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Single-Dose Ciprofloxacin at 100 versus 250 mg for Treatment of Uncomplicated Urinary Tract Infections in Women

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Two single-dose regimens of ciprofloxacin, 100 and 250 mg, were compared in the treatment of uncomplicated urinary tract infections in women. Cure rates 5 days after therapy did not significantly differ, being 16 of 19 (84%) with the 100-mg dose and 17 of 19 (89%) with the 250-mg dose. Ciprofloxacin was well tolerated.

Treatment with single doses of antibiotics of uncomplicated urinary tract infections in women is a well-established therapeutic regimen (1, 4, 12, 15, 20). Therapeutic failures following a single-dose treatment appear to predict complicating factors such as silent pyelonephritis (14), morphologic alterations, dynamic disturbances, or microbial resistance to antibiotics (6, 8, 11, 13).

Ciprofloxacin, a new quinolone drug which can be administered both orally and intravenously, has good antimicrobial activity against microorganisms frequently found in urinary tract infections. The aim of the present study was to evaluate the efficacy of a single dose of ciprofloxacin in the treatment of uncomplicated urinary tract infection. In addition, two oral doses, 250 and 100 mg, were compared to estimate clinical and bacteriological efficacy at the lower-dosage range.

Women 16 years or older attending our outpatient clinic were enrolled in the study if they presented with acute dysuria and frequent micturition of <72 h in duration. Admission criteria included bacteriuria ($>10^2$ CFU/ml) and pyuria ($\geq$10 leukocytes per mm^3). Exclusion criteria were pregnancy, fever of >38°C, serum creatinine of >115 μmol/liter, and a history of antecedent complicated urinary tract infection (e.g., due to obstruction in the urinary tract). Uncomplicated recurrent urinary tract infections did not lead to exclusion. A total blood count, erythrocyte sedimentation rate, serum creatinine, alkaline phosphatase, and glutamate pyruvate transaminase were determined at presentation.

Midstream urine was collected after individual instruction of the patient and was cultivated quantitatively on human blood and MacConkey agar plates. Uropathogenic microorganisms were differentiated according to standard methods, and *Staphylococcus saprophyticus* was identified by the novobiocin method (5). A routine sensitivity test by photometric measurement of the optical density (MS-2 automated antimicrobial susceptibility testing system; Abbott Laboratories, Chicago, Ill.), as well as determinations of MICs by a micromethod (16) in Mueller-Hinton broth and a disk test on Mueller-Hinton agar for ciprofloxacin, was performed for all isolates (2). Patients received either 100 or 250 mg of ciprofloxacin orally at presentation, before any laboratory values were available.

A total of 40 women with a median age of 25.0 years (range, 18 to 61 years) entered the study, 2 of whom had to be excluded because initial cultures were inconclusive (mixed flora). Thirty-eight women completed the study; 19 received 100 mg and 19 received 250 mg of ciprofloxacin orally as a single dose. Laboratory values at presentation revealed an elevated leukocyte count (>10,000/mm^3) in four cases and a leukocytosis with accelerated erythrocyte sedimentation rate (>20 mm/h) in one case in each treatment group. All other laboratory values, including serum creatinine, were normal in all patients.

In both treatment groups, the predominant microorganism isolated from urine was *Escherichia coli*, whereas the other causative microorganisms (*S. saprophyticus*, *Proteus mirabilis*, *Enterobacter cloacae*) were comparatively rare. In one case, both *P. mirabilis* and *S. saprophyticus* were isolated (Table 1).

At the first follow-up 4 to 5 days after the treatment with ciprofloxacin, 5 of 38 (13%) patients had a clinical and bacteriological failure, defined as continuing symptoms, pyuria (>10 leukocytes per mm^3), and the repeated isolation of the same causative microorganisms at concentrations exceeding 10^2 CFU/ml. There were two clinical and bacteriological failures (*E. coli*, *S. saprophyticus*) in the 250-mg groups and three failures in the 100-mg group (*E. coli* twice, *S. saprophyticus* once; Table 1). In the patient who initially presented with *P. mirabilis* and *S. saprophyticus* in concentrations of $>10^5$ CFU/ml, *S. saprophyticus* persisted, whereas *P. mirabilis* was eradicated after 5 days. The five patients with therapeutic failure were subsequently treated with an alternative antibiotic for 2 weeks according to sensitivity results.

At a 4-week follow-up there were two cases with reinfection in the 250-mg group (*E. coli*). In the 100-mg group, one reinfection with *Citrobacter* sp. and one relapse (*E. coli*) were documented. Reinfection was defined as clinical and laboratory evidence of a new infection after a normal first follow-up, whereas relapse was defined as isolation of the original pathogen after a sterile first urine specimen. Identity of microorganisms was assumed when pre- and posttreatment cultures exhibited the same biotype in the API 20E system and the antibiogram.

The MICs of ciprofloxacin for all initial isolates were $\leq$2 mg/liter (range, 0.0037 to 2.0 mg/liter). All isolates were susceptible as determined by the zone diameter of the disk. There was no difference between the MICs for initial cultures and cultures from patients showing persistence or relapse. None of the organisms not responding to treatment developed resistance to ciprofloxacin. No side effects attributable to ciprofloxacin were observed.

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TABLE 1. Microbiological results before and 5 days after therapy with a single dose of ciprofloxacin in 38 episodes of uncomplicated urinary tract infections

Microorganism	No. of isolates:			
	Before therapy		5 Days after therapy	
	100 mg[a]	250 mg	100 mg	250 mg
E. coli	14	17	2	1
P. mirabilis	2[b]			
Enterobacter cloacae	2			
S. saprophyticus	2[b]	2	1	1

[a] n = 19 for each parameter.
[b] One mixed infection.

Four strains of *S. saprophyticus* and four strains of *E. coli* (two each isolated from patients with therapeutic failures and two each from patients with successful therapy) were examined in vitro to evaluate the rate of killing by high-dose (100-mg/liter) ciprofloxacin. Killing curves were performed in Mueller-Hinton broth supplemented with magnesium and calcium. The concentration of ciprofloxacin in broth was 100 mg/liter. A final inoculum of about 10^6 CFU/ml was incubated at 35°C, and quantitative subcultures were repeatedly performed for 24 h. Colony counts were obtained by filtration of 100 μl of the inoculated broth through Micropore membranes (type SM 13806; Sartorius, Göttingen, Federal Republic of Germany). The filters were rinsed with sterile physiological saline to eliminate antibiotic residues and then incubated on Mueller-Hinton agar at 35°C. After 24 h, the number of colonies on the filter was counted at a 16-fold magnification (sensitivity limit, 10^1 CFU/ml). No difference was seen between strains which were eradicated by single-dose therapy and those which persisted, but there was a striking difference between the gram-positive and the gram-negative microorganisms. While colony counts of *E. coli* decreased by at least 3 log CFU/ml within <1 h of exposure to ciprofloxacin, the average time to reduce *S. saprophyticus* by 3 log CFU/ml was 6 h (Fig. 1).

Clinical and microbiological success rates were 89 and 84% after single doses of 250 and 100 mg of ciprofloxacin, respectively. There was no significant difference in success rates between the two dosages examined in this study. Recently, published studies revealed similar treatment results for the effectiveness of single-dose treatment with an average success rate of 85% (range, 65 to 100%) for trimethoprim, trimethoprim-sulfamethoxazole, or amoxycillin (3, 7, 10, 17, 19, 20).

We found no concomitant complicating factors that could explain the treatment failures in our patients, although invasive tests were not performed. In particular, previous episodes of urinary tract infections had been successfully treated by single doses of antibiotics in one case of persistent *S. saprophyticus* infection. Treatment failures were due to neither resistance nor development of resistance to ciprofloxacin in any of our cases.

That 2 of 4 infections caused by *S. saprophyticus* were not cured, while only 3 of 35 infections caused by gram-negative organisms persisted, caused considerable concern. Although this difference did not reach statistical significance because of the small number of cases caused by *S. saprophyticus*, we sought to determine whether there was a systematic difference between the killing rates for *S. saprophyticus* and gram-negative organisms by ciprofloxacin. Our in vitro results illustrate that *E. coli* was rapidly killed by the drug, whereas *S. saprophyticus* was killed at a significantly slower rate. The concentration of ciprofloxacin examined in these experiments, which exceeds the MIC for our tested microorganisms approximately 100-fold, can be expected to be

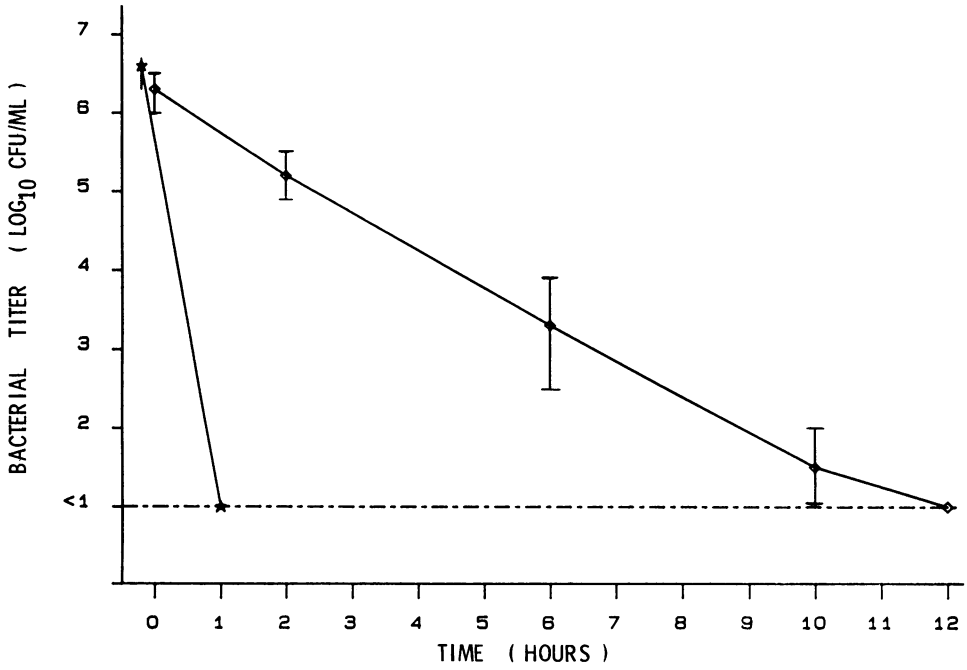

FIG. 1. In vitro killing curves of four *E. coli* (★) and four *S. saprophyticus* (◇) strains with ciprofloxacin (100 mg/liter). *E. coli* and *S. saprophyticus* strains both include two strains isolated from patients with therapeutic failures and two isolates from patients with therapeutic success: 0.0037 ≤ MIC (*E. coli*) ≤ 2.0 mg/liter; 0.125 ≤ MIC (*S. saprophyticus*) ≤ 0.5 mg/liter. The horizontal line represents the sensitivity limit (10^1 CFU/ml) of the assay. Vertical bars represent the range of individual measurements.

maximally bactericidal as shown by previous in vitro studies (18). Since concentrations of ciprofloxacin similar to those used in our in vitro study are found in urine (9, 15), these results suggest a clinically relevant reduction of the bactericidal activity of ciprofloxacin against *S. saprophyticus* compared with *E. coli*. However, the activity of ciprofloxacin does not appear to be the sole important factor for cure, since not all infections caused by *S. saprophyticus* failed to be eradicated and some infections caused by *E. coli* were not cured by a single dose of ciprofloxacin.

Our study shows a high effectiveness of single-dose administration of ciprofloxacin in the treatment of uncomplicated urinary tract infections in women, with the possible exception of infections caused by *S. saprophyticus*. Ciprofloxacin deserves special consideration in cases in which established regimens (amoxycillin, co-trimoxazole) cannot be administered because of a history of allergy or drug resistance.

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