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Prospective, Randomized, Placebo-Controlled Trial of Norfloxacin for the Prophylaxis of Recurrent Urinary Tract Infection in Women

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Thirty women were randomized in a double-blind, placebo-controlled study to receive either norfloxacin, 200 mg orally daily at bedtime, or placebo for the prevention of recurrent bladder infection. Subjects were followed monthly to monitor compliance and symptoms, for urine culture and periurethral and anal canal swabs to monitor colonization, and for blood specimens for hematologic and biochemical studies to monitor safety. During 1 year of follow-up, 10 of 15 placebo subjects and none of 15 norfloxacin subjects developed infection ($P < 0.001$). Adverse effects occurred with equal frequencies in the two groups. For norfloxacin subjects, only 2 (1.6%) of 129 periurethral and 4 (3.1%) of 129 anal canal swabs showed colonization with aerobic gram-negative organisms, while 16 (22%) of 73 periurethral and 47 (64%) of 73 anal canal swabs from placebo subjects showed colonization. Daily therapy with norfloxacin at bedtime is effective in preventing recurrent cystitis. During 1 year of norfloxacin therapy, colonization was infrequent and superinfection with norfloxacin-resistant organisms did not occur.

From 2 to 10% of all women experience recurrent symptomatic bladder infections due to reinfection from the fecal reservoir (13). Extended prophylaxis with a low dose of some antimicrobial agents is effective for the prevention of such infections (9, 10). The efficacy of prophylactic therapy is due to at least two mechanisms: the eradication of gut colonization with aerobic gram-negative organisms which are potential uropathogens, as occurs with trimethoprim-sulfamethoxazole; and intermittent sterilization of the urine, as is observed with nitrofurantoin (14).

The recently introduced quinolone antimicrobial agents have a wide spectrum of activity, including most uropathogens, and achieve high levels in urine for extended time periods. These agents have been extensively investigated for the treatment of urinary tract infections (8). With short courses of therapy, eradication of members of the family *Enterobacteriaceae* from the gut flora has been documented (11), an observation which has been exploited in the use of these agents for the prophylaxis of infection in granulocytopenic patients (3). Thus, these agents should constitute effective prophylaxis for the prevention of recurrent lower urinary tract infection in women. This study was undertaken to assess the effectiveness of norfloxacin for this clinical indication.

MATERIALS AND METHODS

Patient population. Thirty adult women referred to the Infectious Diseases Out-patient Clinics at the Health Sciences Centre and St. Boniface General Hospital, Winnipeg, Manitoba, Canada, were enrolled in this study. Study subjects had had three or more episodes of acute symptomatic urinary tract infection in the 12 months prior to enrollment and were free of urinary tract infection at study entry. Women were excluded if they were under 12 or over 75 years of age or when there was a history of allergy to quinolone antimicrobial agents. All subjects were practicing a reliable means of birth control, did not have serious associated illnesses or infections, and were not receiving concurrent antimicrobial agents. Informed written consent was obtained from all patients enrolled in the study.

Study design. The study was a double-blind, randomized, placebo-controlled trial comparing the efficacy of norfloxacin, 200 mg daily at bedtime, with that of placebo. Study subjects were treated for 12 months or until urinary tract infection recurred. When either symptomatic or asymptomatic urinary tract infection developed, subjects were withdrawn from the study without breaking the randomization code. Patients were monitored at monthly intervals for 12 months or until withdrawal and were questioned about compliance, urinary symptoms, or possible drug-related adverse effects at each visit. Compliance was not assessed beyond interview.

Specimen collection and microbiologic assessment. At each visit a voided midstream urine specimen was obtained for urinalysis, including a quantitative leukocyte count, using the hemacytometer chamber, and urine culture. Periurethral and anal canal swabs were obtained at each visit and inoculated into 1 ml of phosphate-buffered saline (pH 7.4), and organisms were isolated and quantitated as described previously (7). Urine specimens were inoculated onto split plates of blood and MacConkey agar, using the quantitative loop method, and incubated overnight. Organisms isolated were identified by the Microscan (Travenol Canada Inc., Edmonton, Alberta) method. Antimicrobial susceptibilities to norfloxacin for organisms isolated from periurethral and anal canal swabs were determined by using the National Committee for Clinical Laboratory Standards agar dilution method.

A blood specimen for hematologic and biochemical studies to monitor safety was also obtained at each monthly visit.

Definitions and analysis of data. An infection was microbiologically documented when an organism was isolated in quantitative counts of $\geq 10^8$ CFU/liter ($\geq 10^5$ CFU/ml). Infection was symptomatic when the patient complained of irritative symptoms consistent with urinary infection such as dysuria, urgency, or frequency.

Differences between the two study groups in age and periurethral and rectal colonization were examined by using

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TABLE 1. Characteristics and outcome in subjects randomized to receive norfloxacin compared with placebo for prophylaxis of recurrent urinary tract infection

Study group	No. of subjects enrolled	Age (yr) ± SD	No. withdrawn prior to 12 mo		Patient-mo followed	Infections/ patient-yr	Colonization (%)		Adverse effects (no.)			
			Infection	Other			Periurethral	Anal canal	Vaginitis	Skin rash	Gastro-intestinal upset	AST elevation[a]
Norfloxacin	15	53 ± 15	0	4[b]	139	0	2/129 (1.6)	4/129 (3.1)	2	0	0	1
Placebo	15	45 ± 19	8	2[c]	77.5	1.6	16/73 (22)	47/73 (64)	1	1	1	0

[a] AST, Aspartate transaminase.
[b] Two were lost to follow-up (1 mo), one wished to become pregnant (1 mo), and one had a possible adverse drug effect (4 mo).
[c] One was infected at enrollment, and one had an adverse effect requiring study drug discontinuation (2 mo).

the Wilcoxon rank sum test. Life table analysis comparing the placebo and norfloxacin groups was performed by using the Kaplan-Meier method with a log rank estimate of difference.

RESULTS

Fifteen women were randomized to each of the two study groups (Table 1). The mean age in the placebo group tended to be lower than that in the norfloxacin group, but this difference was not significant ($P = 0.13$). Four patients randomized to norfloxacin did not complete 12 months, including one woman with elevated hepatocellular enzymes after 4 months with no identified cause. Liver enzymes returned to normal within 1 week after discontinuation of the study drug. Ten subjects randomized to placebo did not complete the year of therapy, including one with medication discontinued at 2 months for a skin rash. The rash may have been due to concomitant allopurinol.

Eight individuals receiving placebo had the study drug discontinued because of documented urinary tract infection. A ninth placebo subject had a first urinary tract infection at the final visit. In addition, one placebo subject had a symptomatic episode at 7 months with pyuria ($7,360/mm^3$; $7,360 \times 10^6$/liter). No pathogen was identified in significant numbers, but *Escherichia coli* was present at a count of 10^6 CFU/liter (10^3 CFU/ml). The patient subsequently treated herself, with resolution of symptoms, and completed the 5 remaining study months without further episodes. In retrospect, this was considered in the analysis as symptomatic urinary tract infection with low bacterial counts (16). An additional patient in the placebo group who completed 12 months of therapy took two self-medicated single doses during the year of therapy because of perceived symptoms. These occurred at 1 month, when urine culture grew *Staphylococcus epidermidis* (3×10^7 CFU/liter [3×10^4 CFU/ml]) with a cell count of only 3, and at 11 months, when no culture was available prior to therapy. These two episodes were not included as infections in the analysis. No symptomatic or microbiologically documented urinary tract infections were identified in norfloxacin subjects during the study year, and no subject treated herself during norfloxacin treatment. Thus, 10 (71%) of 14 placebo patients monitored for 1 month or longer experienced infection compared with none of 12 norfloxacin patients. Life table analysis of the proportion in each group who remained infection-free during follow-up is shown in Fig. 1. The differences in outcome between the two groups were significant (log rank test, $t = 12.22$; $P < 0.001$).

The infecting organisms in the placebo-treated patients included five *E. coli* (including the episode mentioned above), two *S. epidermidis*, and one each *S. aureus*, *Enterococcus* sp., and mixed *S. epidermidis* and *Enterococcus* sp. infection. Seven infections were symptomatic and three were asymptomatic. All infected subjects had associated pyuria with cell counts ranging from 15 to $4,266/mm^3$ (median, $954/mm^3$) (15×10^6 to $4,266 \times 10^6$/liter [median, 954×10^6/liter]).

Periurethral and anal canal colonization with aerobic gram-negative organisms was identified significantly more frequently in placebo subjects ($P = 0.011$ and 0.0001, respectively) (Table 1). Three colonizing organisms were nonviable and unavailable for susceptibility testing. The MICs for gram-negative organisms isolated from periurethral and rectal swabs are shown in Table 2. On several occasions more than one species or strain of organism was isolated, so the number of organisms exceeds the number of positive swabs. The few aerobic gram-negative organisms colonizing norfloxacin subjects did tend to be organisms for which MICs of norfloxacin were higher than those isolated from placebo subjects.

Three individuals in each group experienced adverse effects which were possibly associated with study medication, including the one in each group with study drug discontinued. In addition, two women receiving norfloxacin and one in the placebo group complained of symptoms of vaginitis, although none required specific therapy or discontinuation of the study drug. One placebo subject complained of intermittent gastrointestinal upset. The subject in whom norfloxacin was discontinued due to an elevation in hepatocellular enzymes was the only individual with hematologic or biochemical abnormalities recognized on routine serum screening.

Eight of 11 subjects who received norfloxacin have become reinfected in subsequent follow-up, from 2 weeks to 7

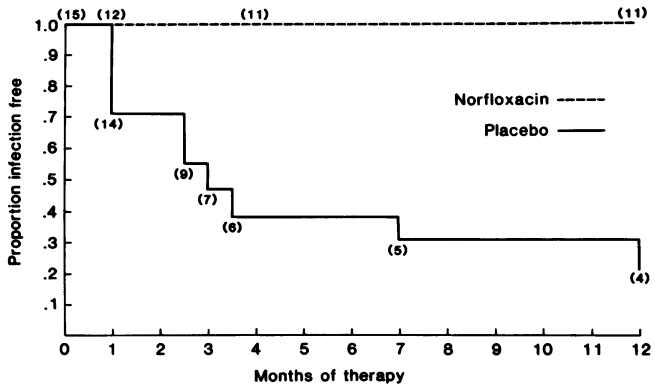

FIG. 1. Life table analysis of infection-free period for women with recurrent urinary tract infection receiving norfloxacin, 200 mg/day at bedtime, or placebo.

TABLE 2. MIC of norfloxacin for aerobic gram-negative organisms isolated from periurethral and rectal swabs during prophylactic therapy with placebo or norfloxacin

Organism	MIC (μg/ml) of norfloxacin with:			
	Placebo		Norfloxacin therapy	
	Periurethral	Anal canal	Periurethral	Anal canal
Escherichia coli	0.063–0.125 (11)[a]	0.063–0.125 (49)		
Klebsiella pneumoniae	0.25 (1)	0.125–0.25 (5)		
Klebsiella oxytoca	0.125 (1)			0.25 (1)
Proteus mirabilis	0.063 (1)	0.063 (2)		
Proteus vulgaris	0.063 (1)			
Citrobacter freundii	0.125 (1)	0.125–0.25 (4)		
Citrobacter spp.	0.125 (1)			
Enterobacter cloacae		0.125 (2)		
Enterobacter agglomerans		0.125 (1)		
Pseudomonas aeruginosa				1.0 (1)
Acinetobacter spp.		4.0 (2)	2.0–4.0 (3)	2.0–4.0 (3)

[a] Number in parentheses is number of strains tested.

months (median, 8 weeks) after discontinuing therapy. Subjects who have not yet become reinfected have been followed for 6, 8, and 12 months posttherapy. The postprophylaxis infecting organisms included four *E. coli*, two *Enterococcus* spp., and 1 each *Enterobacter cloacae* and *Klebsiella pneumoniae*.

DISCUSSION

This study documents the prophylactic efficacy of a quinolone, norfloxacin, for the prevention of recurrent urinary tract infection in women. All 11 women who completed 1 year of therapy remained infection-free on norfloxacin. By comparison, the majority of individuals receiving placebo developed urinary infection, and the infection rate in the placebo group was similar to that previously reported in populations of women with recurrent infection not receiving therapy (10). The drug was well tolerated at the dose used for this extended time period, with adverse effects occurring no more frequently in the treated than in the placebo group. One previous study of norfloxacin compared with placebo for the prevention of recurrent urinary tract infection reported a reinfection rate of 19% of norfloxacin subjects compared with 87% of placebo subjects after 24 weeks of therapy (12). This report was published only in abstract form, and it cannot be ascertained what patient characteristics, if any, can explain the substantially higher infection rate of 19% at 24 weeks compared with 0 at 52 weeks observed in this study.

In addition to preventing symptomatic urinary tract infection, norfloxacin virtually eradicated periurethral and anal canal colonization with aerobic gram-negative organisms. This is consistent with observations from short-term treatment with this antimicrobial agent (5, 11) and with one earlier study in which the antimicrobial agent remained effective in eradicating colonization for 3 months (2). This study extends these earlier investigations by documenting that norfloxacin remains effective in suppressing aerobic gram-negative fecal flora for as long as 1 year of continuous therapy. In addition, a lower dose of norfloxacin was used and antimicrobial therapy remained effective in preventing colonization at this lower dose. When aerobic gram-negative colonization was observed in the norfloxacin group, the organisms isolated, particularly *Acinetobacter* spp., tended to have higher MICs of the antimicrobial agent than those colonizing the placebo group. However, infection with these organisms was not observed, perhaps because the high levels of antimicrobial agent in urine still exceeded the MICs for the organism, preventing bladder infection.

Norfloxacin was compared with placebo in this study. In the placebo group, rapid reinfection, with 60% becoming reinfected by 3 months of entry into the study, was observed. This infection rate is consistent with other studies of prophylaxis for urinary tract infection which have used a placebo comparative arm (1, 7, 16). The consistency of these rates of reinfection without antimicrobial therapy among different studies and the exceedingly high frequency of recurrence suggest that the inclusion of a comparative placebo arm in further studies of urinary tract infection prophylaxis in this population is not appropriate. One of the several antimicrobial regimens of documented efficacy for this clinical indication, including co-trimoxazole, trimethoprim alone, and nitrofurantoin, should be used as the comparative arm for future studies (10).

The dose of norfloxacin we used was 200 mg orally daily. Prophylaxis for urinary tract infection with norfloxacin may remain effective with even less frequent administration. For instance, for trimethoprim-sulfamethoxazole, one-half tablet of antimicrobial agent three times a week at bedtime is an effective prophylactic regimen (6). Further studies are required to determine the minimal effective regimen for norfloxacin. In addition, norfloxacin prophylaxis would be contraindicated in pregnant or lactating women because of the arthropathy observed in immature animals treated with quinolone therapy (4). In the interim, when antimicrobial resistance or patient intolerance to other medication makes other agents undesirable, prophylactic therapy with norfloxacin appears to be an option for the management of nonpregnant women with frequent recurrences of symptomatic lower urinary tract infections.

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