Cefaclor and cefamandole as alternatives to spectinomycin in the treatment of men with uncomplicated gonorrhoea

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SUMMARY Between 25 December 1981 and 11 March 1982, 400 men with uncomplicated gonococcal urethritis were randomly assigned to one of four treatment regimens: spectinomycin 2 g intramuscularly (group A); cefamandole 1 g intramuscularly after probenecid 1 g orally (group B); cefaclor 3 g orally with probenecid 1 g orally (group C); and cefaclor 3 g orally (group D).

The cure rates were 91 of 92 (98·9%) in group A, 68 of 96 (70·8%) in group B, 88 of 92 (95·8%) in group C, and 86 of 96 (89·6%) in group D.

Cefaclor at a dose of 3 g given orally with 1 g probenecid appears to be an effective alternative to spectinomycin 2 g in the treatment of gonorrhoea in areas where strains of penicillinase producing Neisseria gonorrhoeae (PPNG) are prevalent.

Introduction

For many years gonococci from south east Asia including Thailand have been less susceptible to antimicrobials than have isolates of Neisseria gonorrhoeae from other areas of the world. In 1978 Suvannamalik reported that 97·9% of the strains isolated in Bangkok, Thailand, were less sensitive to penicillin. Since penicillinase producing N gonorrhoeae (PPNG) strains were first isolated in 1976 these organisms have been found in a large proportion of all gonococcal isolates in Thailand. In 1981 42·9% to 48·9% of strains of N gonorrhoeae isolated in Bangkok were reported to be PPNG. Spectinomycin 2 g and cefoxitin 2 g plus probenecid 1 g are effective approved single dose treatments for uncomplicated gonococcal infections and are recommended by the United States Public Health Service for the treatment of PPNG infections.

Cefaclor is a semisynthetic cephalosporin which is absorbed when given orally. It differs from cephalxin in the substitution of a chloro group for the methyl group of cephalxin. Cefamandole is another semisynthetic broad spectrum cephalosporin antibiotic but is given parenterally. It is the sodium salt of 7-D-mandelamido-3-[(1-methyl-1H-tetrazol-5yl)-thio[methyl]-3-cepthem-4-carboxylic acid, formate(ester). In vitro sensitivities suggest that cefaclor and cefamandole might be effective alternatives to spectinomycin for treating uncomplicated gonococcal infection. This study was undertaken to determine the efficacy of cefaclor and cefamandole in the treatment of men with uncomplicated gonococcal infections caused by both penicillinase producing N gonorrhoeae (PPNG) and non-PPNG.

Patients and methods

STUDY DESIGN

Men attending the Bangrak Hospital, Bangkok, Thailand, during the period 25 December 1981 to 11 March 1982 who were diagnosed as having uncomplicated gonorrhoea were selected for the study. A total of 400 men, all of whom were Thai, was assigned randomly (using a random number table) to one of four treatment groups. Each group contained 100 patients and treatments were: spectinomycin 2 g intramuscularly (group A); cefamandole 1 g intramuscularly plus 1 g probenecid orally (group B); cefaclor 3 g plus 1 g probenecid orally (group C); and cefaclor 3 g orally (group D).

DIAGNOSIS

Diagnoses were based on the finding of Gram negative intracellular diplococci (GNDC) in Gram stained urethral smears, which were examined in the clinic, and on the results of cultures of specimens
taken from the urethra. These were inoculated directly onto Thayer-Martin medium, incubated at 35°C in an atmosphere of carbon dioxide, and examined after 24 and 48 hours. Blood was also taken from each patient for routine serological tests for syphilis. The diagnosis of gonorrhoea was based on culture of *N gonorrhoeae*. Isolates were confirmed as gonococci by sugar fermentation reactions. The colonies were subcultured for determination of the presence of PPNG by the rapid iodometric method. The confirmed gonococcal isolates were tested later for antibiotic sensitivity by agar plate dilution techniques.

**FOLLOW UP**

Follow up visits were arranged for 1, 4, 7, and 14 days after treatment. Specimens for smear microscopy and culture were taken from the urethra on each occasion. Routine serological tests for syphilis were performed at monthly intervals for three months.

If gonococci persisted or reappeared within 14 days after treatment and further sexual intercourse was denied by the patient treatment was considered to have failed. The reappearance of gonococci after 14 days, irrespective of the patient's history, was considered to be due to reinfection. Those who admitted sexual exposure before the first follow up examination were excluded from the final assessment.

Any patients with microscopical or cultural evidence of gonococcal infection at follow up visits were treated with spectinomycin 2 g or cefotaxime 500 mg given intramuscularly, those treated with cefotaxime were given probenecid 1 g orally before the injection.

**STATISTICAL ANALYSIS**

The unpaired *t* test and the χ² test were used.

### Table 1: Results of four treatment schedules in men with uncomplicated gonorrhoea caused by PPNG and non-PPNG strains

<table>
<thead>
<tr>
<th>Treatment schedule</th>
<th>PPNG strains</th>
<th>Non-PPNG strains</th>
<th>Not tested</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Spectinomycin only (group A):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No assessed</td>
<td>33</td>
<td>59</td>
<td>0</td>
<td>92</td>
</tr>
<tr>
<td>No (%) cured</td>
<td>33 (100)</td>
<td>58 (98·3)</td>
<td>0</td>
<td>91 (98·9)+++</td>
</tr>
<tr>
<td>Probenecid plus cefamandole (Group B):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No assessed</td>
<td>42</td>
<td>53</td>
<td>1</td>
<td>96</td>
</tr>
<tr>
<td>No (%) cured</td>
<td>30 (71·4)</td>
<td>37 (69·8)</td>
<td>1 (100)</td>
<td>68 (70·8)</td>
</tr>
<tr>
<td>Probenecid plus cefaclor (group C):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No assessed</td>
<td>27</td>
<td>64</td>
<td>1</td>
<td>92</td>
</tr>
<tr>
<td>No (%) cured</td>
<td>25 (92·6)</td>
<td>62 (96·9)</td>
<td>1 (100)</td>
<td>88 (95·7)+</td>
</tr>
<tr>
<td>Cefaclor only (group D):</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No assessed</td>
<td>36</td>
<td>59</td>
<td>1</td>
<td>96</td>
</tr>
<tr>
<td>No (%) cured</td>
<td>30 (83·3)</td>
<td>55 (93·2)</td>
<td>1 (100)</td>
<td>86 (89·6)+</td>
</tr>
</tbody>
</table>

*χ² = 2·51 (p<0·01)

**Results**

A total of 400 patients was enrolled in the study. Of these, 24 patients were excluded, seven because *N gonorrhoeae* did not grow in the initial culture and 17 because the patients defaulted after treatment. There were therefore 92 patients in group A, 96 in group B, 92 in group C, and 96 in group D. Table I shows the results of the four treatment schedules.

Of the 400 patients 393 had positive culture results. Of these, 390 isolates were tested for the presence of β-lactamase. PPNG strains were shown in 146 of 390 (37·4%) isolates tested and 244 of 390 (62·6%) were non-PPNG strains.

**ANTIBIOTIC SENSITIVITIES**

Table II shows the minimum inhibitory concentrations (MIC) of spectinomycin, cefaclor, and cefamandole for PPNG and non-PPNG strains tested. The unpaired *t* test was used to determine the significance of the difference between the mean MICs for PPNG and non-PPNG strains. The mean MIC of spectinomycin was 8·26 μg/ml for PPNG strains and 7·8 μg/ml for non-PPNG strains (significant difference *t* = 3·459 *p*<0·01). The mean MIC of cefaclor was 5·29 μg/ml for PPNG and 2·04 μg/ml for non-PPNG strains (significant difference *t* = 11·897 *p*<0·01). The mean MIC of cefamandole was 7·57 μg/ml for PPNG and 2·28 μg/ml for non-PPNG strains (significant difference *t* = 14·375 *p*<0·01).

**SIDE EFFECTS**

One patient who was treated with cefaclor complained of generalised itching all over the body at night after treatment. He was examined on the day after treatment, when he came for follow up, but no
skin lesions were found. One patient who received cefamandole developed palpitations, giddiness, and conjunctivitis 15 minutes after the injection.

Discussion

Although spectinomycin is a drug which produces acceptable cure rates in the treatment of PPNG and is recommended in the treatment of infections with such strains, attempts to find some alternative agent are necessary.4 6 12 13 Many new cephalosporins including cefuroxime, cefotaxime, and cefoxitin, are highly effective in the treatment of gonococcal infections caused by both PPNG and non-PPNG strains.4 5 14-22

Cefaclor is another new cephalosporin which can be given orally and is effective in the treatment of gonococcal urethritis in men in doses of 2-4 g with or without probenecid.23 Harrison reported the success of cefaclor at a total dosage of 7 g without probenecid in separate doses over three days in the treatment of men with uncomplicated gonococcal urethritis caused by both PPNG and non-PPNG strains.24 Tupasi et al reported a cure rate of 93% after a single oral dose of 3 g cefaclor in the treatment of uncomplicated gonococcal infections in women; 27 of them were infected with PPNG strains.25

In this study we found a 4·3% failure rate among men treated with 3 g cefaclor with 1 g probenecid (group C) with a failure rate of 10·4% among those treated with 3 g cefaclor alone (group D). There was no significant difference between the cure rates of both groups. The difference between the cure rates of group C (probenecid and cefaclor) and group A (spectinomycin) was not statistically significant, but the difference between the results of the treatment in group A (spectinomycin) and group D (cefaclor) was statistically significant. The results of treatment in group B (cefamandole) did not look promising as the failure rate was 29%. Cefaclor 3 g with probenecid 1 g (group C) was highly effective in the treatment of infections with PPNG and non-PPNG strains. The difference between the cure rates of both types of strain was not statistically significant. As the failure rate of this group was 4·3% 3 g of cefaclor with 1 g of probenecid should be an adequate substitute for spectinomycin in patients who prefer an oral regimen.

We thank the Eli Lilly Company of Thailand for providing cefaclor and cefamandole used in this study and Miss A Sangpetsong of Chulalongkorn University for her assistance with the statistical analysis.

References


TABLE II Sensitivity of N gonorrhoeae to antibiotics

<table>
<thead>
<tr>
<th>MIC (µg/ml)</th>
<th>Spectinomycin</th>
<th>Cefaclor</th>
<th>Cefamandole</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>PPNG</td>
<td>Non-PPNG</td>
<td>PPNG</td>
</tr>
<tr>
<td>0·064</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>0·12</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>0·25</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>1·0</td>
<td>0</td>
<td>4</td>
<td>8</td>
</tr>
<tr>
<td>2·0</td>
<td>0</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>4·0</td>
<td>0</td>
<td>40</td>
<td>38</td>
</tr>
<tr>
<td>7·5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>8·0</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>10·0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>16·0</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>105</td>
<td>141</td>
<td>135</td>
</tr>
<tr>
<td>&lt;0·5</td>
<td>2</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>&lt;5·0</td>
<td>2</td>
<td>16</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>137</td>
<td>236</td>
<td>136</td>
</tr>
</tbody>
</table>

MIC = minimum inhibitory concentration

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