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Trovafloxacin in Treatment of Rabbits with Experimental Meningitis Caused by High-Level Penicillin-Resistant *Streptococcus pneumoniae*

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The fluoroquinolone trovafloxacin was bactericidal (0.47 ± 0.23 $\Delta\log_{10}$ CFU/ml · h after 10 mg/kg of body weight and 0.78 ± 0.15 $\Delta\log_{10}$ CFU/ml · h after 30 mg/kg) in the treatment of experimental meningitis caused by a highly penicillin-resistant (MIC and minimum bactericidal concentration = 4 and 4 μg/ml) strain of *Streptococcus pneumoniae*. Combinations with ampicillin and rifampin were indifferent compared to single drugs.

Streptococcus pneumoniae is currently the most common cause of bacterial meningitis in the United States and leads to significant morbidity and mortality (21). Penicillin and cephalosporins have been the mainstay of therapy; however, the global spread of multidrug-resistant strains of *S. pneumoniae* has complicated the antimicrobial therapy of meningitis (4, 12). Vancomycin has been used with success against *S. pneumoniae* strains with intermediate- and high-level β-lactam resistance in patients (11) and in animal models of meningitis (3, 13), and it is considered by some to be the drug of choice for this indication. Vancomycin, however, shows a relatively high degree of variability with regard to its penetration into the cerebrospinal fluid (CSF), and recent reports have documented vancomycin failures in humans (26). Therefore, most recommendations for the treatment of penicillin-resistant pneumococcal meningitis involve at least two antibiotics, typically an expanded-spectrum cephalosporin combined with vancomycin or rifampin (11, 18). Dual antibiotic therapy is cumbersome and expensive and bears the potential for increased adverse events. The need for new, more effective antibiotics for the treatment of meningitis caused by resistant pneumococci is obvious.

Quinolones are highly active in vivo against susceptible organisms. They are lipophilic and enter the CSF better than other classes of antibiotics (6, 20). Nonetheless, quinolones have not been used routinely in the treatment of meningitis because of their limited activity against common meningeal pathogens such as *S. pneumoniae* (20). Newer quinolones have improved activity against gram-positive pathogens (10, 22, 23), and some have been shown to be efficacious in experimental meningitis caused by pneumococci (16, 17). Trovafloxacin is a representative of this new group of quinolones with improved activity against many gram-positive pathogens, including *S. pneumoniae* (9). We tested trovafloxacin in a meningitis model in rabbits to determine its efficacy in meningitis caused by a highly penicillin-resistant strain of *S. pneumoniae.*

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In vitro studies. *S. pneumoniae* serotype 23F, used in this study (a generous gift from Alex Tomasz, Rockefeller University, New York, N.Y.), shows high-level penicillin resistance and resistance to other antibiotics (erythromycin and trimethoprim-sulfamethoxazole) and has been shown to spread intercontinentally (1, 14). Trovafloxacin was provided by Pfizer Inc. (Groton, Conn.). Ampicillin, rifampin, and ceftriaxone (Roche Laboratories, Nutley, N.J.) were obtained from commercial sources. MICs and minimum bactericidal concentrations (MBCs) were determined in Todd-Hewitt broth (Difco Laboratories, Detroit, Mich.) by the standard tube macrodilution method with an inoculum of 7×10^6 CFU/ml which was chosen to reflect CSF bacterial titers at the initiation of therapy. The MIC was defined as the lowest concentration inhibiting visible growth after 24 h of incubation at 37°C in room air with 5% CO_2, and the MBC was defined as the lowest concentration killing >99.9% of the initial inoculum. The MICs and MBCs, respectively, of the drugs studied were as follows (in micrograms per milliliter): penicillin, 4.0 and 4.0; ampicillin, 4.0 and 8.0; ceftriaxone, 0.25 and 0.5; rifampin, 0.12 and 0.12; and trovafloxacin, 0.12 and 0.25. The organism was highly resistant to penicillin and ampicillin but was sensitive to ceftriaxone, albeit at a relatively high MIC and MBC. The lowest MICs and MBCs were those of trovafloxacin and rifampin. Thus, this organism was characteristic of penicillin-resistant pneumococci in at least two ways. First, the high-level resistance to penicillin, mediated by alterations of several penicillin-binding proteins in these organisms, was associated with an increase in the MICs and MBCs of other β-lactams, such as ceftriaxone. Second, even though β-lactam-resistant pneumococci are often also resistant to other antibiotics, such as macrolides or trimethoprim-sulfomethoxazole, they typically remain sensitive to quinolones and rifampin (22, 23). These two classes of antibiotics thus represent potential candidates for the therapy of infections caused by β-lactam-resistant pneumococci.

Meningitis model in rabbits. The animal studies were approved by the Committee on Animal Research of the University of California, San Francisco. A modification of the rabbit model of bacterial meningitis described by Dacey and Sande (5) was used. After intramuscular anesthesia with ketamine (30 mg/kg of body weight), xylazine (15 mg/kg), and acepromazine (3 mg/kg), rabbits were infected by direct intracisternal injection of 10^6 CFU of *S. pneumoniae* suspended in 0.3 ml of saline. The inoculum was prepared from bacteria cultured on blood agar plates after several intrathecal passages in rabbits and was stored at −70°C as a suspension in sterile saline. To infect animals, the frozen organisms were thawed, grown in

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TABLE 1. Drug concentrations in CSF and serum in experimental meningitis caused by a highly penicillin-resistant *S. pneumoniae* strain

Drug	Dose (mg/kg)	*n*	1 h			7 h		
			CSF drug concn (μg/ml)	Concn in CSF/MBC	Serum drug concn (μg/ml)	CSF drug concn (μg/ml)	Concn in CSF/MBC	Serum drug concn (μg/ml)
Trovafloxacin	30	8	3.92 ± 1.86	15.7	7.85 ± 2.70	0.23 ± 0.13	0.9	0.87 ± 0.59
	10 (2×)[a]	10	0.47 ± 0.30	1.9	2.42 ± 1.43	0.23 ± 0.23	0.9	0.93 ± 0.83
	10	19	0.37 ± 0.17	1.5	1.62 ± 0.44	0.06 ± 0.05	0.3	0.20 ± 0.28
Ceftriaxone	10	7	1.16 ± 0.42	2.3	16.79 ± 4.24	0.45 ± 0.24	0.9	3.93 ± 0.86
Ampicillin	50 (2×)[a]	7	5.56 ± 1.27	0.7	16.86 ± 2.67	0.62 ± 0.21	0.01	0.71 ± 0.37
Rifampin	10	8	0.75 ± 0.27	6.3	16.89 ± 5.09	0.50 ± 0.18	4.2	6.05 ± 1.93

[a] Two doses given 3 h apart.

Todd-Hewitt broth, diluted to the desired concentration in saline, and injected intracisternally. The accuracy of the inoculum size was routinely confirmed by quantitative cultures. After infection, the animals were returned to their cages. Eighteen hours later, when meningitis had fully developed, animals were anesthetized by intravenous administration of urethane (2 mg/kg) for 7 h. An intra-arterial line was placed for the collection of blood. Before antibiotic therapy was initiated, 0.3 ml of CSF was obtained by puncture of the cisterna magna with a 25-gauge butterfly needle, and initial bacterial titers in CSF were determined by quantitative cultures.

All antibiotics were dissolved in sterile water. Stock antibiotic solutions were diluted in saline and were infused in an ear vein by bolus injection of 1 ml of solution over 2 min. Trovafloxacin, infused as the prodrug CP-116-517, was protected from light during the injection. Several dosages of trovafloxacin were studied in order to assess the dosage dependency of the drug's efficacy: 10 mg/kg as a single dose, used as the standard dose; two doses of 10 mg/kg 3 h apart to main concentrations in CSF higher than the MIC for the entire dosing interval; and 30 mg/kg as a single dose. Comparison groups were treated with ceftriaxone (10 mg/kg once), ampicillin (50 mg/kg in two doses 3 h apart), or rifampin (10 mg/kg once). For rifampin, this dose constitutes the most effective dose in this model (15). A standard dose of trovafloxacin (10 mg/kg once) was also combined with ampicillin or rifampin. Infected control animals received saline.

CSF samples were quantitatively cultured from each animal. Bacterial titers were determined at 0, 1, 3, 5, and 7 h. In addition to samples diluted 10-fold in saline, 50 μl of CSF was plated undiluted, resulting in a detection limit of 2×10^1 CFU/ml. Based on bacterial densities calculated in parallel from undiluted and 1:10-diluted CSF samples, there was no evidence of a carryover effect with any of the antibiotics. In order to account for the limited sensitivity, we assigned the first sterile CSF sample obtained during therapy a value of 1.3 ($\log_{10}$ of the limit of detectability), while any subsequent sterile samples were assigned a value of 0 (15, 16). Bactericidal rates during the 7-h treatment period were calculated from the titers at 0, 1, 3, 5, and 7 h by colinear regression analysis and were expressed as $\Delta\log_{10}$ CFU/ml · h. All results were expressed as mean ± standard deviation. Comparisons between groups were performed by analysis of variance. Statistical significance was determined by Bonferroni tests.

Drug concentrations in serum and in CSF were determined by the agar diffusion method performed in antibiotic medium 11 (Difco Laboratories) in duplicate wells. Standard curves for serum were generated in rabbit serum, while standard curves for CSF were generated in saline containing 5% rabbit serum, approximating the protein content of CSF during meningitis. To minimize variability, the concentrations of drugs in all samples containing the same drug were determined on a single day. Assay variability for individual samples was <10%. *Escherichia coli* (ATCC 10536) was used as the indicator strain for ceftriaxone (limits of detection, 0.25 μg/ml in serum and 0.12 μg/ml in CSF). *Bacillus subtilis* (ATCC 6633) was used as the indicator strain for trovafloxacin, ampicillin, and rifampin. The limits of detection were 0.12 μg/ml in serum and 0.06 μg/ml in CSF for all three drugs.

In vivo results. The present study confirmed previous findings that showed good penetration of fluoroquinolones in general and trovafloxacin in particular into the CSF of rabbits with meningitis (16). Depending on the dosage of trovafloxacin, concentrations in CSF 1 h after administration varied between 19 and 50% of the simultaneous serum concentrations, reflecting penetration rates similar to those found in a previous study with continuous infusion of the drug (Table 1) (16). Ampicillin showed a comparable CSF-to-serum concentration ratio at 1 h (0.33), while the corresponding values for ceftriaxone (0.07) and rifampin (0.04) were considerably lower. The concentrations of trovafloxacin achieved in the CSF exceeded the MBC for the organism 15-fold at the highest dose examined (30 mg/kg) (Table 1). At the lower, clinically more relevant dose of 10 mg/kg, CSF trovafloxacin concentrations exceeded the MBC for the pneumococci by approximately twofold. CSF ceftriaxone concentrations 1 h after injection were 2.3 times higher than the MBC for the organism, while the ratio was 0.7 for ampicillin and 6.3 for rifampin (Table 1). It is important to note that the differences in pharmacokinetics in serum and CSF among the drugs (time to peak and half-lives) make direct comparisons of CSF penetration rates or CSF concentration/MBC ratios after the administration of a single bolus dose difficult.

The three dosages of trovafloxacin studied were all bactericidal compared to untreated controls (Table 2). The high dose of trovafloxacin, 30 mg/kg, produced the highest bactericidal rate (0.78 ± 0.15 $\Delta\log_{10}$ CFU/ml · h), which was significantly higher than that for a single dose of 10 mg/kg (0.47 ± 0.23 $\Delta\log_{10}$ CFU/ml · h; $P < 0.05$ for analysis of variance of the three trovafloxacin groups). Two doses of 10 mg of trovafloxacin per kg 3 h apart increased the bactericidal rate slightly compared to a single dose. After the single dose, CSF bacterial titers were progressively reduced during the first 5 h of therapy, at which time trovafloxacin concentrations in CSF reached approximately 0.1 μg/ml, the equivalent of the MIC. Between 5 and 7 h of therapy, titers in CSF did not continue to decline

TABLE 2. Bactericidal rates in CSF of antibiotics tested in experimental meningitis caused by a highly penicillin-resistant *S. pneumoniae* strain

Treatment group	Dose (mg/kg)	*n*	Initial CSF titer ($\log_{10}$ CFU/ml)[a]	Killing rate ($\Delta\log_{10}$ CFU/ml · h)
Trovafloxacin				
Alone	30	8	6.54 ± 0.56	0.78 ± 0.15[b,c]
	10 (2×)[d]	10	6.04 ± 1.19	0.59 ± 0.21[b,c]
	10	19	6.22 ± 0.75	0.47 ± 0.23[c]
+Ampicillin[e]	50 (2×)[d]	8	6.68 ± 1.45	0.44 ± 0.28[c]
+Rifampin[e]	10	8	5.99 ± 1.18	0.57 ± 0.17[c]
Ceftriaxone	10	7	5.74 ± 0.71	0.23 ± 0.21
Ampicillin	50 (2×)[d]	7	5.44 ± 1.36	0.31 ± 0.27
Rifampin	10	8	6.33 ± 0.52	0.45 ± 0.20[c]
Control		17	5.94 ± 0.60	0.02 ± 0.14

[a] *P* is not significant for any two groups.
[b] *P* is <0.05 compared with the ceftriaxone group.
[c] *P* is <0.05 compared with the control group.
[d] Two doses given 3 h apart.
[e] Given with one trovafloxacin dose of 10 mg/kg.

(data not shown). Thus, trovafloxacin produced a bactericidal effect only while drug concentration in CSF exceeded the MIC. This finding suggests that concentrations of trovafloxacin in CSF should be maintained above the MIC during the therapy of pneumococcal meningitis to optimize the bactericidal effect.

The results of the present study and our previous study with trovafloxacin (16) further indicate that, as with other classes of antibiotics, the height of the peak concentration in CSF is critical for the bactericidal rate. This conclusion is supported by two observations. First, the CSF bactericidal rate during the first 5 h of therapy, the period during which both regimens resulted in concentrations in CSF above the MIC, was significantly higher with 30 mg of trovafloxacin per kg than with 10 mg/kg (1.06 ± 0.13 versus 0.57 ± 0.34 $\Delta\log_{10}$ CFU/ml · h; $P < 0.001$). That this finding is indeed the result of differences in peaks in CSF rather than in area under the concentration-time curve/MIC ratios is indicated by the comparison of the present study and our previous study with trovafloxacin (16). In the previous study, trovafloxacin was administered such that the concentration in CSF exceeded the MBC by almost the same ratio as in the present study (19 versus 16). However, in that study the high concentrations in CSF were maintained during the entire 7-h treatment period, yet the two regimens resulted in almost the same bactericidal rates (0.84 versus 0.78 $\Delta\log_{10}$ CFU/ml · h). Taken together, these results suggest that a peak in CSF exceeding the MBC for the organism approximately 10-fold and concentrations in CSF greater than the MIC during the entire dosing interval will result in optimal bactericidal rates with trovafloxacin. In a human study, concentrations in serum after a 200-mg intravenous dose of trovafloxacin resulted in a mean peak concentration in serum of 2.3 μg/ml (19). Assuming a 20 to 30% rate of penetration into the CSF during meningitis, a concentration in CSF of 0.5 μg/ml can be expected, which is very similar to that achieved in our model after a 10-mg/kg dose. Based on our results, a somewhat higher peak in CSF would be preferable, and the feasibility of initiating therapy with doses of 300 or 400 mg should be tested.

Ampicillin and ceftriaxone were dosed to achieve concentrations in CSF that would exceed the MIC and the MBC for the penicillin-resistant pneumococcus to a degree similar to that of the standard dose of trovafloxacin (Table 1). At these doses, which result in concentrations in CSF on the low end of the range achieved in humans with meningitis, neither ampicillin nor ceftriaxone showed significant bactericidal activity compared to untreated controls (Table 2). However, ampicillin (25) and ceftriaxone (24) showed a strong positive correlation between concentration in the CSF and bactericidal activity in the CSF. It is therefore very likely that both drugs would have been more effective at higher doses. While a direct comparison of the maximal bactericidal rates for the β-lactams and trovafloxacin is not possible based on the present study, previous data indicate that these rates are very similar (16).

Ampicillin is commonly included in the empirical therapy of meningitis to provide coverage for *Listeria monocytogenes* and is synergistic with trovafloxacin in experimental enterococcal endocarditis (2). Its addition to trovafloxacin in the present study did not improve the killing rates compared to those for trovafloxacin alone. Rifampin has been reported to be either indifferent (8) or antagonistic (7) with ceftriaxone in the treatment of penicillin-resistant pneumococcal meningitis. Like ampicillin, rifampin was indifferent in combination with trovafloxacin, similar to the results of a previous study of a quinolone with rifampin in the treatment of experimental pneumococcal meningitis (15).

The excellent CSF penetration and bactericidal activity of trovafloxacin qualify this new quinolone as an attractive antibiotic for the treatment of meningitis caused by susceptible bacteria. Since cross-resistance between quinolones and β-lactams is very uncommon, trovafloxacin appears to be promising for the treatment of meningitis caused by highly penicillin-resistant *S. pneumoniae* (22, 23). This study and previous studies have identified the peak concentration in CSF (16) and half-life in CSF as parameters that allow the estimation of the usefulness of a drug for the treatment of meningitis. If this assessment indicates that the human CSF pharmacokinetic profile is favorable, then a clinical study will be justified.

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