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Comparative Efficacy and Safety of Fosfomycin and Nitrofurantoin in Acute Uncomplicated Lower Urinary Tract Infection in Young Women A Randomized, Open Label, Comparative Study

Research Article

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Abstract

Aim: The aim is to evaluate the comparative efficacy and safety of fosfomycin and nitrofurantoin in acute uncomplicated lower urinary tract infection in young women in our study cohort.

Material and methods: A randomized open label, intention to treat, comparative study was conducted over period of two years. Women were prescribed either nitrofurantoin or fosfomycin and their final outcomes in term of clinical and bacteriological cure were compared.

Results: Both the drugs were found to be equally effective in treating UTI with comparable safety and tolerability.

Keywords: Urinary tract infection, Fosfomycin; Nitrofurantoin

Introduction

Acute uncomplicated lower Urinary Tract Infection (UTI) in an otherwise healthy, non-pregnant woman is one of the most common problems for which young women seek medical attention. More than 30% of all women will experience UTI during their lifetime and the prevalence of UTI in women is approximately 50 times higher than in men. Antimicrobial resistance among uropathogens causing community-acquired UTIs is increasing worldwide.

The use of fosfomycin and nitrofurantoin are returning, owing to their broad-spectrum activity against both gram-positive and gram-negative bacteria. Fosfomycin is a unique antibiotic that is chemically different from any other known antibacterial agent. Nitrofurantoin is bactericidal.

Materials and Methods

A randomized open label, intention to treat, comparative study was conducted in the department of Obstetrics and Gynecology, Asian institute of medical sciences, Faridabad over a period of two years from June 2017 to May 2019.The study was undertaken after prior approval from the institutional ethics committee.

Young females diagnosed with uncomplicated UTI were randomized to receive either 100 mg capsules of nitrofurantoin twice a day for 7 days or a 3 gms single dose of fosfomycin. The diagnosis of uncomplicated UTI was based on clinical history, physical examination, urine analysis and urine culture with susceptibility testing. The clinical and bacteriological response was compared between the patients in the two treatment groups after ten days.

Results

70 women with uncomplicated UTI attending outpatient department formed the subject matter for this study. 35 study subjects were assigned to each group with one group having nitrofurantoin treatment and other having fosfomycin. Relevant finding were

recorded in specially designed pro forma including age, complaints, past history, drugs use to treat UTI, relevant side effects and response to drugs.

Urine culture analysis revealed growth of *E. coli* in 94.3% of the patients in both the treatment groups. Rest of the patients had growth of Klebsiella. Both the groups were similar in terms of the urine culture growth results (p value = 1.0).

Seven patients from the Fosfomycin group (20%) reported side effects, while only four patients in the Nitrofurantoin group.

14.3% of the women had no relief of symptoms. The two study drugs were not different statistically with respect to their relief in symptoms (p value =0.73)

Repeat culture results revealed that 94.3% of the patients in the Fosfomycin group had sterile urine, while 85.7% in the Nitrofurantoin group had sterile urine. The study groups were not statistically different with respect to their findings of repeat urine culture result (p value = 0.37).

In the Fosfomycin group, only two patients (5.7%) required further treatment, while in the Nitrofurantoin group four patients (11.4%) required further treatment. The difference is not statistically significant (p=0.63).

Table 1: Distribution of study subjects according to their age.

Variables	Group	N	Mean (Age in years)	SD	p- value
Age (in years)	Fosfomycin(F)	35	34.77	8.93	0.93
	Nitrofurantoin(N)	35	34.97	10.9	

Table 2: Distribution of study subjects according to their presenting symptoms.

Symptoms	Group		Total	p-value
	Fosfomycin	Nitrofurantoin		
Urgency	3	0	3	0.239
	8.60%	0.00%	4.30%	
Frequency	21	21	42	1
	60.00%	60.00%	60.00%	
Burning micturition	14	18	32	0.47
	40.00%	51.40%	45.70%	
Dysuria	2	1	3	1
	5.70%	2.90%	4.30%	
Pain in Abdomen	13	10	23	0.61
	37.10%	28.60%	32.90%	
Fever	4	4	8	1
	11.40%	11.40%	11.40%	

Table 3: Distribution of study subjects according to their findings of urine culture.

Urine Culture	Group		Total
	Fosfomycin	Nitrofurantoin	
E. Coli	33	33	66
	94.30%	94.30%	94.30%
Klebsiella	2	2	4
	5.70%	5.70%	5.70%
Total	35	35	70
	100.00%	100.00%	100.00%
p- value - 1.0			

Table 4: Distribution of study subjects according to the side effects.

Side Effects	Group		Total
	Fosfomycin	Nitrofurantoin	
Gastritis	0	1	1
	0.00%	2.90%	1.40%
Gastritis and Nausea	1	0	1
	2.90%	0.00%	1.40%
Loose stools	6	0	6
	17.10%	0.00%	8.60%
Nausea	0	3	3
	0.00%	8.60%	4.30%
Nil	28	31	59
	80.00%	88.60%	84.30%
Total	35	35	70
	100.00%	100.00%	100.00%
p- value - 0.51			

Table 5: Distribution of study subjects in the two groups according to the symptom relief.

Relief of Symptoms	Group		Total
	Fosfomycin	Nitrofurantoin	
Failure(no relief of symptoms)	4	6	10
	11.40%	17.10%	14.30%
Cure(relief of symptoms)	31	29	60
	88.60%	82.90%	85.70%
Total	35	35	70
	100.00%	100.00%	100.00%
p- value - 0.73			

Table 6: Distribution of study subjects in the two treatment groups for relief of specific symptoms.

Relief of Symptoms	Group		Total
	Fosfomycin	Nitrofurantoin	
Burning +	1	0	1
	2.90%	0.00%	1.40%
Dysuria +	0	2	2
	0.00%	5.70%	2.90%
Frequency +	2	2	4
	5.70%	5.70%	5.70%
Pain in Abdomen +	1	2	3
	2.90%	5.70%	4.30%
Relieved	31	29	60
	88.60%	82.90%	85.70%
Total	35	35	70
	100.00%	100.00%	100.00%
p- value - 0.49			

Table 7: Distribution of study subjects according to their repeat culture findings.

Repeat Culture	Group		Total
	Fosfomycin	Nitrofurantoin	
E. Coli	1	4	5
	2.90%	11.40%	7.10%
Klebsiella	1	1	2
	2.90%	2.90%	2.90%
Sterile	33	30	63
	94.30%	85.70%	90.00%
Total	35	35	70
	100.00%	100.00%	100.00%
p- value - 0.37			

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Table 8: Distribution of study subjects according to their resistance to study drugs.

Resistance to study drugs	Group		Total
	Fosfomycin	Nitrofurantoin	
No	33	30	63
	94.30%	85.70%	90%
Yes	2	5	7
	5.70%	14.20%	10%
Total	35	35	70
	100.00%	100.00%	100.00%
p- value - 0.23			

Discussion

In the present study, both the treatment groups included 35 patients each. Mean age of cases in the Fosfomycin group was 34.77 ± 8.93 years and of the Nitrofurantoin group was 34.97 ± 10.90 years.

The most common complaint of the patients in our study was frequency, reported by 60% of the patients in both the study groups. The next common complaint was burning micturition, which was observed in 40% in the Fosfomycin group and 51.4% in the Nitrofurantoin group. Pain in the abdomen was the next most common complaint in both the treatment groups. It was reported by 37.1% in the Fosfomycin group and 28.6% in the Nitrofurantoin group. Less common complaints were urgency, fever and dysuria.

Huttner and colleagues did not report specific clinical complaints of their patients, but the median number of symptoms was 3, ranging from 2 to 4 [1]. We have defined clinical improvement as cure (complete resolution of symptoms and signs of UTI without prior failure), failure (need for additional or change in antibiotic treatment due to a UTI or discontinuation due to lack of efficacy or persistence of symptoms). Stein defined clinical response as cure (elimination of all prê therapy symptoms), improvement (most but not all symptoms improved or absent), or failure (not improved from the initial assessment) [2]. In both the treatment groups in their study, 87% of the patients had symptoms for less than 48 hours.

In the present study, 74.3% of the patients in the Fosfomycin group and 80% of the patients in the Nitrofurantoin group had 10 to 20 pus cells. Nagel et al. conducted a retrospective study to evaluate the clinical and economic outcomes of fosfomycin compared to matched controls for the treatment of complicated lower tract and uncomplicated UTI [3]. In their study, 68% of the patients receiving Fosfomycin had more than 10 pus cells, which is similar to our study.

Baseline urine culture analysis in our study revealed *E. coli* growth in 94.3% of the patients in both the treatment groups. Rest of the patients had *Klebsiella* growth. Furthermore, 2 patients in the Fosfomycin group and 5 cases in the Nitrofurantoin group were resistant to drugs. In the study by Huttner et al., of the 487 baseline urine cultures obtained, 377 (77%) were positive, among which, *E. coli* (61%), *Klebsiella* spp (7%),

Enterococcus spp (7%), and *Proteus* spp (5%) predominated [1]. However, in our study only *E-coli* and *Klebsiella* predominated. In the Nitrofurantoin group, 1% were resistant to Nitrofurantoin, 23% resistant to co-trimoxazole, 12% resistant to fluoroquinolone and 6% were Extended Spectrum Beta-Lactamase (ESBL) producers.

Similar to our study,in the study by Stein et al., the predominant pretreatment uropathogen in each group was *E. coli* [2]. Next most common isolates were Proteus mirabilis, *Klebsiella pneumoniae*, and Staphylococcus saprophyticus.

Overall, 94% of pretreatment isolates were susceptible to fosfomycin compared with 83% for nitrofurantoin. Of the *E. coli* isolates, 99% were susceptible to fosfomycin and 90% were susceptible to Nitrofurantoin. Similarly, in our study, 94.3% isolates were susceptible to Fosfomycin and 85.7% were susceptible to nitrofurantoin.

In the present study, seven patients from the Fosfomycin group (20%) reported side effects, while only four patients in the Nitrofurantoin group (12%) reported any side effects. In the Fosfomycin group, one reported gastritis and nausea, and six patients reported loose stools. In the Nitrofurantoin group, one patient reported gastritis and three reported nausea.

Whereas, in the randomized trial by Huttner, 21 of 248 (8%) and 16 of 247 (6%) in the nitrofurantoin and fosfomycin groups, respectively, reported at least one adverse event.1 Stein and colleagues found that the most common adverse effects related to fosfomycin treatment were diarrhea (2.4%), vaginitis (1.8%), and nausea (0.8%) [2]. Common side effects associated with nitrofurantoin treatment were nausea (1.6%), vaginitis (1.6%), dizziness (0.8%), and diarrhea (0.8%). GI adverse events were reported in 3.9% of fosfomycin recipients among women with an uncomplicated lower UTI. Moreover, in a large non-comparative study in 387 women and men with uncomplicated UTIs who received single-dose fosfomycin, adverse events were reported in 4.9 % of patients, with diarrhea, nausea and vomiting occurring in 3.1, 1.3 and 0.5 % of patients, respectively.

We observed that in the Fosfomycin group, 88.6% of the patients reported relief of symptoms, while in the Nitrofurantoin group 82.9% reported relief of symptoms.

Four patients in the Fosfomycin group did not report relief of symptoms, one with burning micturition and pain in abdomen each and two with frequency. In the Nitrofurantoin group, six patients did not report relief of symptoms, two each of dysuria, frequency and pain in the abdomen.

Stein et al. reported that the clinical cure rates were similar with Fosfomycin and Nitrofurantoin at each of the follow-up assessment [2]. Which is comparable to our study. P value 0.73 which is statistically insignificant. At the end of the study, the overall success (cure and improvement) rates were 80% in both the fosfomycin and nitrofurantoin groups. Huttner et al. reported that at 28 days after therapy completion, 171 of 244 patients (70%) receiving nitrofurantoin had maintained clinical resolution versus 139 of 241 (58%) receiving fosfomycin (difference, 12% [95% CI, 4%-21%]; P = 0.004) [1]. Clinical response at the earlier point of 14 days after therapy completion also differed significantly between groups, with 184 of 247 patients (75%) receiving nitrofurantoin experiencing clinical resolution *vs* 162 of 247 (66%) receiving fosfomycin (difference, 9% [95% CI, 1%-17%]; P = 0.03). Patients in either treatment group with early clinical failure (due to the persistence of symptoms rather than recurrence after initial improvement) returned for additional antibiotic therapy at the

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same point after inclusion (mean [SD] of 6.3 [3.8] and 6.5 [3.6] days in the nitrofurantoin and fosfomycin groups, respectively). In our study also, two patients in the Fosfomycin group and four patients in the Nitrofurantoin group required further treatment with antibiotics and the difference is not statistically significant (0.63) Similarly, another double-blind, placebo-controlled trial by comparing a single 3-g dose of fosfomycin *vs* 7 days of nitrofurantoin, 50 mg 4 times daily, in women with clinically confirmed cystitis also found no difference in clinical response at any time point 4 to 42 days after starting treatment as per-protocol analyses which is in tandem to our study [4].

We found that the bacteriological cure rate in the Fosfomycin group was 94.3%, while it was 85.7% in the Nitrofurantoin group. Among the patients in the Fosfomycin group, one patient had *E. coli* and *Klebsiella* growth each. In the Nitrofurantoin group, four patients had growth of *E. coli* and one patient had *Klebsiella* growth.

However, contrary to our study, Huttner et al. reported that patients receiving nitrofurantoin had significantly more bacteriologic success: among those with positive baseline cultures, 146 of 177 (82%) and 121 of 165 (73%) saw no recurrence on day 14 in the nitrofurantoin and fosfomycin groups, respectively (P =.04).68 The difference remained at day 28, when both groups saw an overall decrease in success, with 129 of 175 (74%) and 103 of 163 (63%), respectively (difference, 11% [95% CI, 1%-20%]; P =.04). Stein et al. reported a statistically higher failure rate with fosfomycin 5 to 10 days after the initial treatment dose which is in contrast to our study in which failure rates with Fosfomycin were less compared to nitrofurantoin.2 The bacteriologic cure rates were not statistically different at any of the subsequent follow-up visits. The overall bacteriologic cure rate was 60% for fosfomycin and 59% for nitrofurantoin.

Gupta et al. conducted a study which included non pregnant women aged 18-45 years with acute uncomplicated cystitis, pyuria and a positive urine culture [5]. The women received a single dose of fosfomycin trometamol 3 gm (n = 20), ciprofloxacin 250 mg twice daily for 3 days (n = 25) or nitrofurantoin 100 mg twice daily for 7 days (n = 17), and clinical success rates and bacteriological eradication rates were more than 90 % in all three treatment groups. At the enrolment visit, 94 % of women had rectal colonization with *E. coli*; the prevalence of rectal *E. coli* was significantly ($p < 0.001$) reduced after treatment with fosfomycin and ciprofloxacin, but not nitrofurantoin. This finding is also different from our study. Isolation of two ciprofloxacin-resistant rectal *E. coli* strains from a single patient occurred 10 days after completing treatment with ciprofloxacin. Among patients receiving fosfomycin or nitrofurantoin, all isolated rectal *E. coli* strains were susceptible to the study drug.

Furthermore, we observed that on subsequent urine culture after 10-14 days of treatment, only two patients in the fosfomycin group (5.7%) had resistance to the study drugs, while in the Nitrofurantoin group, five patients (14.2%) reported resistance.

Shah et al. found that out of 97 Multi-Drug Resistant (MDR) gram-negative urinary isolates, multi-drug resistance in *E. coli* was predominant (44.5%) as compared to *K. pneumoniae* (2%). In their study, 98% of MDR *E. coli* isolates were susceptible to fosfomycin and 81% to nitrofurantoin. These results coincided with a study conducted in Taiwan against MDR *E. coli*, where 95.5% and 75.1% isolates were susceptible to fosfomycin and nitrofurantoin respectively which is similar to our study. Bano et al. concluded maximum susceptibility to fosfomycin (100%) and nitrofurantoin (100%) against *K. pneumoniae* in a study conducted in Pakistan.

Few limitations of this study. First, it was conducted as an open-label study, which might have introduced some level of measurement bias. However, interestingly Fosfomycin which was given as a single dose relieved symptoms in a higher number of patients as compared to Nitrofurantoin. Huttner et al. commented that open-label design may influence the patient reported clinical outcomes [1]. A perception of greater treatment intensity (twice a day dose for 7 days) can differentially reduce the frequency of clinical failure in the nitrofurantoin as compared to that in the fosfomycin group, second, clinical response was patient-reported and could have introduced a bias. Lastly, this was a single center study. Epidemiology of uncomplicated UTI might vary at other geographical locations, where the clinical and bacteriological response to Fosfomycin and Nitrofurantoin might change. So the results of the study might not be applicable to other geographical locations. Also, different dosages of Nitrofurantoin are used in different parts of the world. For instance, 100 mg thrice a day is the most frequently used dose in Europe. So it is not clear at this point that the clinical and bacteriological efficacy is dose-dependent.

Conclusion

Both drugs appear to be equally effective, safe and well tolerated in young female with acute uncomplicated UTI.

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