

Double-Blind Study Comparing 3-Day Regimens of Cefixime and Ofloxacin in Treatment of Uncomplicated Urinary Tract Infections in Women

RAUL RAZ,^{1*} ELIMELECH ROTTENSTERICH,² YOSHUA LESHEM,³ AND HAVA TABENKIN³

Infectious Disease Unit¹ Outpatient Clinic Zvulum, Kiryat Motzkin,² and The Family Medicine Unit,³ Central Emek Hospital, Afula, Israel

Received 8 April 1993/Returned for modification 3 June 1993/Accepted 25 February 1994

This double-blind randomized study compared 3-day regimens of cefixime (400 mg once daily) and ofloxacin (200 mg twice a day) in the treatment of urinary tract infections in women. The respective clinical cure rates for the two groups of women were 89 and 92% after 7 days and 81 and 84% after 4 weeks. The respective microbiological cure rates (free of bacteriuria) for the two groups of women were 83 and 86% after 7 days and 77 and 80% after 28 days. A 3-day cefixime regimen seems to be as efficient as a 3-day ofloxacin regimen in the treatment of uncomplicated cystitis in women.

A 3-day regimen of antibiotics appears to be the optimal treatment for uncomplicated cystitis in women. This regimen may be associated with cure rates comparable to those achieved with longer courses of therapy, along with an incidence of adverse effects as low as that seen with single-dose therapy (5).

Short-course, single-dose or 3-day regimens of cotrimoxazole and quinolones are as effective as longer courses of therapy (4); however, beta-lactam antibiotics were more effective when administered for 5 or more days than when given as a 3-day or single-dose course (6).

Cefixime is an oral cephalosporin, with a broad antibacterial spectrum against most community-acquired uropathogens. Peak concentrations in serum of 3 to 4 µg/ml are achieved 3 to 4 h following a 400-mg tablet. The half-life in serum of 3 to 4 h is substantially longer than that of other oral beta-lactam antibiotics. In addition, urinary concentrations after a single daily dose of 400 mg are well above the MICs for 90% of the most common urinary pathogens (1).

The aim of the present study was to evaluate the efficacy of a 3-day regimen of cefixime and to compare it with a similar regimen of ofloxacin in the treatment of women with uncomplicated cystitis.

Women, 16 years of age or older, who had been referred to our Outpatient Clinic with the diagnosis of uncomplicated cystitis were included in this study. The diagnosis of uncomplicated cystitis was based upon both clinical symptoms (dysuria, frequency of urination, and absence of fever or flank pain) and laboratory findings (pyuria [at least 8 leukocytes per mm³/ml] and a positive urinary culture yielding $\geq 10^5$ CFU/ml). Women with a history of pyelonephritis or nephrolithiasis and pregnant or immunocompromised women were excluded from the study.

Clean, voided midstream urine samples were collected and cultured by the Uritest system (Hylab dip slides; Hylab, Rehovot, Israel). All isolates were identified by standard procedures and tested for susceptibility to antimicrobial drugs by the Kirby-Bauer method.

Treatment was given on a randomized and double-blind basis. The cefixime-treated patients received 400 mg of ce-

fixime once daily plus placebo, and the ofloxacin-treated patients received 200 mg of ofloxacin twice a day. Both regimens were given for 3 days.

Each patient was monitored clinically and bacteriologically at 7 and 28 days. The presence of the same microorganism after cessation of treatment (follow-up after 7 days) was defined as a failure. Relapse was defined as a positive culture with the same pathogen after a previous negative culture.

Side effects were recorded by asking each woman at the second follow-up visit about the appearance of any symptoms during the last week and specifically about symptoms related to the drug treatment, such as abdominal disturbances, nausea, vomiting, rash, fever, etc.

Statistical analysis was performed by the chi-square test with the Yates' correction where appropriate, and *P* values of 0.05 were considered statistically significant.

The size of the study group was set so that a clinically significant difference of 20% or more between the efficacy of treatment with cefixime compared with that with ofloxacin, with a two-sided type I error (alpha) of 0.05 and type II error (beta) of 0.2, could be detected.

A total of 106 women were included in the study. Of the 106 women, 54 received cefixime and 52 received ofloxacin and 49 and 50 of these women, respectively, completed the treatment and both follow-up appointments. In the cefixime group, five patients were not included, two because the pretreatment urine culture had less than 10⁵ CFU/ml and three because of a lack of follow-up. In the ofloxacin group, two patients were not included because a lack of follow-up. Clinical characteristics in both groups were similar (Table 1), and the etiological agents are listed in Table 2.

Clinical cures at the 7-day follow-up were achieved in 44 (89%) women treated with cefixime and 46 (92%) women treated with ofloxacin (*P* = 0.9). At the 28-day follow-up, 40 (81%) and 42 (84%) women, respectively, continued to be free of symptoms (*P* = 0.9).

Eradication of microorganisms in urine, 7 days after treatment, was obtained in 41 cefixime-treated women (83%) and 43 ofloxacin-treated women (86%) (*P* = 0.9). Negative cultures at 28 days posttreatment were found in 38 and 40 women, respectively (77 and 80%, respectively; *P* = 0.9).

Side effects (nausea and headache) were reported in only one patient treated with ofloxacin.

* Corresponding author. Mailing address: Infectious Disease Unit, Central Emek Hospital, Afula 18101, Israel.

TABLE 1. Clinical characteristics of patients in the two treatment groups

Characteristic ^a	Value for treatment group	
	Cefixime	Ofloxacin
No. of patients	49	50
Mean age \pm SEM (yr)	48.7 \pm 18.4	48.3 \pm 17.2
Age range (yr)	17–88	16–76
0–2 UTI/yr	34	34
>3 UTI/yr	15	16
No. premenopausal	28	24
No. postmenopausal	21	26

^a UTI, urinary tract infections.

The efficacy of a 3-day treatment with oral narrow-spectrum cephalosporins is controversial. Sandberg et al. (7) reported similar cure rates (80% at an early follow-up, and 75 and 79% at late follow-up), with 1 g of cefadroxil once daily for 3 or 7 days. On the other hand, Greenberg et al. (3) obtained a 68% bacteriological cure rate after treatment with cefadroxil (0.5 g twice a day) for 3 days and a cure rate of 83% when it was given for 7 days, and after 4 weeks, the cure rates were 58 and 70%, respectively.

In an unpublished study with 0.5 g of cefalexin given four times a day for 3 days, we observed cure rates of 88.7% after 7 days and 66.2% after 28 days. However, fluoroquinolones appear to be highly efficient given as a 3-day regimen. Hooton et al. (4) obtained 92 and 89% bacteriological cure rates after 1 and 5 weeks, respectively, with 200 mg of ofloxacin once daily. Similar cure rates were achieved by us in an unpublished study with 100 mg of ofloxacin twice a day (97.5 and 80.2%).

TABLE 2. Microbiological findings

Time and species found	No. of patients with species in treatment group	
	Cefixime	Ofloxacin
Initial		
<i>Escherichia coli</i>	40	39
<i>Klebsiella pneumoniae</i>	3	3
<i>Enterobacter</i> spp.	2	3
<i>Staphylococcus saprophyticus</i>	2	3
<i>Morganella morganii</i>	2	
Failure or relapse		
<i>Escherichia coli</i>	8	6
<i>Klebsiella pneumoniae</i>	1	1
<i>Staphylococcus saprophyticus</i>	1	3
<i>Proteus mirabilis</i>	1	

Two previous studies showed lower cure rates when a single-dose ciprofloxacin (2) or ofloxacin (4) was given to women with *Staphylococcus saprophyticus* bacteriuria. In our study, one of two women with *S. saprophyticus* bacteriuria treated with cefixime and all three women treated with ofloxacin failed. Although there were only a few patients with *S. saprophyticus* who were treated with short-course therapy in this study, it seems that the short-course therapy is inadequate for the treatment of this bacteria.

The results of this study showed similar clinical and microbiological cure rates with both 3-day regimens, cefixime (400 mg once daily) and ofloxacin (200 mg twice a day) (Table 1). The observed small differences of 2 to 3% in the cure rates between the two regimens do not seem to be clinically significant, and this study was not designed to detect such a small difference. A large number of women in each group is needed in order to evaluate the true meaning of this difference.

The results obtained with cefixime in comparison to oral cephalosporins can probably be explained by its longer half-life and higher and prolonged concentration of the drug in urine (1).

The observed slight differences of 2 to 3% in the cure rates between the two regimens do not seem to be clinically significant. In order to define the exact role of cefixime as a short course in the treatment of uncomplicated cystitis in women, further studies are required.

We thank Ronit Almog, Hana Edelstein for statistical assistance, and Frances Nachmani for typing the manuscript.

REFERENCES

- Faulkner, R. D., A. Yacobi, J. S. Barone, S. Kaplan, and M. Silber. 1987. Pharmacokinetics profile of cefixime in man. *Pediatr. Infect. Dis. J.* **6**:963–970.
- Garlando, F., S. Rietiker, M. G. Täuber, M. Fleep, B. Meier, and R. Lüthy. 1987. Single-dose ciprofloxacin at 100 versus 250 mg for treatment of uncomplicated urinary tract infections in women. *Antimicrob. Agents Chemother.* **31**:354–356.
- Greenberg, R. N., P. M. Reilly, K. L. Luppen, W. J. Weinaudt, L. L. Ellington, and M. R. Bollinger. 1986. Randomized study of single-dose, three-day, and seven-day treatment of cystitis in women. *J. Infect. Dis.* **153**:277–282.
- Hooton, T. M., C. Johnson, C. Winter, L. Kuwamura, M. E. Rogers, P. L. Roberts, and W. E. Stamm. 1991. Single-dose and three-day regimens of ofloxacin versus trimethoprim-sulfamethoxazole for acute cystitis in women. *Antimicrob. Agents Chemother.* **35**:1479–1483.
- Johnson, J. R., and W. E. Stamm. 1989. Urinary tract infections in women. *Diagnosis and treatment.* *Ann. Intern. Med.* **111**:906–917.
- Norrby, S. R. 1990. Short-term treatment of uncomplicated lower urinary tract infections in women. *Rev. Infect. Dis.* **12**:458–467.
- Sandberg, T., C. Henning, S. Iwanson, and O. Paulsen. 1985. Cefadroxil once daily for three days or seven days versus amoxicillin for seven days in uncomplicated urinary tract infections in women. *Scand. J. Infect. Dis.* **17**:83–87.