In-vitro antigonococcal activity of rosoxacin (WIN 35213)

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SUMMARY The in-vitro activity of rosoxacin against 173 isolates of *Neisseria gonorrhoeae*, including 17 β -lactamase-producers, was tested by an agar dilution method. Of the isolates, 167 (including 16 of the β -lactamase-producers) were inhibited by 0.06 mg/l of rosoxacin. The remaining six isolates, one of which produced β -lactamase and the others were moderately resistant to penicillin, were inhibited by 0.12-0.25 mg/l of the compound. There was little correlation between the minimum inhibitory concentrations (MICs) of rosoxacin and penicillin, except for isolates with MICs of penicillin of 0.06-1 mg/l, for which correlation was good.

Introduction

Rosoxacin (WIN 35213) is an antibacterial agent chemically related to nalidixic acid (fig 1). Appreciable activity against *Neisseria gonorrhoeae* has been noted¹ (Sterling Winthrop, unpublished data). In this paper we report the activity of rosoxacin against 173 isolates of *N gonorrhoeae*, including 17 β -lactamase-producers, and correlate this activity with that of benzylpenicillin.

Materials and methods

All the isolates of *N gonorrhoeae*, including the β -lactamase-producers, were from patients attending the Department of Genitourinary Medicine at St Thomas' Hospital. Those isolates that did not produce β -lactamase were fresh isolates collected in November 1979.

All isolates were identified by characteristic staining with a specific antigonococcal fluorescent antibody conjugate (Difco). Sugar-fermentation reactions were determined for a number of isolates, including the few that gave weak reactions in the fluorescent antibody test.

Minimum inhibitory concentrations (MICs) were determined by an agar dilution method. Suspensions of gonococci were prepared by scraping bacterial growth off lysed blood agar (Oxoid Diagnostic

FIG 1 The chemical structures of rosoxacin and nalidixic acid.

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Sensitivity Test Agar, CM 271, plus 6% saponin-lysed horse blood) and suspending the organisms in nutrient broth. The inoculum consisted of about 10^4 colony-forming units delivered by a multi-point inoculator. Antibiotics were incorporated, in suitable doubling dilutions, in lysed blood agar and results were read after overnight incubation of the plates in 10% carbon dioxide.

Disc tests were performed by spreading the organism over the surface of a lysed blood agar plate to produce semi-confluent growth. A filter-paper disc containing 5 μ g of rosoxacin was placed on the surface. The diameter of the zone of inhibition was measured after overnight incubation in 10% carbon dioxide.

Results

The range of MICs of rosoxacin was narrow, 0.016–0.25 mg/l, in contrast to that of benzylpenicillin (fig 2). Correlation between the

FIG 2 Comparison of the MICs of benzylpenicillin and rosoxacin. ———— calculated line of best fit when MICs for all isolates were included; — — — — — line of best fit when MICs for isolates that produced β -lactamase were excluded; line of best fit for MICs for isolates with MICs of benzylpenicillin of 0.06–1 mg/l.

MICs of benzylpenicillin and those of rosoxacin was poor (correlation coefficient $r=0.17$) but was better if the β -lactamase-producers were excluded ($r=0.48$). When only isolates with MICs of benzylpenicillin of 0.06–1 mg/l inclusive were considered, correlation between MICs of the two agents was good ($r=0.76$). The geometric mean MIC of rosoxacin for penicillin-sensitive isolates—that is those with MICs of 0.03 mg/l or less—was 0.025 mg/l; for isolates that were moderately resistant to penicillin it was 0.034 mg/l, which was

significantly if only slightly higher ($P=0.001$ by Student's t test). The mean MIC of rosoxacin for the β -lactamase-producers was 0.024 mg/l, which was very similar to that for penicillin-sensitive isolates.

Inverse correlation between the diameter of the zone of inhibition produced by a 5- μ g disc of rosoxacin and the MIC of rosoxacin was poor ($r=-0.24$; fig 3). This may reflect the narrow range of MICs of rosoxacin for gonococci.

FIG 3 Comparison of the MICs of rosoxacin with diameters of the zones of inhibition around 5- μ g discs of rosoxacin.

Discussion

From its in-vitro activity rosoxacin appears to be a promising agent against the gonococcus. However we did not find the compound to be quite so active as did other workers who reported all isolates to be inhibited by 0.05 mg/l (Sterling Winthrop, unpublished data). The sensitivity of β -lactamase-producers to rosoxacin is not surprising since the compound is unrelated to the β -lactams. On the other hand, the good correlation between MICs of rosoxacin and benzylpenicillin for moderately penicillin-resistant gonococci suggests that their penetration barrier to penicillin is also effective to some extent against rosoxacin, as it is against some other agents.^{2,4} Nevertheless, the MICs of rosoxacin for these moderately penicillin-resistant isolates were well below the peak plasma concentrations of rosoxacin, which are about 6 mg/l after a single dose of 300 mg (Sterling Winthrop, unpublished data).

In clinical trials a single dose of 300 mg of rosoxacin has been found to be generally effective in the treatment of acute gonorrhoea (Sterling Winthrop, unpublished data). Treatment failures do not appear to be associated with bacterial resistance.

β -lactamase-producing gonococci were sensitive to rosoxacin, as to several other agents, and should present no problem in therapy. However, non- β -lactamase-producing moderately penicillin-resistant gonococci can be the most difficult to treat. Although rosoxacin was less active against isolates of this type than against other isolates, the reduction in activity was mostly small and should not diminish clinical effectiveness.

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