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Multicenter Randomized Study of Single-Dose Ofloxacin versus Amoxicillin-Probenecid for Treatment of Uncomplicated Gonococcal Infection

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The safety and efficacy of ofloxacin, 400 mg orally, were compared with those of amoxicillin, 3.0 g, plus probenecid, 1.0 g orally, as single-dose therapy in 201 heterosexual patients (101 men and 100 women) with uncomplicated gonococcal infection. Treatment groups were comparable in age, duration of symptoms, number of sexual partners within the previous month, and number of previous episodes of sexually transmitted diseases. The cure rate for men treated with ofloxacin was 98% (47 of 48), and that for women was 100% (52 of 52). Cure rates for both men and women treated with amoxicillin-probenecid were 96% (51 of 53 men; 46 of 48 women). All 13 patients with positive rectal cultures and 7 of 8 patients with positive pharyngeal cultures treated with ofloxacin were cured. Neither regimen reliably eradicated coexistent infection with *Chlamydia trachomatis*. The MIC of ofloxacin for all but two of 198 pretreatment isolates was 0.3 μg/ml or less. The MIC of amoxicillin for 90% of isolates tested was 1.0 μg/ml. Single oral doses of ofloxacin and of amoxicillin plus probenecid were equally effective for treatment of urethral and cervical gonorrhea. Ofloxacin appears promising as treatment for rectal and pharyngeal infection, but studies with larger numbers of patients with rectal or pharyngeal infection or both are required for confirmation. Relative contraindications in children and possibly pregnant women plus the potential for single-step, high-level resistance may limit the usefulness of quinolone therapy for gonorrhea.

Neisseria gonorrhoeae has shown a remarkable propensity for developing resistance to a variety of useful antibiotics, such as penicillin, tetracycline, and spectinomycin, by several different mechanisms (4, 5, 12). Penicillinase-producing *N. gonorrhoeae* (PPNG) now accounts for more than 2% of all reported gonococcal infections in the United States (2). The increasing prevalence of and difficulty in screening for gonococci with plasmid-mediated tetracycline resistance (TRNG) (12) and strains with chromosomally-mediated resistance to penicillin and tetracycline (CMRNG) (5) have also complicated therapy. Tetracycline is no longer recommended by the Centers for Disease Control or the U.S. Public Health Service as sole therapy for gonorrhea, and treatment with the penicillins is inappropriate in some geographic areas (3). Ceftriaxone is currently the drug of choice for treatment in areas where there is a high prevalence of antibiotic-resistant gonococcal strains (3), but it must be administered intramuscularly and is relatively expensive. Ceftriaxone-resistant gonococci have yet to be discovered, but incremental decreases in susceptibility among gonococci to ceftriaxone have been reported (2). These problems underscore the need for continued development of safe, inexpensive, reliable, and easily administered alternative treatments for gonococcal infection, including infection at rectal and pharyngeal sites.

Ofloxacin is a synthetic carboxyquinolone antibiotic with potent bactericidal activity against a broad spectrum of gram-positive and gram-negative bacteria, including *N. gonorrhoeae* (MIC for 90% of isolates tested [MIC_{90}], ≤0.05 μg/ml) (14). Although levels of genital ofloxacin have not been studied, concentrations in plasma should exceed the MIC_{90} for *N. gonorrhoeae* for 36 to 48 h after a single 400-mg dose (11; Ortho Pharmaceuticals, unpublished data). This multicenter, randomized study was performed to compare the safety and efficacy of ofloxacin, 400 mg orally, with that of amoxicillin, 3.0 g, plus probenecid, 1.0 g orally, as single-dose therapy for men and women with uncomplicated gonococcal infection.

MATERIALS AND METHODS

Patient population. Men and nonpregnant, nonnursing women between the ages of 18 and 65 who attended sexually transmitted diseases clinics in Indianapolis, Ind.; Baltimore, Md.; Seattle, Wash.; and Tacoma, Wash., between July 1986 and June 1987 were invited to participate in the study. Men and women were eligible if Gram stain of urethral or cervical exudate contained gram-negative intracellular diplococci. Women were also eligible if a recent screening culture had grown *N. gonorrhoeae* or if contact with a man with gonorrhea within the last thirty days was documented. Patients were excluded from the study if they had (i) a history of allergy to penicillins, quinolones, or probenecid; (ii) clinical evidence for complicated gonococcal infection (pelvic inflammatory disease, epididymitis, or disseminated gonococcal infection); (iii) known syphilis or infection with *Chlamydia trachomatis*; or (iv) therapy with antibiotics with activity against *N. gonorrhoeae* within the previous 14 days. The sexual orientation of each patient and the number of previous sexually transmitted diseases were recorded on the basis of self-reported history.

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Study design and treatment. Patients were treated with ofloxacin, 400 mg orally, or amoxicillin, 3 g, plus probenecid, 1 g orally, according to open preassigned randomization schedules. A medical history, directed physical examination, cultures of exposed sites, and blood and urine tests for toxicity screening were obtained before treatment. Patients were instructed to refrain from sexual activity until after the follow-up visit, 6 to 9 days later. All patients who failed initial therapy were treated with ceftriaxone, 250 mg intramuscularly. All patients were treated for the possibility of concomitant infection with *C. trachomatis* at the conclusion of the study.

Isolation of *N. gonorrhoeae* and *C. trachomatis*. Urethral cultures for *N. gonorrhoeae and C. trachomatis* were obtained from all male patients by inserting a calcium alginate swab 2 to 4 cm beyond the urethral meatus. Endocervical cultures for both organisms were obtained from all female patients with cotton-tipped swabs. Pharyngeal and rectal cultures were obtained if indicated by a history of sexual exposure. At the follow-up visit, 6 to 9 days after treatment cervical and rectal cultures for *N. gonorrhoeae* and cervical cultures for *C. trachomatis* were obtained from all female patients, and urethral cultures for both organisms were obtained from all male patients for the test of cure. Additional cultures were obtained at the follow-up visit from any other sites that were infected initially.

Specimens for gonococcal culture were inoculated immediately onto modified Thayer-Martin medium and incubated at 35°C in candle extinction jars. *N. gonorrhoeae* was identified presumptively by colonial morphology, oxidase reaction, and Gram stain. Presumptive identification was confirmed by using fluorescein-conjugated monoclonal antibodies (Syva Corp., Palo Alto, Calif.) (10), Gonochek II (E Y Laboratories, San Mateo, Calif.) (20), or sugar utilization tests (19). In Baltimore and Indianapolis, isolates were tested for β-lactamase production by the chromogenic cephalosporin method, while in Seattle and Tacoma, the acidometric method was used (17). All isolates were subcultured onto chocolate agar or supplemented GC medium base agar (Difco Laboratories, Detroit, Mich.) with the defined supplements of Kellogg et al. (8) and frozen in tryptic soy broth at −70°C for subsequent antimicrobial susceptibility testing.

Specimens for isolation of *C. trachomatis* were placed immediately into 0.2 M sucrose-phosphate buffer transport media and either stored at 4°C for 4 to 24 h before inoculation or stored at −70°C for up to 3 days until inoculation into cycloheximide-treated McCoy cells in microdilution wells. Growth of *C. trachomatis* was detected by the fluorescein-conjugated monoclonal antibody technique (Micro Trak; Syva Corp.) (6, 16).

Antimicrobial susceptibility testing. MICs of ofloxacin, amoxicillin, penicillin G, and tetracycline HCl for *N. gonorrhoeae* were determined by the agar dilution technique by using GC medium base supplemented with 1% IsoVitaleX (BBL Microbiology Systems, Cockeysville, Md.) and doubling dilutions of antibiotic (14). Gonococci with chromosomally-mediated penicillin resistance were defined on the basis of a MIC of penicillin or amoxicillin of ≥1 μg/ml if β-lactamase production was not detected. TRNG strains were identified presumptively on the basis of a tetracycline MIC of ≥16 μg/ml.

RESULTS

Patient population. A total of 246 patients were enrolled in the study: 40 males and 54 females in Indianapolis, 40 males and 51 females in Seattle-Tacoma, and 40 males and 21 females in Baltimore. Fifteen patients failed to return for appropriate follow-up, and 30 patients had negative cultures for *N. gonorrhoeae* on the initial visit, leaving 201 evaluable patients (82%). At each clinic the two treatment groups were comparable in age, duration of symptoms, number of previous episodes of sexually transmitted diseases (data not shown). Consequently, data from all clinic sites were combined. Although homosexual men were not excluded, all patients enrolled were heterosexual.

TABLE 1. Eradication of *N. gonorrhoeae* after treatment with single-dose ofloxacin or amoxicillin plus probenecid, by site of infection

Infection site	No. cured/no. treated (%) with:	
	Ofloxacin	Amoxicillin plus probenecid
Urethra	48/48 (100)	52/54 (96)
Cervix	50/50 (100)	43/44 (98)
Rectum[a]	13/13 (100)	17/17 (100)
Pharynx	7/8 (88)	7/8 (88)
All sites	118/119 (99)	119/123 (97)

[a] All patients with positive rectal cultures were women.

Efficacy. Cure rates for men and women treated with 400 mg of oral ofloxacin were 98% (47 of 48) and 100% (52 of 52), respectively. Cure rates for both men and women treated with amoxicillin-probenecid were 96% (51 of 53 men; 46 of 48 women). Overall, 99% (99 of 100) patients treated with ofloxacin and 97% (97 of 101) patients treated with amoxicillin-probenecid were cured. All 13 patients with positive rectal cultures and 7 of 8 patients with positive pharyngeal cultures treated with ofloxacin were cured, while all 17 patients with positive rectal cultures and 7 of 8 patients with positive pharyngeal cultures treated with amoxicillin-probenecid were cured (Table 1). Combining data for all infected sites, ofloxacin eradicated infection from 99% (118 or 119) sites compared with 97% (119 of 123) sites for amoxicillin-probenecid (*P* values were not significant). No patients treated with ofloxacin experienced significant toxicity; one patient treated with amoxicillin plus probenecid developed transient tongue swelling.

Antimicrobial susceptibility. Of 242 pretreatment isolates, 190 were available for susceptibility testing; the remainder failed to survive storage or transport. The MIC_{90} of ofloxacin was 0.015 μg/ml (range, 0.004 to 0.125 μg/ml); the MIC of ofloxacin for all but two isolates was 0.03 μg/ml or less. In contrast, the MIC_{90} of amoxicillin was 1.0 μg/ml or less. In contrast, the MIC_{90} of amoxicillin was 1.0 μg/ml (range, 0.015 to 8 μg/ml). Only one β-lactamase-producing strain was isolated, but the amoxicillin MIC was ≥1 μg/ml for strains isolated from 33 patients. All 18 patients with strains for which the amoxicillin MIC was ≥1 μg/ml who were treated with ofloxacin were cured, but 13% (2 of 15) of such patients treated with amoxicillin-probenecid had persistent infection. TRNG strains were not encountered in this study.

Effect of treatment on isolation of *C. trachomatis*. *C. trachomatis* was isolated from 15% (7 of 48) men treated with ofloxacin and 21% (11 of 53) men treated with amoxicillin-probenecid. The overall coinfection rate among men was 18% (18 of 101). After treatment, chlamydia cultures were positive in 43% (3 of 7) men treated with ofloxacin and 55% (6 of 11) men treated with amoxicillin-probenecid. Coexisting chlamydial infection in women was more common: 38% (20 of 52) of women treated with ofloxacin and 31% (15 of 48) of women treated with amoxicillin-probenecid had positive

chlamydial cultures from the cervix, rectum, and/or urethra. The overall coinfection rate among women was 35% (35 of 100). After treatment, chlamydia cultures were positive in 50% (10 of 20) women treated with ofloxacin and 67% (10 of 15) women treated with amoxicillin-probenecid.

DISCUSSION

The emergence of several different forms of antibiotic resistance among gonococci and the geographic variation in prevalence of such organisms has made universal recommendations for therapy difficult (1, 3). Since 1985, the number of reported gonococcal infections caused by PPNG in the United States has increased by more than fourfold (21). Because the agar dilution techniques necessary for accurate antibiotic susceptibility testing have not been widely applied, the proportion of gonococcal infections caused by CMRNG and TRNG is not known. However, within 2 years of the discovery of the first outbreak in North Carolina in 1983, CMRNG strains had been isolated in 23 states (2). Within 18 months of the first description of TRNG strains in the United States, they had been isolated in 17 states (9). In areas where PPNG accounts for ≥1% or CMRNG accounts for ≥5% of all gonococcal isolates, the Centers for Disease Control currently recommend treatment with intramuscular ceftriaxone (250 mg) (3). Although almost uniformly effective for infection at all anatomic sites, ceftriaxone is relatively expensive (approximately $7.50/250-mg dose). The necessity for intramuscular injection makes it less convenient than single-dose oral regimens.

In this study of 201 patients, ofloxacin in a single 400-mg oral dose cured 100% of urethral and cervical gonococcal infections. All 18 patients whose isolates showed at least moderate resistance to amoxicillin (MIC, ≥1 μg/ml) and who were treated with ofloxacin were cured. Only one PPNG isolate and no TRNG strains were isolated during the study. However, in this and other studies, the susceptibility and/or clinical response to ofloxacin was independent of the susceptibilities to β-lactam antibiotics or tetracycline (13, 15). All 13 patients with rectal infection and 7 of 8 patients with pharyngeal infection treated with ofloxacin were cured. Too few rectal and pharyngeal infections were included in the study to permit definitive statistical analysis, but these encouraging preliminary results justify further trials of ofloxacin for treatment of gonococcal infection at extragenital sites. Single-dose therapy with ofloxacin did not reliably eradicate *C. trachomatis*.

Ofloxacin proved as effective as amoxicillin plus probenecid for treatment of genital gonorrhea in both men and women in this large, randomized study. Several of the newer fluorinated quinolones, such as enoxacin, ciprofloxacin, and norfloxacin, in doses ranging from 200 to 800 mg, have been shown to treat uncomplicated genital gonorrhea successfully (7, 14; H. H. Handsfield, J. R. Black, and E. W. Hook III, Rev. Infect. Dis., in press). Single oral dose treatment with ofloxacin or other quinolones may represent an important advantage over parenteral therapy with ceftriaxone in areas where resistance to penicillin and tetracycline appear to have developed. Since tetracycline alone no longer constitutes reliable therapy for gonorrhea in many areas, quinolones may also represent a reasonable alternative for treating patients with allergies to penicillin. In addition, costs for oral quinolone treatment may be considerably lower than those associated with ceftriaxone administration.

However, before the newer quinolones can be recommended for the treatment of gonorrhea, further evaluation of additional patients with rectal or pharyngeal infection or both and further study of the potential in the gonococcus for single-step, high-level resistance to quinolones (18) will be required. For example, widespread use of rosoxacin in the Philippines may have contributed to clinically significant rates of resistance among gonococci to other quinolones such as enoxacin, norfloxacin, and pefloxacin (M. P. Joyce, B. B. Ayling, G. H. Vaughn, D. S. Herip, C. G. Hayes, G. Espinosa, A. Andrada, O. P. Daily, and L. W. Laughlin, 6th Int. Pathogenic Neisseria Conf., Pine Mountain, Ga., 16 to 21 October 1988, abstr. no. E-19). Quinolones may be contraindicated in pediatric patients and in women who may be pregnant. These groups make up a significant percentage of patients with gonorrhea. Finally, the effect of quinolone treatment for gonorrhea on incubating syphilis is not known, although ofloxacin had little or no activity against *Treponema pallidum* in a rabbit model (18a).

In summary, ofloxacin, given as a single 400-mg dose, appears to be effective therapy for genital, and possibly rectal and pharyngeal, gonorrhea. Although the number of antibiotic-resistant strains causing infection in this study was limited, experience from other studies suggests that ofloxacin will be effective for strains expressing penicillin or tetracycline resistance or both as well.

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