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Randomized, Double-Blind Comparison of Ciprofloxacin and Trimethoprim-Sulfamethoxazole for Complicated Urinary Tract Infections

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In a prospective, randomized, double-blind study, the effect of ciprofloxacin (250 mg orally, twice daily) was compared with that of trimethoprim-sulfamethoxazole (160 mg of trimethoprim and 800 mg of sulfamethoxazole orally, twice daily) on 45 patients with complicated urinary tract infections. Pretherapy isolates were all members of the family *Enterobacteriaceae*. Isolates were eradicated from 18 (82%) of 22 patients treated with ciprofloxacin and 12 (52%) of 23 patients treated with trimethoprim-sulfamethoxazole during and 5 to 9 days after therapy ($P = 0.035$). Both groups had similar relapse and reinfection rates at 4 to 6 weeks posttherapy. Adverse effects were mild and reversible, occurring in 1 of 22 in the ciprofloxacin group and 6 of 23 in the trimethoprim-sulfamethoxazole group. Disk diffusion susceptibility tests correlated better with broth macrodilution for ciprofloxacin than for trimethoprim-sulfamethoxazole. Ciprofloxacin is a safe, effective alternative to trimethoprim-sulfamethoxazole for the treatment of complicated urinary tract infections.

Ciprofloxacin has excellent in vitro activity against pathogens commonly causing complicated urinary tract infections, including members of the family *Enterobacteriaceae* (4, 7, 12). Oral ciprofloxacin is well absorbed, reaching concentrations in serum and urine well above the MIC for most urinary pathogens (6, 13, 14). The present study was designed to compare the efficacy and safety of ciprofloxacin and trimethoprim-sulfamethoxazole (TMP-SMX) for the treatment of complicated urinary tract infections caused by susceptible bacteria.

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MATERIALS AND METHODS

Patients at the Omaha Veterans Administration Medical Center with signs or symptoms of urinary tract infection were eligible for enrollment if they had (i) functional or anatomical abnormalities of the genitourinary tract known to promote infection and (ii) urine obtained by clean-catch midstream collection or straight catheterization within 24 h prior to treatment which grew (per milliliter) $>10^5$ CFU of a pathogen susceptible to both ciprofloxacin and TMP-SMX by disk diffusion. Patients with isolates resistant to TMP-SMX received ciprofloxacin in an open protocol (20). Asymptomatic patients were required to have two pretreatment urine cultures, each with $>10^5$ CFU of the same pathogen per ml. Patients were excluded if they were allergic to either medication, were pregnant, or had septicemia or unrelieved urinary tract obstruction. Patients with a severe neurogenic bladder, with a chronic indwelling urinary catheter, with a creatinine level in serum of >3.0 mg/dl, or under concomitant antimicrobial therapy were not eligible.

After written informed consent was obtained, patients were randomized in a double-blind, double-placebo technique to receive a ciprofloxacin tablet (250 mg) and TMP-SMX placebo tablet every 12 h or a TMP-SMX tablet (160 mg of TMP, 800 mg of SMX) and ciprofloxacin placebo tablet every 12 h for 7 days. Laboratory tests (complete blood count, urea nitrogen, creatinine in serum, alkaline phosphatase, total bilirubin, aspartate aminotransferase, alanine aminotransferase, and routine urinalysis) were performed up to 48 h before therapy, on day 3 or 4 of therapy, and within 48 h after therapy. Urine samples were cultured before therapy, on day 3 or 4 of therapy, and between days 5 and 9 posttherapy. Whenever possible, urine samples were cultured 4 to 6 weeks posttherapy. The antibody-coated-bacteria test was performed on bacteria from urine specimens obtained before therapy (8).

The susceptibility of all infecting organisms was determined initially by the standard antibiotic disk technique by using the modified Bauer-Kirby procedure (17). MICs were determined by the standard twofold macrobroth dilution procedure (18) with Mueller-Hinton medium and an inoculum of approximately 10^5 CFU/ml. An organism was considered susceptible to ciprofloxacin if the MIC of ciprofloxacin did not exceed 1 μg/ml. An organism was considered susceptible to TMP-SMX if the MIC of TMP-SMX was ≤1/20 μg/ml and resistant if it was ≥2/40 μg/ml.

Bacteriological responses of the patients were defined as (i) eradication ($<10^4$ CFU/ml during and after therapy); (ii) persistence ($>10^4$ CFU of the original isolate per ml during therapy); (iii) superinfection ($>10^4$ CFU of a different isolate per ml during therapy); (iv) relapse (eradication during therapy, but $>10^4$ CFU of the original isolate per ml posttherapy); and (v) reinfection (eradication during therapy, but $>10^4$ CFU of a different isolate per ml posttherapy). Statistical analysis was performed with Fisher's exact test; $P \leq 0.05$ was chosen as a level of statistical significance.

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TABLE 1. Summary of patients treated with ciprofloxacin or TMP-SMX[a]

Characteristic	No. of patients	
	Ciprofloxacin (n = 22)	TMP-SMX (n = 23)
Diagnosis		
Cystitis	19	22
Asymptomatic	3	1
Chronicity		
Acute	18	16
Chronic	2	5
Recurrent	2	2
Antibody-coated bacteria	16	21
Nosocomial infection	7	6
Complication[b]		
Prostatic hypertrophy	14	15
Neurogenic bladder	3	5
Urethral stricture	1	4
Tumor	2	1
Prior indwelling catheter	0	2
Renal calculus	1	0
Prior prostatectomy	1	0
Bladder neck contracture	0	1
Prostatitis	0	1

[a] In the ciprofloxacin-treated group there were 21 men and 1 woman (mean age, 68 years; range, 38 to 90 years); in the TMP-SMX-treated group there were 22 men and 1 woman (mean age, 72 years; range, 50 to 94 years).

[b] Several patients had more than one complication. One female patient had no detectable structural abnormality, but had a positive antibody-coated-bacteria test.

RESULTS

Of 57 patients enrolled, 12 were excluded. Four had pretherapy urine cultures with $<10^5$ CFU of organisms per ml, four received concomitant antimicrobial therapy for an unrelated infection, in two the pretherapy isolate was resistant to TMP-SMX by disk diffusion, one had a rising creatinine level on TMP-SMX therapy (from 1.9 to 3.6 mg/dl), and one withdrew after one dose with no ill effects from therapy. A total of 22 patients received ciprofloxacin and 23 received TMP-SMX for a mean of 7 days. Demographic data were similar in both groups (Table 1). The antibody-coated-bacteria test was positive in the majority of patients in each group (Table 1).

The pretherapy isolates were all members of the family *Enterobacteriaceae*. These are listed in Table 2, along with their susceptibility to the study drugs.

The bacteriological response to treatment is shown in Table 3. Eradication was obtained significantly more often in the ciprofloxacin-treated (18 of 22) than TMP-SMX-treated (12 of 23) patients (P = 0.035). There were four superinfections in the TMP-SMX-treated patients. Three were caused by enterococcus, and one was caused by *Providencia stuartii*; all four isolates were resistant to TMP-SMX and susceptible to ciprofloxacin. Of the two patients in the TMP-SMX-treated group whose original isolates were sensitive by disk diffusion but resistant by MIC data, one relapsed at 5 to 9 days posttherapy, and the other had persistence during therapy. The early reinfections in the ciprofloxacin-treated group were caused by an *E. coli* strain (one) and a yeast strain (two). Relapses and reinfections at 4 to 6 weeks follow-up occurred at a similar rate in the two treatment groups. The late reinfections in the ciprofloxacin-treated patients were due to coagulase-negative staphylococci (one), enterococcus (one), and enterococcus and *Pseudomonas aeruginosa* (one). All organisms causing early and late relapses were susceptible to ciprofloxacin.

TABLE 3. Bacteriological response to treatment of complicated urinary tract infections with ciprofloxacin

Time	Response	No. (%) of patients	
		Ciprofloxacin (n = 22)	TMP-SMX (n = 23)
During and 5–9 days after therapy	Eradication	18 (82)	12 (52) (P = 0.035)
	Persistence	0 (0)	2 (9)
	Superinfection	0 (0)	4 (17)
	Relapse	1 (5)	5 (22)
	Reinfection	3 (13)	0 (0)
4–6 wk after therapy	Eradication	9 (60)	5 (63) (P = 0.63)
	Relapse	3 (20)	3 (37)
	Reinfection	3 (20)	0 (0)

The results of pretherapy antibody-coated-bacteria testing did not correlate with bacteriological response to therapy. The antibody-coated-bacteria test was positive in 12 of 18 patients in the ciprofloxacin-treated group and 11 of 12 in the TMP-SMX-treated group who showed eradication of their organisms. It was also positive in all 4 failures in the ciprofloxacin-treated group and 10 of 11 failures in the TMP-SMX-treated group.

Adverse effects in patients who received TMP-SMX included pruritus without rash in one patient, which resolved after TMP-SMX was discontinued. One patient developed nausea and vomiting associated with TMP-SMX administration but was able to complete the protocol. Four patients had creatinine levels in serum which rose to ≥0.4 mg/dl above base-line levels during therapy.

TABLE 2. MICs of ciprofloxacin and TMP-SMX for initial isolates

Organism	No. of patients with isolates before treatment with:		MIC range (μg/ml)	
	Ciprofloxacin (n = 22)	TMP-SMX (n = 23)	Ciprofloxacin	TMP-SMX
Escherichia coli	15	9	<0.008–0.125	<0.016/0.313–0.125/2.5
Klebsiella pneumoniae	1	7	0.016–0.063	0.031/0.625–2/40[a]
Proteus mirabilis	2	3	0.032–0.063	0.063/1.25–0.125/2.5
Citrobacter spp.	1	1	<0.008–0.031	0.031/0.625–0.125/2.5
Serratia marcescens	3	0	0.016–0.063	0.063/1.25–0.25/5
Enterobacter spp.	0	2	0.016–0.031	0.031/0.625–32/640[a]
Providencia stuartii	0	1	0.063	0.125/2.5

[a] All isolates were susceptible by the Bauer-Kirby test.

In one ciprofloxacin-treated patient, alkaline phosphatase rose from 57 to 127 IU/liter, aspartate aminotransferase rose from 18 to 93 IU/liter, and alanine aminotransferase rose from 28 to 309 IU/liter. Three days after the study, the patient underwent cholecystectomy, with findings of cholelithiasis and chronic cholecystitis. The relationship of these findings to ciprofloxacin therapy was considered remote.

DISCUSSION

Infection in the urinary tract is common in elderly men, and relapse and reinfection are common in this group (3, 16). Prostate infection or enlargement contributes to this incidence of urinary tract infections (16). Ciprofloxacin is an alkaline and lipid-soluble compound which is concentrated in prostate tissue (2, 5, 11) and eliminated by both renal and extrarenal routes. The concentration of ciprofloxacin achieved in the urine is many times higher than its MIC for most urinary pathogens (4, 13). Our study population consisted primarily of elderly men, all with urologic abnormalities and many with mild renal impairment. Despite these conditions, oral ciprofloxacin was effective, with a bacteriological eradication rate of 82% at early follow-up. Increased penetration of ciprofloxacin into prostate tissue compared with that of TMP-SMX may explain the difference at early follow-up.

The majority of patients in both groups had a positive antibody-coated-bacteria test, usually an indication of upper urinary tract or prostate infections. However, false-positives may occur in patients with proteinuria, recurrent urinary tract infections, or prior kidney infections with antigenically related organisms (22). Subclinical upper tract or prostate infection may have been responsible for a number of our treatment failures, since prostate fluid cultures were not done. A longer course of therapy may have improved the cure rates for both treatment groups (10, 23).

We have shown previously that antacids which contain magnesium or aluminum reduce absorption of ciprofloxacin (19). Six patients in the ciprofloxacin-treated group received antacids, milk of magnesia, or both, and the organisms were eradicated in five.

Our results are comparable to previous evaluations of ciprofloxacin for treatment of complicated urinary tract infections (1, 9, 15, 20). Although these studies all involved complicated urinary tract infections, comparisons are limited by differences in definitions, patient populations, and bacterial pathogens. This study specifically excluded infections due to organisms that were resistant to TMP-SMX by disk diffusion. In other studies, a quinolone has been compared with TMP-SMX for treatment of complicated urinary tract infections. Vellucci et al. used ofloxacin in an open randomized study, with similar results at 24 to 48 h (25). Sabbaj et al. used norfloxacin in an open randomized study and treated patients for 4 to 6 weeks. Eradication rates were higher for norfloxacin than for TMP-SMX, but the difference did not reach statistical significance (21).

Two patients in the TMP-SMX group had pretherapy isolates which were susceptible to TMP-SMX by disk diffusion and resistant by MIC. This difference may have been due to the use of standard unsupplemented Mueller-Hinton agar for Bauer-Kirby disk diffusion. The high concentration of thymidine in Mueller-Hinton agar may interfere with the activity of TMP-SMX in this test. For MICs, Mueller-Hinton broth was supplemented with thymidine phosphorylase to eliminate thymidine interference (24). The discrepancy between disk diffusion and broth dilution susceptibility test results for TMP-SMX was clinically significant in these two patients, both of whom failed with TMP-SMX therapy.

Side effects, including nausea, vomiting, pruritus, and rising creatinine levels, were seen in the TMP-SMX-treated patients. One patient who received ciprofloxacin had rising liver function tests. Ciprofloxacin thus appears to be as safe as TMP-SMX and more effective for treatment of complicated urinary tract infections.

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