Treatment of uncomplicated gonorrhoea in women
Comparison of rosoxacin and spectinomycin

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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 penicillin1 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.

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 azonequinoline 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. Minimum inhibitory concentrations (MICs) of rosoxacin were determined by the standard dilution technique for 88 isolates.

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>
<thead>
<tr>
<th>MIC (μg/ml)</th>
<th>PPNG</th>
<th>Non-PPNG</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.000001</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>0.000002</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>0.000005</td>
<td>7</td>
<td>5</td>
</tr>
<tr>
<td>0.00001</td>
<td>7</td>
<td>9</td>
</tr>
<tr>
<td>0.00002</td>
<td>17</td>
<td>19</td>
</tr>
<tr>
<td>0.00005</td>
<td>23</td>
<td>21</td>
</tr>
<tr>
<td>0.0001</td>
<td>27</td>
<td>24</td>
</tr>
<tr>
<td>0.0002</td>
<td>27</td>
<td>33</td>
</tr>
<tr>
<td>0.0005</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td>0.001</td>
<td>43</td>
<td>50</td>
</tr>
<tr>
<td>0.002</td>
<td>50</td>
<td>55</td>
</tr>
<tr>
<td>0.005</td>
<td>60</td>
<td>62</td>
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<td>74</td>
</tr>
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<td>0.01</td>
<td>83</td>
<td>83</td>
</tr>
<tr>
<td>0.03</td>
<td>100</td>
<td>98</td>
</tr>
<tr>
<td>0.06</td>
<td></td>
<td>100</td>
</tr>
</tbody>
</table>

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.
The differences in side effects with the three regimens were statistically significant \((\chi^2 = 14.17, P < 0.05)\) because of a significant difference in the side effects noted with the 200-mg single dose compared with the 300-mg single dose \((\chi^2 = 11.31, P < 0.05)\) and 300-mg split dose \((\chi^2 = 7.64, P < 0.05)\); there was no difference in the incidence of side effects between the 300-mg single dose compared with the 300-mg split dose \((\chi^2 = 0.56, P > 0.05)\).

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**

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

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.

Roxocacin Tolerance Study

Of the 15 patients in group A who received 300 mg roxocacin on day 1, four developed side effects within 24 hours after roxocacin 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 roxocacin. Thus, only 11 (37%) of those included in the double-blind tolerance study developed side effects after treatment with roxocacin. 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 roxocacin. 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 roxocacin. 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 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. The clinical response to roxocacin 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, 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. Our findings showed that roxocacin, 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 roxocacin 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 roxocacin. 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. 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 roxocacin. 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 indispensable features of their profession prevent any definitive conclusions about the frequency, type, and intensity of side effects attributable to roxocacin 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.
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