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Double-Blind, Randomized Comparison of 24 Weeks of Norfloxacin and 12 Weeks of Norfloxacin Followed by 12 Weeks of Placebo in the Therapy of Complicated Urinary Tract Infection

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We evaluated the benefits of prolonging norfloxacin therapy from 12 to 24 weeks for complicated urinary tract infection in a double-blind, randomized, placebo-controlled study. During the second 12 weeks, norfloxacin was superior to placebo ($P < 0.05$) in suppressing bacteriuria. Adverse effects were common but mostly confined to the initial 12 weeks.

There have been few placebo-controlled, prospective trials of suppressive or eradicative therapy for complicated urinary tract infections, despite recommendations for antimicrobial suppression of bacteriuria in some of these patients (3). We therefore attempted such a trial with norfloxacin using a prospective, double-blind, randomized design. Norfloxacin was administered to all patients for the first 12 weeks, at which point patients were randomized to continue norfloxacin or a placebo for a further 12 weeks.

Patients were considered suitable if they had significant bacteriuria along with either structural abnormalities of the urinary tract or multiple relapses of urinary tract infection with the same pathogen. All the patients were ambulatory, and treatment was given on an outpatient basis. The patients had histories and physical examinations at the beginning of therapy, and evidence of structural defects of the urinary tract was documented. The patients were seen 1 week after commencing therapy and at 2- to 4-week intervals during therapy. Clean-catch midstream urine samples were obtained pretherapy and at each visit during therapy. When appropriate, urine was obtained directly from an ileal conduit with a straight catheter. After written informed consent was obtained, all patients received 12 weeks of norfloxacin (400 mg orally twice a day). Norfloxacin was provided by Merck Frosst Canada, Inc.

Patients who completed 12 weeks of therapy without major adverse effects and without symptomatic persistence of infection were randomized to continue to receive either norfloxacin (400 mg orally twice a day) or an identical placebo twice a day. Follow-up visits continued at 2- to 4-week intervals during treatment as before and at 2 and 6 weeks after the end of treatment. Both patients and physicians remained blinded. The code was maintained in the hospital pharmacy and was only broken if a patient was withdrawn from the study. Upon completion, all charts were reviewed to confirm outcome and adverse effects. Following this, the randomization code was broken.

A total of 21 patients were enrolled in the study. Fifteen of these completed the initial 12 weeks of norfloxacin therapy and were randomized into phase 2. The other six were eliminated from the study at various times for the following reasons. Four developed major adverse effects, at 2, 3, 6, and 9 weeks; one had symptomatic pyelonephritis at 4 weeks; and treatment of one was inadvertently stopped at 5 weeks. The major adverse effects included abdominal pain, diarrhea, nausea, vertigo, and amnesia. Eight patients had various other minor symptoms which were attributed to the drug during the first 12 weeks. These included abdominal pain, diarrhea, headache, vertigo, insomnia, increased appetite, weight gain, edema, myalgia, anorexia, acne, and scintillating scotomata. One patient developed a documented *Candida albicans* vaginitis.

Eight patients began phase 2 on norfloxacin and seven began on placebo. Six norfloxacin patients and five placebo patients had well-documented structural disorders of the urinary tract, such as calculi, ileal conduits, nephrocalcinosis, or prostatic carcinoma with bladder outlet obstruction. Two in each group had had a relapsing infection of the urinary tract despite multiple attempts to eliminate the pathogen. No structural abnormality was evident upon investigation of these latter patients. There were 13 significant bacterial isolates in the treatment group and 7 in the placebo group. This disparity is accounted for by three patients in the treatment group who had multiple pathogens isolated. The organisms are shown in Table 1.

The suppressive effect of norfloxacin was assessed by comparing the prevalences of bacteriuria during phase 2 in both groups (Table 2). Seven of eight patients remained free of bacteriuria in the norfloxacin group, compared with one of seven in the placebo group, a difference that is statistically significant ($P < 0.05$ by Fisher's exact test). Of the six who developed bacteriuria in the placebo group, only one completed the 12 weeks of prescribed placebo. This was a 60-year-old female with analgesic nephropathy and nephrocalcinosis who had asymptomatic bacteriuria caused by *Pseudomonas aeruginosa*. The five others developed symptomatic bacteriuria and were removed from the study at various times. Three of these developed bacteriuria caused

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TABLE 1. Original urinary tract isolates from patients who were randomized into phase 2 of the study

Organism(s)	No. of patients	
	Norfloxacin[a]	Placebo
Pseudomonas aeruginosa	2	4
Escherichia coli	2	1
Other aerobic gram-negative bacilli	6	2
Gram-positive cocci	3	0

[a] Three of the eight patients had multiple pathogens.

by the original pathogen (two after 2 weeks and one after 10 weeks of placebo). Two patients developed symptomatic reinfection with a different pathogen (one at 6 weeks and one at 11 weeks of placebo). No adverse effects were reported from those receiving placebo. In contrast, one major and four minor adverse effects occurred in patients receiving norfloxacin. The major adverse effect was seen at 16 weeks and consisted of a combination of diarrhea, swollen hands, myalgia, and migraine.

TABLE 2. Suppressive effects of norfloxacin versus placebo during the second 12 weeks of the study

Outcome	No. of patients	
	Continued norfloxacin	Placebo
Failure[a]	1	4
Reinfection		2
Remained free of infection	7[b]	1

[a] Failure was defined as bacteriuria caused by the original infecting organism while the patient was receiving norfloxacin or placebo.

[b] One of these seven was withdrawn at 16 weeks because of a major adverse effect. The others completed the course of 24 weeks of norfloxacin.

Patients who have structural abnormalities of the urinary tract have a low infection cure rate. Such infection tends to relapse after antimicrobial therapy even if therapy is administered for prolonged periods. There have been few placebo-controlled, prospective trials of suppressive or eradicative therapy in difficult-to-treat urinary tract infections (1, 2). Our study demonstrated a statistically significant difference between continued therapy and placebo in suppression of bacteriuria. Seven of eight patients remained free of bacteriuria, compared with one of seven on placebo. Antimicrobial suppression of bacteriuria in such patients has been recommended (3), but there have been few placebo-controlled studies validating it. Our results give evidence that norfloxacin suppresses bacteriuria and diminishes symptoms in this population. However, this was not without cost, as both major and minor adverse reactions were commonly encountered.

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