

Comparison of Single-Dose Oral Grepafloxacin with Cefixime for Treatment of Uncomplicated Gonorrhea in Men

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In a randomized open study, 351 male patients with uncomplicated gonorrhea were given single oral doses of grepafloxacin (400 mg) or cefixime (400 mg). In the 299 microbiologically evaluable patients, urethral infections were cured in 99% (147 of 149) of those receiving grepafloxacin and 97% (145 of 150) of those given cefixime. Eradication rates for both regimens were 100% in the 16% (47 of 299) of participants who were infected with penicillin-resistant *Neisseria gonorrhoeae* and 97% in the 21% (62 of 299) of participants infected with tetracycline-resistant strains. Grepafloxacin is a well-tolerated alternative to cefixime for treatment of uncomplicated gonorrhea in males.

Treatment of gonorrhea has been impacted markedly by the widespread and increasing resistance of *Neisseria gonorrhoeae* to antibiotics used for therapy of this condition. Single-dose regimens with the newer oral cephalosporins and quinolones have attracted considerable attention and are now recommended for initial therapy of uncomplicated gonorrhea (2). Grepafloxacin (OPC-17116) is a new, orally administered fluoroquinolone with excellent in vitro activity against *N. gonorrhoeae*, being 4- to 16-fold more potent than ofloxacin against penicillin- and tetracycline-resistant strains (15). It is highly concentrated intracellularly (3) and has pharmacokinetic properties (11, 13) which suggest that single doses may be effective for therapy of male genital tract infections. This study compares the efficacy and safety of a single oral dose of grepafloxacin with those of cefixime in the treatment of uncomplicated gonorrhea in men.

From January 1993 through October 1994, male outpatients aged 16 years or older with uncomplicated gonococcal urethritis were enrolled in the study at 10 participating centers. All participants were required to have a Gram stain of a urethral specimen showing gram-negative diplococci within polymorphonuclear leukocytes or a recent culture positive for *N. gonorrhoeae*. Patients were excluded if they gave a history of allergy to quinolone or cephalosporin antibiotics; had received antibiotics or any other investigational drug within 2 weeks before enrollment; had complicating infection or disease that would compromise treatment evaluation; received concomitant antimicrobial medication other than topical or antifungal agents; received chronic treatment with warfarin, diflunisal, fluconazole, or theophylline; had taken antacids or sucralfate

within 4 h of dosing; or had a known *Chlamydia trachomatis* infection. The study was approved by each center's institutional review board, and all participants gave written informed consent.

Patients were randomized to receive a single 400-mg oral dose of either grepafloxacin or cefixime in an open study. The medication was taken under supervision, and patients were instructed to abstain from unprotected sexual intercourse during the study and to attend a follow-up visit 5 to 10 days later.

Patients were evaluated for dysuria, urethral discharge, and urethral itching at the initial and follow-up visits. Specimens for Gram staining and culture of *N. gonorrhoeae* were obtained from the urethra, pharynx, and, if indicated by patient history, rectum. Specimens were inoculated directly onto Thayer-Martin medium and immediately incubated at 36°C in an atmosphere containing 5% CO₂ for 24 to 48 h. All isolates were identified and tested for beta-lactamase production by standard methods (8, 10). The MICs of grepafloxacin, cefixime, penicillin, and tetracycline were determined by agar dilution (4, 8, 9). Isolates were considered resistant to penicillin and tetracycline if MICs of ≥ 2.0 mg/liter were obtained (9). Isolates with decreased susceptibility to grepafloxacin or cefixime were identified as those for which the MICs were >0.06 mg/liter or >0.25 mg/liter, respectively. A urethral specimen was also taken for chlamydial culture, and blood and urine samples were taken for hematology, biochemistry, syphilis serology, and urinalysis. Efficacy in patients who returned for examination and *N. gonorrhoeae* culture was evaluated 5 to 10 days

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TABLE 1. Eradication rate of *N. gonorrhoeae* by site of infection

Site of infection	Patients cured/patients evaluated (%)	
	Grepafloxacin (400 mg)	Cefixime (400 mg)
Urethra	147/149 (98.7)	145/150 (96.7)
Pharynx	8/8 (100)	10/12 (83.3)
Rectum	1/1 (100)	3/3 (100)
Overall ^a	147/149 (98.7)	145/150 (96.7)

^a Denotes eradication of *N. gonorrhoeae* from all infected sites; some patients had more than one infected site.

TABLE 2. Eradication of penicillin-resistant, tetracycline-resistant, and beta-lactamase-producing isolates of *N. gonorrhoeae* in the urethra

Isolate	Grepafloxacin (400 mg)			Cefixime (400 mg)		
	Eradicated	Tested	Percentage	Eradicated	Tested	Percentage
Penicillin-resistant ^a	25	25	100	22	22	100
Tetracycline-resistant	29	30	96.7	31	32	96.9

^a Includes the subset of four beta-lactamase-producing isolates.

after treatment. Bacteriological responses were classified as eradication or persistence on the basis of the follow-up culture for *N. gonorrhoeae*.

Of 351 patients enrolled in the study, 152 in the grepafloxacin group and 154 in the cefixime group were clinically evaluable. The main reasons for exclusion were failure to return for follow-up (38 patients), negative enrollment cultures for *N. gonorrhoeae* (9 patients), and withdrawal of consent (5 patients) (some patients had multiple reasons for exclusion). The two treatment groups were comparable in terms of age (mean age, 27 years), weight, race (85% black), smoking habits, alcohol consumption, and clinical symptoms of urethritis. The proportion of patients who acknowledged using illicit drugs was 43% in the grepafloxacin group and 32% in the cefixime group ($P = 0.01$), but this did not significantly impact the outcome of treatment.

Of the 351 patients in the study, 149 in the grepafloxacin group and 150 in the cefixime group were microbiologically evaluable. *N. gonorrhoeae* was eradicated from the urethra in 99 and 97% of patients receiving grepafloxacin and cefixime, respectively (Table 1) (95% confidence interval for difference in treatment failure rates, 3.1 to 7.0%). All concomitant pharyngeal or rectal infections treated with grepafloxacin (nine patients) were cured, as were 13 (85%) of 15 such infections treated with cefixime. When all body sites were considered, 99% of patients given grepafloxacin were cured compared with 97% of those treated with cefixime.

Of the 299 pretreatment gonococcal isolates tested, 47 (16%) were resistant to penicillin, 8 (3%) of which produced beta-lactamase, and 62 (21%) were resistant to tetracycline (Table 2). Both regimens were 100% effective in eradicating penicillin-resistant and beta-lactamase-producing isolates and 97% effective in eradicating tetracycline-resistant isolates from the urethra. One *N. gonorrhoeae* isolate had reduced susceptibility to both grepafloxacin and cefixime; this pathogen responded to treatment with cefixime.

Pretreatment *C. trachomatis* cultures were positive in 9.6 (17 of 176) and 12.6% (22 of 175) of men treated with grepafloxacin and cefixime, respectively. At the time of follow-up evaluation, chlamydial cultures remained positive in 8 (42%) grepafloxacin-treated men with *C. trachomatis* coinfection and 14 (64%) men who received cefixime (P , not significant).

Only eight adverse events were reported among the 351 study participants. The most common adverse events in grepafloxacin-treated patients were nausea (4%), headache (3%), and pruritus (2%), while patients receiving cefixime most commonly reported headache (3%) and nausea (2%). Two grepafloxacin-treated patients reported potentially serious adverse events. One developed severe nausea but recovered without treatment for the event. The second patient developed severe balanitis of unknown etiology and was withdrawn from the study. No clinically significant changes were detected in any patient by laboratory tests.

This study shows that grepafloxacin and cefixime are both highly effective for the treatment of uncomplicated gonococcal urethritis in men, even in a population with a high proportion

(37%) of *N. gonorrhoeae* strains resistant to penicillin or tetracycline. Despite in vitro resistance to penicillin or tetracycline, such organisms are highly sensitive to grepafloxacin, with 90% of antibiotic-resistant clinical isolates being inhibited by 0.004 mg/liter (15). Moreover, the degree of sensitivity is unaffected whether the penicillin or tetracycline resistance is chromosomally or plasmid mediated.

In recent years, increasing fluoroquinolone resistance has been noted by the Centers for Disease Control and Prevention Gonococcal Isolate Surveillance Project; however, high-level fluoroquinolone resistance remains quite rare in the United States (4). While monitoring of in vitro susceptibility reveals slowly decreasing sensitivity, empirical observations indicate that these drugs remain highly effective for the treatment of uncomplicated gonorrhea, and thus, fluoroquinolones continue to be recommended (along with cefixime and ceftriaxone) as the preferred therapy for uncomplicated gonorrhea. Our data suggest that grepafloxacin is just as active as currently recommended fluoroquinolone antibiotics.

Grepafloxacin is also active against *C. trachomatis* both in vitro (6, 14) and in experimental animal models (6). This organism is the most important cause of nongonococcal urethritis, accounting for about 40% of cases (1). Grepafloxacin MICs for strains of *C. trachomatis* range from 0.03 to 0.12 mg/liter and, based on minimum bactericidal concentrations, it is up to 64 to 128 times more active than ciprofloxacin and tetracycline (14). The very high and prolonged intracellular concentrations achieved by grepafloxacin (3) suggest that these antichlamydial effects may be of clinical use. Beta-lactam antibiotics are not recommended for chlamydial infections and, of the marketed quinolones, only ofloxacin (12) has acceptable efficacy against *C. trachomatis*.

An optimal regimen for gonorrhea treatment should be efficacious for infections at different anatomic sites (5). However, pharyngeal infection responds less well to some antibiotics than do genital or rectal infections (7). In this study, grepafloxacin was successful in treating all concomitant extragenital infections, including pharyngeal gonorrhea, although the number of patients was small. Further assessments of larger study populations are necessary to verify our findings with respect to pharyngeal and rectal infections in men. However, further clinical studies have confirmed the efficacy of grepafloxacin therapy for women with cervical gonorrhea and for nongonococcal urethritis or cervicitis (unpublished data).

We conclude that a single dose of grepafloxacin is a well-tolerated and effective regimen for the treatment of uncomplicated gonococcal infections in men. It has the potential to be considered as empiric therapy for such infections caused by *N. gonorrhoeae* strains that are either penicillin or tetracycline resistant.

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