Comparison of Three-Day Temafloxacin with Seven-Day Ciprofloxacin Treatment of Urinary Tract Infections in Women

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Background. Temafloxacin is a new broad-spectrum arylfluoroquinolone antimicrobial with an extended serum half-life.

Methods. In this large, multicenter, double-blind clinical trial, 404 women with acute, uncomplicated urinary tract infections (UTI) were randomized to receive temafloxacin 400 mg once daily for 3 days, or ciprofloxacin 250 mg twice daily for 7 days. Clinical and microbiologic evaluations were repeated at 4 to 5 days after initiation of treatment, at the end of therapy, and at 5 to 9 days posttreatment. One hundred fifteen patients who received temafloxacin and 105 patients who received ciprofloxacin met the eligibility criteria for efficacy evaluation. The predominant urinary pathogens were *Escherichia coli, Proteus mirabilis,* and coagulase-negative staphylococci. No pretherapy isolate was resistant to either study drug.

Results. Bacteriologic eradication was observed in 112 (97%) of 115 women treated with temafloxacin and 101 (96%) of 105 women treated with ciprofloxacin. Clinical cure rates at 5 to 9 days posttreatment were 90% (the remaining 10% improved) with temafloxacin and 95% (the remaining 5% improved) with ciprofloxacin. Adverse effects associated with treatment occurred in 24 (12%) women who received temafloxacin and 31 (15%) women who received ciprofloxacin. Headache (2% with temafloxacin and 2% with ciprofloxacin), nausea (3% with temafloxacin and 6% with ciprofloxacin), and somnolence (4% with temafloxacin and 3% with ciprofloxacin) were reported most often. Only three and five patients who were treated with temafloxacin and ciprofloxacin, respectively, discontinued treatment because of adverse effects.

Conclusions. In this study, a 3-day treatment regimen using a single daily 400-mg dose of temafloxacin was found to be as effective as a 7-day course of ciprofloxacin in women with acute uncomplicated UTI.

Key words. Temafloxacin; ciprofloxacin; clinical trials; urinary tract infection. *J Fam Pract 1992; 34:180-184.*

The fluorinated piperazinyl quinolones (fluoroquinolones) are a new generation of 4-quinolone antimicrobials with increased activity against urinary pathogens including *Enterococcus faecalis* and *Pseudomonas aeruginosa.*[1] In addition to their broad spectrum of activity, emergence of bacterial resistance during therapy of urinary tract infections (UTI) with these antibiotics is rare.[2] These antimicrobials also possess excellent pharmacokinetic profiles. They are orally absorbed, attain high tissue and urinary concentrations, and have a long elimination half-life.[3] These properties, coupled with a low incidence of significant adverse reactions, make these newer fluoroquinolones attractive agents for the treatment of UTI.[4]

Temafloxacin is a new arylfluoroquinolone antimicrobial agent. It has a broad spectrum of activity and possesses increased potency against gram-positive species and intracellular pathogens compared with the other new fluoroquinolone antibiotics.[5,6] This compound was synthesized to impart high water solubility, good tissue penetration, and a long serum half-life.[7] Temafloxacin is very active in vitro against urinary pathogens, and initial animal and clinical investigations suggest that it is a highly effective agent for the treatment of UTI.[8,9] In this large, multicenter clinical trial, we compared the safety and efficacy of temafloxacin with that of ciprofloxacin in the treatment of women with acute uncomplicated UTI.

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Methods

Women with symptoms of acute UTI (dysuria, urinary frequency or urgency, suprapubic pain) and pyuria (>5 white blood cells per high power field) were enrolled into a multicenter, randomized, double-blind clinical trial from primary care ambulatory clinics (see Acknowledgments). The protocol and informed consent documents were approved by the institutional review boards. Written informed consent was obtained from each patient. Patients younger than 18 years of age, pregnant, with a known allergy to quinolone compounds, receiving other antibiotics, with renal or liver disease, or with structural or functional abnormalities of the urinary tract were excluded from this study. Acute UTI was defined as the presence of greater than or equal to 10^4 CFU (colony-forming units)/mL of a urinary pathogen in a clean-catch midstream urine specimen. All isolates were identified, and disk susceptibilities to ciprofloxacin and temafloxacin were interpreted according to standard criteria.[10,11]

In addition to a pretreatment history and physical examination, all patients underwent laboratory evaluation, including a complete blood count, urinalysis, and blood chemistries. Clinical and laboratory evaluations were repeated 4 to 5 days after the initiation of treatment. Follow-up assessments of urinary tract signs and symptoms as well as urine cultures were repeated at the end of therapy and 5 to 9 days posttreatment. Patients were assigned by random-number code to receive either temafloxacin, 400 mg once daily for 3 days, followed by 4 days of placebo, or ciprofloxacin, 250 mg twice daily, for 7 days. This treatment regimen of ciprofloxacin was chosen because it is highly effective in the treatment of UTI.[12,13] Each patient was given a diary card to record drug administration and untoward effects. Drug compliance as determined by pill counts and the patient's diary card was documented during and at the end of therapy. Adverse events were also assessed at each visit.

The therapeutic outcome was assessed 5 to 9 days after completion of therapy. Those patients with greater than or equal to 10^4 CFU/mL of a pretreatment urinary pathogen, susceptible to both study drugs, who received at least 3 days of therapy were considered for efficacy evaluation. Excluded patients, dropped from the study, were treated with an alternative drug. All patients enrolled were included in the evaluation of drug-induced side effects. Clinical responses were defined as: *cure:* elimination of all pretherapy signs or symptoms; *improvement:* signs and symptoms were less severe but not completely resolved; and *failure:* no improvement in signs or symptoms during the study. Bacteriologic responses were defined as: *eradication:* elimination of the pretherapy pathogen; *persistence:* the pretherapy pathogen was not eliminated following a course of treatment; and *recurrence:* the presence of a urinary pathogen after initial eradication. Recurrent infections were considered to represent either a relapse if the organism that was isolated was the same species as the pretherapy isolate or a reinfection if a different species was isolated. Fisher's exact test for probability was used for statistical comparison of cure rates and adverse effects observed in the two treatment groups.

Table 1. Patient Characteristics in the Two Treatment Groups

Characteristic	Treatment Group: Temafloxacin No. (%)	Treatment Group: Ciprofloxacin No. (%)
Enrolled	197 (49)	207 (51)
Age (years)		
<65	160 (81)	163 (79)
≥65	37 (19)	44 (21)
Previous UTI (past 12 months)		
0	149 (75.5)	161 (78)
1	47 (24)	42 (20)
2 or more	1 (0.5)	4 (2)
Excluded patients		
No pathogen	55 (28)	61 (29)
Intermediate susceptibility	10 (5)	10 (5)
Lost to follow-up	14 (7)	26 (13)
Noncompliance	3 (2)	5 (2)
Evaluated patients	115 (58)	105 (51)

UTI denotes urinary tract infection.

Results

Of the 404 women entered into this study, 197 received temafloxacin and 207 received ciprofloxacin. The patient characteristics of the two treatment groups were comparable (Table 1). The mean age was 44 years in both groups. Thirty-seven (19%) women in the temafloxacin group and 44 (21%) women in the ciprofloxacin group were 65 years old or older. A previous UTI during the past year was documented in 24% and 22% of patients who received temafloxacin and ciprofloxacin, respectively. One hundred-fifteen (58%) patients who received temafloxacin and 105 (51%) patients who received ciprofloxacin met the eligibility criteria for efficacy evaluation. Lack of a pretherapy urinary pathogen was the most common cause that excluded patients from the evaluation of efficacy of these two drugs.

The predominant urinary pathogen isolated in this study was *Escherichia coli.* This organism was cultured from 92 (80%) patients who received temafloxacin and 90 (86%) patients who received ciprofloxacin. The sec-

Table 2. Comparison of Outcomes in the Two Treatment Groups

Outcome	Temafloxacin (%)	Ciprofloxacin (%)
Clinical response		
Overall cure	90	95
<65 years old	92	98
≥65 years old	81	88
Improvement	10	5
Failure	0	0
Bacteriologic response		
Eradication	97	96
Persistence	1	2
Recurrence		
Relapse	2	2
Reinfection	0	0

ond most common pathogen isolated was *Proteus mirabilis,* followed by coagulase-negative staphylococci and *Klebsiella pneumoniae.* None of the pretherapy urinary isolates was resistant to ciprofloxacin or temafloxacin, although 20 pathogens exhibited intermediate susceptibility to the study drugs. Bacteriologic eradication was observed in 112 (97%) women treated with temafloxacin and 101 (96%) women treated with ciprofloxacin. Persistent organisms included *E coli* in two patients treated with ciprofloxacin, and *Pseudomonas aeruginosa* in one patient treated with temafloxacin. Two patients in each group had a posttreatment bacteriologic recurrence. Two patients who received temafloxacin and one who received ciprofloxacin had a relapse with *E coli,* and one patient who received ciprofloxacin had a relapse with *P mirabilis.* None of the organisms isolated from posttreatment cultures was resistant to the study antibiotics.

No clinical failures occurred in this study. Of those women who received temafloxacin, 90% were clinically cured, and 10% improved after 5 to 9 days of treatment. A similar response occurred with ciprofloxacin, with 95% of patients cured and 5% improved 5 to 9 days after treatment. The cure rates in the two treatment groups were not statistically different. Cure rates were higher among those women younger than 65 years old in both treatment groups. Overall, 94% of women younger than 65 years old were cured by 5 to 9 days after treatment compared with 85% of women 65 years old or older (Table 2).

The incidence and type of adverse effects reported by patients was similar in the two treatment groups. Adverse effects associated with treatment occurred in 24 (12%) women who received temafloxacin and in 31 (15%) women who received ciprofloxacin. Headache, nausea, and somnolence were reported most often (Table 3). Three (1.5%) patients who received temafloxacin and five (2.4%) patients who received ciprofloxacin discontinued treatment because of adverse effects. Gastrointestinal complaints were most often the reason for discontinuing the antibiotics. No clinically significant hematological or biochemical alterations were observed with either study drug.

Table 3. Adverse Events Associated with the Use of Temafloxacin and Ciprofloxacin

Event	Temafloxacin (n = 197) No. (%)	Ciprofloxacin (n = 207) No. (%)
Drug-related adverse events	24 (12.2)	31 (15)
Stopped treatment	3 (1.5)	5 (2.4)
Nervous system		
Headache	4 (2)	3 (1.4)
Somnolence	7 (3.6)	7 (3.4)
Dizziness	1 (0.5)	1 (0.5)
Hyperkinesia	1 (0.5)	0 (0)
Digestive system		
Nausea	6 (3)	12 (5.8)
Diarrhea	3 (1.5)	3 (1.4)
Dyspepsia	2 (1)	3 (1.4)
Skin rash	0 (0)	1 (0.5)
Urogenital		
Yeast vaginitis	2 (1)	5 (2.4)

Discussion

An increasing number of oral antimicrobial agents have become available over the past few years for the treatment of urinary tract infections. Many of these newer antibiotics have improved pharmacokinetics and tolerance but are considerably more expensive than agents traditionally used to treat uncomplicated infections. The major impetus for the development and use of newer drugs has been the increasing prevalence of antimicrobial resistance to older agents, even among community-acquired pathogens.[14,15] Current resistance rates to older drugs, such as ampicillin, cephalexin, and nitrofurantoin, range from 10% to 40%. Therapy with trimethoprim-sulfamethoxazole continues to be effective, but increasing rates of resistance have also been observed with this antimicrobial combination.[15] Resistance rates of 5% to 10% have been observed for trimethoprim-sulfamethoxazole against urinary isolates of *E coli* in our outpatient clinics. Of the newer oral agents currently available, the fluoroquinolones provide the greatest potency against urinary isolates. In addition, resistance to these antimicrobials has rarely been observed in clinical trials.[2] Whether these agents should be used in place of older antibiotics will depend on local resistance patterns as well as individual patient variables.

The appropriate length of treatment for women with acute uncomplicated UTI has been extensively studied over the past decade. A 7-to-10-day course of treatment has been considered standard therapy but is associated with increased cost and a higher incidence of untoward effects compared with shorter courses of treatment. Single-dose therapy has the advantages of convenience, low cost, and decreased side effects, but not all antibiotics are useful as single-dose therapy.[16] Only agents with an extended half-life, such as trimethoprim-sulfamethoxazole, were subsequently found to be clinically useful as single-dose therapy.[17] The use of single-dose trimethoprim-sulfamethoxazole was further investigated in two large clinical trials of women with acute cystitis.[18,19] In these studies a higher relapse rate occurred with only a single dose of trimethoprim-sulfamethoxazole compared with that occurring after a 10-day course of therapy. On the other hand, this superior cure rate was at the expense of a significantly higher incidence of adverse effects. It has now been suggested that an intermediate duration of treatment, 3 to 5 days, would be optimal for treatment of women with uncomplicated UTI. This intermediate length of treatment was supported in a recent analysis of clinical trials of short-term treatment of uncomplicated UTI in women.[20] This review found that a 3-day course of treatment with trimethoprim-sulfamethoxazole was as effective as longer courses of therapy, but no more toxic than single-dose treatment. It was further concluded that β-lactam antibiotics should be administered for 5 or more days.

The use of fluoroquinolones in the treatment of various infections has now become common practice.[21] These antimicrobials are especially suited for the treatment of UTI, including prostatitis and complicated cases involving multiple antibiotic-resistant pathogens.[2] The newer fluoroquinolones may also decrease the risk of recurrent urinary infections in women owing to their ability to effectively suppress vaginal and periurethral flora.[22] Numerous clinical trials have been conducted that compare the safety and efficacy of these agents with that of conventional antibiotics in the treatment of UTI.[2] Although extensive experience with single-dose therapy has not been accumulated, several studies support short-course (3 to 5 days) therapy with fluoroquinolones for uncomplicated infections in women.[23] The short-term therapeutic efficacy observed with temafloxacin in this study is similar to results obtained using 3-day treatment courses with other fluoroquinolones.[24–26] An important difference in this study compared with other clinical trials was that temafloxacin was administered only once daily.

The newer fluoroquinolones are generally well tolerated and have similar adverse effect profiles.[27] Untoward effects occur less frequently and are usually less severe than those observed with nalidixic acid. Gastrointestinal side effects occur most commonly and have been reported in 5% to 25% of patients.[28] Less commonly observed adverse effects include central nervous system (CNS) stimulation, such as anxiety and insomnia, skin rash, and joint stiffness. In this study, temafloxacin was found to be very safe, and only three patients discontinued therapy because of an adverse effect. The most common side effects reported in those receiving temafloxacin were nausea, headache, and somnolence. Only two other CNS side effects were reported. One woman complained of dizziness and one reported hyperkinesia. Adverse effects involving the musculoskeletal system were not observed. Overall, the incidence of side effects observed with temafloxacin treatment in this trial is comparable to other antibiotics that have been studied for the treatment of women with UTI.[20]

In conclusion, a 3-day treatment course using a single daily dose of temafloxacin was found to be highly effective and well tolerated in women with acute uncomplicated UTI and comparable to a 1-week treatment regimen of ciprofloxacin.

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