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Quinolone Antibiotics in Therapy of Experimental Pneumococcal Meningitis in Rabbits

ROLAND NAU,† TIBOR SCHMIDT, KEITH KAYE, JEFF L. FROULA, AND MARTIN G. TÄUBER*

Infectious Diseases Laboratory, San Francisco General Hospital, and the Department of Medicine, University of California, San Francisco, San Francisco, California

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Using a rabbit model of pneumococcal meningitis, we compared the pharmacokinetics and bactericidal activities in cerebrospinal fluid (CSF) of older (ciprofloxacin, ofloxacin) and newer (levofloxacin, temafloxacin, CP-116,517, and Win 57273) quinolones with those of the β-lactam ceftriaxone. All quinolones penetrated into the inflamed CSF better than ceftriaxone, and the speed of entry into CSF was closely related to their degrees of lipophilicity. At a dose of 10 mg/kg · h, which in the case of the quinolones already in use in clinical practice produced concentrations attainable in the sera and CSF of humans, ciprofloxacin had no antipneumococcal activity ($\Delta\log_{10}$ CFU/ml · h, +0.20 ± 0.14). Ofloxacin ($\Delta\log_{10}$ CFU/ml · h, −0.13 ± 0.12), temafloxacin ($\Delta\log_{10}$ CFU/ml · h, −0.19 ± 0.18), and levofloxacin ($\Delta\log_{10}$ CFU/ml · h, −0.24 ± 0.16) showed slow bactericidal activity (not significantly different from each other), while CP-116,517 ($\Delta\log_{10}$ CFU/ml · h, −0.59 ± 0.21) and Win 57273 ($\Delta\log_{10}$ CFU/ml · h, −0.72 ± 0.20) showed increased bactericidal activities in CSF that was comparable to that of ceftriaxone at 10 mg/kg · h ($\Delta\log_{10}$ CFU/ml · h, −0.80 ± 0.17). These improved in vivo activities of the newer quinolones reflected their increased in vitro activities. All quinolones and ceftriaxone showed positive correlations between bactericidal rates in CSF and concentrations in CSF relative to their MBCs. Only when this ratio exceeded 10 did the antibiotics exhibit rapid bactericidal activities in CSF. In conclusion, in experimental pneumococcal meningitis the activities of new quinolones with improved antipneumococcal activities were comparable to that of ceftriaxone.

Pneumococci resistant to several antibiotics are becoming a worldwide challenge. In many areas at least 10% of pneumococcal isolates, including those isolated from cerebrospinal fluid (CSF), show reduced susceptibility to penicillin (15, 17, 34). Penicillin resistance in pneumococci is often associated with an increase in the MICs of other β-lactam antibiotics, and the failure of cefotaxime and ceftriaxone in the treatment of meningitis caused by penicillin-resistant *Streptococcus pneumoniae* has been observed (1, 7).

Quinolones are rapidly bactericidal in vitro and in vivo for susceptible organisms in a highly concentration-dependent way (4, 5). Because of their lipophilicity, quinolones enter the CSF better than other classes of antimicrobial agents (3, 26). However, quinolones have infrequently been used in the past for the therapy of meningitis. They are relatively contraindicated in children, the age group most susceptible to the development of meningitis, and the currently approved quinolones possess only marginal activities against important meningeal pathogens such as *S. pneumoniae*, other streptococci, and *Listeria monocytogenes* (26).

In recent years, new quinolones with improved activities against gram-positive pathogens, including *S. pneumoniae*, have been developed (9, 11, 29, 30). These quinolones remain active against β-lactam-resistant pneumococci and are therefore potentially useful for the therapy of pneumococcal meningitis caused by penicillin- and cephalosporin-resistant strains (29, 30). The new quinolone clinafloxacin was the most active single agent against two β-lactam-resistant pneumococci in a recent study of experimental meningitis (8). In light of this potential of quinolones for the therapy of meningitis, we used a well-standardized model of pneumococcal meningitis and several quinolones with different levels of activity against pneumococci to define the parameters that determine the pharmacokinetics and efficacies of quinolones in the CSF of rabbits with pneumococcal meningitis.

* Corresponding author. Mailing address: Infectious Diseases Laboratory/SFGH, Box 0811, University of California, San Francisco, 3rd & Parnassus Avenues, San Francisco, CA 94143. Phone: (415) 206-8844. Fax: (415) 206-6015.

† Present address: Department of Neurology, Georg-August-University, 37075 Göttingen, Germany.

MATERIALS AND METHODS

Test organism. A penicillin-susceptible *S. pneumoniae* type 3 strain originally isolated from an adult with meningitis was used in all experiments (32). After several intrathecal passages in rabbits, infected CSF was cultured for 24 h on blood agar plates, bacteria were suspended in sterile saline, and aliquots were kept at −70°C. To infect the animals, the frozen organisms were thawed, diluted to the desired concentration (3×10^6 CFU/ml) in saline, and injected intracisternally. The accuracy of the inoculum size was routinely confirmed by quantitative cultures.

Antimicrobial agents. Ofloxacin and levofloxacin were provided by Johnson & Johnson (Arlington, Tex.), temafloxacin was provided by Abbott Laboratories (Abbott Park, Ill.), CP-99,219 for in vitro studies and the bis-L-alanyl prodrug of CP-99,219 (CP-116,517) for in vivo experiments were provided by Pfizer Inc. (Groton, Conn.), and Win 57273 was provided by Sterling Winthrop Inc. (Collegeville, Pa.). Ciprofloxacin (Ciproxin; Miles Inc., West Haven, Conn.) and ceftriaxone (Rocefin; Hoffmann-LaRoche Inc., Nutley, N.J.) were obtained from commercial sources. Some of the results for ofloxacin obtained in a different context have already been reported (21).

Susceptibility tests. MICs and MBCs were measured in Todd-Hewitt broth (Difco Laboratories, Detroit, Mich.) by the standard tube macrodilution method with an inoculum of 1×10^5 to 5×10^5 CFU/ml. 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. The lowest drug concentration that killed ≥99.9% of the inoculum was defined as the MBC.

Rabbit model. The animal studies were approved by the Committee on Animal Research of the University of California, San Francisco. A modification of the model previously described by Dacey and Sande (2) was used. After intramuscular anesthesia with ketamine (30 mg/kg of body weight), xylazine (15 mg/kg), and acepromazine (3 mg/kg), New Zealand White rabbits (weight, 2 to 3 kg each) were infected by direct intracisternal injection of 10^6 CFU of *S. pneumoniae* suspended in 0.3 ml of saline. The animals were then returned to their cages. Eighteen hours later, when they had meningitis, they were anesthetized by the intravenous administration of urethane (2 g/kg) for 7 h. Before initiating anti-

biotic therapy, 0.3 ml of CSF was obtained by puncturing the cisterna cerebellomedullaris with a 25-gauge butterfly needle, and the initial bacterial titers in CSF were determined by quantitative cultures.

Drug administration. At neutral pH, CP-99,219 has limited solubility in aqueous solutions. Therefore, CP-116,517, a hydrophilic prodrug of CP-99,219 which is transformed in serum into the parent compound within minutes (10), was used for the intravenous preparation. CP-116,517 and ceftriaxone were dissolved in small volumes of sterile water, levofloxacin was dissolved in 10^{-3} M HCl (final drug concentration 10 mg/ml), and Win 57273 was dissolved in 0.1 M NaOH (final drug concentration, 40 mg/ml). The freshly prepared stock solutions and the commercially available solutions of ciprofloxacin and ofloxacin were diluted in 0.9% saline and were infused through a peripheral ear vein. Infusion rates were 10 ml/h, and the duration of therapy was 7 h. Preceding the constant infusion, a bolus determined in preliminary experiments to rapidly produce steady-state concentrations in serum was administered. Infected control rabbits received the same volume of saline. Quinolones were protected from light during the infusion.

Sample collection and processing. Blood (from an indwelling ear artery catheter contralateral to the ear receiving the antibiotic infusion) and cisternal CSF were sampled at 1, 3, 5, and 7 h of therapy. Bacterial titers in CSF were determined by quantitative culture of undiluted and 10-fold-diluted samples on blood agar plates. In animals treated with ceftriaxone, broad-spectrum β-lactamases (β-lactamase, *Bacillus cereus* 569/H9; Calbiochem Corp., La Jolla, Calif.) were added to the CSF samples to minimize a possible carryover effect. With quinolones, no evidence of a carryover effect was detected by parallel plating of undiluted and 1:100-diluted CSF from randomly chosen animals receiving high doses of the different quinolones or by the routine comparison of serial dilutions of CSF samples with high bacterial titers. To determine antibiotic concentrations, blood and CSF samples were centrifuged at 2,000 × *g* for 5 min, and the supernatants were stored at −70°C.

Calculation of bacterial killing. Ten microliters of CSF was plated undiluted for each sample. The detection limit by this method was therefore 10^2 CFU/ml. In order to account for this limited sensitivity, we assigned the first sterile CSF sample obtained during therapy a value of 2 (the limit of detectability), while a subsequent sterile sample was assigned a value of 0. Bacterial titers at 0, 1, 3, 5, and 7 h were used to calculate the bactericidal rate by log-linear regression analysis, which was expressed as $\Delta\log_{10}$ CFU per milliliter · hour.

Antibiotic assays. Drug concentrations in serum and CSF were determined in duplicate wells by the agar well diffusion method performed in antibiotic medium 11 (Difco Laboratories). Standard curves for serum were generated in serum, while standard curves for CSF were generated in saline containing 5% rabbit serum, approximating the protein content of CSF during meningitis. To minimize the effect of interday variability, the concentrations of drug 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 quantitation, 0.25 μg/ml in serum and 0.125 μg/ml in CSF). Quinolone concentrations were determined with *Bacillus subtilis* ATCC 6633 as the indicator strain. The limits of quantitation in serum and CSF were 0.25 μg/ml for ciprofloxacin, 1 μg/ml for ofloxacin, 0.5 μg/ml for levofloxacin, and 0.125 μg/ml for CP-99,219 and Win 57273.

Pharmacodynamic analysis. The ratio of the mean CSF quinolone concentration to the MBC was related to the bactericidal activity by means of a sigmoid E_{max} model. The mean concentration in CSF/MBC of the different quinolones at the investigated doses (with the exception of the inactive low dose of ciprofloxacin) and the corresponding bactericidal activities were taken for unweighted least-squares regression by the equation $E = E_{max} \cdot C^H \cdot (E_{50} + C^H)^{-1}$ and the program MKMODEL, version 4 (Biosoft, Cambridge, United Kingdom), where E is the estimated bactericidal rate, E_{max} is the maximum bactericidal rate; C is the mean concentration in CSF/MBC ratio, E_{50} is the C producing half-maximal killing, and H is the Hill coefficient indicating the steepness of the sigmoid curve.

Statistical analysis. All results are expressed as means ± standard deviations. Comparisons between groups were performed by one-way analysis of variance; in the case of significance this was followed by Student's *t* tests corrected for multiple comparisons by the Bonferroni correction. Correlations were calculated by the linear regression method.

RESULTS

In vitro susceptibility. Ciprofloxacin and ofloxacin had the highest MICs (1 μg/ml), while those of levofloxacin and temafloxacin were 1 dilution lower (Table 1). CP-99,219 (MIC, 0.06 μg/ml) and Win 57273 (MIC, 0.03 μg/ml) had MICs comparable to that of ceftriaxone (MIC, 0.03 μg/ml). MBCs were within 2 dilutions of the MIC for all study drugs (Table 1).

TABLE 1. In vitro activities of the antibiotics studied against the *S. pneumoniae* strain used in the meningitis model

Drug	MIC (μg/ml)	MBC (μg/ml)
Ciprofloxacin	1	4
Ofloxacin	1	2
Levofloxacin	0.5	1
Temafloxacin	0.5	1
CP-99,219	0.06	0.25
Win 57273	0.03	0.06
Ceftriaxone	0.03	0.06

Pharmacokinetics. For all experimental drugs, the initial dose studied was 10 mg/kg · h, which was chosen because in the case of the clinically available drugs ciprofloxacin and ofloxacin it produced levels in serum comparable to those achievable in the serum of humans. At this dose, the steady-state concentrations of the different quinolones in serum varied: the highest concentrations in serum were observed with Win 57273, while ciprofloxacin and CP-99,219 (the active compound of CP-116,517) achieved the lowest concentrations in serum (Table 2). All drugs showed increasing concentrations in CSF for several hours into therapy, while the concentrations in serum remained stable (Table 2). At between 5 and 7 h, the concentrations of all antibiotics in CSF changed minimally (data not shown), and we therefore used the CSF-to-serum drug concentration ratio at 7 h to estimate the level of steady-state penetration into CSF. The penetration rates were higher for levofloxacin and ofloxacin (0.4 to 0.6) than for the other quinolones, which all had similar penetration rates (Table 2). Of note, of the quinolones examined ofloxacin and levofloxacin had the lowest levels of protein binding (~10%) (3). Indeed, there was an inverse trend ($r = -0.67$; $P < 0.1$) between the level of penetration at steady state of the different quinolones into CSF and their reported degrees of binding to human proteins (ciprofloxacin, 40%; temafloxacin, 26%; CP-99,219, 70%; Win 57273, 95%) (10, 12, 23). The speed of drug entry into CSF, as estimated by the ratio of the concentration in CSF at 1 h to that at 7 h, showed marked variation. It was slower for ceftriaxone (ratio of the concentration in CSF at 1 h to that at 7 h, 0.11) than for any of the quinolones (ratios were as follows: CP-99,219, 0.86; Win 57273, 0.76; ofloxacin, 0.67; levofloxacin, 0.65; temafloxacin, 0.62; and ciprofloxacin, 0.36). There was a strong positive correlation ($r = 0.91$; $P < 0.01$) between the velocity of entry into CSF and the reported lipophilicity of an antibiotic ($\log_{10}$ octanol/water partition coefficient at neutral pH for CP-99,219, 0.28 [10]; Win 57273, 1.12 [19]; ofloxacin and levofloxacin, −0.44 [31]; temafloxacin, 0.46 [12]; ciprofloxacin, −1.11 [12]; ceftriaxone, −4.30 [18]). No significant correlation was observed between the speed of entry and protein binding ($r = -0.18$; P was not significant).

In vivo activity. For comparison of the in vivo activities of the different study drugs, we analyzed the bactericidal activities in CSF of all drugs at the standard dose of 10 mg/kg · h. At this dose, ciprofloxacin did not inhibit bacterial growth in CSF (not different from the growth rate in saline-treated control animals; Table 3). All other antibiotics showed significant bactericidal activities ($P < 0.05$) compared with those of controls, but two groups with different degrees of activity emerged. Ofloxacin, levofloxacin, and temafloxacin showed moderate activity, with no significant difference between these three antibiotics, while CP-116,517, Win 57273, and ceftriaxone were significantly more bactericidal ($P < 0.05$), again without a significant difference between the three drugs in this group (Table 3). For each drug, increasing or decreasing the dose led to a corresponding change in the bactericidal activity which was statistically significant when compared with the bactericidal activity of the 10-mg/kg · h dose (Table 3). The relation-

TABLE 2. Concentrations of different quinolones and ceftriaxone in serum and CSF of rabbits with experimental meningitis caused by *S. pneumoniae*

Drug	Dose (mg/kg · h)	No. of animals	Concentration (μg/ml) in:					C^a in CSF at 7 h/C in serum at 7 h	C in CSF/MBC[b]
			Serum at 1 h	CSF at 1 h	Serum at 7 h	CSF at 7 h	CSF (mean)		
Ciprofloxacin	10	8	6.9 ± 2.1	0.5 ± 0.2	7.5 ± 2.4	1.6 ± 0.7	1.0 ± 0.5	0.21	0.25
	40	8	36.5 ± 9.4	3.5 ± 0.9	42.5 ± 16.6	10.7 ± 1.7	7.2 ± 2.3	0.25	1.8
Ofloxacin	10	14	11.3 ± 2.5	3.2 ± 1.3	13.2 ± 2.5	5.3 ± 1.6	3.8 ± 1.7	0.40	1.9
	40	10	42.4 ± 8.5	16.0 ± 3.3	48.6 ± 15.5	29.3 ± 7.5	23.0 ± 5.5	0.60	11.5
Levofloxacin	10	5	10.9 ± 3.7	4.2 ± 1.5	11.4 ± 4.2	6.9 ± 2.4	5.6 ± 1.5	0.61	5.6
	40	5	50.8 ± 4.7	17.3 ± 1.3	56.5 ± 9.4	27.9 ± 6.1	21.8 ± 3.6	0.49	21.8
Temafloxacin	10	8	9.0 ± 2.5	1.5 ± 1.5	11.5 ± 4.1	3.4 ± 1.4	2.4 ± 1.5	0.30	2.4
	40	9	36.1 ± 5.2	7.3 ± 1.7	45.8 ± 15.1	14.0 ± 2.6	11.0 ± 2.1	0.31	11.0
CP 99,219[c]	10	8	7.0 ± 1.6	1.6 ± 0.7	6.5 ± 2.3	1.8 ± 0.5	1.7 ± 0.5	0.27	6.8
	40	8	21.5 ± 6.0	3.8 ± 0.8	20.7 ± 13.7	4.3 ± 1.5	4.7 ± 1.1	0.21	18.8
Win 57273	2.5	8	6.0 ± 2.0	1.4 ± 0.5	6.3 ± 1.6	1.8 ± 1.0	1.7 ± 0.6	0.29	28.3
	10	10	21.1 ± 6.2	5.2 ± 1.2	21.2 ± 5.3	6.3 ± 2.1	5.8 ± 2.0	0.30	96.7
Ceftriaxone	1	12	12.1 ± 4.3	0.13 ± 0.1	14.1 ± 3.7	1.3 ± 1.2	0.74 ± 0.7	0.09	12.3
	10	12	61.9 ± 11.8	0.8 ± 0.6	57.1 ± 8.7	7.3 ± 6.4	5.0 ± 3.5	0.13	83.3

[a] C, concentration.
[b] Mean concentration in CSF/MBC.
[c] Infused as the prodrug CP-116,517.

ship between dose and bactericidal activity was further confirmed by correlating the mean concentration in the CSF of individual animals with the bactericidal activity. The positive correlation between these two parameters was significant for all drugs except CP-116,517 (ciprofloxacin, $r = 0.59$; ofloxacin, $r = 0.92$; levofloxacin, $r = 0.75$; temafloxacin, $r = 0.89$; CP-116,517, $r = 0.40$; Win 57273, $r = 0.75$). We then analyzed the relationship between CSF drug concentrations and bactericidal activity in CSF for the examined quinolones as a group by normalizing the concentration in CSF to the MBC of each drug. The relation between bactericidal activity and the corresponding concentration in CSF/MBC ratio was adequately described for the whole group by a sigmoid E_{max} model. In this model, the maximum bactericidal rate was 0.70 (coefficient of variation, 16.1%), the mean concentration in CSF/MBC ratio producing half-maximal killing was 3.9 (coefficient of variation, 39.8%), and the Hill coefficient was 1.94.

TABLE 3. Bacterial killing in CSF by different quinolones and ceftriaxone in experimental meningitis caused by *S. pneumoniae*[a]

Drug	Dose (mg/kg · h)	Initial titer in CSF ($\log_{10}$ CSF/ml)	Bactericidal activity ($\Delta\log_{10}$ CFU/ml · h)
Saline ($n = 20$)		5.64 ± 076	+0.22 ± 0.09
Ciprofloxacin	10	5.48 ± 0.71	+0.20 ± 0.14
	40	5.41 ± 0.9	−0.24 ± 0.26
Ofloxacin	10	5.84 ± 0.69	−0.13 ± 0.12
	40	5.15 ± 0.97	−0.63 ± 0.12
Levofloxacin	10	6.31 ± 1.1	−0.24 ± 0.16
	40	5.68 ± 0.85	−0.73 ± 0.16
Temafloxacin	10	5.67 ± 0.94	−0.19 ± 0.18
	40	5.73 ± 0.78	−0.81 ± 0.12
CP-116,517	10	6.18 ± 0.87	−0.59 ± 0.21
	40	5.98 ± 0.75	−0.84 ± 0.25
Win 57273	2.5	5.54 ± 0.41	−0.35 ± 0.10
	10	5.41 ± 0.54	−0.72 ± 0.20
Ceftriaxone	1	5.97 ± 0.75	−0.57 ± 0.24
	10	5.39 ± 0.66	−0.80 ± 0.17

[a] At 10 mg/kg · h, ceftriaxone = Win 57273 = CP-116,517 > temfloxacin = levofloxacin = ofloxacin > ciprofloxacin = controls ($>P < 0.05$). $P < 0.05$ for comparison of the different dosages for each drug.

DISCUSSION

The development of new quinolones that have substantially improved in vitro activities against gram-positive pathogens, including pneumococci, prompted us to characterize in detail the activity of this class of antibiotics in a model of pneumococcal meningitis. Although our experiments were performed with our standard pneumococcal strain that is penicillin susceptible (32, 33), the results are likely to be relevant for the treatment of meningitis caused by β-lactam-resistant pneumococci as well, since quinolone activity is not affected by the development of resistance to penicillin or cephalosporins (29, 30).

Previous experimental and clinical studies have indicated that quinolones reach higher concentrations in CSF relative to the concentrations in serum than β-lactam antibiotics (5, 8, 26). The present study confirms this finding for all of the quinolones studied, including the new compounds CP-99,219 and Win 57273. At the 7-h time point, all quinolones showed concentrations in CSF in excess of 20% of the simultaneous concentrations in serum, whereas the value was 9 to 13% for ceftriaxone. The other β-lactams studied in the same model also consistently failed to achieve penetration rates similar to

those observed with the quinolones (32, 33). The passive entry of antibiotics into the CSF is largely determined by the lipophilicity of a drug, its binding to serum proteins, and its molecular size (22, 24). The overall lipophilicity of quinolones is likely responsible for their good penetration into CSF compared with the penetration of the more hydrophilic β-lactams. The lipophilicity of individual quinolones furthermore appeared to be the predominant determinant of the speed or velocity of entry into CSF during the time of steady-state concentrations in serum. Entry velocity and steady-state penetration into CSF appeared to be independent parameters for each drug (e.g., ofloxacin and levofloxacin had high levels of penetration at steady state and low penetration velocities, whereas CP-99,219 had a high penetration velocity and low levels of penetration at steady state). Our results suggest that a very low level of protein binding favored a high level of steady-state penetration into CSF when we compared individual quinolones.

Older quinolones have excellent activity against gram-negative organisms and have been successfully used for the treatment of gram-negative bacillary meningitis in animal models (13, 26, 27). In humans, a favorable outcome has been reported after therapy with ciprofloxacin for central nervous system infections caused by *Pseudomonas* spp. (14, 20). On the other hand, the activities of the quinolones available for clinical use are insufficient for treating central nervous system infections caused by gram-positive organisms (26). In our model, ciprofloxacin doses resulting in concentrations in CSF of about 1 μg/ml not only were not bactericidal but failed to show even bacteriostatic activity. It is tempting to speculate that this lack of activity against pneumococci in CSF is related to the anecdotal observations of patients who developed pneumococcal meningitis while being treated with ciprofloxacin for other infections (16). Quinolones with slightly improved in vitro activities against the pneumococcus (ofloxacin, levofloxacin, and temafloxacin) showed moderate bactericidal activities at concentrations in CSF that can be achieved in the CSF of humans. Whether this degree of activity is sufficient to adequately treat pneumococcal meningitis is uncertain, but it appears likely that it is sufficient to prevent the development of pneumococcal meningitis during therapy for other infections. The two newest quinolones studied appeared to have significantly improved in vivo activities against the pneumococcus. At a dose of 10 mg/kg · h, both Win 57273 and CP-116,517 were not significantly less effective than ceftriaxone at the same dose.

With β-lactam antibiotics, we and others have found a consistent positive correlation between concentrations in CSF relative to the MBC and bactericidal activity in CSF. Maximum bactericidal activity occurred at concentrations in CSF of at least 10 to 30 times greater than the MBC (32, 33). A similar correlation between the concentration in CSF relative to in vitro activity and the bactericidal rate in CSF was found for quinolones in the present study. Mean concentrations in CSF below about four times the MBC were generally associated with only moderate bactericidal rates in CSF. Using the sigmoid E_{max} model, we estimated a maximal bactericidal rate for these drugs of $-0.70\ \Delta\log_{10}$ CFU/ml · h. A mean concentration in CSF 3.9 times greater than the MBC was necessary to produce a half-maximal bactericidal rate. Win 57273 at the low dose examined appeared to be less effective than estimated by its concentration in CSF/MBC ratio. Win 75273 showed the highest level of protein binding of all of the quinolones examined in the present study (~95%) (23), and it is conceivable that binding to CSF proteins affected its bactericidal activity at lower doses. Such an effect on highly protein-bound drugs has previously been suggested in a study of the use of cephalosporins for the treatment of experimental meningitis (25).

In vitro studies with *E. coli* exposed to different concentrations of quinolones demonstrated maximum bacterial killing rates at concentrations between 30 and 40 times greater than the MIC. At higher concentrations, the drugs lost some of their bactericidal activity (28). This was thought to be due to the inhibition of protein synthesis by very high doses of quinolones, resulting in bacteria less susceptible to the lethal effects of the drug. In the present study, most drugs achieved maximal concentrations in CSF in excess of the MBC of between 10- and 30-fold (corresponding to MIC ratios of between 20- and 60-fold). At these concentrations, no reduction in bacterial killing but rather a concentration-dependent increase in bacterial killing was observed for all quinolones. These results indicate that with the concentrations in CSF examined in the model described here, which exceeded in part those likely to be observed in humans, no paradoxical bactericidal effect occurred. Similarly, in the rat model of *Pseudomonas* sepsis, a small increase in survival was observed when the peak concentration in serum/MIC ratio was increased from 21 to 42 (4).

In conclusion, contrary to the low levels of activity of older quinolones against pneumococci at concentrations achievable in the CSF, the investigation of new quinolones in the rabbit model of *S. pneumoniae* meningitis demonstrated rapid bactericidal activity comparable to that achieved with ceftriaxone. This improved effectiveness was a reflection of the markedly improved in vitro activities of these new drugs and of their favorable pharmacokinetics in CSF. Since resistance to β-lactams does not affect the activities of quinolones, new quinolones appear to be promising for the therapy of pneumococcal meningitis caused by organisms resistant to β-lactams. Clinical studies will have to substantiate this beneficial activity and assess the safety profiles of these drugs in the therapy of meningitis.

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