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Susceptibilities of Penicillin-Susceptible and -Resistant Strains of *Streptococcus pneumoniae* to RP 59500, Vancomycin, Erythromycin, PD 131628, Sparfloxacin, Temafloxacin, Win 57273, Ofloxacin, and Ciprofloxacin

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The MICs of four new quinolones, sparfloxacin (AT-4140, CI-978), PD 131628 (the active form of the prodrug CI-990), temafloxacin, and Win 57273, compared with those of ciprofloxacin and ofloxacin were tested against 53 penicillin-susceptible, 35 penicillin intermediate-resistant, and 51 penicillin-resistant pneumococci. Susceptibility to RP 59500, a new streptogramin, was also tested and compared with those to the quinolones, erythromycin, and vancomycin. All MICs were determined by a standardized agar dilution method by using Mueller-Hinton agar supplemented with sheep blood. Quinolone, vancomycin, and RP 59500 susceptibilities were not affected by susceptibility or resistance to penicillin. For Win 57273, the MICs for 50% (MIC_{50}) and 90% (MIC_{90}) of strains tested were 0.015 and 0.03 μg/ml, respectively. MIC_{50}s of both sparfloxacin and PD 131628 were 0.25 μg/ml, and MIC_{90}s were 0.5 μg/ml. The MIC_{50} of temafloxacin was 0.5 μg/ml, and the MIC_{90} was 1.0 μg/ml. By comparison, ofloxacin and ciprofloxacin both yielded MIC_{50}s of 1.0 μg/ml and MIC_{90}s of 2.0 μg/ml. RP 59500 yielded an MIC_{50} of 0.5 μg/ml and an MIC_{90} of 1.0 μg/ml and was only 1 doubling dilution less active against 17 erythromycin-resistant strains. Vancomycin was active against all strains (MIC_{50}, 0.25 μg/ml; MIC_{90}, 0.5 μg/ml). All four experimental quinolones as well as RP 59500 show promise for therapy of infections with penicillin-resistant and -susceptible pneumococci.

Streptococcus pneumoniae continues to be a significant cause of morbidity and mortality in humans. Although this organism was originally exquisitely susceptible to penicillin, the last two decades have witnessed the emergence of strains resistant to penicillin as well as other antimicrobial agents in many parts of the world (2, 34, 37).

Under certain conditions, nonmeningitic infections caused by *S. pneumoniae* for which penicillin MICs are intermediate and resistant may be successfully treated with high doses of β-lactam antibiotics, such as penicillin. However, treatment may not always be successful. High doses of potentially toxic alternative antibiotics may lead to unwanted side effects (37). In contrast, clinical failure of penicillin in the treatment of meningitis caused by intermediate penicillin-resistant strains approaches 80%, and no cases of meningitis caused by penicillin-resistant strains have responded to penicillin (34).

The existing quinolones, such as ciprofloxacin and ofloxacin, are less potent against gram-positive than against gram-negative aerobic organisms (3). This study examines the in vitro antipneumococcal activities of four new quinolones, sparfloxacin (CI-978, AT-4140), PD 131628 (the active form of the prodrug CI-990), Win 57273, and temafloxacin, with expanded activity against gram-positive organisms compared with the activities of ofloxacin and ciprofloxacin. The activity of RP 59500, a new streptogramin antibiotic, was also tested and compared with those of the quinolones, erythromycin, and vancomycin.

One hundred thirty-nine clinical isolates of *S. pneumoniae*, which were obtained from blood, cerebrospinal fluid (CSF), nasopharynx, or sputum, were used in this study. The organisms comprised 53 penicillin-susceptible, 35 penicillin intermediate-resistant, and 51 penicillin-resistant strains. Penicillin-susceptible strains (MICs, <0.1 μg/ml) were obtained from the University Hospitals of Cleveland and Hershey Medical Center. The majority of penicillin intermediate-resistant (MICs, 0.1 to 1.0 μg/ml) and -resistant (MICs, ≥2 μg/ml) strains were isolated in South Africa and Spain. Organisms were identified by colonial morphology and susceptibility to optochin, bile solubility, and capsular typing (21, 34). MICs of sparfloxacin, PD 131628 (Parke-Davis Pharmaceuticals, Ann Arbor, Mich.), temafloxacin, erythromycin (Abbott Laboratories, Chicago, Ill.), Win 57273 (Sterling Research Laboratories, Rensselaer, N.Y.), ofloxacin (Ortho Pharmaceuticals, Raritan, N.J.), ciprofloxacin (Miles Laboratories, West Haven, Conn.), RP 59500 (Rhône-Poulenc Rorer Laboratories, Paris, France), and vancomycin (Lilly Laboratories, Indianapolis, Ind.) were determined by the agar dilution method with an inoculum of 10^4 CFU per spot by using Mueller-Hinton agar (BBL) supplemented with 5% sheep blood (27). For MIC testing, suspensions with a turbidity equivalent to that of a 0.5 McFarland standard were prepared by suspending growth from blood agar plates in 2 ml of Mueller-Hinton broth. Suspensions were further diluted 1:100 to obtain a final inoculum of 10^4 organisms in 2 μl. Plates were inoculated by using a Steers replicator with 3-mm-diameter inoculating pins and were incubated overnight at 37°C. Quality control strains (*Staphylococcus aureus* ATCC 29213, *Escherichia coli* ATCC 25922, *Enterococcus faecalis* ATCC 29212, and a known penicillin-susceptible strain of *S. pneumoniae*, WRU 294) were included in each run.

Susceptibility data are presented in Table 1. All six quinolones showed similar susceptibility patterns against

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TABLE 1. In vitro susceptibilities of 139 pneumococci

Antimicrobial agent	MIC (μg/ml)		
	Range	50%	90%
Penicillin G			
Susceptible (53)[a]	0.008–0.06	0.015	0.03
Intermediate (35)	0.125–1.0	0.25	1.0
Resistant (51)	2.0–4.0	2.0	4.0
Erythromycin			
Penicillin susceptible	<0.06–2.0	<0.06	2.0
Penicillin intermediate	<0.06–>128	<0.06	>128.0
Penicillin resistant	>0.06–>128	0.25	>128.0
Erythromycin susceptible	<0.06–1.0	<0.06	0.25
Erythromycin resistant	16.0–>128	>128.0	>128.0
Sparfloxacin[b]	<0.004–2.0	0.25	0.5
PD 131628[b]	<0.004–2.0	0.25	0.5
Temafloxacin[b]	0.125–1.0	0.5	1.0
Win 57273[b]	<0.004–0.125	0.015	0.03
Ofloxacin[b]	0.5–4.0	1.0	2.0
Ciprofloxacin[b]	0.25–4.0	1.0	2.0
RP 59500			
Penicillin susceptible	<0.125–2.0	0.25	1.0
Penicillin intermediate	<0.125–2.0	0.5	1.0
Penicillin resistant	<0.125–2.0	1.0	1.0
Erythromycin susceptible	<0.125–2.0	0.5	1.0
Erythromycin resistant	1.0–2.0	1.0	2.0
Vancomycin[b]	<0.03–1.0	0.25	0.5

[a] Values in parentheses are number of strains tested.
[b] Values for penicillin-susceptible, intermediate-resistant, and -resistant strains were identical.

penicillin-susceptible, intermediate-resistant, and -resistant strains. Win 57273 was the most active; this was followed by sparfloxacin and PD 131628 and then temafloxacin. Both ciprofloxacin and ofloxacin were less active against pneumococci, with MICs clustering around their respective breakpoints. All strains were susceptible to RP 59500 (MICs, ≤2 μg/ml); the MICs for 50% (MIC_{50}s) and 90% (MIC_{90}s) of strains tested were 0.5 and 1.0 μg/ml, respectively. MIC_{50}s and MIC_{90}s of RP 59500 against 17 erythromycin-resistant pneumococci (MICs ≥ 16 μg/ml) were 1 and 2 μg/ml, respectively, i.e., 1 doubling dilution higher than those seen against 122 erythromycin-susceptible strains. All strains were susceptible to vancomycin. All penicillin-susceptible strains were susceptible to erythromycin (MIC_{90}s of 2 μg/ml), but greater rates of erythromycin resistance were observed against penicillin intermediate-resistant and penicillin-resistant strains (MIC_{90}s of >128 μg/ml for both groups). Erythromycin-resistant strains made up 7 of 35 of penicillin intermediate-resistant (20.0%) and 10 of 51 of penicillin-resistant (19.6%) strains.

In recent studies, in vitro activity superior to that of penicillin G against penicillin-resistant strains of *S. pneumoniae* has been demonstrated for cefotaxime, cefoperazone, imipenem, ceftriaxone, vancomycin, coumermycin, novobiocin, daptomycin, and teicoplanin (3, 13, 23, 34, 38, 39). Results of this study add PD 131628, sparfloxacin, temafloxacin, Win 57273, and RP 59500 to this list. All quinolones as well as RP 59500 had in vitro activities which were unaffected by the penicillin susceptibility status of pneumococcal strains.

Data on the distribution of ciprofloxacin in the body have been reported (16, 17, 40). Following a 500-mg oral dose of ciprofloxacin, peak concentrations in serum of 1.9 to 2.9 μg/ml are obtained, with a terminal half-life of 3.3 to 4.9 h. Corresponding values after a 600-mg oral dose of ofloxacin are 11 μg/ml and 7.0 h, respectively (16, 17). Although the overall susceptibility of ciprofloxacin against resistant and susceptible pneumococci in our study approached the susceptibility breakpoint (9, 24, 35), a good response to ciprofloxacin in the treatment of respiratory tract infections, including those caused by penicillin-resistant strains, has been reported by some investigators (30). However, there is no general agreement on the latter finding. Although ciprofloxacin has been used in the treatment of *Pseudomonas aeruginosa* ventriculitis (18), the levels achievable in uninflamed CSF (0.13 to 0.3 μg/ml, in comparison with levels in serum of 2.09 to 3.04 μg/ml) show that levels of drug may not be adequate for gram-positive organisms (25). By comparison, peak ofloxacin concentrations in serum of 2.0 to 3.5 μg/ml were found immediately after a 200-mg intravenous infusion, and peak concentrations in serum of 1.7 to 4.0 μg/ml were found 1 to 2 h after oral administration of the same dose. Peak concentrations of 0.4 to 1.0 μg/ml were observed in CSF 2 to 4 h after infusion or oral administration. However, low or no bactericidal titers against *S. pneumoniae* were obtained in CSF (6).

Sparfloxacin is a chemically novel fluoroquinolone with broad spectra of activity against gram-positive and -negative bacteria, including *Legionella* species and *Bacteroides fragilis*. The activity of sparfloxacin against gram-positive organisms is higher than those of ofloxacin and ciprofloxacin (8, 22, 26). Peak concentrations of sparfloxacin in human plasma of 0.44, 0.65, and 1.4 μg/ml were observed 2.5 to 4.5 h following single oral doses of 100, 200, and 400 mg, respectively; the elimination half-life was approximately 16 to 17 h for the three single doses given above. Except for brain, CSF, and testes, levels in rat tissue are 2- to 10-fold higher than levels in plasma (32). After multiple oral doses of 300 mg in humans, mean sparfloxacin levels of 0.56 μg/ml were found in CSF, whereas levels of 1.52 μg/ml were found in serum (5). PD 131628, a new aminopyrrolidine-substituted naphthyridine quinolone, also possesses a high level of in vitro activity against gram-positive as well as gram-negative bacteria (7). No human pharmacokinetic data are available for PD 131628 (5).

Temafloxacin is a new aryl fluoroquinolone with expanded activity against gram-positive and -negative organisms and *Legionella* species (4, 15, 28). The peak concentration of temafloxacin in human serum after oral administration is significantly higher than that of ciprofloxacin. In humans, steady-state peak levels in plasma after 600-mg twice-daily dosing are attained approximately 2 h postdose, with the mean peak level reaching 7.1 μg/ml (range, 4.5 to 9.7 μg/ml). Thereafter, concentrations decline slowly to a mean of 3.4 μg/ml (range, 2.3 to 4.6 μg/ml) at 12 h, with the mean plasma elimination half-life being 8.4 h. Preliminary concentrations of temafloxacin in human CSF after two oral 600-mg doses do not point to clinical use (14, 28, 33).

Win 57273 is a new broad-spectrum 7-dimethylpyridinyl quinolone with greater activity against gram-positive organisms than the activity of ciprofloxacin or ofloxacin; the compound is also active against *Legionella* species (10, 19, 20, 31). Pharmacokinetic data in rats revealed maximum

concentrations of drug in serum of 1.53, 3.49, and 16.5 μg/ml after subcutaneous, oral, and intravenous administration of doses of 25 mg/kg of body weight, respectively; terminal half-lives with these three dosage routes were 1.9, 2.8, and 7.5 h, respectively. No data on cerebrospinal penetration or human pharmacokinetic data for Win 57273 are available (29), and further development of this drug may be in doubt.

RP 59500 is a new injectable streptogramin that is made up of a combination of derivatives of pristinamycin I_A and pristinamycin II_A. RP 59500 is very active against gram-positive cocci (with the exception of enterococci), gram-positive aerobic rods, *Neisseria gonorrhoeae*, *Legionella* species, and anaerobes (1, 11, 12, 36). Pharmacokinetic studies in humans are in progress. Erythromycin resistance is increasingly seen in pneumococci (21), and antimicrobial agents that are active against these strains, including RP 59500 and the newer quinolones, will assume greater clinical importance.

Results of this study combined with existing pharmacokinetic data in humans indicate a potential place for all four experimental quinolones as well as RP 59500 in the treatment of nonmeningitic infections caused by penicillin-susceptible or -resistant pneumococci. More pharmacokinetic data in humans are required before conclusions about the value of quinolones against meningitis caused by these strains can be drawn.

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