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Activities of Three Investigational Fluoroquinolones (BAY y 3118, DU-6859a, and Clinafloxacin) against *Neisseria gonorrhoeae* Isolates with Diminished Susceptibilities to Ciprofloxacin and Ofloxacin

C. J. CARLYN,† L. J. DOYLE, C. C. KNAPP, M. D. LUDWIG, AND J. A. WASHINGTON*

Department of Clinical Pathology, Section of Microbiology, The Cleveland Clinic Foundation, Cleveland, Ohio 44195-5140

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Between 1 January 1992 and 31 December 1993, our laboratory, as part of the Gonococcal Isolate Surveillance Project, found that 39 of 673 isolates of *Neisseria gonorrhoeae* from one local sexually transmitted diseases clinic demonstrated decreased susceptibilities to both ciprofloxacin and ofloxacin. The MICs of BAY y 3118, DU-6859a, and clinafloxacin at which 90% of the gonococci with decreased susceptibility to ciprofloxacin and ofloxacin were inhibited were all 0.016 μg/ml, which was eightfold higher than those for ciprofloxacin-susceptible gonococci. Our report substantiates prior observations that diminished susceptibility to one quinolone is often associated with diminished susceptibility to other quinolones.

Quinolones, including ciprofloxacin and ofloxacin, are currently recommended by the Centers for Disease Control and Prevention as alternative therapy for uncomplicated *Neisseria gonorrhoeae* infection. Their excellent in vitro activity, oral bioavailability, penetration into genitourinary fluids and tissues, safety, and efficacy and the convenience of a single oral dose have made them excellent choices for alternative therapy. Numerous studies have demonstrated their efficacy to be comparable to or better than that of ceftriaxone (2, 10, 14, 15).

In vitro studies have demonstrated that mutants of *N. gonorrhoeae* with reduced susceptibility to the quinolones could be selected when susceptible isolates were serially passed through increasing concentrations of ofloxacin (7, 16). In 1991, small numbers ($n = 17$) of wild-type isolates of *N. gonorrhoeae* with diminished susceptibilities to ciprofloxacin and ofloxacin were encountered in Ohio, Hawaii, Texas, Alaska, California, New Mexico, and Massachusetts (8). Since that time, only Ohio and Hawaii have shown a persistence of these isolates. Of note, at the time of the report in the 1994 *Morbidity and Mortality Weekly Report*, Hawaii had encountered only three more cases while Ohio had had 25 additional cases of gonococcal infections due to isolates with diminished quinolone susceptibility (3). Since the Hawaiian isolates are of Southeast Asian origin (3), it appears that the Ohio isolates may be endemic and may represent a unique phenomenon in the United States.

As a sentinel site for the Gonococcal Isolate Surveillance Project of the Centers for Disease Control and Prevention, our laboratory tested 673 gonococcal isolates from one local, urban sexually transmitted diseases clinic between 1 January 1992 and 31 December 1993. Of these 673 isolates, 39 (5.8%) had MICs greater than the susceptible breakpoint of ≤0.06 μg of ciprofloxacin per ml recommended by the National Committee for Clinical Laboratory Standards (13).

* Corresponding author. Mailing address: Department of Clinical Pathology, Section of Microbiology, The Cleveland Clinic Foundation, 9500 Euclid Ave., Cleveland, OH 44195-5140. Phone: (216) 444-4435. Fax: (216) 445-6984.

† Present address: 739 Thimble Shoals Blvd., Suite 101, Newport News, VA 23606.

The purpose of this study was to test the 39 local isolates with reduced ciprofloxacin susceptibility against five quinolones, including two established and three investigational fluoroquinolones, by the standard agar dilution method utilizing GC agar base as recommended by the National Committee for Clinical Laboratory Standards (13). The five drugs tested and their sources were ciprofloxacin and BAY y 3118 (Miles Pharmaceuticals, West Haven, Conn.), ofloxacin (Ortho-McNeil Pharmaceuticals, Raritan, N.J.), DU-6859a (Daichi, Tokyo, Japan), and clinafloxacin (Parke-Davis, Ann Arbor, Mich.). The concentrations tested ranged from 0.002 to 2.0 μg/ml. Twenty susceptible isolates and *N. gonorrhoeae* ATCC 4226 were also tested in the same manner. All isolates were also tested against penicillin, tetracycline, and ceftriaxone. The MICs of ciprofloxacin, ofloxacin, clinafloxacin, BAY y 3118, and DU-6859a for *N. gonorrhoeae* ATCC 4226 were 0.004, 0.008, ≤0.002, ≤0.002, and ≤0.002 μg/ml, respectively. All MICs for *N. gonorrhoeae* ATCC 4226 were within range.

The 39 isolates with decreased quinolone susceptibility required MICs of ciprofloxacin that were four- to sevenfold higher than those for the susceptible isolates (Table 1). The MICs at which 90% of the isolates tested were inhibited (MIC_{90}s) were 0.25 and ≤0.002 μg of ciprofloxacin per ml, respectively, for these groups (Table 1). The MICs of ofloxacin for the isolates with decreased quinolone susceptibility were five- to eightfold higher than those for the fully susceptible isolates (Table 1). The MIC_{90}s for these groups were 0.5 and 0.016 μg of ofloxacin per ml, respectively. The MIC_{90}s of BAY y 3118, DU-6859a, and clinafloxacin were all ≤0.002 μg/ml for ciprofloxacin-susceptible isolates and 0.016 μg/ml for those with decreased ciprofloxacin susceptibility (Table 1). Despite the higher MICs, all isolates were susceptible to these investigational quinolones, according to the proposed interpretive criteria for clinafloxacin and DU-6859a (5, 12). There are no published criteria for defining susceptibility of gonococci to BAY y 3118 as yet; however, for the purposes of this study, we have adapted the interpretive criteria that have been published for *Moraxella catarrhalis* and *Haemophilus* species (6).

None of the 39 isolates with decreased quinolone susceptibility were susceptible to penicillin, compared with 16% pen-

TABLE 1. Activity of antimicrobial agents against isolates of *Neisseria gonorrhoeae*

Organism type (no. of isolates) and drug	MIC range[a]	MIC_{50}	MIC_{90}
Susceptible to ciprofloxacin (20)			
Ciprofloxacin	≤0.002–0.004	≤0.002	≤0.002
Ofloxacin	0.004–0.016	0.004	0.016
BAY y 3118	≤0.002	≤0.002	≤0.002
DU-6859a	≤0.002	≤0.002	≤0.002
Clinafloxacin	≤0.002	≤0.002	≤0.002
Penicillin	0.03–32.0	0.25	16.0
Tetracycline	0.25–32.0	1.0	32.0
Ceftriaxone	≤0.001–0.015	0.004	0.015
Less susceptible to ciprofloxacin (39)			
Ciprofloxacin	0.064–0.25	0.125	0.25
Ofloxacin	0.125–1.0	0.125	0.5
BAY y 3118	0.004–0.016	0.004	0.016
DU-6859a	≤0.002–0.016	0.008	0.016
Clinafloxacin	0.004–0.032	0.004	0.016
Penicillin	0.5–4.0	2.0	2.0
Tetracycline	0.25–2.0	1.0	1.0
Ceftriaxone	0.015–0.125	0.06	0.06

[a] Units for MIC data are micrograms per milliliter.

icillin susceptibility among the ciprofloxacin-susceptible isolates. All of the penicillin-resistant isolates were β-lactamase negative (Cefinase; Becton Dickinson Microbiology Systems, Cockeysville, Md.). Only 2.5% of the isolates with diminished quinolone susceptibility were susceptible to tetracycline, in contrast with 32% among ciprofloxacin-susceptible isolates. Furthermore, although all isolates were susceptible to ceftriaxone, the 39 isolates with diminished quinolone susceptibility required MICs of ceftriaxone that were four- to eightfold higher than those for the ciprofloxacin-susceptible isolates (Fig. 1).

We found other reports in the literature which parallel our observations of cross-resistance between quinolones, beta-lactams, and tetracycline as well as diminished susceptibility to ceftriaxone. Additional susceptibility tests of the Cleveland isolates at the Centers for Disease Control and Prevention found them to have decreased susceptibility to enoxacin, lomefloxacin, and norfloxacin (3). Zenilman et al. (18) evaluated the susceptibilities of 200 gonococcal isolates to ciprofloxacin, ofloxacin, and OPC-17116 and found that those with chromosomally mediated resistance to penicillins and tetracycline required increased mean MICs of the quinolones. MICs of ceftriaxone were similarly higher for those isolates. Among 2,141 Australian isolates examined, 43 had decreased susceptibility to quinolones that was associated with higher levels of resistance to the beta-lactams and tetracycline (16).

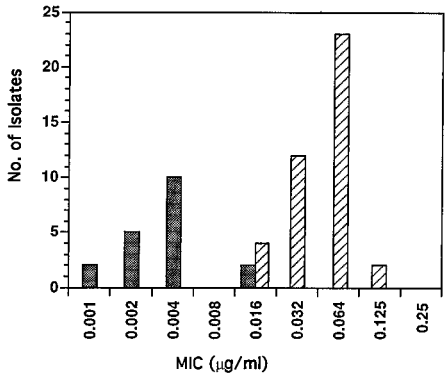

FIG. 1. Ceftriaxone MICs for ciprofloxacin-susceptible (▨) and less-susceptible (▨) *N. gonorrhoeae* isolates.

Jephcott and Turner (11) reported 18 isolates from across the United Kingdom submitted to the Public Health Laboratory Service National Gonorrhea Reference Unit with ciprofloxacin MICs of 0.05 to 0.25 μg/ml. Only two of these isolates had been acquired in the United Kingdom, while the rest were derived from Southeast Asia, Spain, the Canary Islands, and the West Indies. Of the 18 isolates, 17 were resistant to penicillin; of these, 16 were β-lactamase positive. Three of 23 quinolone-resistant isolates reported by Grandsen et al. (9) from London during 1989 had been acquired in the Philippines, while 19 were acquired in the United Kingdom.

Clendennen et al. (4) reported only one isolate resistant to ciprofloxacin in 1991 in the Philippines; however, resistance was defined by an MIC of ≥4 μg/ml. In fact, the MIC_{90} for susceptible organisms was 0.25 μg/ml. They did observe that the MIC_{90} of norfloxacin, although still considered within the susceptible range, was 16-fold higher than that reported in 1982.

The first reported cases of fluoroquinolone resistance in gonococci in North America were published in 1989 by Yeung and Dillon (17) from Ontario, Canada. Four resistant isolates were recovered from men who had acquired their infection outside of Canada, including Thailand and the Philippines.

There is scant information about the relationship between in vitro susceptibility of gonococci to ciprofloxacin and clinical efficacy. None of the 39 Cleveland patients was treated with a quinolone, and all denied use of quinolones within the preceding two weeks. To our knowledge, there have been no reports of quinolone treatment failure of gonorrhea in North America. Treatment failures have occurred in other parts of the world in cases where gonococcal isolates have required ciprofloxacin MICs of >0.125 μg/ml (1, 8). In a large study from Rwanda, treatment failure rates were 2.3% when the MIC of norfloxacin was ≤0.03 μg/ml, 9.3% when the MIC was 0.06 μg/ml, and 25% when the MIC was ≥0.125 μg/ml (1). Similarly, there were two treatment failures in the United Kingdom in patients given ciprofloxacin (single dose of 250 mg) for treatment of gonococci with ciprofloxacin MICs of 0.06 μg/ml (9).

In conclusion, although we have little to no clinical data on the clinical significance of gonococcal isolates in Cleveland with diminished susceptibilities to fluoroquinolones, the appearance of such isolates may preclude the empiric use of ciprofloxacin or ofloxacin as alternative therapy for the treatment of uncomplicated gonococcal infection. Unfortunately, the decreased susceptibilities of our isolates to ciprofloxacin and ofloxacin were also seen, albeit at lower concentrations, with newer, more active fluoroquinolones.

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