Single oral dose of cefaclor for the treatment of infections with penicillinase-producing strains of Neisseria gonorrhoeae

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SUMMARY A single oral dose of 3 g cefaclor was effective in the treatment of uncomplicated gonococcal infection in women due to penicillinase-producing strains of Neisseria gonorrhoeae (PPNG). Cefaclor was equally active in vitro against both PPNG (MIC range, 0·01-1·0μg/ml) and non-PPNG strains (MIC range, 0·005-2·0μg/ml). As empirical treatment cefaclor was effective in 53 of 57 (93%) patients compared with ampicillin, to which only 37 of 53 (69·8%) patients responded. This difference was attributed to the 40% incidence of PPNG in the patients studied; as expected, such patients responded poorly to ampicillin.

Introduction

Cefaclor is an acid-stable semisynthetic cephalosporin which differs from its parent substance, cephalexin, in the substitution of a chloro group in the 3 position. Like cephalexin, cefaclor is absorbed orally but has the advantage of greater in-vitro activity against pathogens, particularly Haemophilus influenzae and Neisseria gonorrhoeae and their β-lactamase-positive strains.1,2 Compared with other cephalosporins cefaclor was second only to cefuroxime in its activity against N gonorrhoeae.2 Preliminary studies of the treatment of gonococcal urethritis in men have shown cefaclor to be effective in doses ranging from 2-4 g with or without probenecid.3 Its efficacy in infections with penicillinase-producing N gonorrhoeae (PPNG) has not yet been studied. The purpose of this study was to determine the efficacy of cefaclor in the treatment of uncomplicated gonococcal infections in women, particularly those due to PPNG. The results of empirical treatment of gonococcal infection with this drug were compared to those with the standard oral dose of ampicillin. Minimum inhibitory concentrations (MIC) of cefaclor, ampicillin, and penicillin against the isolates of N gonorrhoeae were measured and correlated with the response to treatment.

Patients and methods

STUDY DESIGN
Prostitutes with uncomplicated gonococcal infection confirmed by culture on screening volunteered to join the study after the protocol had been explained. Written informed consent was obtained and the study was conducted in accordance with the guidelines for human experimentation of the Declaration of Helsinki and the Committee on Research, Ethics, and Development of the UP Health Sciences Center. Pretreatment culture specimens were obtained from the cervix, urethra, rectum, and pharynx, after which patients were assigned to either treatment group by random allocation using a table of random numbers.

The patients were admitted to the clinic for three days after treatment to observe for possible side effects and, more importantly, to preclude reinfection before test-of-cure cultures were obtained on the second and third post-treatment days. Only patients with confirmed gonococcal infection based on a positive pretreatment culture result were evaluated. Treatment was considered to have failed if post-treatment culture results were still positive for N gonorrhoeae.

TREATMENT REGIMENS
Treatment consisted of a single oral dose of either 3 g cefaclor or 3·5 g ampicillin with 1 g probenecid. Patients who were randomly allocated to the ampicillin group and from whose pretreatment cultures PPNG were subsequently isolated were retreated...
with spectinomycin 2 g intramuscularly after post- 
treatment culture results were obtained and immedi- 
ately before discharge.

**STATISTICAL ANALYSIS**

Fisher’s exact test and the $\chi^2$ test with Yates’s correc- 
tion were used.

**BACTERIOLOGICAL TECHNIQUES**

* N. gonorrhoeae* was isolated and identified according to 
standard procedures. Penicillinase production by 
the isolated strains of *N. gonorrhoeae* was determined 
by the rapid iodometric test and confirmed by the 
chromogenic cephalosporin method of O’Callaghan. 
The MICs of cefaclor, ampicillin, and penicillin were 
determined by the agar dilution method using stan- 
dard procedures.

**OTHER LABORATORY INVESTIGATIONS**

Complete blood cell count, urine analysis, and serum 
alanine aminotransferase (ALT), blood urea 
nitrogen, and serum creatinine concentrations were 
determined before treatment and 24 hours later.

**Results**

**STUDY POPULATION**

A total of 122 patients were initially enrolled in the 
study; those in each treatment group were compar- 
able for age, weight, and sexual exposure. Since peni- 
cillinase production of the infecting strain could not 
be determined from the pretreatment culture at the 
time of the patient’s inclusion into the study, the 
patients were not grouped according to this criterion. 
Thus, using random allocation, it was solely by 
chance that more patients with PPNG strains were 
assigned to the cefaclor treatment group.

Twelve patients, including four given cefaclor and 
eight given ampicillin, were excluded from the study 
because of negative pretreatment culture results. 
Interestingly, in one such patient given cefaclor with 
a negative pretreatment culture result, post-treatment 
cultures from the cervix and rectum subsequently 
gave a heavy growth of PPNG. Despite the pre- 
cautions taken against reinfection during the study, 
this could not be totally excluded, as the patient may 
have left the clinic without the knowledge of the 
clinical staff.

The ages of the remaining 110 patients ranged 
from 15 to 34 years with a mean of 20 years, and 
weights ranged from 36·3 kg to 61·3 kg with a mean of 
45·5 kg. Thirty-eight of 110 (34·5%) patients were 
symptomatic; 44 patients were infected with PPNG 
and 66 with non-PPNG strains of *N. gonorrhoeae*. 
Twenty-seven of the former and 30 of the latter were 
treated with cefaclor and the remainder received 
ampicillin.

**TREATMENT**

Thirty-five of the 57 (93%) patients treated with 
cefaclor responded to treatment compared with 37 of 
53 (69·8%) patients treated with ampicillin. This 
difference was statistically significant ($\chi^2 = 8·416$, 
P<0·01). Of patients with PPNG infections, all 27 
responded to cefaclor while 16 of 17 (94·1%) failed 
to respond to ampicillin (table I). The single patient 
who responded to ampicillin had only a few colonies 
of PPNG in her pretreatment culture from the 
urethra; after treatment no organisms were cultured 
from this site. In patients with non-PPNG infections 
the therapeutic response was significantly better with 
ampicillin ($P = 0·038$ by Fisher’s exact test) since no 
failure was noted with this drug compared with four 
failures out of 30 (13·3%) with cefaclor.

**MINIMUM INHIBITORY CONCENTRATIONS**

The correlation between the treatment response with 
cefalor and the corresponding MICs of cefaclor for 
the infecting strains are shown in table II. Four treat- 
ment failures occurred among patients infected with

### TABLE I: Results of treatment in 122 patients with 
uncomplicated gonococcal infection

<table>
<thead>
<tr>
<th>Treatment outcome</th>
<th>PPNG</th>
<th>Non-PPNG</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cefaclor (n = 61)*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td>27</td>
<td>26</td>
<td>53</td>
</tr>
<tr>
<td>Failure</td>
<td>0</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Ampicillin (n = 61)*</td>
<td>1</td>
<td>36</td>
<td>37</td>
</tr>
<tr>
<td>Response</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Failure</td>
<td>16</td>
<td>0</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td>16</td>
<td>0</td>
<td>16</td>
</tr>
</tbody>
</table>

*Of the two treatment groups, four and eight patients were excluded 
from the analysis as their pretreatment culture results were negative 
for *N. gonorrhoeae*.

PPNG = penicillinase-producing *N. gonorrhoeae*; 
n = No of patients treated

### TABLE II: Minimum inhibitory concentrations of infecting 
*N. gonorrhoeae* strain from patients treated with cefaclor in relation to treatment failures

<table>
<thead>
<tr>
<th>MIC (µg/ml)</th>
<th>PPNG</th>
<th>Non-PPNG</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Treated</td>
<td>Failed</td>
</tr>
<tr>
<td>=0·025</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>0·1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>0·2</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>0·5</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>1·0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>≥2·0</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

PPNG = penicillinase-producing *N. gonorrhoeae*; ND = not done
non-PPNG strains; of these, two had MICs of 1.0 \( \mu \text{g/ml} \), one of 0.5 \( \mu \text{g/ml} \), and one of 0.1 \( \mu \text{g/ml} \). Two of 25 (8%) patients whose infecting strains had MICs of \( <0.5 \mu \text{g/ml} \) cefaclor failed to respond compared with two of five (40%) with MICs of \( \geq 1.0 \mu \text{g/ml} \) cefaclor; this difference was not statistically significant \((p = 0.019\) by Fisher's exact test). Sixteen patients who failed to respond to ampicillin had infecting strains of PPNG with MICs ranging from 4.0-\( >64 \mu \text{g/ml} \) of ampicillin.

The MICs of cefaclor, ampicillin, and penicillin for the isolates are shown in table III. The MICs of the three antibiotics were not determined in a few of the isolates, which could not be retrieved from the stock cultures. The MIC range of cefaclor for PPNG strains was 0.01-1.0 \( \mu \text{g/ml} \) with 84.2% of isolates inhibited by 0.5 \( \mu \text{g/ml} \) and was similar to that for non-PPNG strains at 0.005-2.0 \( \mu \text{g/ml} \) with 87.1% of isolates inhibited by 0.5 \( \mu \text{g/ml} \). Cefaclor was slightly more active in vitro than ampicillin and penicillin against non-PPNG strains; the ampicillin MIC range was 0.05-8.0 \( \mu \text{g/ml} \) with 79% of isolates inhibited by 0.5 \( \mu \text{g/ml} \) while the penicillin MIC range was 0.01-4.0 \( \mu \text{g/ml} \) with 75% of isolates inhibited by 0.5 \( \mu \text{g/ml} \). The PPNG strains were uniformly resistant to ampicillin and penicillin with MIC ranges of 4.0-\( >64 \mu \text{g/ml} \) and 16.0-\( >64 \mu \text{g/ml} \) respectively.

### SIDE EFFECTS
Three of 57 (5.3%) patients given cefaclor had side effects of dizziness (one) and dizziness, headache, and nausea (two). In contrast, only one of 53 (1.9%) patients given ampicillin complained of dizziness.

Ten patients treated with cefaclor showed changes in blood analysis (eosinophilia in six, leucopenia in two, leucocytosis in one, and a mildly raised ALT concentration in one) compared with 14 treated with ampicillin (eosinophilia in seven, leucopenia in three, leucocytosis in two, and a mildly raised ALT concentration in two).

### Discussion
With the recently reported isolation of a spectinomycin-resistant strain of PPNG\(^8\) an appraisal of the efficacy of the cephalosporins as an alternative treatment for gonococcal infection has become imperative. Despite earlier discouraging results of the treatment of gonorrhoea with older cephalosporins, such as cephaloridine, cefazolin, and cephalaxin,\(^9-12\) newer congeners (notably cefuroxime and cefamandole) and a cephemycin, cefoxitin, have shown excellent in-vitro activity against *N gonorrhoeae*.\(^13\) Cefuroxime and cefoxitin have been highly effective in the treatment of gonococcal infections, including those due to PPNG.\(^4,14\) In addition to these drugs, our study shows that cefaclor, an oral cephalosporin, has excellent in-vitro activity against *N gonorrhoeae* and was effective at a dose of 3g in the treatment of uncomplicated gonococcal infections in women particularly those due to PPNG. Its oral route of administration is an important advantage over cefuroxime and cefoxitin, which may make it more acceptable to patients. As empirical treatment before the results of tests for penicillinase production of the infecting strain were known, cefaclor was more efficacious than ampicillin (93% responded to cefaclor compared with 69.8% to ampicillin). This significant difference \((\chi^2 = 8.416, p<0.01)\) is attributed to the 40% incidence of PPNG infections in the patients studied. As expected, such patients responded poorly to \(\beta\)-lactamase-sensitive drugs like ampicillin and penicillin.

The treatment failure rate among patients infected with non-PPNG strains was 13.3% with cefaclor compared with zero failure with ampicillin. In-vitro data suggest that cefaclor should be as effective as ampicillin, so that the significant difference \((p = 0.038\) by Fisher's exact test) in the treatment results might be attributed to differences in the pharmacokinetics of the two drugs, most likely enhanced by the concomitant administration of probenecid with ampicillin. Pharmacokinetic studies indicate that while cefaclor is rapidly absorbed in the gastrointestinal tract, it is cleared more rapidly than cephalaxin from the serum\(^15\) and has a half-life of 0.76 hours after a 1-g dose with no detectable con-

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**Table III** Cumulative percentage of isolates inhibited by increasing concentrations of cefaclor, ampicillin, and penicillin

<table>
<thead>
<tr>
<th>MIC (( \mu \text{g/ml} ))</th>
<th>Cefaclor</th>
<th>Ampicillin</th>
<th>Penicillin</th>
</tr>
</thead>
<tbody>
<tr>
<td>( &lt;0.005 )</td>
<td>1-6</td>
<td>7-7</td>
<td>26-2</td>
</tr>
<tr>
<td>0-01</td>
<td>2-6</td>
<td>1-6</td>
<td>10-8</td>
</tr>
<tr>
<td>0-05</td>
<td>5-3</td>
<td>4-8</td>
<td>22-2</td>
</tr>
<tr>
<td>0-1</td>
<td>31-6</td>
<td>38-7</td>
<td>33-8</td>
</tr>
<tr>
<td>0-2</td>
<td>36-8</td>
<td>58-1</td>
<td>46-2</td>
</tr>
<tr>
<td>0-5</td>
<td>84-2</td>
<td>87-1</td>
<td>75-4</td>
</tr>
<tr>
<td>1-0</td>
<td>100</td>
<td>98-4</td>
<td>87-7</td>
</tr>
<tr>
<td>2-0</td>
<td>100</td>
<td>98-4</td>
<td>95-4</td>
</tr>
<tr>
<td>4-0</td>
<td>100</td>
<td>98-4</td>
<td>100</td>
</tr>
<tr>
<td>8-0</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>16-0</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>32-0</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
<tr>
<td>( \geq 64 \mu \text{g/ml} )</td>
<td>100</td>
<td>100</td>
<td>100</td>
</tr>
</tbody>
</table>

*Isolates not retrieved from stock cultures for MIC determination.

PPNG = penicillinase-producing *N gonorrhoeae*.
centrations six hours later. Conceivably, probenecid given with cefaclor in the treatment of gonococcal infection may ensure higher and prolonged concentrations of cefaclor. This potential benefit remains to be determined.

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References


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