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Treatment of Uncomplicated Gonorrhea with Rosoxacin

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In a randomized, double-blind, dose-ranging study, single oral doses of rosoxacin were used to treat 126 patients with uncomplicated genital or anorectal gonorrhea. *Neisseria gonorrhoeae* was eradicated from 5 (28%) of 18 men treated with 100 mg, compared with 101 (94%) of 108 men and women treated with 200 mg, 300 mg, or 400 mg ($P < 0.001$). Susceptibility to rosoxacin was determined for 6 pretreatment gonococcal isolates from these patients and for 194 stored clinical isolates; 296 (98.7%) of these 300 isolates, including 10 strains of penicillinase-producing *N. gonorrhaeae*, required a minimal inhibitory concentration of ≤0.062 μg/ml. Urethral or cervical infection with *Chlamydia trachomatis* coexisted with gonococcal infection in 14 (22%) of 63 patients and persisted in 7 of 10 patients treated with rosoxacin. Postgonococcal urethritis developed in 11 (34%) of 32 men who were monitored for 12 to 30 days. Sixty-four subjects (51%) developed transient dizziness, drowsiness, altered visual perceptions, or other symptoms suggestive of central nervous system dysfunction after treatment with rosoxacin, but these symptoms were not clearly dose related. Rosoxacin in doses of ≥200 mg appears to be effective for single-dose treatment of uncomplicated gonorrhea, but further studies of its possible central nervous system toxicity are indicated.

The emergence of penicillinase-producing *Neisseria gonorrhoeae* (PPNG) (4, 10) has prompted investigation of additional treatment regimens with potential efficacy for infection with these strains. In addition, each of the regimens recommended by the U.S. Public Health Service (3) for treatment of uncomplicated gonnorhea has problems of toxicity, intolerance, reduced efficacy for infection of some anatomic sites, lack of efficacy for coexisting infection with *Chlamydia trachomatis*, or cost. Rosoxacin, a new orally administered quinolone antimicrobial agent, is highly active in vitro against beta-lactamase-negative and -positive strains of *N. gonorrhoeae*, with a reported minimal inhibitory concentration (MIC) of ≤0.125 μg/ml (5, 8). A single oral dose of 250 mg of rosoxacin results in a mean peak plasma level of 6.4 μg/ml after 2 h, with a half-life of about 5 h (8). These features suggest that rosoxacin might offer an alternative to ampicillin and amoxicillin as an effective orally administered single-dose treatment for gonorrhea caused by beta-lactamase-negative *N. gonorrhoeae*, with the potential added advantage of efficacy for infections due to PPNG. We carried out a cooperative, randomized, double-blind, dose-ranging study designed to examine the efficacy and tolerance of single doses of 100 mg, 200 mg, 300 mg, or 400 mg of rosoxacin for uncomplicated infection caused by beta-lactamase-negative *N. gonorrhoeae*. We also examined the in vitro activity of rosoxacin against 300 clinical isolates of *N. gonorrhoeae*, including 106 strains isolated in this study.

MATERIALS AND METHODS

Study population. Men and women aged ≥18 years who attended sexually transmitted disease clinics in Seattle or Denver and had urethral or endocervical smears showing intracellular gram-negative diplococci or who had culturally documented untreated genital or anorectal gonorrhea were invited to participate. Patients with signs or symptoms of complicated gonococcal infection were excluded, as were pregnant or nursing women and patients who had been treated with antimicrobial drugs within the preceding 2 weeks. Patients from whom *N. gonorrhoeae* was not subsequently isolated were excluded from analysis. Patients were classified by race according to self-description and by sexual preference on the basis of sexual contacts within the preceding 2 months.

Isolation of *N. gonorrhoeae*. In Denver, urethral cultures for *N. gonorrhoeae* were obtained from men, and endocervical and anal canal specimens were obtained from women. In Seattle, pharyngeal, anal canal, and urethral or endocervical specimens were obtained from all subjects. Specimens were inoculated immediately onto modified Thayer-Martin medium and in-

cubated at 36°C in candle extinction jars within 30 min. *N. gonorrhoeae* was identified by standard techniques, including sugar utilization reactions.

Antimicrobial susceptibility testing. All isolates of *N. gonorrhoeae* were stored by freezing at −70°C in a 1:1 mixture of Trypticase soy yeast broth (BBL Microbiology Systems) and horse serum or in 20% glycerol in Mueller-Hinton broth for later susceptibility testing. MICs of rosoxacin were determined for 106 pretreatment gonococcal isolates from this therapeutic trial, for 184 stored strains of beta-lactamase-negative gonococci originally isolated in Seattle, and for 10 PPNG strains isolated in the Philippines. MICs were measured by the agar dilution technique as described previously (11), using GC agar base containing 1% IsoVitaleX (BBL Microbiology Systems), 1% hemoglobin, and twofold dilutions of rosoxacin. Production of beta-lactamase was tested by the iodometric technique (2).

Isolation of *C. trachomatis*. Endocervical and urethral specimens for isolation of *C. trachomatis* were obtained from the Seattle subjects. Urethral specimens were obtained from men by passage of calcium alginate-tipped urethrogenital swabs 2 to 3 cm beyond the meatus. For women, urethral and cervical specimens were obtained with Dacron-tipped swabs. All swabs were immediately placed in transport medium and frozen at −70°C for later inoculation into tissue culture. Isolation was carried out by using cycloheximide-treated cells in a microtiter system, as reported previously (12), modified by use of cycloheximide-treated rather than irradiated McCoy cells.

Treatment and study design. Men were treated with single doses of 100 mg, 200 mg, 300 mg, or 400 mg of rosoxacin; women were treated with single doses of 200 mg, 300 mg, or 400 mg. All subjects received identically appearing capsules containing rosoxacin, lactose placebo, or both; the manufacturer provided coded capsules for each subject, and treatment was assigned according to computer-generated randomization schedules for men and women. Cure or failure was defined by the results of repeat cultures for *N. gonorrhoeae* 3 to 8 days after treatment.

Subjects studied in Seattle were instructed to return for a second follow-up visit 14 to 21 days after treatment for repeat cultures for *C. trachomatis* and assessment for postgonococcal urethritis in men. Postgonococcal urethritis was defined as the presence (12 to 30 days after treatment) of purulent or mucopurulent urethral discharge or a Gram-stained urethral smear showing ≥5 polymorphonuclear leukocytes per ×1,000 microscopic field (1) without intracellular gram-negative diplococci, and a negative culture for *N. gonorrhoeae*. Patients were instructed to abstain from sexual contact until after the final visit. Written informed consent was obtained from all subjects.

To screen for toxicity, complete blood counts, platelet counts, urinalyses, and assays of serum glutamic-oxalacetic transaminase, blood urea nitrogen, creatinine, alkaline phosphatase, and total bilirubin were performed immediately before therapy and at the first follow-up visit. Potential acute central nervous system toxicity of rosoxacin was assessed by three methods: (i) approximately one-third of the subjects were observed hourly in the clinic for 4 h after treatment, after which they underwent neurological screening examinations and were asked to describe any untoward symptoms; (ii) the remainder of the subjects were given checklists of symptoms, including "dizziness," "drowsiness," "change in eyesight," and "other," to be returned at the first follow-up visit; and (iii) all subjects were interviewed regarding these and similar symptoms at the first follow-up visit.

Statistical methods. Fisher's exact test or chi-square analysis was used for discrete variables, and Student's *t*-test was used to compare continuous variables.

RESULTS

Eradication of *N. gonorrhoeae*. A total of 73 men and 66 women were treated with rosoxacin; 67 men and 59 women were infected and returned for the first follow-up visit, and subsequent data analyses were limited to these 126 patients. Their mean age was 26.0 years; there were 54 whites, 55 blacks, 13 persons of hispanic origin, and 4 persons of other races; 13 men were homosexual. There were no significant differences between patients treated with the various doses of rosoxacin with respect to demographic factors, sexual orientation, or sites of infection.

Table 1 shows the results of treatment of genital and anorectal gonococcal infection. Rosoxacin doses of ≥200 mg eradicated urethral gonococcal infection from 45 (92%) of 49 men, compared with 5 (28%) of 18 men treated with 100 mg ($P < 0.001$). Symptoms or signs of urethritis persisted in all men in whom treatment failed. *N. gonorrhoeae* was isolated from the anal canals of two men, each of whom was treated with 300 mg of rosoxacin and had negative anal canal cultures at follow-up. Endocervical gonococcal infection was eradicated from 54 (95%) of 57 women, all of whom received ≥200 mg of rosoxacin. Anorectal gonococcal infection was present in 22 (39%) of 57 women with endocervical infection and in two others with negative endocervical cultures; all 24 anorectal infections were eradicated. Thus, endocervical or anorectal infection was eradicated from both sites in 56 (95%) of 59 women. The overall cure rate for men and women with genital or anorectal gonococcal infection treated with ≥200 mg of rosoxacin was 101 (94%) of 108 cases.

Pharyngeal gonococcal infection persisted in one of four women and was first detected after treatment in one man, who denied interim sexual exposure and kissing. The two patients with persistent pharyngeal infection received 200 mg and 400 mg, and the three whose pharyngeal infections were cured received 300 mg or 400 mg of rosoxacin.

Susceptibility of *N. gonorrhoeae* to rosoxacin. MICs of rosoxacin were determined

TABLE 1. *Results of rosoxacin treatment of uncomplicated genital and anorectal gonococcal infections*

Site of infection	No. cured/no. treated at following rosoxacin dose (mg):				
	100	200	300	400	Total
Men					
Urethra	5/18 (28)[a]	15/17 (88)	14/15 (93)	16/17 (94)	50/67 (75)
Rectum	NA[b]	NA	2/2 (100)	NA	2/2 (100)
Total	5/18 (28)	15/17 (88)	14/15 (93)	16/17 (94)	50/67 (75)[c]
Women					
Endocervix	NA	22/22 (100)	14/16 (88)	18/19 (95)	54/57 (95)
Rectum	NA	7/7 (100)	8/8 (100)	9/9 (100)	24/24 (100)
Total	NA	22/22 (100)	16/18 (89)	18/19 (95)	56/59 (95)

[a] Percent cured is shown within parentheses.
[b] NA, Not applicable.
[c] $P < 0.001$, 100 mg versus ≥200 mg.

for 106 pretreatment genital isolates of *N. gonorrhoeae* from patients in this study, for 184 stored clinical isolates of beta-lactamase-negative *N. gonorrhoeae*, and for 10 clinical isolates of PPNG originally isolated in the Philippines (Table 2). Of 300 isolates, 296 (98.7%) (including the 10 PPNG strains) were inhibited by ≤0.062 μg/ml. One isolate, from a Denver patient, required an MIC of 1.0 μg/ml. When all rosoxacin regimens were combined, the MICs for pretreatment gonococcal isolates from patients in our treatment study correlated with the outcome (Fig. 1); the geometric mean MIC for 87 isolates from patients who were cured of genital infection was 0.041 μg/ml, compared with 0.058 μg/ml for 19 pretreatment genital isolates from subjects whose treatment failed ($P < 0.02$). Treatment failed to eradicate all three gonococcal strains that required MICs of ≥0.125 μg/ml; the patients whose isolates required MICs of 0.125 μg/ml and 1.0 μg/ml were each treated with 100 mg of rosoxacin, and the person infected with the isolate requiring an MIC of 0.25 μg/ml received 400 mg of rosoxacin. MICs for pretreatment and posttreatment gonococcal isolates from subjects whose treatments failed were identical or differed by only one dilution in each case. No PPNG strains were isolated in the treatment study.

Eradication of *C. trachomatis* and prevention of postgonococcal urethritis. *C. trachomatis* was isolated before treatment from the urethras of 6 (18%) of 33 men and from the endocervices of 8 (27%) of 30 women with gonococcal infection. Chlamydial infection persisted after treatment with rosoxacin in 7 of 10 men and women from whom repeat cultures were obtained, and *C. trachomatis* was first isolated after treatment from another woman who denied sexual reexposure. Persistence of *C. trachomatis* was unrelated to the dose of rosoxacin. Postgonococcal urethritis occurred in 11 (34%) of 32 men reexamined 12 to 30 days after treatment, including 5 of 5 men from whom *C. trachomatis* was isolated before treatment.

TABLE 2. *In vitro susceptibility of N. gonorrhoeae to rosoxacin*

MIC (μg/ml)	Treatment study isolates[a]				Stored isolates[b]				Total (n = 300)	
	Denver		Seattle		Seattle		Philippines			
	No.	%[c]	No.	%	No.	%	No.	%	No.	%
≤0.016	8	17	0	0	8	4	6	60	22	7.3
0.031	21	60	25	43	100	59	0	60	146	56.0
0.062	17	96	32	98	75	99	4	100	128	98.7
0.125	0	96	1	100	1	100	0	100	2	99.3
0.25	1	98	0	100	0	100	0	100	1	99.7
0.5	0	98	0	100	0	100	0	100	0	99.7
>1.0	1	100	0	100	0	100	0	100	1	100

[a] All study isolates were beta-lactamase nonproducers.
[b] Stored isolates from Seattle were beta-lactamase-negative; those from the Philippines were beta-lactamase-positive.
[c] All percentages are cumulative.

Toxicity. Symptoms compatible with central nervous system dysfunction, including dizziness, drowsiness, altered visual perceptions, and "high" feelings occurred in 64 (51%) of 126 subjects. As shown in Table 3, the frequency of symptoms was not clearly related to dose, although the lowest risk (33%) was in men treated with 100 mg, and highest (58%) was in patients treated with 400 mg. These symptoms were classified as mild (not interfering with normal activity) in 56 (88%) of the 64 symptomatic subjects, and severity was not dose related. Onset occurred 10 min to 18 h after ingestion of rosoxacin, and usually was sooner in patients treated with 300 mg or 400 mg (mean, 0.93 h) than in those treated with 100 mg or 200 mg (mean, 2.03 h) ($P < 0.10$). The median duration of symptoms was

3 h (mean, 4.5 h; range, 10 min to 48 h). One man, treated with 300 mg, complained of moderately severe dizziness and had signs of central ataxia (inability to walk heel-to-toe) that resolved after 4 h. No other objective neurological abnormalities were observed, although several patients who complained of drowsiness after receiving rosoxacin were observed to fall asleep in the clinic waiting rooms. There were no differences in time to onset, severity, or duration of these symptoms with respect to sex, race, or age, but the overall risk was higher in the Denver population (42 of 63 patients, 67%) than in the Seattle population (22 of 63 patients, 35%) ($P < 0.001$). No significant hematological, biochemical, or urinary abnormalities occurred in any subject.

DISCUSSION

In this study, single oral doses of ≥200 mg of rosoxacin eradicated 101 (94%) of 108 cases of uncomplicated genital or anorectal gonococcal infection. In contrast, the 100-mg dose failed to cure 13 (72%) of 18 men with gonococcal urethritis. Limson et al. (7) reported 100% cure rates for 30 men with gonorrhea who were treated with 400 mg, 600 mg, or 800 mg of rosoxacin divided into two doses 4 h apart.

This study confirms the high level of in vitro activity of rosoxacin against beta-lactamase-negative and -positive strains of *N. gonorrhoeae*, but also shows that relative resistance (MIC ≥ 1.0 μg/ml) may occasionally be encountered. Although infections due to PPNG were not treated in this study, the in vitro activity of rosoxacin against these strains suggests a strong potential for efficacy for penicillin-resistant gonorrhea. Thus, rosoxacin in doses of ≥200 mg should be studied in controlled trials to compare its efficacy with that of other regimens for uncomplicated infections caused by beta-lactamase-positive and -negative *N. gonorrhoeae*; such trials are currently under way in several centers.

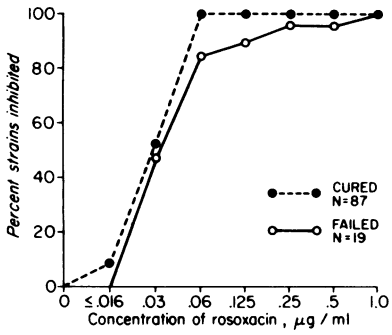

FIG. 1. *MICs of rosoxacin for pretreatment genital isolates of N. gonorrhoeae from 87 patients who were cured and 19 patients in whom gonococcal infection persisted after treatment with rosoxacin.*

Despite a recent report (5) showing modest in vitro inhibitory activity of rosoxacin against *C. trachomatis* (MIC = 5.0 μg/ml) and *Ureaplasma urealyticum* (MIC = 2 to 8 μg/ml), the regimens studied share an important disadvantage with all other reported single-dose regimens for gonorrhea in that they neither eradicated coexisting genital infection with *C. trachomatis* nor prevented postgonococcal urethritis in men. The prevalence of genital chlamydial infection in this study is consistent with previous reports demonstrating chlamydial infection in about 20% of men (6) and 35% of women with gonorrhea (12).

The high rate of symptoms suggestive of central nervous system dysfunction in this study is tempered by the fact that the reported symptoms are highly subjective and that the patients were forewarned about them. The difference in frequency between the Seattle and Denver patients may reflect intercenter differences in interpretation of subtle symptoms, as may the lack of a clear relationship to dose. On the other hand, the time to onset of symptoms was correlated with the dose of rosoxacin; many patients gave clear descriptions of abrupt onset of symptoms with peak severity at times that corresponded with reported peak blood levels, and at least one subject had objective evidence of ataxia. Double-blind studies comparing rosoxacin with placebo or with other single-dose treatments for gonorrhea will be required to assess

TABLE 3. *Incidence of side effects of rosoxacin consistent with central nervous system dysfunction*[a]

Patient group	No. with side effects/no. treated at following rosoxacin dose (mg):				
	100	200	300	400	Total
Men	6/18 (33)[b]	10/17 (59)	6/15 (40)	11/17 (65)	33/67 (49)
Women	NA[c]	10/22 (45)	11/18 (61)	10/19 (53)	31/59 (53)
Total	6/18 (33)	20/39 (51)	17/33 (52)	21/36 (58)	64/126 (51)

[a] Dizziness, lightheadedness, drowsiness, visual disturbances, and "high" feelings.
[b] Percentage with side effects is shown within parentheses.
[c] NA, Not applicable.

the true frequency and severity of these symptoms and the extent to which they may limit the usefulness of this otherwise promising compound.

ACKNOWLEDGMENTS

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Volume 20, no. 5, p. 625: The affiliations of Franklyn N. Judson and King K. Holmes should be transposed.

Page 625: The receipt and acceptance dates should be transposed.

Page 625, abstract, line 5: "Susceptibility to rosoxacin was determined for 6" should read "Susceptibility to rosoxacin was determined for 106."

Page 628, column 2, line 29: Reference 12 should be reference 9.

Dose-Ranging Study of Ceftriaxone for Uncomplicated Gonorrhea in Men

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Volume 20, no. 6, p. 840, column 1, line 24: "0.50 μg/ml" should read "0.35 μg/ml."

In Vitro Susceptibility of *Campylobacter fetus* subsp. *jejuni* to *N*-Formimidoyl Thienamycin, Rosaramicin, Cefoperazone, and Other Antimicrobial Agents

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Volume 20, no. 6, p. 850, column 2, line 26: "Bactericidal activity was defined original inoculum, determined by quantitative subcultures" should read "Bactericidal activity was defined as a reduction of 99% of the colonies in the original inoculum, determined by quantitative subcultures."