

Antibacterial Activities of OPC-17116, Ofloxacin, and Ciprofloxacin against 200 Isolates of *Neisseria gonorrhoeae*

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Received 31 March 1993/Returned for modification 9 June 1993/Accepted 29 July 1993

OPC-17116 is a new fluoroquinolone with potent activity against aerobic and anaerobic organisms. We evaluated the susceptibilities of 200 clinical gonococcal isolates including organisms with plasmid and chromosomally mediated resistance to β -lactams and tetracycline. The antibiotics studied included OPC-17116, ofloxacin, ciprofloxacin, penicillin, tetracycline, erythromycin, azithromycin, and ceftriaxone. All isolates tested were susceptible to the quinolone class of antibiotics. The MICs of ciprofloxacin, ofloxacin, and OPC-17116 for 90% of isolates tested were 0.004, 0.03, and 0.004 $\mu\text{g/ml}$, respectively. For organisms with chromosomally mediated resistance to penicillin and tetracycline, geometric mean MICs of all antibiotics including the quinolones were increased.

Antimicrobial resistance in *Neisseria gonorrhoeae* has evolved into a major public health problem, resulting in a shift from traditional penicillin- and tetracycline-based therapies to the use of cephalosporins and quinolones (5). Therefore, when evaluating in vitro activity, the inclusion of antimicrobial agent-resistant isolates is important.

OPC-17116 is a newly developed fluoroquinolone with potent in vitro activity against both aerobic and anaerobic gram-positive and gram-negative species (2, 4) and penetrates extensively into tissues (1). Because of these characteristics, OPC-17116 has the potential to be a useful antimicrobial agent in the treatment of genitourinary tract infections, including sexually transmitted bacterial infections caused by *N. gonorrhoeae* and *Chlamydia trachomatis*.

We evaluated the activities of OPC-17116, ciprofloxacin, ofloxacin, azithromycin, erythromycin, penicillin, tetracycline, and ceftriaxone against 200 strains of *N. gonorrhoeae*. Included in this isolate panel was a high proportion of organisms with plasmid-mediated penicillin resistance (penicillinase-producing *N. gonorrhoeae* [PPNG]), plasmid-mediated tetracycline resistance (tetracycline-resistant *N. gonorrhoeae* [TRNG]), and chromosomally mediated resistance (CMR) to penicillin and tetracycline.

The following antimicrobial agents in standard reagent powder form were supplied by the indicated manufacturers; OPC-17116 was from Otsuka America Pharmaceuticals (Rockville, Md.), ciprofloxacin was from Miles Laboratories (West Haven, Conn.), ofloxacin was from Ortho Pharmaceuticals (New Brunswick, N.J.), ceftriaxone was from Hoffmann-La Roche (Nutley, N.J.), azithromycin was from Pfizer (New York, N.Y.), tetracycline was from Lederle (Pearl River, N.Y.), and penicillin was from Lilly (Indianapolis, Ind.). Gonococcal isolates were obtained from sexually transmitted disease clinics in Baltimore as part of the surveillance program in 1990 and 1991 done by the Centers for Disease Control and Prevention (7). Antimicrobial resistance was classified as PPNG, TRNG, CMR, or susceptible by a

variation of the classification scheme of the Centers for Disease Control and Prevention and the National Committee for Clinical Laboratory Standards (3). Organisms with CMR were classified as those for which penicillin and tetracycline MICs were $\geq 1.0 \mu\text{g/ml}$; these represent multi-drug-resistant isolates. Of the 200 strains evaluated, 37 had plasmid-mediated penicillin resistance (PPNG), 34 had plasmid-mediated tetracycline resistance (TRNG), 21 were PPNG-TRNG combination strains, 70 had CMR, and 38 were susceptible isolates. The quality control organisms F18, F29, F45, and 76061782 of the Centers for Disease Control and Prevention were included in all susceptibility runs. All strains were confirmed as *N. gonorrhoeae* by using monoclonal fluorescent-antibody reagents (Gonocheck; Syva, Palo Alto, Calif.). Agar dilution susceptibility testing (3) was performed by using GC Agar II Base (BBL, Cockeysville, Md.) supplemented with 1% IsoVitalX (BBL). MIC frequency distributions and statistical calculations were performed by using PC-SAS 6.03 software (SAS Institute, Cary, N.C.).

Results of the susceptibility evaluation are given in Table 1. Organisms with plasmid-mediated resistance (PPNG, TRNG, and PPNG-TRNG) were uniformly susceptible to all antibiotics tested except penicillin and tetracycline. However, the MICs of some active antimicrobial agents such as tetracycline for these organisms with plasmid-mediated penicillin resistance were typically greater than those for organisms in the susceptible group. For example, the geometric mean MIC of tetracycline was 2.0 $\mu\text{g/ml}$ for PPNG organisms, whereas it was 0.694 $\mu\text{g/ml}$ for the susceptible group of organisms.

All organisms were susceptible to ceftriaxone. MICs of ceftriaxone were greater than those reported in previous studies from 1987 to 1989 (6). Between 1987 and 1989, the MIC of ceftriaxone for 50% of organisms tested (MIC_{50}) was 0.004 $\mu\text{g/ml}$; in 1990 and 91, the MIC_{50} was 0.015 $\mu\text{g/ml}$. The geometric mean MIC of ceftriaxone for CMR organisms was significantly greater than those for the plasmid-mediated organisms or susceptible strains ($P < 0.001$ by t test of the logarithm of the MIC for each comparison). Similarly, MICs

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TABLE 1. MIC distributions for 200 isolates of *N. gonorrhoeae*^a

Isolate and drug	MIC ($\mu\text{g/ml}$)			
	Geometric mean	50%	90%	Range
PPNG (<i>n</i> = 37)				
OPC	0.002	0.002	0.004	0.001–0.008
OFX	0.014	0.015	0.015	0.008–0.06
CIP	0.004	0.004	0.004	0.002–0.015
AZI	0.072	0.060	0.25	0.03–0.25
ERY	0.195	0.125	0.5	0.03–2
PEN	29.8	32	64	4–64
TET	2.0	1	1	0.5–4
CTR	0.006	0.008	0.008	0.002–0.03
PPNG-TRNG (<i>n</i> = 21)				
OPC	0.002	0.002	0.002	0.001–0.008
OFX	0.016	0.015	0.015	0.008–0.03
CIP	0.003	0.004	0.004	0.002–0.004
AZI	0.039	0.03	0.06	0.03–0.125
ERY	0.138	0.125	0.125	0.125–0.5
PEN	32.0	32	32	16–64
TET	19.4	16	32	16–32
CTR	0.006	0.008	0.008	0.004–0.008
TRNG (<i>n</i> = 34)				
OPC	0.002	0.002	0.004	0.002–0.004
OFX	0.014	0.008	0.015	0.008–0.015
CIP	0.003	0.004	0.004	0.002–0.004
AZI	0.116	0.125	0.25	0.06–0.5
ERY	0.401	0.50	0.50	0.125–0.5
PEN	0.360	0.25	1.0	0.125–0.5
TET	27.1	32	32	16–32
CTR	0.008	0.008	0.015	0.004–0.015
Susceptible (<i>n</i> = 38)				
OPC	0.002	0.002	0.004	0.001–0.008
OFX	0.013	0.015	0.015	0.008–0.03
CIP	0.003	0.004	0.004	0.002–0.008
AZI	0.093	0.125	0.25	0.03–0.5
ERY	0.288	0.25	1.00	0.03–4
PEN	0.210	0.25	0.5	0.03–1
TET	0.694	1.0	1.0	0.125–2
CTR	0.005	0.004	0.008	0.001–0.03
CMR (<i>n</i> = 70)				
OPC	0.004	0.004	0.004	0.002–0.008
OFX	0.033	0.03	0.06	0.015–0.06
CIP	0.008	0.008	0.015	0.002–0.015
AZI	0.037	0.25	0.25	0.06–0.5
ERY	0.870	1.0	2.0	0.25–2.0
PEN	1.656	1.0	4.0	1.0–8.0
TET	2.019	2.0	4.0	1.0–4.0
CTR	0.025	0.015	0.06	0.008–0.125

^a OPC, OPC-17116; OFX, ofloxacin; CIP, ciprofloxacin; AZI, azithromycin; ERY, erythromycin; PEN, penicillin; TET, tetracycline; CTR, ceftriaxone; PPNG, plasmid-mediated penicillinase-producing *N. gonorrhoeae*; TRNG, plasmid-mediated tetracycline-resistant *N. gonorrhoeae*; CMR, chromosomally mediated-resistant (penicillin and tetracycline) *N. gonorrhoeae*.

of the macrolides, erythromycin, and azithromycin were highest for the organisms with CMR.

The quinolones that we tested were highly active against all organisms. When compared with the geometric mean MICs for susceptible organisms, the geometric mean MICs were higher for the organisms with CMR ($P < 0.05$ by *t* test for OPC-17116, ofloxacin, and ciprofloxacin). MIC₅₀s and MIC₉₀s were typically one to two dilutions higher for the organisms with CMR than for the drug-susceptible group. Little or no difference in susceptibility to quinolones was observed in organisms with plasmid-mediated resistance

(PPNG, TRNG, PPNG-TRNG) compared with that in the drug-susceptible strains.

OPC-17116 was consistently the most active quinolone against all categories of organisms. For organisms with CMR, the geometric mean MICs of OPC-17116, ciprofloxacin, and ofloxacin were 0.004, 0.008, and 0.03 $\mu\text{g/ml}$, respectively. The range of MICs seen for this group of organisms was narrowest for OPC-17116 (0.002 to 0.008 $\mu\text{g/ml}$), representing a total of three consecutive dilutions.

All of the 200 gonococcal isolates tested in the present study, including all of the penicillin- and tetracycline-resis-

tant isolates, were susceptible to the quinolones ofloxacin, ciprofloxacin, and OPC-17116.

Among the organisms with plasmid-mediated resistance to penicillin and tetracycline, decreased susceptibility to quinolones was not observed. Organisms with CMR had markedly decreased susceptibilities to all antimicrobial agents. Ceftriaxone MICs were higher for this sample than for isolates from previous years, probably representing the continued evolution of low-level resistance, which has been observed previously (6). Organisms with CMR also had decreased susceptibilities to the macrolides, including azithromycin.

Susceptibility to the quinolone class of antimicrobial agents was similarly decreased in organisms with chromosomally mediated penicillin and tetracycline resistance; however, the range of MICs still fell well within the potential therapeutic range (3). No high-level quinolone resistance was observed.

The mechanism of CMR in *N. gonorrhoeae* has been classically described as a result of altered penicillin-binding proteins in the cell membrane. Resistance to one class of antibiotics in organisms with CMR is closely correlated with decreased susceptibility to other antibiotics. Since quinolones presumably do not bind to penicillin-binding proteins, alternative mechanisms of resistance deserve further investigation.

In summary, the quinolone class of antimicrobial agents is clearly the most active against penicillin- and tetracycline-resistant isolates of *N. gonorrhoeae*. Since they are orally administered, they offer an attractive therapeutic option for patients with gonococcal infections.

We thank Koren Waters for assistance in preparing the manuscript and Karen Bean for continued support.

This work was supported by a grant from Otsuka America.

J. M. Zenilman is a scholar of the American Foundation for AIDS Research.

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