin-resistant strains and because of the concern that dexamethasone therapy might reduce penetration of antibiotics into the cerebrospinal fluid (CSF). We addressed these issues with our rabbit meningitis model by studying two pneumococcal isolates that were resistant to penicillin and ceftriaxone and susceptible to vancomycin and rifampin. Ceftriaxone, vancomycin, and rifampin were given alone or in combination, with or without coadministration of dexamethasone. Treatment was started 12 to 14 h after intracisternal inoculation of ~10^4 CFU of one of the organisms. Rifampin concentrations in serum and CSF were similar, regardless of whether dexamethasone was given, whereas those of ceftriaxone were somewhat lower at each time point in animals given dexamethasone. The penetration of vancomycin into CSF was consistently and substantially reduced with dexamethasone treatment, which resulted in a delay in CSF sterilization not observed in non-dexamethasone-treated animals. When rifampin was used with ceftriaxone for treatment of meningitis caused by the more resistant strain, bacteriologic cure occurred promptly, with or without dexamethasone therapy. In areas with high rates of occurrence of resistant pneumococcal strains, we believe initial empiric therapy of bacterial meningitis should include two antibiotics: ceftriaxone and either rifampin or vancomycin. When dexamethasone is used, the combination of ceftriaxone and rifampin is preferred for therapy.

Dexamethasone has been shown to improve the long-term outcome in infants and children with bacterial meningitis, especially meningitis caused by *Haemophilus influenzae* type b (19, 20, 27, 28). Its role in the management of *Streptococcus pneumoniae* meningitis is uncertain, although a retrospective study of 97 infants and children (18) and a prospective trial in 106 older patients (15) with pneumococcal meningitis suggested a satisfactory effect. With routine use of conjugate *Haemophilus* vaccines in many countries, meningitis caused by this organism has virtually disappeared (1, 4, 6, 23, 26, 29), leaving the pneumococcus and meningococcus as the principal causes of meningitis in these areas.

Attention has recently focused on management of pneumococcal meningitis because of the emergence of penicillin- and cephalosporin-resistant strains (7, 8, 10, 11). For example, 8% of *S. pneumoniae* strains isolated from Dallas, Tex., pediatric patients in 1981 to 1983 were resistant to penicillin (MIC ≥ 0.06 µg/ml) and none was resistant to cephalosporin (16). By contrast, in 1991 and 1992, 11.6 and 8% of Dallas isolates were resistant to penicillin and to cefotaxime or ceftriaxone (MIC ≥ 0.5 µg/ml), respectively (14), and in 1993 18.5 and 12.9% of 54 pneumococcal isolates were penicillin resistant and cefotaxime or ceftriaxone resistant, respectively. There have been many reports of failure of penicillin and cephalosporin therapy for meningitis caused by these resistant pneumococcal strains (2, 3, 5, 14, 31). As a result, other antimicrobial agents, principally vancomycin or rifampin, have been added to the initial empiric regimens, especially when pneumococcal disease is suspected (14, 34). The combination of ceftriaxone and vancomycin

showed synergistic killing of resistant pneumococci in the rabbit meningitis model (12), and this regimen has been suggested for routine initial therapy of bacterial meningitis until results of culture and susceptibility studies are available.

Because of concerns about the highly variable concentrations of vancomycin in cerebrospinal fluid (CSF) after parenteral administration (22, 34) and about possible reduced penetration of vancomycin into CSF when dexamethasone is concomitantly given, the present study was undertaken. The impact of dexamethasone therapy on the decrease of clearance of resistant pneumococci from CSF in our meningitis model was assessed by using several antimicrobial regimens.

MATERIALS AND METHODS

Bacterial strains. Two *S. pneumoniae* strains isolated from infants with meningitis for whom conventional therapy failed were used (12, 14). The strains were grown overnight on blood agar plates. The plates were washed with phosphate-buffered saline (PBS), and aliquots of the resultant suspension were frozen at −70°C. To prepare the inoculum, aliquots were diluted in PBS to a concentration of approximately 2×10^5 CFU/ml, and a 250-µl inoculum was intracisternally administered into each rabbit.

Meningitis model. The well-characterized rabbit meningitis model (17, 21, 24, 32), modified from the original description of Dacey and Sande (9), was used. Briefly, New Zealand White male rabbits weighing 2 to 2.5 kg were intramuscularly anesthetized with ketamine (40 mg/kg of body weight) and acepromazine (3 mg/kg) before each procedure. After a dental acrylic helmet was attached to the cranium, each rabbit was immobilized in a stereotactic frame. A 25-gauge spinal needle was introduced into the cisterna magna and 250 µl of CSF was

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TABLE 1. MICs and MBCs for the two strains used[a]

Drug	Strain JM		Strain JG	
	MIC	MBC	MIC	MBC
Penicillin	1	1	2	2
Ceftriaxone	1	1	4	4
Vancomycin	0.25	0.5	0.25	0.25
Rifampin	0.016	0.03	0.008	0.03

[a] All values are micrograms per milliliter and were determined by microdilution using Mueller-Hinton broth supplemented with 3 to 5% lysed horse blood.

withdrawn, and an equal volume of fluid containing approximately 5×10^4 CFU was inoculated. After 12 to 14 h, therapy was started (0 h). At different times (0, 5, 10, 24, and 36 h), 100 to 300 μl of CSF was obtained. Bacterial concentrations were quantified by plating serial dilutions on sheep blood agar plates and incubating them in 5% CO_2 at 35°C for 24 h. The lowest limit of bacterial detection was 10 CFU/ml. For the statistical analysis, a value of 1 CFU/ml (0 $\log_{10}$) was assigned to the negative cultures. The remaining CSF was centrifuged at 5,000 rpm for 10 min (Savant; Instruments, Inc., Farmingdale, N.Y.), and the supernatant was stored at −70°C for determination of antibiotic concentrations. Blood samples (0.5, 5, 5.5, and 10 h) and additional CSF samples (1 and 6 h) were withdrawn and stored as described above for determination of the antibiotic concentrations.

Treatment. The following antibiotics were evaluated: vancomycin (20 mg/kg; Eli Lilly & Co., Indianapolis, Ind.), rifampin (10 mg/kg; Marion Merrell Dow Inc., Kansas City, Mo.), and ceftriaxone (75 mg/kg; Roche Laboratories, Nutley, N.J.). The antibiotics were given intravenously, vancomycin and rifampin every 5 h for three doses and ceftriaxone at 0 and 10 h. These antibiotic dosages were selected to achieve peak and trough concentrations in CSF similar to those in humans during the first 24 h of therapy. Additionally, half of the animals received dexamethasone intravenously (1 mg/kg; Luitpold Pharmaceutical Inc., Shirley, N.Y.) just before and 10 h after the initiation of antimicrobial therapy.

Antibiotic measurement. Vancomycin and rifampin concentrations were determined by disk diffusion microbioassays using *Bacillus subtilis* ATCC 6633 and *Micrococcus lutea* ATCC 9341, respectively (30). Ceftriaxone values were measured by reverse-phase high-performance liquid chromatography. The lower limits of detection were 0.7, 0.08, and 0.5 μg/ml in CSF and 0.7, 0.3, and 12.5 μg/ml in serum for vancomycin, rifampin, and ceftriaxone, respectively. The higher limit for the ceftriax-

one concentration in serum was the result of a greater dilution of serum made to detect larger concentrations than are found in CSF.

Statistical analysis. Student's t test or one-way analysis of variance (Newman-Keuls multiple-comparisons test) and two-tailed Fisher exact tests were used for parametric data and comparison of positive and negative cultures, respectively. The number of animals ranged from 6 to 10 per treatment group. A P of <0.05 was considered significant.

RESULTS

The MICs and MBCs of the antibiotics used are shown in Table 1. The CSF and serum antibiotic concentrations obtained after the first dose and the percentages of antibiotic penetration into CSF are presented in Table 2. Values obtained after the second dose were similar to those after the first dose with the exception of vancomycin, for which there were significantly lower peak concentrations in CSF in dexamethasone-treated versus non-dexamethasone-treated animals (1.5 ± 0.5 versus 2.5 ± 1.0 μg/ml, respectively; $P = 0.042$). A similar trend for CSF vancomycin concentrations was seen for both peak and trough values in the first specimens as well. Furthermore, the percentage of vancomycin penetration into CSF was consistently lower in dexamethasone-treated animals. The ceftriaxone concentrations in CSF and CSF penetration were lower in dexamethasone-treated animals at all times studied; however, the differences in concentrations were not statistically significant compared with the values for non-dexamethasone-treated rabbits. The concentrations and penetration of rifampin were unaffected by dexamethasone administration.

Therapy in animals inoculated with JM strain. Figure 1 shows the results of therapy expressed as CFU per milliliter in CSF for the different regimens, ceftriaxone, vancomycin, and

TABLE 2. Mean antibiotic concentrations in CSF and serum and percentages of antibiotic penetration into CSF in rabbits with pneumococcal meningitis[a]

Antibiotic	Peak concn in CSF/peak concn in serum	% Penetration	Trough concn in CSF/trough concn in serum	% Penetration
Ceftriaxone				
Without DMX	5.5 (3.7)/275 (59)	2.1 (1.0)	2.7 (1.7)/28 (13)[b]	13.8 (5.7)
With DMX	5.6 (3.1)/228 (57)	2.5 (1.1)	2.1 (0.9)/29 (8)[b]	7.9 (4.1)
Vancomycin				
Without DMX	1.6 (0.9)/29 (14)	5.3 (2.8)	1.7 (0.9)/4.5 (3.7)	53.1 (20.3)
With DMX	1.1 (0.7)/34 (11)	3.4 (1.4)	1.3 (0.8)/3.6 (1.2)	39.3 (27.8)
Rifampin				
Without DMX	0.14 (0.05)/7.1 (1.6)	2.0 (0.7)	0.08 (0.0)/2.7 (1.6)	4.3 (1.7)
With DMX	0.23 (0.13)/7.3 (0.9)	3.1 (1.7)	0.09 (0.01)/1.8 (0.6)	5.4 (2.3)

[a] All values are means, with standard deviations given in parentheses. Concentrations are given in micrograms per milliliter.
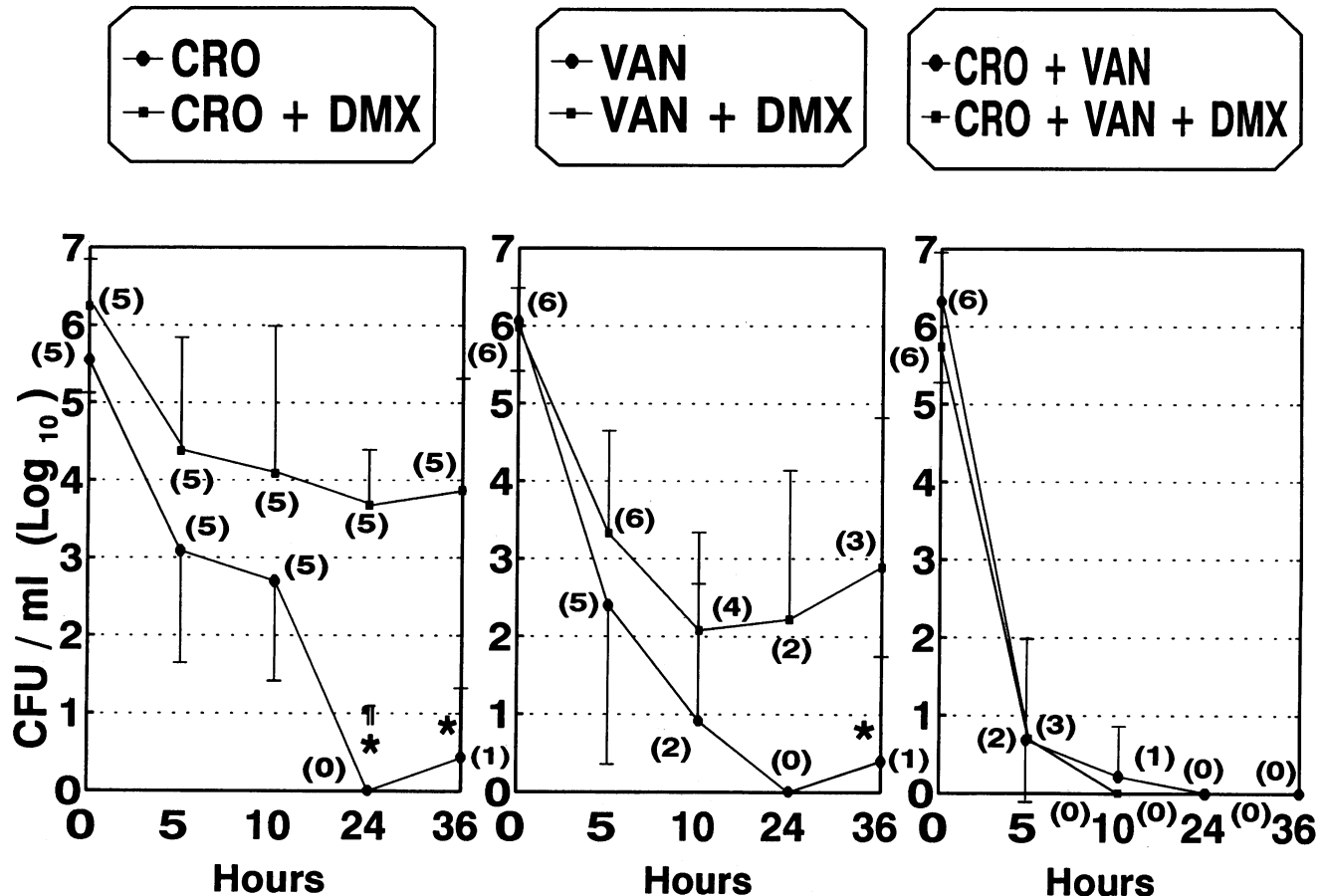[b] Before the second dose.

FIG. 1. Bacterial concentrations in CSF (means ± standard deviations, in CFU per milliliter) and numbers of positive cultures (in parentheses) after intracisternal inoculation of JM strain. CRO, ceftriaxone; DMX, dexamethasone; VAN, vancomycin. * and ¶, $P < 0.05$ between non-DMX-treated and DMX-treated animals in CFU per milliliter and number of positive cultures, respectively.

the combination (vancomycin and ceftriaxone) with or without dexamethasone. When vancomycin or ceftriaxone was given with dexamethasone, a delay in clearance of organisms from CSF was seen and CSF cultures were positive significantly more often than those for non-dexamethasone-treated animals. The combination of vancomycin and ceftriaxone was effective in sterilizing CSF cultures by 10 h, and there were no differences in CFU per milliliter and number of positive cultures at each time point for dexamethasone-treated and non-dexamethasone-treated animals.

Therapy in animals inoculated with JG strain. When JG strain, with higher MICs and MBCs of penicillin and cephalosporin, was used, there was no decrease in the number of CFU per milliliter when ceftriaxone therapy was given alone or in combination with dexamethasone (data not shown). For rabbits treated with dexamethasone and either vancomycin or vancomycin and ceftriaxone, clearance decreased and the numbers of positive CSF cultures at all time points increased compared with the results for animals not receiving dexamethasone (Fig. 2). The combination of ceftriaxone and rifampin was effective in sterilizing CSF cultures, regardless of whether dexamethasone was given.

Because ceftriaxone and rifampin were so effective, additional experiments were performed in which animals infected with JG strain were treated for 7 days and in which half of the rabbits were given dexamethasone (1 mg/kg of body weight

every 12 h) for the first 4 days. Animals were treated intravenously with rifampin (20 mg/kg every 12 h) for 7 days and with ceftriaxone (75 mg/kg every 12 h) for the first 2 days only. CSF samples were obtained at 0, 24, and 48 h following initiation of antibiotics, on the last day of treatment (day 7), and 2 and 5 days after the last dose of rifampin. Antibiotic concentrations and penetration into CSF were similar to those shown previously, and there were no significant differences in values for dexamethasone-treated and non-dexamethasone-treated animals. The mean $\log_{10}$ CFU per milliliter (± standard deviations) before antibiotic therapy were 6.6 ± 0.6 and 6.5 ± 0.5 in dexamethasone-treated and non-dexamethasone-treated animals, respectively. After the first day of treatment, all CSF cultures were sterile, including those obtained 2 and 5 days after rifampin therapy was stopped.

DISCUSSION

As a rule, antimicrobial therapy for bacterial meningitis is most effective when the antibiotic concentration in CSF exceeds the MBC of the pathogen by approximately eightfold or more (21, 33). The rabbit meningitis model has been useful in evaluating antimicrobial regimens for meningitis therapy with the caveat that the dosage of the tested drugs be adjusted to achieve concentrations in rabbit serum that are comparable to those expected in humans. This was achieved in the present
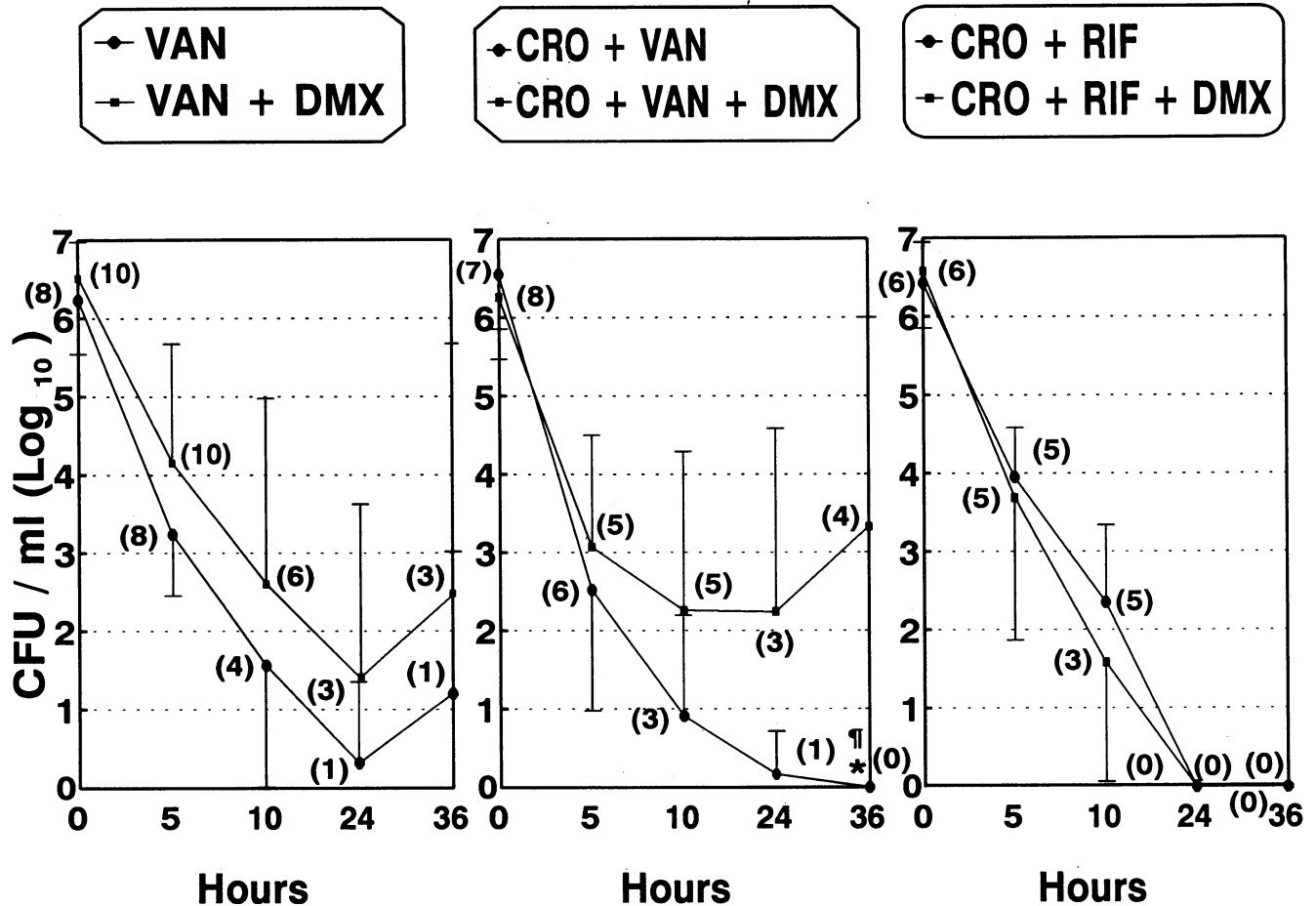
FIG. 2. Bacterial concentrations in CSF (means ± standard deviations, in CFU per milliliter) and numbers of positive cultures (in parentheses) after intracisternal inoculation of JG strain. VAN, vancomycin; DMX, dexamethasone; CRO, ceftriaxone; RIF, rifampin. * and ¶, $P < 0.05$ between non-DMX-treated and DMX-treated animals in CFU per milliliter and number of positive cultures, respectively.

study with the three antibiotics assessed, given either singly or in combination.

The penetration of rifampin into CSF was relatively unaffected by coadministration of dexamethasone, whereas the ceftriaxone concentrations in CSF and penetration into CSF were lower in the dexamethasone-treated animals. The concentrations of vancomycin were substantially and consistently reduced by steroid therapy in all experiments, and the CSF vancomycin concentrations attained failed to achieve a sufficient multiple of the MBC of the organism to produce a consistent bacteriologic cure. This was also true for some of the animals treated with ceftriaxone and dexamethasone. The bacteriologic efficacy of ceftriaxone or vancomycin therapy as measured by concentrations of organisms in CSF at various times after the start of treatment was reduced by dexamethasone, especially against the less resistant JM strain. Combined ceftriaxone and vancomycin therapy was effective in animals infected with the JM strain whether or not dexamethasone therapy was given, illustrating the synergistic activity of these drugs against pneumococci (12, 13). This was not the case for the more ceftriaxone-resistant JG strain when dexamethasone was coadministered. The lack of bacteriologic efficacy in the latter experiments can be explained by lower concentrations of both antibiotics, especially vancomycin, in CSF with dexamethasone therapy, resulting in diminished bactericidal activity as

recently shown in vitro by time-kill studies with the JG and JM pneumococcal strains (13).

We previously studied rifampin therapy alone or in combination with ceftriaxone or vancomycin in experimental pneumococcal meningitis (12) and in time-kill experiments (13) using the JM and JG strains. Rifampin therapy resulted in slow killing of pneumococci in vivo, and the addition of either ceftriaxone or vancomycin resulted in an indifferent effect in the in vivo and in vitro systems. In the present experiments, dexamethasone therapy did not adversely influence the eradication of pneumococci from CSF when rifampin and ceftriaxone were administered. Additionally, animals injected with the JG strain and treated with rifampin and ceftriaxone for 2 days and then with rifampin alone for 5 days had uniformly sterile CSF cultures during therapy and at 2 and 5 days after rifampin therapy was discontinued.

If dexamethasone is used for the first 2 to 4 days of therapy for meningitis (19, 27, 28), which we recommend, from our studies it appears prudent to use initially the combination of ceftriaxone and rifampin to avoid the possibility of delayed sterilization of CSF cultures and an adverse outcome that could result if ceftriaxone and vancomycin are used. Although this recommendation is based on results from our rabbit meningitis model, there are data for humans that corroborate, in part, these results. Viladrich and associates (34) treated

adults with meningitis caused by resistant strains of *S. pneumoniae* with vancomycin and dexamethasone. They reported highly variable trough concentrations of vancomycin in serum and CSF, and clinical failure occurred more often in the patients with low or undetectable vancomycin concentrations in CSF.

Management of meningitis caused by resistant pneumococcal strains is evolving, and no one regimen should be considered standard therapy at this time. Regardless of the regimen chosen for initial empiric therapy, we believe that a second lumbar puncture should be performed approximately 24 to 36 h after the start of treatment to document bacteriologic cure, and susceptibility studies of pneumococcal isolates should be carried out in accordance with the recently published recommendations of the National Committee on Clinical and Laboratory Standards (25).

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