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Single-Dose Fosfomycin Trometamol versus 5-Day Cephalexin Regimen for Treatment of Uncomplicated Lower Urinary Tract Infections in Women

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A randomized study was conducted to assess the clinical and microbiological efficacies of a single 3-g dose of fosfomycin trometamol for the treatment of uncomplicated lower urinary tract infections in women compared with a 5-day regimen of cephalexin at 0.5 g four times daily. One hundred twelve women, all of whom had documented infections with bacteria sensitive to both antibiotics, were included. Fifty-eight women received fosfomycin trometamol, and 54 women received cephalexin. The two groups did not differ in age, severity, or duration of current urinary tract infection, menstrual status, sexual activity, or use of contraceptives. Ninety percent of pathogens in the fosfomycin trometamol group and 81% in the cephalexin group were *Escherichia coli* (the difference is not significant [NS]). A clinical evaluation at the 5-day follow-up showed that 91% of the women in each group were free of symptoms, while five women in each group were considered therapy failures and were treated by another antibiotic course. A microbiological evaluation at the 5-day follow-up showed a 91% eradication rate in the fosfomycin trometamol group and an 83% eradication rate in the cephalexin group (NS). At the 1-month follow-up, a clinical evaluation demonstrated prolonged resolution in 86 and 78%, respectively, of the participating women (NS). A microbiological evaluation at 1 month demonstrated prolonged eradication in 47 (81%) women treated with fosfomycin trometamol and in 37 (68%) women treated with cephalexin (NS). Three and six women, respectively, had relapsed. No adverse reactions were reported by the fosfomycin trometamol-treated women, while three women treated with cephalexin reported mild adverse reactions but completed the study period. Fosfomycin trometamol in a single 3-g dose is as effective as a 5-day regimen of cephalexin for the treatment of uncomplicated lower urinary tract infection in women.

A majority of urinary tract infections present as acute uncomplicated cystitis. The question of the optimal antimicrobial agent that should be used in such circumstances and the appropriate length of therapy has been exhaustively dealt with in the past but without clear-cut conclusions. It is well recognized today that 3-day regimens are as effective as 7-day regimens, with fewer side effects and a lower cost (14). These advantages can be enhanced by single-dose therapy, but more frequent relapses have been reported with several drugs, including the fluoroquinolones (1, 11). Fosfomycin trometamol, a stable and bioavailable salt of fosfomycin, has been proposed as an effective single-dose drug for the treatment of urinary tract infections in several groups of patients, including children and pregnant women (2, 5, 9, 12). The spectrum of activity of fosfomycin appears to cover all the common pathogens of uncomplicated urinary tract infections (3). Fosfomycin trometamol achieves high urinary concentrations with a prolonged antibacterial activity in the urine of up to 48 h (7). In view of local high resistance rates of urinary pathogens for amoxycillin and trimethoprim-sulfamethoxazole and the high cost of the fluoroquinolones, this study evaluated the clinical and microbiological efficacies of a single-dose therapy of fosfomycin trometamol compared with 5-day treatment with cephalexin for uncomplicated urinary tract infections in women.

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MATERIALS AND METHODS

Women, 16 years of age or older, suffering from acute uncomplicated cystitis with positive leukocyte esterase test results, who had not been treated with antibiotic agents in the previous 4 weeks, were included in this study. The diagnosis of uncomplicated cystitis was based upon clinical symptoms of dysuria, frequency and urgency of urination, and the absence of fever or flank pain, accompanied by pyuria (more than eight leukocytes per mm^3 per ml) and a positive urinary culture yielding $\geq 10^5$ CFU of a microorganism sensitive to both fosfomycin trometamol and cephalexin per ml. Excluded from the study were women with known anatomic or functional renal abnormalities, patients with diabetes mellitus, pregnant or immunocompromised women, and women with known allergy to cephalosporins. Women with a history of urinary tract infection in the previous 5 weeks were excluded as well.

Clean voided midstream urine was collected and cultured by using the Uritest system (Hylab [Rehovot, Israel] dip slides). All isolates were identified by standard procedures and tested for susceptibility to antimicrobial drugs by the Kirby-Bauer method. The disc diffusion susceptibility test for fosfomycin trometamol was done with paper filter discs impregnated with fosfomycin trometamol (200 μg) and glucose-6-phosphate (50 μg). Susceptible zones with respective discs were defined as greater or equal to 16 mm.

Each patient gave informed consent. Data on previous urinary tract infections, duration of symptoms of the previous episode, relation to sexual activity, menstrual status, and use of contraceptives were obtained. Candidates were randomly as-

TABLE 1. Clinical characteristics

Characteristic	Value for group	
	Fosfomycin trometamol	Cephalexin
Total no. of subjects	58	54
Age (mean, range, SD) (yr)	40.6, 17–85, 16.3	37.2, 18–80, 15.1
Duration of symptoms (mean no. of days)	3.4	2.7
No. of subjects with 1st episode/no. with recurrent episode	33/25	35/19
No. of subjects with 0–2 UTI[a]/yr	41	44
No. of subjects with >3 UTI/yr	17	10

[a] UTI, urinary tract infections.

signed by a computer to nonblind treatment with either a single 3-g dose of fosfomycin trometamol or 5-day therapy of four daily doses of 500 mg of cephalexin.

Each patient was monitored clinically and bacteriologically at days 5 and 28. The presence of the same microorganism at day 5 (short follow-up) was considered a failure. Relapse was defined as a positive culture with the same pathogen after a previous negative culture. Microbiological cure was defined as complete eradication. Adverse reactions were recorded at the day 5 follow-up by specifically asking about any symptoms that might have been related to drug treatment, such as gastrointestinal disturbances, rash, fever, etc.

Statistical analysis used standard χ^2 with Yates' correction when appropriate and the Fisher exact test. P values of 0.05 were considered statistically significant.

RESULTS

A total of 130 women were initially recruited for the study, of whom 7 were excluded because of negative initial urine cultures and 11 were excluded because of initial resistance to one of the antibiotic agents (2 to fosfomycin, 9 to cephalexin, none to both); 58 women received fosfomycin trometamol and 54 received cephalexin. All 112 women completed the follow-up period. Clinical characteristics of both treatment groups were similar (Table 1). The etiological agents are listed in Table 2. No significant differences between the two groups in terms of sexual activity, menstrual status, or use of contraceptives or in the subjective evaluation by the subjects of the severity of the current episode on a scale of 1 to 4 were found.

At the short follow-up (day 5) (Table 3), clinical cure was achieved in 53 women (91%) in the fosfomycin trometamol-treated group and 49 women (91%) in the cephalexin group (the difference is not significant [NS]). Clinical failure at the short follow-up was observed in five women in each therapy group; these women received another antibiotic course. In each case of short-follow-up clinical failure a bacterium was cultured (Table 2). *Escherichia coli* was the only pathogen isolated in the 5-day-follow-up urine cultures from the fosfomycin trometamol-treated women and in one of the positive urine cultures from women in the cephalexin group. All bacterial isolates from the fosfomycin trometamol group were sensitive to both antimicrobial agents, while in the cephalexin group one isolate of *Enterobacter cloacae* was resistant to both antibiotic agents.

At the 1-month follow-up (Table 3), 50 women (86%) in the fosfomycin trometamol group and 42 women (78%) in the cephalexin group were free of symptoms (NS). Six and eight women, respectively, had reinfections (NS), and thus, microbiological cure rates were 81% for the fosfomycin trometamol group and 68% for the cephalexin group. Three and six women, respectively, had relapses (NS). *E. coli* was the only pathogen isolated from the fosfomycin group and in five of six of the relapses in the cephalexin group. In both groups, the pathogens isolated at the 1-month follow-up were fosfomycin trometamol sensitive, while two isolates among the cephalexin-treated women were cephalexin resistant.

No association between age and clinical and microbiological evaluations at the short and 1-month follow-ups was found for either treatment groups. None of the women treated with fosfomycin trometamol reported any major or minor adverse reactions, while three women in the cephalexin group complained of mild vaginal irritation at the 5-day follow-up evaluation.

On the basis of the sizes of the study groups, the type II (beta) error for detecting a clinically significant difference of 20% or more between the efficacies of the fosfomycin and cephalexin protocols with a single-sided type I (alpha) error of 0.05 was 0.3.

DISCUSSION

The advantages of single-dose therapies for uncomplicated urinary tract infections in women are numerous, resulting in better compliance, fewer side effects, lower risk for development of bacterial resistance, and presumably, significant reduction in drug costs (1). Narrow-spectrum cephalosporins and amoxycillin are not suitable for single-dose therapies (10, 11).

TABLE 2. Microbiological findings

Bacterium	No. of subjects					
	Pretreatment		Short-follow-up failures		Long-follow-up relapse/reinfection	
	FOSFO[a]	CEPH[b]	FOSFO	CEPH	FOSFO	CEPH
Escherichia coli	50	42	5	1	3/3	5/0
Klebsiella pneumoniae	5	5		1		
Proteus mirabilis	2	3		1		1/0
Morganella morganii		1		1		
Pseudomonas aeruginosa		1				
Enterobacter cloacae	1			1		0/1
Citrobacter diversus		2				
Streptococcus faecalis						0/1

[a] FOSFO, fosfomycin trometamol.
[b] CEPH, cephalexin.

TABLE 3. Clinical and microbiological responses

Outcome	No. of subjects (%)	
	Fosfomycin (n = 58)	Cephalexin (n = 54)
Clinical cure		
5-day follow-up	53 (91)	49 (91)
1-month follow-up	50 (86)	42 (78)
Microbiological cure		
5-day follow-up	53 (91)	45 (83)
1-month follow-up	47 (81)	37 (68)

Single-dose therapeutic protocols with trimethoprim-sulfamethoxazole or fluoroquinolones have achieved best results, but because of high resistance rates, trimethoprim-sulfamethoxazole can no longer be used for the empirical treatment of uncomplicated urinary infections in many areas (11, 13, 14). Moreover, 3-day regimens have been shown to result in fewer recurrences (10, 11, 13), and thus, single-dose regimens are generally not recommended for empirical treatment of acute uncomplicated cystitis in women (14).

Nevertheless, new drugs should be tested for that purpose, and fosfomycin trometamol, because of its high urinary concentrations and prolonged urinary antibacterial activity after a single oral dose of 3 g (2–4, 7, 9), appears to be very suitable for single-dose therapies. Fosfomycin trometamol has been shown to be effective in several clinical situations (5, 10, 12), including studies that have shown that single-dose fosfomycin trometamol is as effective as multiple-dose norfloxacin (5, 6).

The study presented above compared the clinical and microbiological efficacies of a 5-day regimen of cephalexin (0.5 g four times daily) and a 3-g single dose of fosfomycin trometamol for the treatment of uncomplicated lower urinary tract infections in women. Clinical and microbiological evaluations at the 5-day and 1-month follow-ups were similar for both protocols, with relatively low relapse rates (Table 3). This study could not demonstrate any statistically significant superior results with fosfomycin trometamol, but a trend towards better clinical results, with fewer relapses and, possibly, a lower rate of resistance development, appears to exist for this drug. The clinical and microbiological efficacies achieved by fosfomycin trometamol in the present study (91% each at the short follow-up and 86 and 81%, respectively, at the long follow-up) are similar to the efficacies achieved by multiple-dose fluoroquinolones regimens (5, 6, 8).

Although the power of this study was only moderate, it would appear that fosfomycin trometamol may offer good clinical and microbiological efficacies and, thus, may be suitable for an initial empirical single-dose therapeutic regimen for treatment of uncomplicated lower urinary tract infections in women.

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