Different Doses of Cefetamet Pivoxil (Ro 15-8075) in the Treatment of Acute Uncomplicated Gonococcal Urethritis in Men

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In an open, dose-finding study, a 100% cure rate was observed in patients suffering from uncomplicated gonococcal urethritis who were treated with a single oral dose of either 1.2 g (n = 10), 0.8 g (n = 11), or 0.4 g (n = 10) of cefetamet pivoxil. The MICs of cefetamet for all gonococcal strains ranged from 0.001 to 0.12 µg/ml, and the MIC for 90% of the strains tested was 0.008 µg/ml. Cefetamet pivoxil was ineffective against Chlamydia trachomatis in 3 of 31 patients. Side effects were minor.

The incidence of plasmid- and chromosome-mediated drug resistance of Neisseria gonorrhoeae to treatment with penicillin or tetracycline has become a serious worldwide problem (1, 6, 9, 13, 14). The development of an alternative antimicrobial therapy is therefore justified. Intramuscular treatment of patients with broad-spectrum cephalosporins has proved to be highly effective in the eradication of penicillinase-producing N. gonorrhoeae (PPNG) and nonpenicillinase-producing N. gonorrhoeae (non-PPNG) and is therefore the therapy of first choice in our clinic (8, 12).

Cefetamet pivoxil (Ro 15-8075) is a new oral cephalosporin. When given orally with food, approximately 50% of this prodrug ester is absorbed in the intestinal tract and is hydrolyzed into the active free acid cefetamet (2, 3). A single oral dose of 1.5 g of cefetamet pivoxil results in a maximum concentration in plasma of 7.4 ± 1.3 µg/ml after approximately 5 h. The elimination half-life is 2.3 h. Cefetamet is eliminated predominantly via the kidneys. Thus, its elimination is influenced considerably by renal function.

Cefetamet pivoxil possesses an effective in vitro activity against PPNG and non-PPNG, with MICs ranging from 0.0015 to 0.125 µg/ml, a MIC for 50% of the strains tested of 0.007 µg/ml, and a MIC for 90% of the strains tested of 0.015 µg/ml (investigational drug brochure, F. Hoffmann-La Roche & Co. AG, Basel, Switzerland, 1988). A cure rate of 100% has been reported for patients suffering from gonorrhea who were treated with a single oral dose of 1.2, 1.5, or 0.4 g of cefetamet pivoxil (2). Cure rates of 94, 89, and 81% have been reported for patients treated with 1.0, 0.8, and 0.5 g of this drug, respectively (2).

This study was an open, step-by-step dose-finding study, beginning with a high dose of cefetamet pivoxil (1.2 g) and, when the 1.2-g dose was found effective, continuing with lower doses (0.8 and 0.4 g). This study was approved by the Medical Ethics Committee of the University Hospital Rotterdam-Dijkzigt.

Men older than 18 years and suffering from acute uncomplicated gonococcal urethritis were enrolled in this study after informed consent was obtained. They were all outpatients at the sexually transmitted disease clinic of the University Hospital. Each had a positive urethral discharge showing gram-negative diplococci at the pretreatment visit. Patients known or suspected to be allergic to cephalosporins or penicillins, patients with a history or current clinical evidence of a severe disease (e.g., renal insufficiency, hepatic deficiency, or syphilis), and patients who were treated with other antibiotics within the preceding 15 days were excluded from this study. Fourteen patients were treated with 1.2 g, 16 were treated with 0.8 g, and 11 were treated with 0.4 g of cefetamet pivoxil, which was given as a single oral dose.

All patients were requested to return for follow-ups 2 to 3 days and 7 to 8 days after therapy and to refrain from sexual contact during the study period. At each visit, a patient history was taken and a physical examination was performed. The following laboratory tests were also performed: a Gram stain of the urethral discharge, a urine sediment test for the presence of leukocytes in the first-void urine, cultures for N. gonorrhoeae and Chlamydia trachomatis, a general blood test, and liver and kidney function determinations. A blood sample was also taken at the pretreatment visit only for a Treponema pallidum hemagglutination test, a fluorescent treponemal antibody absorption test, and a Venereal Disease Research Laboratory test.

Samples for N. gonorrhoeae cultures were collected from the urethra, the pharynx, and, for homosexual patients, the rectum. The swabs were placed into Stuart transport media and plated within 4 h onto selective medium consisting of GC agar base (Oxoid Ltd.) supplemented with 2% hemoglobin (Oxoid) and 1% IsoVitalex (BBL Microbiology Systems).

Specimens for C. trachomatis cultures were collected from the urethra. If not cultured immediately, the specimens were stored at −70°C. C. trachomatis was cultured with DEAE-dextran and cycloheximide-pretreated HeLa 229 cell monolayers. Fluorescent staining was performed with a monoclonal antibody (Microtrak; Syva Co.) after 48 h without subpassage (10).

All gonococcal strains were tested for the production of β-lactamase by using the chromogenic cephalosporin (nitrocefin) test (4).

MICs of the free acid cefetamet and penicillin G for N. gonorrhoeae were determined by the agar dilution technique with twofold dilutions between 128 and 0.001 µg/ml (9).

A total of 41 men were enrolled in this study. Of these, 31 patients were evaluable; the other 10 were not evaluable because they did not return for follow-ups.

Two of 31 evaluable patients were positive serologically for syphilis at the pretreatment visit (T. pallidum hemagglutination test, +; fluorescent treponemal antibody absorption test, +; Venereal Disease Research Laboratory test, −).
Their test results were in accordance with their histories of treated late latent syphilis.

*N. gonorrhoeae* was isolated only from the urethra of each patient before treatment. At follow-ups, this bacterium was absent in all evaluable patients treated with 1.2, 0.8, or 0.4 g of cefetamet pivoxil.

*C. trachomatis* was isolated from 2 of the 31 evaluable patients before and from 3 (one in each dose group) of the 31 patients after therapy. Cefetamet pivoxil appeared to be ineffective against this microorganism. In this study, patients with concomitant chlamydial infections were additionally treated with 100 mg of doxycycline twice a day for 7 days after the second follow-up.

The MICs of the free acid cefetamet and penicillin G for *N. gonorrhoeae* strains were determined for a total of 41 patients (Table 1). The MICs of cefetamet for all strains ranged from 0.001 to 0.12 μg/ml and were comparable to those found by an earlier study (investigational brochure, Hoffmann-La Roche). One patient who was treated with 1.2 g of cefetamet pivoxil had a slightly elevated total bilirubin level 7 days after therapy. This adverse effect was probably not caused by cefetamet pivoxil because of the pharmacokinetics of this drug and because laboratory findings 2 days after treatment were normal. One patient who was treated with 0.4 g of cefetamet pivoxil complained of itch in the scrotum before therapy which increased in intensity after therapy.

Since *N. gonorrhoeae* was isolated only from the urethra in our study population, the efficacy of cefetamet pivoxil against oropharyngeal or rectal gonorrhea could not be evaluated.

The brief follow-up period precludes any conclusion concerning postgonococcal urethritis in our study. Postgonococcal urethritis would appear 2 to 3 weeks after treatment of gonorrhea (5).

Our preliminary findings may indicate that cefetamet pivoxil is a safe and effective drug for the treatment of uncomplicated gonococcal urethritis caused by PPNG and non-PPNG. The efficacy and the safety of cefetamet pivoxil against *N. gonorrhoeae* compare well with those of other oral cephalosporins (7, 11). In this study, a single oral dose of 0.4 g of cefetamet pivoxil was sufficient to cure uncomplicated gonococcal urethritis. However, further investigation with a larger group of patients should be conducted to confirm the beneficial effect of this drug in the treatment of uncomplicated gonococcal urethritis.

We thank B. Tank for correcting the English text.

**TABLE 1. MICs for *N. gonorrhoeae* strains**

<table>
<thead>
<tr>
<th>Compound</th>
<th>Strains (no. of patients)</th>
<th>MIC (μg/ml)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range</td>
<td>50%</td>
</tr>
<tr>
<td>Cefetamet</td>
<td></td>
<td></td>
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<tr>
<td>Non-PPNG (34)</td>
<td>0.001–0.12</td>
<td>0.004</td>
</tr>
<tr>
<td>PPNG (7)</td>
<td>0.004–0.015</td>
<td>0.008</td>
</tr>
<tr>
<td>All (41)</td>
<td>0.001–0.12</td>
<td>0.004</td>
</tr>
<tr>
<td>Penicillin G</td>
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<td></td>
</tr>
<tr>
<td>Non-PPNG (34)</td>
<td>0.002–2</td>
<td>0.03</td>
</tr>
<tr>
<td>PPNG (7)</td>
<td>2–16</td>
<td>8</td>
</tr>
<tr>
<td>All (41)</td>
<td>0.002–16</td>
<td>0.06</td>
</tr>
</tbody>
</table>

* 50% and 90%, MIC for 50 and 90% of strains tested, respectively.

**LITERATURE CITED**