Br J Vener Dis 1982;**58**:231-5

Treatment of uncomplicated gonorrhoea in women

Comparison of rosoxacin and spectinomycin

OFELIA V CALUBIRAN, LITA B CRISOLOGO-VIZCONDE, THELMA E TUPASI, CLEOTILDE A TORRES, AND BENJAMIN M LIMSON

From the Infectious Disease Section, Department of Medicine, University of Philippines College of Medicine, Manila, Philippines

SUMMARY A comparative study of the new antibacterial agent, rosoxacin, a quinoline derivative, with spectinomycin was made in women with uncomplicated cervical, urethral, pharyngeal, and rectal gonorrhoea. Rosoxacin was given in three oral regimens: 200 mg in a single dose, 300 mg in a single dose, and 300 mg in two doses of 150 mg four hours apart. All culture results 72 hours after administration were negative for *Neisseria gonorrhoeae* in all 81 women compared with 107 of 109 who received 2 g spectinomycin intramuscularly.

Thirty-five of the women successfully treated with rosoxacin harboured penicillinase-producing strains of *N gonorrhoeae* (PPNG) and 46 non-penicillinase-producing (non-PPNG) strains. Fifty of the women treated with spectinomycin had PPNG strains and 59 non-PPNG strains. Mild self-limiting side effects, principally dizziness, occurred in varying frequency with rosoxacin, but these were difficult to evaluate owing to the characteristics of the patient population and the conditions under which the study was conducted.

Introduction

The emergence in 1957 of gonococcal strains with decreased sensitivity to penicillin[1,2] and in 1979 of penicillinase-producing *Neisseria gonorrhoeae* (PPNG)[3,4] together with recent reports of spectinomycin-resistant mutants,[5,6] particularly in PPNG,[7] have created an urgent need for alternative treatment regimens for gonococcal infections. Rosoxacin, 1-ethyl-1, 4-dihydro-4-oxo-7 (4-pyridyl)-3 quinoline carboxylic acid, is a new synthetic agent with good in-vitro activity against *N gonorrhoeae,* both PPNG and non-penicillinase-producing (non-PPNG) strains. Clinical data show that its use in gonococcal infections is promising but they need to be expanded.[8-10] This study was thus designed to evaluate the clinical efficacy and tolerance of various doses of rosoxacin and to compare them with those of spectinomycin in the treatment of uncomplicated gonorrhoea in women.

Address for reprints: Dr T E Tupasi, Infectious Disease Section, Department of Medicine, University of the Philippines College of Medicine, Pedro Gil Street, Manila, Philippines

Accepted for publication 15 February 1982

Patients and methods

STUDY POPULATION

The study population consisted of prostitutes with uncomplicated gonococcal infection seen at the Balibago Social Hygiene Clinic, Angeles City, between June and August 1980. Patients were enrolled in the study if urethral or cervical screening cultures grew *N gonorrhoeae.* Written informed consent was obtained from each patient before random allocation to a treatment group using a table of random numbers.

Criteria for exclusion from the study included azoquinoline allergy, serious systemic disease, or antimicrobial treatment within the previous week. Women who were pregnant were included only in the group treated with spectinomycin.

STUDY DESIGN

Dose-ranging study

Patients were allocated to treatment with rosoxacin or spectinomycin according to a table of random numbers. A total of 81 women received oral rosoxacin; 32 were given a 200-mg single dose, 21 a 300-mg single dose, and 28 300 mg in two doses of 150 mg four hours apart. One hundred and nine

women received 2 g spectinomycin intramuscularly. The rosoxacin and spectinomycin groups were comparable in age (18-25 years) and weight (38·5-73·0 kg).

Rosoxacin tolerance study

A double-blind crossover oral tolerance study was undertaken in 30 patients divided into two groups of 15 women each. One group (group A) received 300 mg rosoxacin as a single dose on day 1 and a matching placebo tablet on day 2 whereas the other group (group B) received placebo on day 1 and a single dose of 300 mg rosoxacin on day 2.

TREATMENT RESPONSE AND SIDE EFFECTS

The patients were treated in a large ward during the study to ensure follow-up and preclude reinfection before evaluation of treatment results. All patients were asked about their alcohol intake and drug habits, but accurate histories were not always obtainable because of the unreliability of the patient population and their reluctance to admit to the use of drugs.

Cases included in the final analysis of efficacy consisted only of those who had positive pretreatment culture results and interpretable post-treatment culture results. Treatment was considered a failure if *N gonorrhoeae* was isolated from any of the post-treatment cultures.

During the three days of treatment, the patients were interviewed and examined at frequent intervals for signs and symptoms of possible side effects. Direct questions about specific symptoms, particularly those related to the central nervous system, were asked and a positive or negative response obtained. All patients were questioned in the presence of others. At no time in the study was there a need to break the code because of side effects or for other reasons. Side effects were monitored in all patients studied.

LABORATORY TECHNIQUES

Before treatment and three days after, culture specimens were obtained with a cotton swab from the pharynx, urethra, endocervix, and rectum. Specimens were inoculated directly on to modified Thayer-Martin medium and incubated at 35°C in an atmosphere of 5% carbon dioxide. Gonococci were identified by colonial morphology, Gram stain, and oxidase reaction. Isolates from the pharynx were confirmed by sugar fermentation tests. All strains were tested for β-lactamase production by the chromogenic cephalosporin test.[11] Minimum inhibitory concentrations (MICs) of rosoxacin were determined by the standard dilution technique for 88 isolates.[12]

Laboratory monitoring for rosoxacin toxicity included complete blood counts, urine analysis, and measurements of blood urea nitrogen, serum creatinine, serum aspartate aminotransferase, and glucose 6-phosphate dehydrogenase before and 24 hours after treatment. Electrocardiograms were obtained in 20 patients who received a single dose of 300 mg rosoxacin at six and 24 hours after treatment.

Results

SENSITIVITY OF GONOCOCCAL ISOLATES TO ROSOXACIN

The cumulative susceptibility to rosoxacin of 30 PPNG and 58 non-PPNG strains is shown in table I. The range of MICs for the isolates was 0·000001-0·06 μg/ml, with a mean of 0·015 μg/ml for PPNG strains and 0·03 μg/ml for non-PPNG strains. Only one PPNG isolate had an MIC of 0·06 μg/ml of rosoxacin.

TABLE I *Cumulative percentage of N gonorrhoeae isolates inhibited by varying concentrations of rosoxacin*

MIC (μg/ml)	*PPNG*	*Non-PPNG*
0·000001	3	3
0·000002	7	3
0·000005	7	5
0·00001	7	9
0·00002	17	19
0·00005	23	21
0·0001	27	24
0·0002	27	33
0·0005	33	34
0·001	43	50
0·002	50	55
0·005	60	62
0·008	73	74
0·01	83	83
0·03	100	98
0·06		100

MIC = minimum inhibitory concentration; PPNG = pencillinase-producing *N gonorrhoeae;* non-PPNG = non-penicillinase-producing *N gonorrhoeae*

TREATMENT

Rosoxacin

Cervical, urethral, rectal, and pharyngeal culture results after treatment were negative in all 81 patients treated with the three regimens of rosoxacin (table II). All had urethral and endocervical infections; additionally, two patients had a pharyngeal infection while 34 had a rectal infection. Thirty-five (43%) patients with infection due to PPNG strains were cured; 17 received a 200-mg single dose, seven a 300-mg single dose, and 11 a 300-mg split dose. Similarly, all 46 (57%) patients with non-PPNG strains were cured; 15 received a 200-mg single dose, 14 a 300-mg single dose, and 17 a 300-mg split dose.

TABLE II *Efficacy of rosoxacin and spectinomycin treatment in uncomplicated gonococcal infections*

Regimen	PPNG		Non-PPNG	
	No treated	*% Cured*	*No treated*	*% Cured*
Rosoxacin				
200-mg single dose	17	100	15	100
300-mg single dose	7	100	14	100
300-mg split dose	11	100	17	100
Spectinomycin	50	100	59	97

PPNG = penicillinase-producing *N gonorroeae;* non-PPNG = non-penicillinase-producing *N gonorrhoeae*

Spectinomycin

Cervical, urethral, rectal, and pharyngeal culture results after treatment were negative in all but two of the 109 patients treated with spectinomycin (table II). Of those who responded to treatment, all had urethral and endocervical infections; additionally, one had a pharyngeal infection and 32 rectal infections. The difference between the cure rates with rosoxacin and spectinomycin was not statistically significant ($\chi^2 = 0{\cdot}29$; $P > 0{\cdot}05$). There was no difference in the symptomatic response of the two groups. Of those with evaluable symptoms, two of the 51 (4%) patients treated with spectinomycin showed no improvement in symptoms compared with two of the 50 (40%) patients treated with rosoxacin. In both groups those who did not respond symptomatically nonetheless had negative post-treatment culture results for *N gonorrhoeae.*

SIDE EFFECTS

Rosoxacin

The incidence of apparent side effects reported by patients receiving one of the three dosages of rosoxacin are given in table III. Eleven patients were excluded from the evaluation of side effects, since 10 were already taking drugs which affected the central nervous system. Nineteen of 25 (76%) patients taking a single dose of 300 mg, 20 of 30 (67%) taking a split dose of 300 mg, and 17 of 49 (35%) taking a single dose of 200 mg reported one or more side effects. The differences in side effects with the three regimens were statistically significant ($\chi^2 = 14{\cdot}17$, $P < 0{\cdot}05$) because of a significant difference in the side effects noted with the 200-mg single dose compared with the 300-mg single dose ($\chi^2 = 11{\cdot}31$, $P < 0{\cdot}05$) and 300-mg split dose ($\chi^2 = 7{\cdot}64$, $P < 0{\cdot}05$); there was no difference in the incidence of side effects between the 300-mg single dose compared with the 300-mg split dose ($\chi^2 = 0{\cdot}56$, $P > 0{\cdot}05$).

In all but three instances, these side effects were mild and self-limiting. In all but one of the patients they affected the central nervous system: dizziness in 53, vertigo in 20, drowsiness in 17, headache in 19, euphoria in two, and hallucination in one. In addition, two patients taking a single dose of 300 mg had blurred vision. Nausea was reported by five patients taking a single dose of 300 mg, three a split dose of 300 mg, and two a single dose of 200 mg. Most patients with dizziness had mild symptoms and only those taking a single dose of 300 mg (three patients) reported "severe" dizziness. Apart from this there was no correlation between the intensity of the dizziness and the dose of rosoxacin. In most patients the duration of dizziness was less than four hours with all regimens. The incidence of more prolonged dizziness (over four hours) was not correlated with dosage. The symptoms were generally well tolerated and no treatment or restriction of activity was required. No changes in vital signs or physical findings occurred that were thought to be related to the drug.

TABLE III *Side effects in 104 patients taking three different doses of rosoxacin*

	Rosoxacin			
	200-mg single dose	*300-mg single dose*	*300-mg split dose*	*Total**
No enrolled	50	26	39	115
No evaluated	49	25	30	104
No (%) with one or more adverse reaction	17 (35)	19 (76)	20 (67)	
No (%) with adverse reaction of the CNS	17 (35)	18 (72)	20 (67)	
No (%) with blurred vision	0 (0)	2 (4·1)	0 (0)	
No (%) with nausea	2 (4.1)	5 (20)	3 (10)	

CNS = central nervous system

*The total of 115 enrolled includes 81 patients who were evaluated for efficacy as well as 34 who did not meet the criteria for efficacy but were evaluated for side effects

Spectinomycin

Side effects after spectinomycin treatment occurred in 19 of 187 (10%) patients evaluated for safety. These included moderate pain at injection site in nine, headache in eight, dizziness in five, and rashes with pruritus in one.

ROSOXACIN TOLERANCE STUDY

Of the 15 patients in group A who received 300 mg rosoxacin on day 1, four developed side effects within 24 hours after rosoxacin treatment while one had side effects on day 2 after receiving the placebo. Of the 15 patients in group B who received a placebo on day 1, one developed symptoms on day 1 within 24 hours of administration, while seven developed symptoms on day 2 within 24 hours of receiving rosoxacin. Thus, only 11 (37%) of those included in the double-blind tolerance study developed side effects after treatment with rosoxacin. All the 30 patients studied had negative culture results for *N gonorrhoeae* after treatment.

LABORATORY TESTS

No significant changes were noted in blood counts, blood urea nitrogen, serum creatinine, or glucose 6-phosphate dehydrogenase after treatment with rosoxacin. A slight transient increase in serum aspartate transaminase values occurred in six patients. Mild transient haematuria was noted in four patients and pyuria increased in eight. Of the 20 patients given a 300-mg single dose in whom electrocardiography was performed, two developed sinus arrhythmia six hours after treatment; in one patient this arrhythmia had reverted to normal 18 hours later.

Discussion

All 81 cases of uncomplicated gonorrhoea in these female patients, including 35 PPNG infections, were cured by rosoxacin. This shows that all the three regimens were effective in producing a bacteriological cure. Our data conform with those of earlier studies showing a 100% cure rate with a 300-mg dose. The result with the 200-mg dose was better than the 66·7% cure rate previously reported[8] and significantly better than the results obtained in male patients where no cure was noted in eight cases (unpublished data). A lower dose of 100 mg has been tried in Europe, but in the first three cases treatment failed; thus it is considered to be unacceptable.[8] The clinical response to rosoxacin was consistent with its excellent in-vitro activity, with MICs of 0·06 μg/ml or less for non-PPNG as well as for PPNG strains.

This study was undertaken in a locality where PPNG accounts for 30-40% of gonococcal infections,[13-15] which could not have been eradicated by penicillin treatment. This high incidence has led to the increased use of spectinomycin, which may result in the selection of spectinomycin-resistant mutants.[7 16 17] Our findings showed that rosoxacin, either in a 200-mg single dose, 300-mg single dose, or 300-mg split dose, compared favourably with spectinomycin in the treatment of uncomplicated gonorrhoea in women. Since rosoxacin may be given orally in a single dose it appears to be a reasonable alternative to spectinomycin, particularly when penicillin-resistant gonorrhoea is prevalent.

An obvious disadvantage of this drug is the high incidence of side effects, as seen in this study. The apparent incidence appeared to increase with dosage. The frequency of apparent side effects in the double-blind tolerance study, however, was about one-half that in the open-dose study among patients who received the same 300-mg single dose of rosoxacin. The discrepancy between these two groups, studied under the same conditions and taking the same dosage, cannot be explained, and may well illustrate the difficulty in drawing conclusions from these findings. Moreover, the incidence of reported side effects in this study was much higher than that found in other studies conducted in several hundred patients in Europe, the USA, South America, and other Asian countries (unpublished data). In addition, a lower incidence of side effects of 14% was noted in Filipino men receiving a 300-mg single dose in a concurrent study.[18] Although the difference in mean body weights between the male and female Filipinos (65·6 kg compared with 47·5 kg respectively) might be considered to be a contributory factor, there appeared to be no correlation between apparent side effects and body weight within the group of women receiving a single dose of 300 mg rosoxacin. The mean body weight in those reporting notable side effects was 46·7 kg compared with 46·2 kg in those with no or negligible apparent side effects. Thus, the influence of body weight is not clear.

The evaluation of these apparent side effects, primarily dizziness, was difficult because of the very nature of the study population and the methods used to determine them. These limitations were to be expected since the study was undertaken among prostitutes, who are highly susceptible to suggestion and yet in whom only direct questioning could be used to obtain answers about side effects. The fact that alcohol and drug abuse are indispensible features of their profession prevent any definitive conclusions about the frequency, type, and intensity of side effects attributable to rosoxacin in this study, since by themselves these two abuses may account for some of the side effects complained of. What is clear is that the side effects are generally mild and self-limiting.

This project was supported by the National Research Council of the Philippines and the Winthrop-Stearns Philippines. The study was conducted in accordance with the guidelines for human experimentation set forth by the Declaration of Helsinki and the Committee on Research, Ethics and Development of the UP Health Sciences Center.

References

1. Thayer JD, Field FW, Magnuson HJ, *et al.* Sensitivity of gonococci to penicillin and its relation to treatment failures. *Antibiot Chemother* 1957; **7**: 306-10.
2. Curtis FR, Wilkinson AE. A comparison of the in-vitro sensitivity of gonococci to penicillin with the results of treatment. *Br J Vener Dis* 1958; **34**: 70-82.
3. Ashford WA, Golash RG, Heming VG. Penicillinase-producing *Neisseria gonorrhoeae. Lancet* 1976; ii: 657-8.
4. Phillips I. Beta-lactamase-producing, penicillin-resistant gonococcus. *Lancet* 1976; ii: 656-7.
5. Thornsberry C, Jaffe J, Brown ST, *et al.* Spectinomycin-resistant *Neisseria gonorrhoeae. JAMA* 1977; **237**: 2405-6.
6. Shtibel R. Resistance of cultures of *Neisseria gonorrhoeae* to spectinomycin. *Can Med Assoc J* 1978; **119**: 1006.
7. Center for Disease Control. Spectinomycin-resistant penicillinase-producing *Neisseria gonorrhoeae. Morbidity and Mortality Weekly Report* 1981; **30**: 221-2.
8. Sterling-Winthrop Research Institute. *A Summary of Laboratory and Clinical Data for Rosoxacin Oral.* New York: Rensselaer, 1979.
9. O'Connor JR, Dobson RA, Came PE, *et al.* Rosoxacin: a new synthetic agent for the treatment of systemic Gram-negative infections. *Proceedings of the 11th International Congress of Chemotherapy and 19th Interscience Conference on Antimicrobial Agents and Chemotherapy.* Washington DC: American Society for Microbiology, 1979.
10. Limson BM, Macasaet RK. Rosoxacin (Win 35, 213), a new antigonococcal agent: double-blind study of three dose regimens. *Phil J Int Med* 1979; **17**: 123-7.
11. O'Callaghan CH, Kirby SM, Morris A, *et al.* Correlation between hydrolysis of the lactam bond of cephalosporin in nucleus and expulsion of the 3 substituent. *J Bacteriol* 1972; **110**: 988-91.
12. Biddle JW, Swenson JM, Thornsberry C. Disc agar diffusion antimicrobial susceptibility tests with β-lactamase-producing *Neisseria gonorrhoeae. J Antibiot* 1978; **31**: 352-8.
13. Crisologo LB, Torres CA, Tupasi TE. Problems and tentative solutions in the control of gonorrhea in the community. *Phil J Int Med* 1979; **17**: 112-5.
14. Siegel MS, Perine PL, Westbrook WG, *et al.* Epidemiology of penicillinase-producing *Neisseria gonorrhoeae:* In: Brooks GS, Gotschlich EC, Holmes KK, *et al,* eds. *Immunology of Neisseria gonorrhoeae.* Washington DC: American Society for Microbiology, 1978; 75-9.
15. Tupasi TE, Calubiran OV, Torres CA. Single oral dose of cefaclor for the treatment of infections with penicillinase-producing strains of *Neisseria gonorrhoeae. Br J Vener Dis* 1982; **58**: 176-9.
16. Reyn A, Schmidt H, Trier M, *et al.* Spectinomycin hydrochloride (Trobicin) in the treatment of gonorrhoea. *Br J Vener Dis* 1973; **48**: 58-61.
17. Maness MJ, Foster GC, Sparking PF. Ribosomal resistance to streptomycin and spectinomycin in *Neisseria gonorrhoeae. J Bacteriol* 1974; **120**: 1293-9.
18. Limson BM, Macasaet RK. Single oral dose rosoxacin in the treatment of gonorrhea in males. *J Int Med Res* 1982; **10**: 42.