Comparative Double-Blind Study of 200- and 400-mg Enoxacin Given Orally in the Treatment of Acute Uncomplicated Urethral Gonorrhea in Males

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In a double-blind randomized study, 155 male patients with uncomplicated urethral gonorrhea were given 200 mg (one capsule with 200 mg and one capsule with placebo; n = 77) or 400 mg (two capsules with 200 mg; n = 78) of enoxacin orally. The cure rates in the 200- and 400-mg treatment groups were 90 and 92%, respectively. The enoxacin MIC for the isolated Neisseria gonorrhoeae strains ranged from 0.015 to 0.12 μg/ml. Postgonococcal urethritis was diagnosed in 29 (42%) patients in the 200-mg treatment group and 19 (26%) patients in the 400-mg treatment group. Side effects (nausea, headache, and vomiting) occurred in 2 (3%) of the 77 patients in the 200-mg treatment group and in 3 (4%) of the 78 patients in the 400-mg treatment group.

The increasing resistance of Neisseria gonorrhoeae to penicillins and tetracycline calls for new therapeutic agents. The 4-quinolone group has yielded some derivatives that are active against N. gonorrhoeae and can be given orally. Cure rates of up to 100% have been reported in previous studies with ciprofloxacin in the treatment of uncomplicated urogenital gonorrhea in males (12) and with enoxacin in the treatment of uncomplicated urogenital gonorrhea in females (4, 13). In vitro studies have shown that enoxacin, one of the new quinolone agents, is effective against N. gonorrhoeae with MICs of 0.03 to 0.25 μg/ml (8). Our double-blind randomized study involved clinical evaluation of the treatment of uncomplicated urethral gonorrhea in males with a single oral dose of either 200 or 400 mg of enoxacin.

MATERIALS AND METHODS

Patient population. All patients were men attending the outpatient clinic for sexually transmitted diseases at the University Hospital Rotterdam-Dijkzigt. Patients who were under 18, had disseminated gonococcal infections, had solitary rectal or pharyngeal gonococcal infections, had syphilis, liver, or kidney diseases, had allergies to quinolones, and were recently treated with enoxacin or on theophylline medication were excluded. This was a double-blind study. A randomization list ensured that patients received a single oral dose of either 400 mg of enoxacin in two 200-mg capsules or 200 mg of enoxacin in one 200-mg capsule and one placebo capsule. The capsules were taken with water under the supervision of a nurse. The patients were advised to abstain from sexual contacts throughout the follow-up period.

All subjects gave oral informed consent before they were enrolled, and the study was approved by the committee for the protection of human subjects at the University Hospital Rotterdam-Dijkzigt.

Venereological study. A standard history was taken, and all patients underwent the following tests before and after therapy. Gram stains were made of the discharge, and samples for Chlamydia trachomatis and N. gonorrhoeae cultures were taken from the urethra. N. gonorrhoeae culture samples were taken from the pharynx (and from the rectum in homosexual men), and the sediment of 10 to 15 ml of the first-voided urine was collected. Blood was drawn for Venereal Disease Research Laboratory (VDRL), fluorescent treponemal antibody (FTA-ABS), and TPHA tests (only before therapy) and general hematologic, liver, and kidney function determinations. Therapy was started if gram-negative diplococci were found in the Gram stain or if N. gonorrhoeae was isolated from the culture.

The effect of therapy was evaluated 7 to 14 days after patients began to receive medication. Postgonococcal urethritis was diagnosed if, at follow-up, more than 10 leukocytes per field were seen in the sediment of the first-voided urine at a magnification of 250× and the Gram stain contained no intracellular gram-negative diplococci. At follow-up, all patients were asked about side effects and whether dysuria or discharge was still present.

N. gonorrhoeae cultures. For N. gonorrhoeae cultures, samples were taken with a carbon-impregnated cotton swab and, after transport in Stuart medium, transferred within 6 h to a selective medium which consisted of GC agar base (Oxoid Ltd., London, England) supplemented with 2% hemoglobin (Oxoid Ltd.) and 1% IsoVitaleX (BBL Microbiology Systems, Cockeysville, Md.).

MICs of enoxacin, tetracycline, penicillin, ampicillin, and cefuroxime for the N. gonorrhoeae strains were determined by an agar dilution technique on gonococcal agar base (11) with twofold serial antibiotic dilutions between 4 and 0.004 μg/ml and a bacterial inoculum of 10^6 CFU/spot. All N. gonorrhoeae strains were tested for beta-lactamase production using the chromogenic cephalosporin (nitrocephin) test (5). Susceptibility to spectinomycin was tested by the disk diffusion method. Auxotyping of the N. gonorrhoeae strains was performed at the National Institute of Public Health and Environmental Hygiene (1). Pairs showing similarity before and after therapy were sent to the Centers for Disease

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Control for lectin agglutination (9) and serotyping (3) tests as described previously.

**C. trachomatis** cultures. For *C. trachomatis* cultures, samples were taken by inserting white-cotton-tipped metal swabs deep into the urethra, rotating them, and suspending them in buffer containing 0.2 M sucrose and 0.02 M phosphate with 10% fetal calf serum, 25 mg of gentamicin per ml, and 25 U of nystatin per ml. Samples were frozen to −70°C within 6 h of being obtained. *Chlamydiae* were cultured on HeLa 229 monolayers washed with DEAE-dextran in 96-well microtiter plates. Staining was done with fluorescent monoclonal antibodies (Syva Inc.) after 48 h of incubation (10). Subpassage was not performed.

**Statistical analysis.** Results were statistically analyzed by the two-tailed Fisher exact test.

**RESULTS**

Of the 243 patients treated, 88 (36%) could not be evaluated, 45 in the 200-mg and 43 in the 400-mg treatment group. Reasons included failure to report for follow-up (47 patients), follow-up later than 2 weeks (17 patients), sexual contact during the study (11 patients), capsule vomited immediately after ingestion (1 patient), negative *N. gonorrhoeae* culture at start of study (3 patients), and material not obtained for *N. gonorrhoeae* culture at follow-up (9 patients).

**Treatment with 200 mg of enoxacin.** In the 200-mg treatment group, 77 patients were available for evaluation; 69 (90%) patients were culture negative for *N. gonorrhoeae* at follow-up. Of the 77 patients with positive initial *N. gonorrhoeae* cultures, the strains were isolated from the urethra in all 77; none were isolated from the rectum or the pharynx.

The auxotyping patterns of the *N. gonorrhoeae* strains obtained from six treatment failures were identical (Table 1). In two failures, one or both strains were no longer available for auxotyping. The typing patterns of pre- and posttreatment strains obtained from two nonassessable patients (one for sexual contact during the study and one for follow-up later than 2 weeks) showed similarity in auxo- and serotyping. One pair showed a similar and one pair a different lectin agglutination pattern (Table 1). Five (6%) of the 77 *N. gonorrhoeae* strains isolated produced penicillinase; the cure rate for this group of patients was 100%.

**TABLE 1. MICs of enoxacin for *N. gonorrhoeae* strains isolated before and after therapy with enoxacin and their typing patterns**

<table>
<thead>
<tr>
<th>Patient group and enoxacin dose (mg)</th>
<th>Pretreatment strains</th>
<th>Posttreatment strains</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>MIC (µg/ml)</td>
<td>Auxotype*</td>
</tr>
<tr>
<td>Assessable</td>
<td>200</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>200</td>
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<tr>
<td></td>
<td>200</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>0.03</td>
</tr>
<tr>
<td>Nonassessable</td>
<td>400</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>400</td>
<td>0.06</td>
</tr>
<tr>
<td></td>
<td>400</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>400</td>
<td>0.03</td>
</tr>
</tbody>
</table>

* NR Phe, not requiring and inhibited by phenylalanine; Pro−, proline requiring; Amac−, amino acid mixture requiring (1); NR, no requirement.
* NT, Not typable.

Postgonococcal urethritis (PGU) was diagnosed in 29 (42%) of the 69 patients negative for *N. gonorrhoeae* at follow-up. *C. trachomatis* was isolated from the urethra in 8 (28%) of the 29 patients; only 3 of them still had complaints. Samples from 20 patients (69%) were *C. trachomatis* negative, and only 5 of these patients still had complaints. In one symptomatic case, no *C. trachomatis* culture was obtained. In four cases, *C. trachomatis* was isolated in the absence of urinary sediment changes. One (1%) patient complained of nausea and one (1%) of headache and nausea.

**Treatment with 400 mg of enoxacin.** In the 400-mg treatment group, 78 patients were available for evaluation; 72 (92%) patients were culture negative for *N. gonorrhoeae* at follow-up. Of the 78 patients with positive *N. gonorrhoeae* cultures, the strains were isolated from the urethra in 78, the rectum in 2, and the pharynx in 0.

The auxotyping patterns of the *N. gonorrhoeae* strains from two treatment failures were identical (Table 1). In four failures, one or both strains were no longer available for auxotyping. The typing patterns of pre- and posttreatment strains obtained from two nonassessable patients (one for follow-up later than 2 weeks and one for capsule vomited immediately after ingestion) showed similarity in auxo- and serotyping. One pair showed a similar and one pair a different lectin agglutination pattern (Table 1). Two strains isolated from two patients after therapy had enoxacin MICs of 1 and 2 µg/ml. The pretreatment strain of the first patient was no longer available for MIC determination. The pretreatment strain of the latter patient showed a MIC of 0.03 µg/ml (Table 1).

None of the strains produced penicillinase. Two patients also had a positive rectal gonococcal culture. The follow-up cultures were negative for both patients.

PGU was diagnosed in 19 (26%) of the 72 patients negative for *N. gonorrhoeae* at follow-up. *C. trachomatis* was isolated from the urethra in 9 (47%) of the 19 patients; only 2 of these patients still had complaints, whereas 10 (53%) samples from asymptomatic patients were *C. trachomatis* negative. In five cases, *C. trachomatis* was isolated in the absence of urinary sediment changes. Two (3%) patients complained of nausea, and one (1%) vomited a few minutes after ingestion of the medication.

**C. trachomatis** cultures. Before therapy, *C. trachomatis*
TABLE 2. In vitro susceptibility of N. gonorrhoeae strains isolated before treatment with enoxacin

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>MIC (μg/ml)*</th>
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<tr>
<td></td>
<td>Range 50%</td>
</tr>
<tr>
<td>Enoxacinb</td>
<td>0.015–0.12</td>
</tr>
<tr>
<td>Penicillinb</td>
<td>0.015–4</td>
</tr>
<tr>
<td>Ampicillin</td>
<td>0.03–4</td>
</tr>
<tr>
<td>Cefuroximeb</td>
<td>0.008–2</td>
</tr>
<tr>
<td>Tetracyclineb</td>
<td>0.06–4</td>
</tr>
</tbody>
</table>

* 50% and 90%, MIC for 50 and 90% of isolates, respectively.

** Tested against all strains, including six penicillinase-producing strains (n = 134).

† Tested against non-penicillinase-producing strains only (n = 128).

was isolated from 17 (11%) of the 155 patients and after therapy from 26 (17%).

Abnormal laboratory findings. The following abnormal laboratory findings were obtained for the 200-mg treatment group: enlarged plaques in two (3%) patients, a slightly increased serum glutamic oxalacetic transaminase value in two (3%), slight anisocytosis in two (3%), and a few macrocytes in one (1%). The only abnormal finding for the 400-mg treatment group was a slightly increased serum glutamic pyruvic transaminase value in one (1%) patient.

Antimicrobial susceptibility and typing patterns. Eleven (5%) of the 239 N. gonorrhoeae strains isolated produced penicillinase. The MICs of enoxacin ranged from 0.004 to 0.12 μg/ml. The enoxacin MIC for 90% of isolates was 0.06 μg/ml (Table 2). One N. gonorrhoeae strain showed an increase in the MIC of 0.03 to 2 μg/ml after treatment with 400 mg of enoxacin.

The lectin agglutination patterns and serotyping of each of the eight pre- and posttreatment pairs of isolates obtained from assessable patients were identical (Table 1).

DISCUSSION

A study of 12 healthy control volunteers (16) demonstrated peak plasma levels of 1.2 μg/ml after a single dose of 200 mg and 2.1 μg/ml after 400 mg of enoxacin. The half-life of enoxacin is ca. 5 h. In view of the good results of our previous pilot study with enoxacin (4), the above-mentioned data, and low MICs of enoxacin for N. gonorrhoeae, we decided to investigate this quinolone in a large group of patients suffering from uncomplicated gonorrhea.

The cure rate found in this study, 90% in the 200-mg treatment group and 92% in the 400-mg treatment group, was lower than that in our previous study of enoxacin with identical doses in the treatment of uncomplicated female urogenital gonorrhea (13). The cure rates in the latter study were 98.7% in the 200-mg treatment group and 100% in the 400-mg treatment group.

Although the MICs of enoxacin for penicillinase-producing and non-penicillinase-producing N. gonorrhoeae strains were low (0.3 to 0.12 μg/ml) and agreed with those determined in previous studies (2, 4, 8) the cure rates in both groups of treated males were lower than expected from other studies with quinolones (4, 12, 13). Pre- and posttreatment isolates were available from six treatment failures in the 200-mg group and two failures in the 400-mg group. Auxotyping, serotyping, and lectin agglutination patterns were the same for each pair of N. gonorrhoeae strains obtained before and after therapy. This suggests either failure of therapy or reinfection with the same strain. In sex therapy failures auxotyping was impossible, and no conclusions about whether the strains were the same before and after therapy could be drawn. The fact that in two nonassessable patients the pre- and posttreatment pairs of strains showed the same auxo- and serotyping and lectin agglutination patterns underscored the importance of additional typing methods.

The MICs of enoxacin for one N. gonorrhoeae strain rose from 0.03 μg/ml before therapy to 2 μg/ml after therapy with 400 mg of enoxacin.

van Klingereren et al. (14) demonstrated that the sensitivity in vitro of N. gonorrhoeae strains to quinolones may show a 10-fold to 100-fold decrease compared with the parent strain at a frequency of 1 in 10^6 to 10^7. These findings indicate that resistance to quinolones can develop in vivo.

Enoxacin in a single oral dose is not effective against C. trachomatis; this is in accordance with the high MICs of enoxacin against C. trachomatis (MIC for 90% of isolates, 16 μg/ml) and data reported for other antibiotics given in a single dose (6, 7, 15). This probably explains the PGU in 42% of the 200-mg treatment group and 26% of the 400-mg treatment group. Like Oriel et al. (7), we found a larger number of positive C. trachomatis cultures after therapy than before.

The low percentage of positive C. trachomatis cultures (28 to 47%) for patients suffering from PGU is probably due to the short follow-up period. It is possible that some patients may have persistent urethral leukocytosis due to gonorrhea alone. Also, enoxacin may cause temporary suppression of C. trachomatis. Of the PGU patients, 31% in the 200-mg treatment group and 10% in the 400-mg treatment group still had complaints. These low percentages are probably also due to the short follow-up period. The peak incidence of symptomatic PGU occurs 2 to 3 weeks after treatment.

The differences in cure of gonococcal infections between the 200-mg treatment group and the 400-mg treatment group were not statistically significant (P > 0.05). The differences in PGU rate were not statistically significant either (P > 0.05). The side effects observed (headache and nausea) were mild and transient.

Abnormal laboratory findings occurred more often in the 200-mg treatment group than in the 400-mg treatment group, demonstrating that there was no dose-dependent relation with the medication given.

Our conclusion is that enoxacin is an effective drug in the treatment of uncomplicated male urethral gonorrhea, although the cure rate in this study was lower than that in previous studies of female patients and previous studies with other quinolones (13).

LITERATURE CITED


