

Rosoxacin in the Therapy of Uncomplicated Gonorrhea

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In this randomized, multicentered study, 157 males and 130 females with laboratory-confirmed, uncomplicated anogenital *Neisseria gonorrhoeae* infections were evaluated to determine the efficacy and safety of a single 300-mg oral dose of rosoxacin versus 3.5 g of ampicillin plus 1 g of probenecid. A total of 130 males and 101 females were evaluated. Rosoxacin cured 90.3% ($P = 0.053$) and 94.1% ($P = 0.62$), respectively, whereas ampicillin was effective in 98.5 and 98% of males and females, respectively. All 39 patients with anorectal infections were cured. One penicillinase-producing *N. gonorrhoeae* strain was isolated and was eradicated with rosoxacin. Of 212 pretreatment isolates tested, 201 were inhibited by 0.06 μg or less of rosoxacin per ml. The MICs of rosoxacin for the remaining 11 isolates ranged up to 0.5 $\mu\text{g}/\text{ml}$. The incidence of adverse effects was relatively high (29% for the rosoxacin group versus 18% for the ampicillin group), but none of the reactions required medical intervention nor did they result in serious sequelae.

Rosoxacin is a novel quinolone derivative chemically related to nalidixic acid. It is active in vivo and in vitro against most gram-negative pathogens including *Neisseria gonorrhoeae*. The MIC of rosoxacin for β -lactamase-positive and -negative strains of *N. gonorrhoeae* is $\leq 0.125 \mu\text{g}/\text{ml}$ (4, 8). The pharmacokinetics of this drug make it favorable for treating gonorrhea: a single 300-mg oral dose achieves a peak serum concentration of 5 $\mu\text{g}/\text{ml}$ at 2.5 h, with a half-life of 4 h (J. R. O'Conner, R. A. Dobson, P. E. Came, and R. B. Wagner, Program Abstr. Intersci. Conf. Antimicrob. Agents Chemother. 19th, Boston, Mass., abstr. no. 511, 1979).

These properties suggest that rosoxacin may offer an alternative single-dose therapy for uncomplicated gonorrhea due to both non-penicillinase- and penicillinase-producing strains. Rosoxacin as single oral doses of 300 and 200 mg has been used successfully in 28 of 28 males and 87 of 87 females infected with genital or anorectal penicillinase-producing (PP) *N. gonorrhoeae* in the Philippines, Indonesia, Kenya, and North America (2; Winthrop Laboratories, personal communication).

The purpose of this study was to evaluate the safety and efficacy of a single 300-mg oral dose of rosoxacin versus ampicillin plus probenecid in the treatment of uncomplicated gonorrhea in men and women. We also determined the MIC of rosoxacin for 212 pretreatment isolates of *N. gonorrhoeae*.

MATERIALS AND METHODS

This randomized, multicentered, cooperative trial was carried out simultaneously in Edmonton, London, Toronto, and Montreal, Canada.

Males and females, 18 years of age and over, who had culture-proven genital or anorectal gonorrhea and consented to participate were enrolled. Patients with signs and symptoms of complicated gonococcal infection, a history of antimicrobial allergy, antibiotic therapy within the preceding

2 weeks, or pregnancy were excluded. Patients were only entered into the study once.

N. gonorrhoeae cultures were obtained from the urethra of all males and the endocervix of all females. Additional specimens from the pharynx and anal canal were obtained when clinically indicated or as part of the routine of each clinic. Specimens were either placed in Stuart transport medium or directly inoculated onto appropriate medium (Thayer Martin, modified New York City, or Edmonton Provincial Laboratory) (1) and incubated at 36°C under a CO₂ environment for 36 to 48 h. Isolates presumptively identified as *N. gonorrhoeae* were confirmed by standard techniques, including sugar utilization reactions and the presence of oxidase-positive, gram-negative diplococci which demonstrated brilliant fluorescence when stained by the direct fluorescent-antibody technique. Production of β -lactamase was tested by either the rapid iodometric technique or the chromogenic cephalosporin test (3). MICs were measured by the agar dilution technique as described previously by Wiesner et al. (9).

A computer-generated balance randomization chart for men and women was provided to each center. Patients were assigned, in order of entry, to receive either a single 300-mg oral dose of rosoxacin or 3.5 g of ampicillin plus 1 g of probenecid. The trial was not double blind. Cure was defined as negative cultures for *N. gonorrhoeae* 3 to 8 days after treatment.

To assess drug toxicity pre- and posttreatment, we carried out complete blood counts, platelet counts, a multichannel 12 biochemical screen, and urinalysis. Adverse reactions were determined by direct questioning at the follow-up visit and were classified by their effect on the central nervous system (CNS), gastrointestinal (GI) system, or other body system. CNS dysfunction included dizziness, drowsiness, headache, euphoria, and altered visual perception whereas GI adverse effects included diarrhea, nausea, or vomiting.

The Cochran-Mantel-Haenszel mean score test was applied to the data, and no statistically significant differences were demonstrated between study centers; therefore, all data were pooled for final evaluation. The Fisher exact test was used to examine differences in responses between

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TABLE 1. Results of rosoxacin and ampicillin plus probenecid treatment of uncomplicated genital and anorectal gonococcal infections

Site of infection	No. cured/no. treated (%) with:	
	Rosoxacin	Ampicillin plus probenecid
Men		
Urethra	56/62 (90.3) ^a	67/68 (98.5)
Anal canal	0/0	2/2 (100)
Women		
Endocervix	48/51 (94.1) ^b	49/50 (98)
Anal canal	16/16 (100)	21/21 (100)
Total	104/113 (92) ^c	116/118 (98.3)

^a $P = 0.053$.^b $P = 0.62$.^c $P = 0.031$.

drugs, whereas the chi-square test was utilized to assess adverse reactions.

RESULTS

Results from the five study centers have been combined for each sex. Of 157 males entered, 13 could not be evaluated due to protocol violation and a further 14 could only be evaluated for safety. Therefore, 144 males were evaluated for safety and 130 for efficacy. A total of 130 females were entered with 16 protocol violators and a further 13 only evaluable for safety. In total, 114 females were evaluated for safety and 101 for efficacy. The patients evaluable for safety but not efficacy (protocol violators) either had a negative pretreatment culture, were reexposed to an untreated sexual partner, or did not return for their test of cure within the specified time frame.

Rosoxacin was administered to 71 men and 59 women with the remaining 73 males and 55 females receiving ampicillin plus probenecid. The median age was 25 years for men and 21 for women. There were no significant differences among patient groups with respect to demographic factors.

Table 1 outlines the results of treatment for genital and anorectal infection. Rosoxacin eradicated urethral gonococcal infection in 56 (90.3%) of 62 men compared with 67 (98.5%) of 68 men cured with ampicillin plus probenecid ($P = 0.053$). Symptoms or signs of urethritis persisted in 6 of 7 men in whom treatment failed. The one asymptomatic culture-positive male had received rosoxacin and was symptomatic before treatment. Two men with anorectal gonorrhoea were cured with ampicillin plus probenecid.

Endocervical gonococcal infection was eliminated in 48 (94.1%) of 51 women treated with rosoxacin compared with 49 (98%) of 50 females receiving ampicillin and probenecid ($P = 0.62$). Gonococcal eradication from the anal canal was

achieved in all 16 women receiving rosoxacin and in all 21 receiving ampicillin plus probenecid.

The overall cure rate for men and women with genital or anorectal infection treated with rosoxacin was 104 (92%) of 113, whereas 116 (98.3%) of 118 were cured with ampicillin plus probenecid ($P = 0.031$).

N. gonorrhoeae was isolated from the pharynx of five males. Rosoxacin eradicated the organism from one of two patients and ampicillin plus probenecid was successful in two of the three remaining patients. In females, rosoxacin cured four of five pharyngeal infections, whereas ampicillin plus probenecid eliminated the organism in a further three of five women.

MICs of rosoxacin were determined for 212 pretreatment isolates (Table 2). Of these isolates, 201 (94.8%) were inhibited by ≤ 0.06 $\mu\text{g/ml}$. One PP *N. gonorrhoeae* isolate had a MIC of 0.03 $\mu\text{g/ml}$, and the patient was cured with rosoxacin. The relationship between MICs and cure rates was analyzed, and no consistent trends were found. There was no apparent MIC-cure rate correlation although the number of drug failures was small. MICs for pre- and posttreatment isolates from patients who failed therapy were identical or differed by only one dilution in two cases.

Overall, 29% of rosoxacin-treated patients and 18% of ampicillin-plus-probenecid-treated patients developed adverse effects (Table 3). None of the reactions required medical intervention nor did they result in any serious sequelae. CNS side effects occurred in 31% of females and 28% of males treated with rosoxacin compared with 2% of females and 5% of males, receiving ampicillin plus probenecid. Dizziness was the commonest reaction reported. Six rosoxacin reactions were classified as severe by the patient. Onset occurred 20 min to 4 h after administration of the drug, with the mean duration of symptoms being 5 h (range, 2 min to 72 h). The difference in CNS side effects experienced by the rosoxacin and ampicillin plus probenecid groups is highly statistically significant ($P < 0.001$).

GI disturbances occurred in 5% of females and 4% of males treated with rosoxacin, whereas 11% of females and 15% of males receiving ampicillin plus probenecid reported GI adverse effects. Two men administered ampicillin plus probenecid reported their reaction as severe. The time of onset of GI side effects after administration of ampicillin plus probenecid was generally >4 h with a mean duration of 28 h (range, 30 min to 6 days). The difference in GI side effects observed in the rosoxacin and ampicillin plus probenecid groups is statistically significant ($0.05 > P > 0.02$). However, the difference in overall adverse reactions is not significant ($P > 0.20$). No significant hematological, biochemical, or urinary abnormalities occurred in any patients.

DISCUSSION

The results of this multicentered trial indicate that rosoxacin is an effective agent in the therapy of uncomplicated genital and anorectal gonorrhoea. However, it is of marginal

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

Isolates from:	No. inhibited (%) ^a at an MIC ($\mu\text{g/ml}$) of									
	≤ 0.015	0.02	0.03	0.04	0.06	0.08	0.1	0.25	0.5	
Men	7 (6)	19 (23)	50 (67)	3 (70)	26 (93)	6 (98)			2 (100)	
Women	10 (10)	12 (22)	24 (46)	4 (51)	46 (97)		1 (98)		2 (100)	
Total	17 (8)	31 (22.6)	74 (57.5)	7 (60.8)	72 (94.8)	6 (97.6)	1 (98.1)		4 (100)	

^a All percentages are cumulative.

TABLE 3. Incidence of adverse reactions to rosoxacin and ampicillin plus probenecid

Adverse reaction	No. with side effect (%)			
	Rosoxacin		Ampicillin plus probenecid	
	Women (n = 59)	Men (n = 71)	Women (n = 55)	Men (n = 73)
CNS	18 (31)	20 (28) ^a	1 (2)	4 (5)
GI	3 (5)	3 (4) ^b	6 (11)	11 (15)
Other ^c	1 (2)	1 (1)	2 (4)	3 (4)
Total ^d	18 (31)	20 (28) ^e	8 (15)	15 (21)

^a $P < 0.001$.

^b $0.05 > P > 0.02$.

^c Includes wheezing and muscle weakness.

^d One patient may be counted in more than one category.

^e $P > 0.20$.

significance in the therapy of male gonococcal urethritis when compared with ampicillin plus probenecid and is clearly not an improvement over ampicillin plus probenecid in endocervical gonococcal infections. Overall, a single 300-mg oral dose of rosoxacin cured 104 (92%) of 113 patients including one case of PP *N. gonorrhoeae*. In contrast, 3.5 g of ampicillin plus 1 g of probenecid cured 116 (98.3%) of 118 patients. These results compare favorably to those reported by other authors (2, 5, 6, 7). Handsfield et al. reported a 94% cure rate for men and women treated with 200, 300, or 400 mg of rosoxacin (5).

This study, including one β -lactamase-producing strain, confirms the high level of in vitro activity of rosoxacin against *N. gonorrhoeae*. A review of the literature outlines the potential usefulness of rosoxacin in the therapy of PP *N. gonorrhoeae*. Data originates from seven centers in the Philippines, Indonesia, Kenya, and North America (2; Winthrop Laboratories, personal communication). A total of 115 patients (28 men and 87 women) with uncomplicated urogenital gonorrhea secondary to PP *N. gonorrhoeae* have been treated with a single oral dose of rosoxacin. A 300-mg dose of rosoxacin was administered to 28 males and 67 females with the remaining 20 females receiving 200 mg. All patients with genital and anorectal disease were cured. Four patients with pharyngeal infection also had the organism eradicated. The MIC range for 52 isolates from these studies was 0.008 to 0.31 $\mu\text{g/ml}$ with 94.2% inhibited by 0.06 $\mu\text{g/ml}$. These results present an exciting prospect for the availability of an effective single oral dose agent for the therapy of PP *N. gonorrhoeae*. The results of rosoxacin therapy for uncomplicated gonorrhea due to PP *N. gonorrhoeae* are superior to those achieved for non-PP *N. gonorrhoeae* strains. At this time, the reasons for this remain unclear, but it must be remembered that the total number of patients treated is small and that data originates from seven independent centers. Addi-

tional well-designed clinical trials examining this issue should be undertaken.

Overall, five of seven patients with gonococcal pharyngeal infections treated with rosoxacin were cured. Clearly, this number is too small to arrive at any conclusions.

The high incidence of adverse effects may be partially explained by their subjective nature, taking into account that patients were forewarned about their nature and then directly questioned on adverse effects. The incidence of rosoxacin CNS-related side effects was high; however, they were of short duration, tended to be mild, and cleared without sequelae. The GI side effects from ampicillin plus probenecid were of much longer duration although they also cleared without medical intervention.

Unfortunately, although rosoxacin is active in vitro against both *Chlamydia trachomatis* and *Ureaplasma urealyticum* when administered as single-dose therapy, it is not effective in eradicating coexisting genital infection with *C. trachomatis* (5).

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