Norfloxacin in the Therapy of Uncomplicated Gonorrhea

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In an open study, 70 patients with uncomplicated anogenital Neisseria gonorrhoeae infection were evaluated to determine the efficacy and safety of a single oral dose of norfloxacin (800 mg). Norfloxacin cured all 31 male urethral and 25 endocervical infections. All 63 isolates of N. gonorrhoeae tested were inhibited by 0.05 μg of norfloxacin per ml.

Norfloxacin is a new orally administered quinolone derivative chemically related to nalidixic acid. It is active in vivo and in vitro against most gram-negative pathogens, including Neisseria gonorrhoeae. The norfloxacin MIC for 90% of strains tested for beta-lactamase-positive and -negative strains of N. gonorrhoeae is 0.06 and 0.015 μg/ml, respectively (5, 6, 8, 10). The pharmacokinetics of this drug makes it favorable for treating gonorrhea: a single oral dose of 400 or 800 mg of norfloxacin results in mean peak levels in serum of 1.58 and 2.45 μg/ml, respectively, at 1 to 2 h. The half-life of norfloxacin is 7 h (7).

These characteristics suggest that norfloxacin may offer an alternative single-dose therapy for uncomplicated gonorrhea caused by both non-penicillinase- and penicillinase-producing strains. Norfloxacin at 1,200 mg divided into two equal oral doses 4 h apart was used successfully to treat uncomplicated gonococcal urethritis in 28 of 28 men with penicillinase-producing N. gonorrhoeae and 31 of 31 men with non-penicillinase-producing N. gonorrhoeae (2).

The purpose of this open study was to evaluate the safety and efficacy of a single 800-mg oral dose of norfloxacin for the treatment of uncomplicated gonorrhea in men and women. The study was performed at the Edmonton Sexually Transmitted Disease Clinic from June to September 1984.

Males and females, 12 years of age and over, who had culture-proven genital or anorectal gonorrhea and consented to participate were enrolled. Patients with signs and symptoms of complicated gonococcal infection, a history of antimicrobial allergy, antibiotic therapy within the preceding 3 days, or pregnancy were excluded. Patients were entered into the study only once.

N. gonorrhoeae cultures were obtained from the urethra of all males and the endocervix and rectum of all females. Pharyngeal specimens were obtained when epidemiologically indicated by a history of orogenital contact. Specimens were directly inoculated onto Edmonton Provincial Laboratory medium (1) and incubated at 36°C under a CO₂ environment for 36 to 48 h. Isolates presumptively identified as N. gonorrhoeae were confirmed by standard techniques, including sugar utilization reactions and the presence of oxidase-positive, gram-negative diplococci which demonstrated brilliant fluorescence when stained by the direct fluorescent antibody technique. Production of beta-lactamase was tested by the rapid isometric technique. MICs were measured by the agar dilution technique as previously described by Wiesner et al. (9).

The patients were administered a single oral dose of norfloxacin (800 mg in two 400-mg tablets). Cure was defined as negative cultures for N. gonorrhoeae 3 to 5 days after treatment.

To assess drug toxicity pre- and posttreatment, we performed complete blood counts, platelet counts, a multichannel 12 biochemical screen, and urinalysis. Adverse reactions were determined by direct questioning at the follow-up visit and were classified by their effect on the central nervous system, gastrointestinal system, or other body systems. Central nervous system dysfunction included dizziness, headache, and tingling in the fingers, and gastrointestinal system adverse effects included anorexia, abdominal discomfort, diarrhea, and constipation.

Of 43 males entered in the study, 9 could not be evaluated due to protocol violation and a further 3 could be evaluated only for safety. Therefore, 34 males were evaluated for safety and 31 were evaluated for efficacy. A total of 27 females were entered, with 2 protocol violators; 25 females were evaluated for safety and efficacy. The patients evaluable for safety but not efficacy either had a negative pretreatment culture, were reexposed to an untreated sexual partner, or did not return for their test of cure within the specified time.

The median age for the 43 men and 27 women entered in the study was 24.8 and 22.8 years, respectively. There were no significant differences among patient groups with respect to demographic features.

The results of treatment for genital and anorectal infection are shown in Table 1. Norfloxacin eradicated urethral gonorrhea in all the 31 men evaluated for efficacy. Similarly, endocervical gonococcal infection was eliminated in 25 of 25 women, and gonococcal eradication from the anal canal was achieved in all 6 women.

The overall cure rate for men and women with genital and anorectal infection treated with norfloxacin was 100% (62/62). N. gonorrhoeae was isolated from the pharynx of two males and one female. Norfloxacin failed to cure the female.

The MICs of norfloxacin were determined for 63 pretreatment isolates. All were inhibited by 0.05 μg/ml. The MICs for pre- and posttreatment isolates from the one treatment failure (pharyngeal infection) were identical. All strains were susceptible to ≤1 μg of penicillin, ≤2 μg of tetracycline, and ≤16 μg of spectinomycin per ml.

Although the identification of gonococcal urethritis was not part of this study, three men had evidence of this infection at the time of their test of cure. This diagnosis was based on a urethral smear demonstrating >5 polymorphonu-
clear leukocytes in more than one high-power field. Two of these patients had positive cultures for Chlamydia trachomatis. These men were subsequently cured with a 7-day course of tetracycline hydrochloride (500 mg four times a day).

Overall, 20.3% (12/59) of the patients developed adverse effects (Table 2). None of the reactions required medical intervention, nor did they result in any serious sequelae. Central nervous system side effects occurred in four of seven females and two of five males. Gastrointestinal disturbances occurred in three females and three males. No significant hematological, biochemical, or urinary abnormalities occurred in any patients.

The results of this trial indicate that norfloxacin is an effective agent in the therapy of uncomplicated genital and anorectal gonorrhea. Although no beta-lactamase-positive strains were included in this study, the previously reported trial of Crider et al. (2) demonstrated the usefulness of this agent against penicillinase-producing N. gonorrhoeae. At a dosage of 1,200 mg divided into two equal oral doses 4 h apart, 28 of 28 men with urethritis caused by beta-lactamase-positive N. gonorrhoeae were cured. This trial also cured two of two cases of beta-lactamase-negative gonococcal pharyngitis.

Norfloxacin demonstrates limited in vitro activity against C. trachomatis (3) and is unlikely to be useful in patients with urethritis that is caused by this organism or in patients with concurrent infections with C. trachomatis and N. gonorrhoeae. In our series of 31 men, 3 had postgonococcal urethritis at the time of test of cure. Two of these individuals were culture positive for C. trachomatis.

Our high incidence of adverse effects may be partially explained by their subjective nature, taking into account that patients were forewarned about their nature and then directly questioned on adverse effects. All adverse effects were of short duration, mild, and cleared without sequelae. It is interesting that the study of Crider et al. (2) reported no adverse effects among U.S. military personnel, whereas Hooper and Wolfson’s review (4) of fluoroquinolones gave a figure of 10%. In the latter review, it was again stressed that the effects rarely were severe or required cessation of therapy.

As oral agents with the inherent advantages of improved patient compliance and low toxicity, the quinolones appear to possess characteristics that could make them the drugs of choice for uncomplicated gonococcal infections caused by beta-lactamase-positive and -negative strains. The recent emergence of non-penicillinase-producing gonococci that are highly resistant to penicillin poses a new threat for which norfloxacin may be the solution.

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<table>
<thead>
<tr>
<th>TABLE 2. Incidence of adverse reactions to norfloxacin</th>
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<tbody>
<tr>
<td>Adverse reaction</td>
</tr>
<tr>
<td>Dizziness</td>
</tr>
<tr>
<td>Tingling in hands</td>
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<tr>
<td>Diarrhea</td>
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<tr>
<td>Constipation</td>
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<td>Abdominal discomfort</td>
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LITERATURE CITED


TABLE 1. Results of norfloxacin treatment of uncomplicated gonococcal infections

<table>
<thead>
<tr>
<th>Site of infection</th>
<th>No. of patients cured/no. treated</th>
<th>Women</th>
<th>Men</th>
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<tbody>
<tr>
<td>Urethra</td>
<td>31/31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Endocervix</td>
<td>25/25</td>
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<tr>
<td>Anal canal</td>
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<tr>
<td>Pharynx</td>
<td>2/2</td>
<td>0/1</td>
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