

Treatment of uncomplicated gonorrhoea with rosoxacin (acrosoxacin)

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SUMMARY An open study was designed primarily to evaluate the efficacy of rosoxacin in the treatment of gonorrhoea caused by penicillinase producing *Neisseria gonorrhoeae* (PPNG) and non-PPNG strains. A total of 199 patients (99 men and 100 women) satisfactorily completed follow up examinations, 50 men and 50 women having received rosoxacin 300 mg orally and the remainder having received kanamycin 2 g intramuscularly. Rosoxacin achieved an overall cure rate of 94% (96.7% for PPNG and 90% for non-PPNG strains). In patients treated with kanamycin the overall cure rate was 89.9% (92.7% for PPNG and 83.3% for non-PPNG strains). A correlation between treatment failures and minimum inhibitory concentrations (MICs) of rosoxacin was noted in non-PPNG strains but not in PPNG strains. Side effects which were mild and self limiting were noted in 15 of 100 patients treated with rosoxacin. The high failure rates associated with non-PPNG strains requiring MICs of 0.125 mg/l and the observation of a substantial rise in the MICs for isolates after treatment is of concern. Otherwise, rosoxacin in a single dose of 300 mg appears to be safe and effective for the treatment of uncomplicated gonorrhoea.

Introduction

Gonococcal strains, especially those in the Far East, have been able to develop increasing levels of resistance to penicillin. This has been further complicated by the emergence of penicillinase producing *Neisseria gonorrhoeae* (PPNG) strains, which were first isolated in Singapore in 1976. Since then PPNG strains have become endemic, and in 1982 accounted for 2413 cases or 34.5% of all gonococcal isolates in Singapore. Like many countries in the Far East, Singapore has witnessed increasing failure rates with penicillin, and there is a constant need to evaluate new antimicrobials.

Rosoxacin is a quinolone antimicrobial agent structurally related to nalidixic acid. In vitro tests have confirmed that rosoxacin has potent activity against a broad spectrum of Gram negative bacteria including *N gonorrhoeae*. It is well absorbed by the oral route, with serum concentrations reaching 6.2 mg/l one hour after a single 300 mg dose.¹ This is well above the reported minimum inhibitory concentrations (MICs) of 0.015-0.125 mg/l for PPNG and non-PPNG strains.²

This study was designed to determine the efficacy of rosoxacin in the treatment of PPNG and non-PPNG infections. Comparisons were made with patients treated with kanamycin, an agent used commonly in Singapore for the treatment of gonorrhoea.

Patients and methods

STUDY POPULATION

Two hundred patients with acute gonorrhoea (100 men and 100 female prostitutes) were included in the trial. Patients with a history of hypersensitivity to quinolone and azaquinolone drugs, renal disease, urinary tract obstruction, liver and biliary disease, central nervous system disease, gastrointestinal disease, disseminated gonococcal infections, uncontrolled diabetes mellitus, or serious haemopoietic disease were excluded. Pregnant women and patients who had received antimicrobial treatment less than 72 hours before the start of the trial were also excluded.

DIAGNOSES

Gonorrhoea was diagnosed on the finding of Gram negative intracellular diplococci in stained smears or on the isolation of *N gonorrhoeae* on culture, or on both. Men whose urethral smears gave positive

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results were entered into the trial. All diagnoses were confirmed by culture and included infections caused by PPNG and non-PPNG strains. Only women with gonococcal cervicitis due to PPNG strains were recruited into the study. Gonococcal isolates were identified by their colonial morphology on modified Thayer-Martin medium, oxidase reaction, and Gram stained microscopical appearance. Penicillinase production was tested for in all isolates by the paper acidometric method.³

TREATMENT

Fifty men and 50 women received a single 300 mg dose (two 150 mg capsules) of rosoxacin while the remaining 100 patients received 2 g of kanamycin in a single intramuscular injection.

FOLLOW UP AND TESTS OF CURE

The patients were assessed on day 3 or 4 and day 14 after treatment. Urethral smears and cultures were obtained from the men and only cervical cultures from the women at each visit. Treatment was considered to have failed if the culture gave positive results on day 3 or 4 and the patient denied further sexual intercourse. If gonococci were isolated on day 14 and the patient admitted sexual intercourse reinfection was assumed to have occurred. Serum was tested for cardiolipin antibodies, using the Venereal Diseases Research Laboratory (VDRL) test, before and six weeks and three months after treatment.

Results

TREATMENT RESPONSE

Table I shows the details of treatment response. One man did not attend for follow up tests and was excluded from the study, leaving 99 men and 100 women for assessment.

The overall cure rate with rosoxacin was 94% (96.7% for PPNG and 90% for non-PPNG strains) while the overall cure rate with kanamycin was

89.9% (92.7% for PPNG and 83.3% for non-PPNG strains). Although rosoxacin achieved a better overall cure rate than kanamycin, the difference was not significant ($\chi^2 = 0.64$; $0.5 > p > 0.1$). The numbers involved, however, were small. Rosoxacin was also more successful in eradicating PPNG infections in women (98% cure rate) than in men (90% cure rate), the reason for which is not clear.

SIDE EFFECTS

Side effects were reported by 15 of the 100 patients treated with rosoxacin; 12 complained of dizziness, one of malaise, one of drowsiness, and one of gastritis. All these side effects were mild and transient.

ANTIBIOTIC SUSCEPTIBILITY

Antibiotic susceptibility tests were performed on 129 PPNG and 70 non-PPNG isolates. The MICs of rosoxacin were measured by the agar plate dilution method described previously.⁴ Table II shows that the range of MICs was identical (0.008-0.125 mg/l) for PPNG and non-PPNG strains. Their geometric means were 0.0304 and 0.03525 mg/l respectively.

TABLE II Number of strains of *N gonorrhoeae* inhibited by various concentrations of rosoxacin

Strains	Minimum inhibitory concentrations (mg/l):				
	0.008	0.016	0.03	0.06	0.125
PPNG (n = 129)	9	10	27	59	24
Non-PPNG (n = 70)	6	14	17	26	7

We examined the MICs of rosoxacin and benzyl penicillin for 29 PPNG and 70 non-PPNG isolates. When all isolates were considered together, correlation between the MICs of both agents was poor (correlation coefficient (r) = 0.24). The correlation was equally poor when PPNG and non-PPNG isolates were considered separately (r = 0.26 and 0.18 respectively).

TABLE I Treatment response of 99 men and 100 women (29 men and all women infected with PPNG strains to rosoxacin or kanamycin

Treatment	Strains	No (%) cured			No (%) treatment failures	
		Men	Women	Total	Men	Women
Rosoxacin 300 mg	PPNG (n = 10m, 50f)	9 (90.0)	49 (98.0)	58 (96.7)	1 (10.0)	1 (2.0)
	Non-PPNG (n = 40m)	36 (90.0)	0	36 (90.0)	4 (10.0)	0
	Total (n = 100)			94 (94.0)		
Kanamycin 2g	PPNG (n = 19m, 50f)	16 (84.2)	48 (96.0)	64 (92.7)	3 (15.7)	2 (4.0)
	Non-PPNG (n = 30m)	25 (83.3)	0	25 (83.3)	5 (16.7)	0
	Total (n = 99)			89 (89.9)		

Table III shows the results of rosoxacin treatment and the MICs for gonococcal isolates from 40 of the men treated with rosoxacin. Treatment failed to eradicate three (43%) of seven non-PPNG strains with MICs of 0.125 mg/l compared with one (3%) of 33 non-PPNG strains with MICs of 0.008-0.06 mg/l.

TABLE III Correlation of *in vitro* susceptibility of non-PPNG isolates from 40 men and *in vivo* response to rosoxacin (percentages in parentheses)

Response to treatment	Minimum inhibitory concentrations (mg/l):	
	0.125	0.008-0.06
Success	4 (57.1)	32 (97.0)
Failure	3 (42.9)	1 (3.0)

The correlation between treatment response and the MICs of non-PPNG strains is further illustrated in the figure. Such a correlation did not emerge when we examined the MICs of PPNG isolates from the remaining 10 men and 50 women (see table IV).

We measured MICs for isolates obtained after treatment from patients who were treatment failures. Two isolates showed a significant rise in the MIC: one (a non-PPNG strain) showed an increase from 0.125 mg/l before treatment to 4 mg/l after treatment, and another (a PPNG strain) showed an increase from 0.06 mg/l to 2 mg/l.

Discussion

The ability of gonococci to evolve into more resistant strains and the emergence of penicillinase producing strains emphasise the need to evaluate new

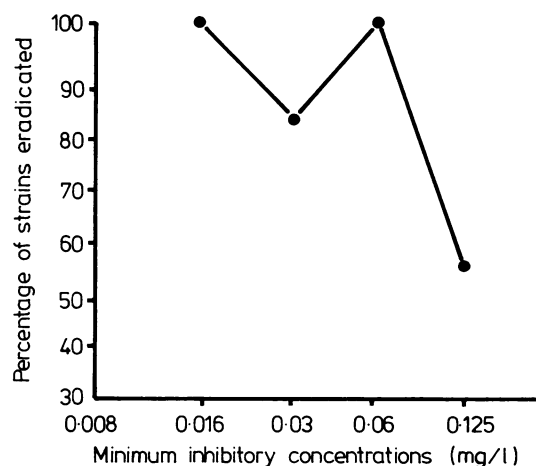


FIGURE Correlation of *in vitro* susceptibility of non-PPNG strains and response to rosoxacin.

TABLE IV Correlation of *in vitro* susceptibility of PPNG isolates from 10 men and 50 women and *in vivo* response to rosoxacin (percentages in parentheses)

Response to treatment	Minimum inhibitory concentrations (mg/l):	
	0.125	0.008-0.06
Success (Men) (Women)	3 11	6 38
Failure (Men) (Women)	0 0	1 1

14 (100) 44 (95.7)
0 2 (4.3)

antimicrobial agents. Owing to variations in the antimicrobial susceptibility of strains between regions, an antimicrobial agent shown to be effective in clinical trials conducted in one region still needs to be evaluated in the population for which it is intended before its use can be recommended. Many antibiotics, such as tetracyclines and co-trimoxazole, which were found to be effective in the treatment of gonorrhoea in other countries have been found to be less effective in Singapore.⁵

In this study, an overall cure rate of 94% was obtained with rosoxacin, which eradicated 96.7% of infections caused by PPNG strains and 90% caused by non-PPNG strains. Comparable results have been reported, with overall cure rates of 94-100% using similar doses of rosoxacin.⁶⁻¹⁰

Handsfield *et al* reported that treatment with rosoxacin failed to eradicate all three non-PPNG strains that required MICs of ≥ 0.125 mg/l.⁶ The patients whose isolates required MICs of 0.125 mg/l and 1.0 mg/l were each treated with 100 mg of rosoxacin while the remaining patient infected with an isolate requiring a MIC of 0.25 mg/l received 400 mg of rosoxacin. Although the dosages used are different from those used in this study, our results and theirs suggest that non-PPNG strains requiring MICs of 0.125 mg/l or higher may be resistant. Warren *et al* found a good correlation between the MICs of benzyl penicillin and rosoxacin for isolates moderately resistant to penicillin (MICs of benzyl penicillin of 0.06-1 mg/l),¹¹ and suggested that the penetration barrier of gonococci moderately resistant to penicillin may also be effective to some extent against rosoxacin. Our results, however, showed that there was little correlation between the MICs of the two agents. Nevertheless, a penetration barrier to rosoxacin exists, though this may be distinct from that effective against penicillin. Penetration may be improved by using larger or additional doses of rosoxacin. Further studies would be necessary to evaluate the efficacy of such regimens. Our results also suggest that PPNG strains in Singapore are more susceptible to rosoxacin regardless of the MICs.

This study confirms that rosoxacin has good overall efficacy against *N gonorrhoeae*. Rosoxacin permits simple, single dose oral treatment and is well tolerated. Side effects were mild and transient, but nevertheless, patients should be warned about them. One observation which caused some concern was a significant rise in the MIC for isolates obtained after treatment from two patients whose treatment had failed. All patients whose treatment failed were interviewed again and although we cannot absolutely exclude the possibility of reinfection, we felt it was unlikely for the following reasons. The first follow up test was performed only 72 hours after treatment. Secondly, the patients were interviewed again and reminded of the objectives of this study and the importance of truthfulness, and we therefore have no reason to doubt their word. We were not, however, able to serotype the strains and therefore it was impossible to ascertain whether the increase in MIC represented selection of more resistant clones or induction of resistance. The possible mechanism should be investigated.

In conclusion, the use of rosoxacin may be considered in areas where PPNG strains are prevalent, but its use should be limited to centres with good follow up facilities.

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