Norflaxin Versus Trimethoprim-Sulfafomethoxazole in the Therapy of Uncomplicated, Community-Acquired Urinary Tract Infections

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In a prospective, randomized trial, norflaxin (400 mg perorally, twice a day) was compared with trimethoprim-sulfafomethoxazole (160-800 mg perorally, twice a day) in 45 patients with uncomplicated urinary tract infections. Escherichia coli was the most common isolate. Infections due to Enterobacter spp., Proteus mirabilis, Pseudomonas spp., and Staphylococcus spp. were also treated. Norflaxin was equivalent in effectiveness and safety to trimethoprim-sulfafomethoxazole, with a cure rate of 91% at the 5- to 9-day posttherapy visit and 88% at the 4- to 6-week posttherapy visit. It was well tolerated and had a low incidence of side effects.

Norflaxin, a new orally absorbed quinolone antibiotic, is related to nalidixic acid but has a broader spectrum of activity that includes Staphylococcus saprophyticus, enterococci, Escherichia coli, Serratia marcescens, and Pseudomonas aeruginosa, including aminoglycoside-resistant strains (4, 8, 9). Resistance to norflaxin does not develop as readily as previously reported to occur with nalidixic acid (4, 8, 9). Urinary concentrations of approximately 30 to 150 μg/ml are found 8 to 10 h after a single 400-mg oral dose, allowing twice-daily dosage (1, 3, 5, 13).

Consequently, we undertook a clinical study to determine the efficacy and safety of norflaxin compared with trimethoprim-sulfafomethoxazole (SXT) in the treatment of uncomplicated community urinary tract infections.

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Women over 18 years old who were not pregnant or lactating and who had urinary tract infections were eligible for study. Urinary tract infections were defined by the following symptoms: frequency or urgency of urination, dysuria, suprapubic pain, or malodorous urine with pyuria (>10 leukocytes per high-power field) and >10³ bacteria per ml on a pretreatment midstream clean-catch urine culture. Patients with pyelonephritis (flank pain, rigors, or temperature of >100.4°F [ca. 38°C]) or allergy to either medication were excluded from study. Signed informed consent was obtained from each patient before the study.

Patients were prospectively randomized to receive either norflaxin (400 mg perorally, twice a day) or SXT (160-800 mg perorally, twice a day) for 7 to 10 days. The medical history and physical examination (including visual acuity, color blindness, amsler grid, visual fields, and neurological examination) were recorded on a standard data form. Patients were reevaluated on days 2 to 4 of therapy, 5 to 9 days posttherapy, and, when possible, 4 to 6 weeks posttherapy. Laboratory studies (complete blood count, liver enzymes, blood urea nitrogen, and creatinine) were obtained within 48 h before therapy and 5 to 9 days posttherapy. Patients noted subjective response to therapy as well as any side effects in daily diaries. Isolates were identified and disk susceptibilities to SXT and norflaxin were interpreted according to standard criteria (11, 16). Isolates were considered susceptible to norflaxin if there was a ≥17-mm zone of inhibition (16, 17).

Forty-five patients were enrolled; 23 received norflaxin, and 22 received SXT. Demographic data were similar for both groups. Patients ranged in age from 19 to 75 years. One patient in the norflaxin group was non-evaluable, since the pretreatment culture yielded no growth.

The bacteria isolated from pretreatment cultures are listed in Table 1. Of the original isolates, only one, an E. coli, was resistant to SXT and one, a Pseudomonas fluorescens, was resistant to norflaxin. Both these patients received SXT. Cure, defined as the absence of symptoms and eradication of bacteriuria on both the 2- to 4-day on-therapy visit and the 5- to 9-day posttherapy visit, was achieved in 19 of 22 (86%) control patients and in 20 of 22 (91%) patients receiving norflaxin. In the SXT group, one patient was reinfeeted with two types of diphtheroids, one was reinfeeted with a Citrobacter freundii strain that was resistant to SXT, and one patient had persistent infection with an SXT-resistant E. coli. In the norflaxin group, one diabetic patient had a reinfection with diphtheroids and one had a relapse of infection with her original and still susceptible E. coli and coinfection with a group B streptococcus that was resistant to norflaxin. Posttherapy follow-up cultures (4 to 6 weeks) were obtained in 34 patients, 17 from each group. In 13 of 17 (71%) in the SXT group and 15 of 17 (88%) in the norflaxin group, there was persistent cure. In the SXT group there was one patient who experienced a late relapse with a susceptible E. coli and three patients who had late reinfections with new organisms (one with K. oxytoca, one with E. coli, and one with Enterobacter aerogenes and a coagulase-negative Staphylococcus sp.). In the norflaxin group there was one late relapse with E. coli and one late reinfection with a coagulase-negative Staphylococcus sp. that was resistant to norflaxin.

Adverse reactions or side effects were seen in five (23%) women in the SXT group (three had headaches, one had diarrhea, and one had nausea). One patient with headache discontinued taking the medication. In the norflaxin group, 14% of patients experienced side effects (one had headaches, one had headaches, nausea, and insomnia and discontinued...
TABLE 1. Bacteria isolated from pretreatment urine cultures in 43 study patients

<table>
<thead>
<tr>
<th>Organism</th>
<th>No. of isolates in patients receiving:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SXT (n = 22)</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>18</td>
</tr>
<tr>
<td>Enterobacter agglomerans</td>
<td>2</td>
</tr>
<tr>
<td>Proteus mirabilis</td>
<td>1</td>
</tr>
<tr>
<td>Pseudomonas fluorescens</td>
<td>1</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>1</td>
</tr>
<tr>
<td>Staphylococcus saprophyticus</td>
<td>1</td>
</tr>
<tr>
<td>No pathogen isolated</td>
<td>1</td>
</tr>
</tbody>
</table>

the medication; and one had insomnia and abdominal pain and also discontinued the medication). No adverse laboratory effects were seen in either group.

Although SXT is frequently prescribed for urinary tract infection, a number of patients will have resistant isolates or give a history of allergy or adverse reaction to sulfonamides (12, 14–16). Our study showed that norfloxacin was clinically and microbiologically as effective as SXT in the therapy of uncomplicated, community-acquired urinary tract infections. Cure was achieved in 91% of norfloxacin-treated patients at the 5- to 9-day posttherapy visit, and 88% continued to be asymptomatic and have negative urine cultures 4 to 6 weeks posttherapy. European studies (2, 6, 7, 10, 14) showed similar results, but several were either uncontrolled or gave sparse methodology. Clinical side effects (nausea, headache, insomnia) were seen in 23% of the SXT group and 14% of the norfloxacin group. None of these adverse reactions was serious in nature. Most of our patients had infections with susceptible E. coli. Further clinical trials should be conducted to determine the effectiveness of norfloxacin in patients with complicated urinary tract infections and those with antibiotic-resistant bacteria.

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LITERATURE CITED