

Long-Term Prophylaxis with Norfloxacin versus Nitrofurantoin in Women with Recurrent Urinary Tract Infection

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A total of 102 women with recurrent urinary tract infections were included in this open randomized study; 55 received 200 mg of norfloxacin daily and 47 received 50 mg of nitrofurantoin daily over 6 months. Fifty-three and 41 women from the norfloxacin- and nitrofurantoin-treated groups, respectively, completed the 6-month follow-up period. Forty-four (81%) of the norfloxacin-treated patients and 27 (65%) of the nitrofurantoin-treated patients remained free of symptoms ($P = 0.05$), and urine samples from 49 (92.4%) and 29 (70.7%) of the patients, respectively, were sterile ($P < 0.005$). Side effects occurred with similar frequencies in both groups (15 and 17%) but were more severe in the women who received nitrofurantoin. Despite the better results obtained with norfloxacin, the difference in the costs of the two agents must be considered.

Recurrent urinary tract infection (UTI) is a common problem affecting approximately 6 to 10% of women of all ages. Most of those affected have a normal urogenital tract, and most of the infections are caused by recurrent colonization of the periurethral area by microorganisms from the intestinal flora with subsequent ascension to the bladder (6).

Effective antibiotic regimens to prevent recurrent UTIs have used low doses of trimethoprim-sulfamethoxazole, trimethoprim alone, nitrofurantoin, and cephalosporins over a prolonged period of time (5).

The new fluoroquinolones are ideal agents for the treatment of UTIs because of their broad-spectrum activity against most uropathogens and their ability to achieve high levels in the urinary tract. Numerous studies have shown their efficacy in the treatment of complicated and uncomplicated UTIs (1, 7), but few studies have evaluated their effectiveness as prophylactic agents (3, 4).

The present study was designed to evaluate the efficacy and safety of prolonged use of a low dose of norfloxacin and to compare these results with those obtained with a prolonged treatment with nitrofurantoin in the prevention of recurrent UTI in women. A feature of this study is the inclusion of women with recurrent UTIs who had different

diseases, urinary or gynecological abnormalities, and menstrual status of the patients were recorded. Pregnant women and those who were planning pregnancy were excluded.

A clear-voided midstream urine specimen was collected from each patient and cultured with the Uritest system (Nylab dip slides; Rehovot, Israel). Once a negative urine culture was obtained, the women were randomized by an open schedule into two groups: one group received 200 mg of norfloxacin nightly and the second group received 50 mg of nitrofurantoin nightly. Both groups were treated for 6 months.

All patients were seen once a month or when symptoms relating to UTIs appeared. Urine cultures were performed on each visit, and clinical bacteriological infections were recorded. Hematological, liver, and renal function tests were performed before initiation of treatment and at 2, 4, and 6 months after treatment began. All possible drug-related side effects were also recorded.

An infection was defined as the isolation of an organism in quantitative counts of ≥ 105 CFU/ml. Symptomatic infection was defined as being present when the women complained of dysuria, frequency of micturation (or urgency), and/or suprapubic tenderness.

TABLE 1. Clinical characteristics of the two treated groups

| Treatment group (n) | Mean age (yr) | No. of women with: | | Mean no. of episodes ^a | No. of women with underlying diseases | | | No. of women with the following menstrual status: | |
|------------------------|------------------|-----------------------|----------------|--------------------------------------|--|-------------------|-----------------------------|--|---------------|
| | | Cystitis | Pyelonephritis | | Diabetes mellitus | Urinary stones | Prolapse urinary bladder | Premenopausa | Postmenopausa |
| Norfloxacin (55) | 51.2 | 39 | 16 | 3.1 | 15 | 4 | 8 | 17 | 38 |
| Nitrofurantoin (47) | 54.6 | 40 | 7 | 3 | 7 | 2 | 6 | 19 | 28 |

^a During the 6 months before treatment.

clinical characteristics, such as postmenopausal diabetes and urinary stones.

Women, 16 years of age or older, who had been referred to two of our outpatient clinics with a history of three or more documented episodes of UTI during the last 6 months were included in this study. Clinical characteristics, underlying

Demographic differences between the two groups and the microbiological and clinical responses were analyzed by the chi-square test, and P values less than or equal to 0.05 were considered statistically significant.

A total of 102 women were enrolled in the study; 55 received norfloxacin and 47 received nitrofurantoin. Fifty-three and 41 women, respectively, completed the 6-month follow-up period. The clinical characteristics of both groups are summarized in Table 1.

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TABLE 2. Clinical and microbiological responses after the 6-month follow-up period^a

| Treatment group (n) | Mean no. of episodes ^b | No. (%) of women: | |
|------------------------|--------------------------------------|---------------------|-----------------------|
| | | Free of symptoms | With sterile urine |
| Norfloxacin (53) | 0.07† | 44 (81)* | 49 (92.4)† |
| Nitrofurantoin (41) | 0.34 | 27 (65) | 29 (70.7) |

^a Asterisk indicates $P = 0.05$; dagger indicates $P < 0.005$.

^b During the 6-month follow-up period.

Forty-four (81%) women in the norfloxacin-treated group and 27 (65%) in the nitrofurantoin-treated group remained free of symptoms ($P = 0.05$), and the urine samples of 49 (92.4%) and 29 (70.7%) of the women, respectively, were sterile ($P \leq 0.005$). The incidence of UTIs after initiation of prophylaxis dropped dramatically in both groups, from 3.1 episodes per 6 months before treatment to 0.02 episode per 6 months after prophylaxis for the norfloxacin-treated women and from 3 episodes per 6 months to 0.3 episode per 6 months for the nitrofurantoin-treated women ($P < 0.005$) (Table 2).

Side effects from the medications occurred with similar frequencies in both groups (15 and 17% for the norfloxacin- and nitrofurantoin-treated women, respectively) but were more severe among the women who received nitrofurantoin, leading to discontinuation of the drug for four women (Table 3). No organisms resistant to norfloxacin were found, but in two women treated with nitrofurantoin, resistant uropathogens appeared.

During the study period no hematological, liver, or kidney abnormalities developed.

The efficacy of a prophylactic antimicrobial regimen in women with recurrent UTI is based on two mechanisms: (i) the eradication of members of the family *Enterobacteriaceae* from the intestine and the vagina, as occurs with treatment with trimethoprim-sulfamethoxazole, and (ii) intermittent sterilization of the urine, as is observed with treatment with nitrofurantoin (3).

Norfloxacin, like other fluoroquinolones, produces both effects. Nicolle et al. reported a 1-year comparative study of the effects of 200 mg of norfloxacin given daily versus those of a placebo on women with recurrent UTI (3). They demonstrated that norfloxacin was indeed effective in suppressing growth of members of the family *Enterobacteriaceae* in rectal cultures and that it also achieved bactericidal levels in the bladder, resulting in intermittent sterilization of the urine.

TABLE 3. Side effects

| Treatment group (n) | No. of patients: | | | | Total no. (%) of patients showing symptoms |
|------------------------|---|-------------------|----------------|--------------------------------|--|
| | Requiring cessation of treat- ment | With urticaria | With nausea | With vaginal candidiasis | |
| Norfloxacin (55) | 0 | 4 | 0 | 4 | 8 (15) |
| Nitrofurantoin (47) | 4 | 4 | 4 | 1 | 7 (17) |

Our study adds new data on the role of the quinolones in the prevention of UTI in women. Norfloxacin and nitrofurantoin were both effective in preventing UTI, but norfloxacin was 15 times more efficacious. We speculate that the better results obtained with norfloxacin are attributable to its ability to eradicate the fecal microorganisms and to sterilize the urine, while nitrofurantoin is capable of performing only the latter.

The main objections against long-term antibiotic chemoprophylaxis relate to the emergence of resistant strains and to the increase in unacceptable side effects. In the present study, no resistant isolates emerged with the use of norfloxacin, and only two resistant isolates emerged with the use of nitrofurantoin.

The frequency of side effects was similar for both drugs (approximately 15%); however, the severity was greater with nitrofurantoin. Severe gastrointestinal symptoms led to discontinuation of therapy for four nitrofurantoin-treated women, compared with no symptoms in norfloxacin-treated women.

This study confirms the high efficacy and safety of a 200-mg dose of norfloxacin taken daily for 6 months in the prevention of recurrent UTI in women. Previous data have shown that trimethoprim-sulfamethoxazole taken three times weekly was also highly effective (4). We presume that norfloxacin might also be effective in a lower-frequency dosage. Control studies are needed to test this possibility.

Because of the higher cost of the fluoroquinolones, we recommend reserving their use for women with UTIs with multiresistant organisms, for patients exhibiting intolerance, or for women for whom use of nitrofurantoin or trimethoprim-sulfamethoxazole has failed.

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