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Comparative Trial of Norfloxacin and Trimethoprim-Sulfamethoxazole in the Treatment of Women with Localized, Acute, Symptomatic Urinary Tract Infections and Antimicrobial Effect on Periurethral and Fecal Microflora

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Forty-three women with acute, symptomatic urinary tract infections were randomized to receive either norfloxacin (400 mg) twice daily or trimethoprim-sulfamethoxazole (160-800 mg) twice daily for 10 days. Of the 43 patients, 7 (16%) had low-count bacteriuria and pyuria and were included in the evaluation. *Escherichia coli* was isolated in 72% of the infections, whereas coagulase-negative staphylococci were isolated in 14%. All isolates were susceptible to the assigned study drug. The MICs for 90% of the strains susceptible to norfloxacin and trimethoprim-sulfamethoxazole were ≤2 and ≤0.8-16 μg/ml, respectively. The cure rates for norfloxacin and trimethoprim-sulfamethoxazole were 95 and 90%, respectively. There were 17 patients with presumptive upper tract infections; only 1 of these relapsed after therapy. The effects on the periurethral flora were similar in both groups, but the infecting organism was eradicated from the fecal flora in 93% of the patients treated with norfloxacin and in 57% of the patients treated with trimethoprim-sulfamethoxazole. More early reinfections occurred in the trimethoprim-sulfamethoxazole group, with resistant organisms appearing in urine and in the periurethral and fecal flora in all cases. Three patients in each group experienced adverse clinical effects, but these were more severe in the trimethoprim-sulfamethoxazole group. No adverse hematological or biochemical changes were noted. From these results, we concluded that norfloxacin is at least as effective as trimethoprim-sulfamethoxazole in the therapy of acute, symptomatic urinary tract infections in women.

Urinary tract infection continues to be one of the most common clinical entities affecting women today. The great majority of these urinary tract infections can be adequately treated with an effective, orally absorbed antimicrobial agent. Norfloxacin, a new oral quinoline carboxylic acid antimicrobial agent, has been shown to be more active in vitro than currently available oral agents against a wide variety of aerobic gram-negative bacilli, including *Pseudomonas aeruginosa*, and gram-positive bacterial isolates, including coagulase-negative staphylococci and enterococci (4, 5, 8, 14). It is structurally related to nalidixic acid, the clinical use of which has been limited by the frequent occurrence of side effects and the rapid in vivo development of bacterial resistance (19, 21).

Norfloxacin, however, is rapidly absorbed orally and achieves very high levels in urine (peak, >400 μg/ml after a dose of 400 mg), making it a more ideal agent for the therapy of urinary tract infections (26). Trimethoprim-sulfamethoxazole has been extensively used for the therapy of urinary tract infections with great success and minimal adverse effects (1, 2, 9, 11–13), but it is less effective against infections caused by organisms such as *P. aeruginosa* and enterococci.

This study was designed as a prospective, randomized comparison of the efficacy, tolerance, and safety of orally administered norfloxacin and trimethoprim-sulfamethoxazole in the therapy of acute urinary tract infections. The influence of these drugs on microflora in the periurethra and the anal canal was also compared.

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MATERIALS AND METHODS

Patient selection. Candidates for this study were ambulatory female outpatients with clinical symptoms and signs suggestive of acute upper (fever, flank pain or tenderness) or lower (dysuria, urgency or frequency) urinary tract infections and significant bacteriuria. Significant bacteriuria was defined as a midstream urine culture bacterial count of $\geq 10^5$ CFU/ml of urine, with or without significant pyuria (≥10 leukocytes per mm^3) (23). However, patients with counts of $<10^5$ CFU/ml but more than 10^2 CFU/ml with significant pyuria were also entered (18, 24). Patients were excluded from the study if there was (i) allergy to nalidixic acid or its derivatives, to the sulphonamides, or to trimethoprim, (ii) pregnancy, (iii) renal dysfunction, or (iv) structural abnormalities of the urinary tract. In addition, patients who were infected with organisms known to be resistant to either study drug, who had had antimicrobial therapy within 72 h before entry, or who had serious systemic disease or infections were also excluded.

After written, informed consent was obtained, patients were randomized to receive two tablets of either norfloxacin (400 mg) or trimethoprim-sulfamethoxazole (160-800 mg) twice daily for 10 days. Norfloxacin was provided by Merck Frosst Canada, Inc., and the trimethoprim-sulfamethoxazole used was in the form of Bactrim (Hoffmann-La Roche Inc.).

Patient assessment. Patients were assessed clinically before therapy, during therapy at days 3 to 5, and after the completion of therapy at days 5 to 9 and at 4 to 6 weeks. A clean-catch midstream urine sample for bacteriological culture and antimicrobial susceptibility testing was obtained before therapy and at each follow-up visit, along with swabs from the periurethral and anal canal areas. Hematological

and biochemical parameters of blood and urine were also monitored at each visit for assessment of drug toxicity.

Bacteriology. An absolute leukocyte count and antibody-coated bacteria (ACB) testing were performed on all urine specimens as previously described (10). Swabs from the periurethra and anal canal were cultured aerobically and processed as previously described (12). All organisms present on cultures from the periurethra and anal canal were identified. Coagulase-negative staphylococci which were not novobiocin susceptible (*Staphylococcus saprophyticus*) were designated as *S. epidermidis*. Antimicrobial susceptibility testing was performed by the disk diffusion method and also by the agar dilution method for determination of MICs (8, 17, 25). For susceptibility testing, trimethoprim-sulfamethoxazole was used in a ratio of 1:20. Biotyping of *Escherichia coli* was performed to distinguish between reinfection and relapse (3).

Definitions. Cure was defined as improvement of symptoms, eradication of the infecting organism, and disappearance of pyuria with no recurrence at days 5 to 9 and at 4 to 6 weeks after the completion of therapy. Failure or persistence was defined as the continued presence of the pretherapy infecting organism, with or without pyuria, during therapy. Relapse was defined as the recurrence of infection with the same organism after therapy, whereas reinfection was defined as recurrence of infection with a different organism after therapy.

Organisms were reported as ACB positive if there was uniform fluorescence of at least five bacteria per slide with a nonfluorescing negative control. Nonspecific fluorescence was reported if there was also fluorescence in the negative control and ACB status could not be determined (10).

Susceptibility to norfloxacin and trimethoprim-sulfamethoxazole was defined as zone diameters of ≥17 and ≥16 mm, respectively, or MICs of ≤16 and ≤3.2-64 μg/ml, respectively, or both.

Statistical analysis of proportions was carried out with the Fisher exact test.

RESULTS

Forty-three symptomatic patients were entered and randomized to either treatment group (Table 1). A total of 36 patients had midstream urine bacterial counts of $\geq 10^5$ CFU/ml, and 25 of these had significant pyuria. Seven patients had midstream urine bacterial counts of 10^3 to 10^5 CFU/ml; all of these had significant pyuria, and four were infected with ACB-positive organisms. More patients in the norfloxacin group had a positive ACB test than in the trimethoprim-sulfamethoxazole group (10).

The data on the infecting organisms are presented in Table 2. *E. coli* was the most frequently recovered isolate, accounting for 31 (72%) of all isolates, whereas coagulase-negative staphylococci accounted for 6 (14%) of all isolates. All isolates were susceptible to norfloxacin, and 37 (86%) were susceptible to trimethoprim-sulfamethoxazole. Since all patients were acutely symptomatic, many were entered into the study before the results of susceptibility tests were available. Only gram-negative organisms were resistant to trimethoprim-sulfamethoxazole. The range of MICs for susceptible organisms was ≤0.125 to 16 and ≤0.2-4 to 3.2-64 μg/ml for norfloxacin and trimethoprim-sulfamethoxazole, respectively, with 90% of the susceptible isolates tested having MICs of ≤2 and ≤0.8-16 μg/ml, respectively.

There was no significant difference in the outcome of therapy for both treatment groups ($P = 0.5$) (Table 3). All patients in the low-count bacteriuria groups ($<10^5$ CFU/ml) were cured. Of the 12 patients whose infecting organisms were positive by ACB testing, 11 were cured with norfloxacin, and 5 of 5 were cured with trimethoprim-sulfamethoxazole. All the patients in both groups whose infecting organisms were ACB negative were cured. The patient treated with trimethoprim-sulfamethoxazole and whose infecting organism persisted (failure) was infected with an *E. coli* strain which remained susceptible to trimethoprim-sulfamethoxazole throughout therapy. This patient had a long history of recurrent episodes of acute pyelonephritis, with changes on intravenous pyelogram consistent with chronic pyelonephritis. Repeated ACB testing of this organism showed nonspecific fluorescence. The one relapse in the norfloxacin group was due to an ACB-positive *Klebsiella pneumoniae* infection which reappeared, along with symptoms and significant pyuria, 5 days after the completion of therapy. It retained its susceptibility to norfloxacin. In the trimethoprim-sulfamethoxazole group, the one relapse was due to an *E. coli* infection which was initially susceptible to trimethoprim-sulfamethoxazole but was not available for

TABLE 1. Characteristics of the population receiving norfloxacin or trimethoprim-sulfamethoxazole

Characteristic	Treatment	
	Norfloxacin	Trimethoprim-sulfamethoxazole
No. of patients entered	22	21
Mean age (range) (yr)	39.7 (19–72)	37.2 (19–66)
MSU[a] $\geq 10^5$ CFU/ml	18	18
MSU $<10^5$ CFU/ml	4	3
No. of patients with pyuria		
≥10 WBC[b]/mm^3	17	15
<10 WBC/mm^3	3	4
Not done	2	2
ACB status		
Positive	12	5
Negative	10	10
Nonspecific fluorescence	0	3
Not done	0	3

[a] MSU, Midstream urine bacterial count.
[b] WBC, Leukocytes.

TABLE 2. Infecting organisms with antimicrobial susceptibility

Infecting organism	No. of patients with infections susceptible to[a]:	
	Norfloxacin (n = 22)	Trimethoprim-sulfamethoxazole (n = 21)
Escherichia coli	14	17
Klebsiella pneumoniae	2	1
Enterobacter cloacae	1	0
Pseudomonas aeruginosa	1	0
Staphylococcus saprophyticus	2	1
Staphylococcus epidermidis	2	1
Streptococcus faecalis	0	1

[a] In the norfloxacin treatment group, all 22 patients were infected with organisms that were susceptible to norfloxacin, and 16 of these patients were infected with organisms that were susceptible to co-trimoxazole; in the trimethoprim-sulfamethoxazole treatment group, all 21 patients were infected with organisms that were susceptible to both norfloxacin and co-trimoxazole.

TABLE 3. Outcome of therapy for patients receiving norfloxacin or trimethoprim-sulfamethoxazole

Treatment (no. of patients)	No. (%) of patients			
	Cured	Failed	Relapsed	Reinfected
Norfloxacin (22)	21 (95)	0	1	4
Trimethoprim-sulfamethoxazole (21)	19 (90)	1	1	3

susceptibility testing when it reappeared 12 days after the completion of therapy. ACB testing was not performed on this organism. There were four reinfections in the norfloxacin group (*E. coli*, 3; *Streptococcus faecalis*, 1). Two appeared at 12 and 16 days after the completion of therapy, and two appeared at 5 weeks after the completion of therapy. The three reinfecting organisms which were available for testing were all susceptible to norfloxacin and trimethoprim-sulfamethoxazole. The three reinfections in the trimethoprim-sulfamethoxazole group appeared at 4, 6, and 12 days after the completion of therapy and were due to organisms which were resistant to trimethoprim-sulfamethoxazole but susceptible to norfloxacin (*E. coli* 2; *S. epidermidis*, 1).

Serial cultures from the periurethra and anal canal were obtained from 18 patients in each group (Table 4). The infecting organism was eradicated from the periurethral flora in 15 of 16 patients in the norfloxacin group and 14 of 16 patients in the trimethoprim-sulfamethoxazole group. Eradication of the infecting organism from flora in the anal canal occurred in 14 of 15 (93%) patients treated with norfloxacin and 8 of 14 (57%) patients treated with trimethoprim-sulfamethoxazole. This difference was significant ($P = 0.03$). Two patients in both groups who experienced reinfections were noted to have the reinfecting organism in flora in the periurethra and anal canal either during therapy or at the time reinfection was detected. *S. faecalis* was noted in cultures from the periurethra or the anal canal or both, either pretherapy or at days 3 to 5 of therapy, in seven and eight patients in the norfloxacin and trimethoprim-sulfamethoxazole groups, respectively. Of these, four in each group had persistence of this organism in flora in the periurethra or the anal canal or both throughout therapy. One patient in the norfloxacin group showed the transient appearance of *P. aeruginosa* in flora in the anal canal during therapy, with subsequent eradication. One other patient in this group also showed the transient appearance of *P. aeruginosa* in flora in the periurethra and anal canal after the completion of therapy. This organism was susceptible to norfloxacin and resistant to trimethoprim-sulfamethoxazole. Neither patient developed a urinary tract infection with these organisms. No patient in the trimethoprim-sulfamethoxazole group showed the appearance of *P. aeruginosa* in flora in the periurethra or anal canal.

There were three patients in each group who experienced adverse clinical effects. In the norfloxacin group, one patient developed dizziness and two developed nausea. These were mild, however, and did not warrant discontinuation of therapy. In the trimethoprim-sulfamethoxazole group, one patient developed a severe headache after 3 days of therapy and two patients developed a generalized skin rash after a single dose and after 3 days of therapy, respectively. These were severe enough to warrant discontinuation of therapy, but all three patients were cured of their infections. There were no biochemical or hematological abnormalities noted in the 43 patients throughout the study.

TABLE 4. Influence of norfloxacin and trimethoprim-sulfamethoxazole on microflora in the periurethra and anal canal

Treatment	No. of patients in whom:				
	Serial cultures performed	Infecting organism present		Infecting organism eradicated	
		Periurethra	Anal canal	Periurethra	Anal canal
Norfloxacin	18	16	15	15	14
Trimethoprim-sulfamethoxazole	17	16	14	14	8[a]

[a] $P = 0.03$ (Fisher exact test).

DISCUSSION

The results of this trial suggest that norfloxacin in a 10-day course is at least as effective as trimethoprim-sulfamethoxazole in the therapy of women with acute, symptomatic, upper or lower urinary tract infections (Table 3). Patients with presumptive upper urinary tract involvement (ACB positive) showed similar responses to both drugs. Symptomatic patients with low-count bacteriuria and pyuria also met our criteria for urinary tract infections, as suggested by Stamm et al. and Platt, and were included in our evaluation (18, 23, 24). Norfloxacin and trimethoprim-sulfamethoxazole were similar in their abilities to eradicate the infecting organism from flora in the periurethra, but norfloxacin was significantly better in the eradication of the infecting organism from flora in the anal canal (Table 4). It may be of significance that the three reinfections in the trimethoprim-sulfamethoxazole group appeared earlier than those in the norfloxacin group and were due to trimethoprim-sulfamethoxazole-resistant organisms, two of which were present in flora in the anal canal. Previous studies have shown a marked reduction in periurethral and fecal *Enterobacteriaceae*, with little or no development of resistance even on long-term, low-dose prophylaxis (15, 20, 22). Murray et al., however, have demonstrated the emergence of high-level resistance to trimethoprim-sulfamethoxazole in patients on daily prophylaxis of travelers diarrhea (16). The patient population in our study included women with recurrent urinary tract infections, many of whom had received trimethoprim-sulfamethoxazole therapy in the past. It is therefore likely that the emergence of resistant organisms in the fecal flora may in part be due to repeated antibiotic treatment. In this regard, norfloxacin, a new effective agent, may have a distinct advantage. However, there was no difference in the eradication of *S. faecalis* from flora in the anal canal in either treatment group.

There were no abnormalities of hemoglobin, leukocyte count, or renal or liver function in either treatment group throughout our study. However, norfloxacin was much better tolerated than trimethoprim-sulfamethoxazole, which had severe adverse effects necessitating its discontinuation in some patients.

The in vivo susceptibilities of the organisms to norfloxacin in this study correlated very well with the in vitro susceptibility data and show that this drug should be useful in urinary tract infections caused by a variety of gram-negative and gram-positive organisms. Other clinical comparative studies of norfloxacin and trimethoprim-sulfamethoxazole in the treatment of urinary tract infections have shown similar results for efficacy, safety, and tolerance (6, 7). However,

there was no evaluation of the effect of these drugs on flora from the periurethra and anal canal or report of the development of antimicrobial resistance in either treatment group. The in vivo development of resistance to norfloxacin, particularly in relation to the fecal reservoir, must be further evaluated.

In this initial investigation, we have demonstrated comparable efficacy between norfloxacin and trimethoprim-sulfamethoxazole in the therapy of uncomplicated, acute, symptomatic, upper and lower urinary tract infections in conventional doses. We must now investigate the potential applications of norfloxacin in other forms of urinary tract infections, especially those for which trimethoprim-sulfamethoxazole has been shown to be effective. These include single-dose therapy and long-term prophylaxis for recurrent urinary tract infections (2, 9, 12, 13). The much wider spectrum of activity of norfloxacin is advantageous and should make it particularly useful in the therapy of complicated urinary tract infections due to multiply resistant organisms or for suppression of infection in patients with urinary tract abnormalities. Further studies are also required with norfloxacin in these clinical settings.

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