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In Vitro Activity of a New Fluoroquinolone, CP-99,219, against Strains of *Neisseria gonorrhoeae*

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The susceptibilities of 216 strains of *Neisseria gonorrhoeae* to a new fluoroquinolone, CP-99,219 were determined. For strains for which the MICs of ciprofloxacin were ≤0.06 μg/ml, the MICs at which 90% of the isolates are inhibited (MIC_{90}s) of CP-99,219, ciprofloxacin, and ofloxacin were 0.008, 0.015, and 0.03 μg/ml, respectively. For strains for which the MICs of ciprofloxacin were 0.125 to 0.5 μg/ml, the MIC_{90}s of CP-99,219, ciprofloxacin, and ofloxacin were 0.06, 0.25, and 0.5 μg/ml, respectively. For strains for which the MICs of ciprofloxacin and ofloxacin were 2.0 μg/ml, the MIC of CP-99,219 was 0.25 μg/ml.

Although the number of reported cases of gonorrhea in the United States has decreased since the mid-1980s, the proportion caused by antimicrobial agent-resistant strains of *Neisseria gonorrhoeae* has increased (2, 4). Because of penicillin and tetracycline resistance in *N. gonorrhoeae*, the Centers for Disease Control and Prevention recommended in 1993 that broad-spectrum cephalosporins and fluoroquinolones be used to treat uncomplicated gonorrhea (1). Strains exhibiting decreased susceptibilities to ciprofloxacin and ofloxacin have been reported from Asia, the United Kingdom, the United States, and Canada (3–8). A strain that failed to respond to treatment with ciprofloxacin (500 mg) for which the MIC of ciprofloxacin was 1.0 μg/ml has been isolated in Australia (12). The emergence of resistant strains may limit the future usefulness of fluoroquinolones; more-active agents will be required to kill all gonococcal strains. We determined the in vitro activity of a new fluoroquinolone, CP-99,219, against *N. gonorrhoeae* strains, including strains with decreased susceptibilities to ciprofloxacin.

A total of 216 strains of *N. gonorrhoeae* were tested. These strains represented five distinct resistance phenotypes according to their susceptibilities to penicillin and tetracycline, β-lactamase production (penicillinase-producing *N. gonorrhoeae* [PPNG]), and the presence of the TetM determinant (strains with plasmid-mediated resistance to tetracycline [TRNG]) as defined previously (10, 11) (Table 1) and included 183 strains for which the MIC of ciprofloxacin was ≤0.06 μg/ml, 30 strains for which the MICs of ciprofloxacin were 0.125 to 0.5 μg/ml, and 3 strains for which the MIC of ciprofloxacin was 2.0 μg/ml. PPNG strains included 35 of 69 (50.7%), 17 of 69 (24.6%), and 16 of 69 (23.2%) strains possessing 3.2-, 4.4-, or 3.05-MDa plasmids, respectively. All PPNG strains with plasmid-mediated resistance to tetracycline due to the TetM determinant (PP/TR strains) possessed a 3.2-MDa plasmid.

The strains were isolated in the following 23 localities in the United States: Honolulu, Hawaii (44 strains); Cleveland, Ohio (25 strains); Baltimore, Md. (20 strains); West Palm Beach, Fla. (14 strains); New Orleans, La. (13 strains); Atlanta, Ga. (12 strains); Birmingham, Ala. (12 strains); Cincinnati, Ohio (12 strains); Orange County and San Diego, Calif. (11 strains each); Long Beach County, Calif. (7 strains); Boston, Mass. (5 strains); San Antonio, Tex. (5 strains); Denver, Colo. (4 strains); Muskegon, Mich. (3 strains); Nassau County, N.Y. (3 strains); Philadelphia, Pa. (3 strains); Phoenix, Ariz. (3 strains); Portland, Oreg. (3 strains); San Francisco, Calif. (3 strains); Seattle, Wash. (1 strain); St. Louis, Mo. (1 strain); and Tacoma, Wash. (1 strain). The strains belonged to a total of 45 auxotype/serovar (A/S) classes as follows: Pen^s isolates, 19 A/S classes; strains with chromosomally mediated resistance to penicillin and tetracycline (CMRNG), 16 A/S classes; PPNG, 33 A/S classes; TRNG, 13 A/S classes); and PP/TR strains, 12 A/S classes.

Agar dilution susceptibilities to ciprofloxacin, ofloxacin, and CP-99,219 were determined as described previously (10, 11). The antimicrobial agents were obtained as standard powders for in vitro susceptibility testing from Miles, West Point, Conn. (ciprofloxacin); Ortho Pharmaceutical Corp., Raritan, N.J. (ofloxacin); and Pfizer Central Research, Groton, Conn. (CP-99,219). Susceptibilities were determined on GC II agar base medium (Becton Dickinson, Cockeysville, Md.) supplemented with 1% IsoVitaleX (Becton Dickinson) and containing twofold dilutions of each antimicrobial agent. Inocula were prepared by suspending growth from chocolate agar medium in Mueller-Hinton broth to a density equivalent to a 0.5 McFarland standard and were diluted 1:10 in Mueller-Hinton broth. Media were inoculated with a multipoint replicator (Cathra Systems; Automed, Arden Hills, Minn.), which delivered an inoculum of approximately 10^4 CFU (9). A plate without antibiotics was included to indicate growth of all isolates. Plates were incubated for 24 h at 35 to 36°C in a CO_2-enhanced (5%) atmosphere. *N. gonorrhoeae* ATCC 49226, which met the acceptable quality control range recommended by the National Committee for Clinical Laboratory Standards (9), and three additional gonococcal strains (F-28 [spectinomycin resistant], F-45 [CMRNG], and P681E [PP/TR]) were included in each susceptibility test run (10, 11). The MIC of an agent for each isolate was defined as the lowest concentration inhibiting growth to ≤1 CFU. The MICs were interpreted according to the recommendations of the National Committee for Clinical Laboratory Standards (9).

The MIC at which 90% of the isolates are inhibited (MIC_{90}s) for ciprofloxacin-susceptible (MIC, ≤0.06 μg/ml)

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TABLE 1. Resistance phenotypes of *N. gonorrhoeae* strains tested for in vitro susceptibility to selected fluoroquinolone agents

Resistance phenotype[a]	Total no. of isolates	No. of isolates for which ciprofloxacin MIC (μg/ml) was:		
		≤0.06	0.125–0.5	2.0
Pen^s	30	28	2	
CMRNG	79	57	22	
PPNG	74	66	5	3
PP/TR	15	15		
TRNG	18	17	1	
Total	216	183	30	3

[a] Pen^s, strains for which the penicillin and tetracycline MICs were <2.0 μg/ml. CMRNG (β-lactamase-negative strains lacking the TetM determinant) includes 39 strains for which the penicillin and tetracycline MICs were ≥2.0 μg/ml and 40 strains for which the penicillin or tetracycline MIC was ≥2.0 μg/ml and the corresponding tetracycline or penicillin was <2.0 μg/ml.

strains belonging to the Pen^s, TRNG, and PP/TR resistance phenotypes was 0.004 μg/ml for ciprofloxacin and CP-99,219 compared with 0.015 μg/ml for ofloxacin (Table 2). In contrast, the MIC_{90}s for CMRNG were of 0.008 μg/ml for CP-99,219, 0.015 μg/ml for ciprofloxacin, and 0.03 μg/ml for ofloxacin. Overall, for PPNG isolates for which the MIC of ciprofloxacin was ≤0.06 μg/ml, the MIC_{90} of CP-99,219 was 0.008 μg/ml, the MIC_{90} of ciprofloxacin was 0.015 μg/ml, and the MIC_{90} of ofloxacin was 0.03 μg/ml. PPNG strains with 4.4- or 3.05-MDa plasmids had susceptibilities similar to those of CMRNG, whereas the MICs for PPNG strains possessing a 3.2-MDa plasmid were similar to those for the Pen^s, TRNG, and PP/TR strains. For strains for which the MIC of ciprofloxacin was ≥0.125 μg/ml, the MIC_{90} of ciprofloxacin and ofloxacin was 0.5 μg/ml and the MIC_{90} of CP-99,219 was 0.06 μg/ml. For strains for which the MIC of ciprofloxacin was 2.0 μg/ml, the MIC of CP-99,219 was 0.25 μg/ml.

CP-99,219 is more active in vitro than fluoroquinolones that are currently recommended for the primary treatment of uncomplicated gonorrhea (1). However, strains exhibiting decreased susceptibilities to ciprofloxacin also showed decreased susceptibilities to CP-99,219. Thus, the clinical application of CP-99,219 will depend on results of future clinical efficacy studies. The results of this study demonstrate that gonococcal strains belonging to different resistance phenotypes vary in their susceptibilities to fluoroquinolones and support our previous recommendations (10, 11) that newer antimicrobial agents be evaluated against isolates that represent all resistance phenotypes, particularly CMRNG. It is more important that strains adequately represent gonococcal resistance phenotypes than diverse geographic origins which may not include all resistance phenotypes. As fluoroquinolone agents are used widely to treat a wide spectrum of genitourinary infections, including uncomplicated and complicated gonococcal infections such as pelvic inflammatory disease, laboratories should

TABLE 2. Distribution, by ciprofloxacin MIC and resistance phenotype, of in vitro susceptibilities of 216 strains of *N. gonorrhoeae* to ciprofloxacin, ofloxacin, and CP-99,219

Ciprofloxacin MIC (μg/ml), resistance phenotype(s), and agent[a]	No. of isolates	No. of strains for which MIC (μg/ml) was:											MIC (μg/ml)[b]	
		≤0.001	0.002	0.004	0.008	0.015	0.03	0.06	0.125	0.25	0.5	1.0	≥2.0	50%	90%
2.0															
PPNG	3														
Ciprofloxacin													3		
Ofloxacin													3		
CP-99,219										3					
0.125–0.5															
Pen^s + TRNG	3														
Ciprofloxacin									1	1	1				
Ofloxacin										2	1				
CP-99,219						1	2								
CMRNG + PPNG	27														
Ciprofloxacin									10	2	10			0.5	0.5
Ofloxacin									1	7	19			0.5	0.5
CP-99,219				2			7	18						0.06	0.06
≤0.06															
Pen^s + TRNG + PP/TR	60														
Ciprofloxacin			49	11										0.002	0.004
Ofloxacin				2	46	12								0.008	0.015
CP-99,219		4	30	26	1									0.002	0.004
CMRNG	57														
Ciprofloxacin			5	9	24	18	1							0.015	0.015
Ofloxacin				1	4	35	17							0.03	0.03
CP-99,219			16	32	9									0.002	0.008
PPNG	66														
Ciprofloxacin			34	7	15	8	1	1						0.002	0.015
Ofloxacin				2	37	4	20	1	2					0.008	0.03
CP-99,219		7	33	17	7	1		1						0.002	0.008

[a] Pen^s, strains for which the MICs of penicillin and tetracycline were <2.0 μg/ml. CMRNG includes isolates for which the MICs of penicillin and tetracycline were ≥2.0 μg/ml and isolates for which the MIC of penicillin or tetracycline was ≥2.0 μg/ml with corresponding MIC of tetracycline or penicillin, respectively, of <2.0 μg/ml (10, 11).

[b] 50% and 90%, MICs for 50 and 90% of strains, respectively.

monitor the in vitro susceptibilities of gonococci to detect emerging resistance to the fluoroquinolones.

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