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Treatment of Non - Complicated Lower Urinary Tract Infection in Pregnancy: Single Dose Fosfomycin Tromethamine Versus Multiple Dose Nitrofurantoin

Murat ÖZEL, Oktay KAYMAK, Nüvit BİRGİLİ, Şevki ÇELEN, Mine ERDOĞAN, Nuri DANIŞMAN

Ankara, Turkey

OBJECTIVE: To evaluate the efficacy of single-dose fosfomycin tromethamine (FT) treatment in pregnant women with uncomplicated lower urinary tract infection (UTI).

STUDY DESIGN: In this study, 421 pregnant women with established, symptomatic, uncomplicated lower UTI were randomly allocated to receive either a single dose of FT (Monurol®, Zambon Group S.p.A, Milan-ITALY) (n=217) or a 7-day course of nitrofurantoin (n=204). The treatment was found to be effective if urine culture was negative 15 days after therapy.

RESULTS: Microbiological cure was achieved in 205 (94.5%) patients treated with FT and 164 (80.4%) patients treated with nitrofurantoin ($p<0.05$). Pathogen microorganisms were predominantly E.coli (199 in FT and 183 in NF group) followed by Klebsiella (18 in FT and 21 in NF group).

CONCLUSION: The treatment of acut lower UTI in pregnant women is essential. FT is an effective, safe, single dose treatment choice in the management of uncomplicated lower UTI in pregnant women.

Key Words: Urinary tract infections, Pregnancy, Fosfomycin tromethamine, Nitrofurantoin

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Introduction

Pregnancy is not responsible for a major increase in the development of urinary tract infection (UTI) but appears to enhance the development of pyelonephritis in women who have bacteriuria even asymptomatic.[1,2] About one of every 20 pregnant women have more than 106 microorganisms per ml in the urine and some 20-40% of them develop acute pyelonephritis.[3,4]

Factors predisposing the pregnant women to bacteriuria and UTI are:

1. Increased urinary content of aminoacids, vitamins and other nutrients which creates a suitable medium for bacterial growth,

2. Stasis of the urine both due to the dilatation of ureters and impaired emptying of urinary bladder,

3. Increase of urine pH.

Therefore, all bacteriuric pregnant women should receive an appropriate antimicrobial treatment whether symptomatic or asymptomatic. In pregnant patients, the most frequently isolated uropathogen is Escherichia coli. Other responsible microorganisms include Klebsiella, Enterobacter, Proteus, Staphylococcus epidermidis, Staphylococcus saprophyticus, Enterococcus faecalis and group B Streptococcus.[5]

The goal must be to maintain a sterile urine throughout pregnancy in order to avoid complications with UTIs. Shortest possible course of antimicrobial agents should be used to minimize the risk of toxicity both for the mother and the fetus, because evidence supports that continious therapy has no advantages over a short-course or single-dose treatment.[6]

Fosfomycin tromethamine (FT) is a fosfomycin formula which keeps the microbiological properties while improving the bioavailability when taken orally.[7,8] It is bactericidal in urine at therapeutic doses and neither mutagenic nor teratogenic; it is pre-and postnatally nontoxic.[9] There is generally no cross-resistance between FT and other classes of antibacterial agents such as beta-lactams and aminoglycosides. FT is excreted unchanged in both urine and feces therefore it causes high urinary levels of the active compound which remains higher than the minimum inhibitory concentration for 36-48 h. Following a 3 g oral administration of FT, the urinary concen-

Zekai Tahir Burak Woman Health Education and Research Hospital, Division of Perinatology, Ankara

Address of Correspondence: *Murat Özel*
Ahmet Taner Kışlalı Mah. Park Cad.
No:52 Rönesans Evleri B Blok, Çayyolu
Ankara
drmuratozelztb@hotmail.com

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trations are initially very high (>700 mg/I up to 12 h) and mean concentration at 24-28 h after dosing was about 150 mg/I.[10] Fosfomycin tromethamine has received FDA approval in the United States and is a category 'B' drug.

Hence, a randomized trial has been planned comparing single-dose treatment with fosfomycin tromethamine versus conventional therapy with nitrofurantoin in pregnant women with uncomplicated lower UTI.

Material and Method

Pregnant patients with the signs and symptoms of acute cystitis attending the antenatal clinic of Zekai Tahir Burak Woman Health Education and Research Hospital, Ankara, Turkey between June and November 2009 were enrolled if they were found to have significant bacteriuria of the same microorganism with more than 10 CFU/ml in a urine culture of a midstream urine specimen, collected using the clean-catch method. Patients who have signs or symptoms suggestive of pyelonephritis or giving a history of hypersensitivity reaction to study drugs were excluded from the study.

After informed consent had been obtained for each patient, 421 patients in total were subdivided into two groups, and were randomly allocated to receive either a single dose of fosfomycin tromethamine (Monurol™)- one sachet of 3 gr as active antibiotic dissolved in a glass of water taken preferably at night on an empty stomach (n=217) or a 7-day course of nitrofurantoin 100 mg b.i.d (n=204).

The bacteriological efficacy of the studied drugs was evaluated 15 days after the therapy. The treatment was found to be effective if there was no positive urine culture obtained 15 days after the initiation of the therapy.

In case of treatment failure, the patient who can not be treated by the drug administered was switched to the other drug.

Any possible drug-related adverse reaction was carefully recorded.

A computer generated ramdomization list was used for random allocation of the patients. Continuous data were expressed as mean ± SD and were analyzed with student T test. Categorical data were expressed as number and percentages and analyzed with the Pearson chi-square test. Distribution normality was shown using Kolmogorov-Smirnov test. All tests were two-sided and a probability value of <0.05 represented statistical significance. All statistical analysis was performed with SPSS 16.0 (SPSS, Chicago, IL).

Results

The mean maternal age and gestational week for 217 patients in FT group were 24.26±4.6 (18-37) and 22.78±4.2 (7-36) respectively; and for 204 patients in NF group were 25.24±4.8 (18-36) and 23.64±4.4 (7-37) respectively. Thus, both treatment groups were comparable regarding maternal and gestational ages (p>0.05).

The pathogens isolated are shown in table 1. The distribution of the pathogen microorganisms was homogen in both groups. They were predominantly E.coli (199 in the FT group and 183 in NF group) followed by Klebsiella (18 in the FT group and 21 in NF group).

Table 1. Uropathogens isolated in pregnant patients with UTI

Isolated uropathogens	Fosfomycin (n)	Nitrofurantoin (n)
Escherichia coli	199	183
Klebsiella	18	21
Total	217	204

Microbiological cure from the isolated microorganisms was observed in 205 (94.5%) patients treated with fosfomycin tromethamine and 164 (80.4%) patients treated with nitrofurantoin (Table 2). Cure rate of FT was signicicantly higher than the cure rate obtained by using NF (p<0.05).

Table 2. Bacteriological cure in pregnant women with UTI

Therapy	Dosage	cure (cured/total)	%
Fosfomycin	3 g/single dose	205/217	94.5
Nitrofurantoin	100mg bid/7 days	164/204	80.4

p<0.05

Of the 12 patients can not be treated by using FT, the isolated microorganisms were E.coli in 10 cases and Klebsiella in two cases. In 12 FT failures the treatment was switched to standart dose of NF and all were cured. Among the 40 patients can not be treated by using NF, isolated microorganisms were E.coli in 34 cases and Klebsiella in six cases. In 40 NF failures the treatment was switched to single dose of oral FT and 37 were cured. Three patients cured by ampiciline.

Both drugs were well tolerated by the patients with only minor and transient side-effects, mainly nausea.

Discussion

Multidrug resistance of uropathogens to antimicrobial agents is a progressively increasing problem in recent years. The rate of resistance to nitrofurantoin in recent surveys in USA and Canada was 1.1% among 1142 isolates of E.coli from outpatients urinary isolates. However, among 115 clinical isolates of E.coli which produce extended spectrum beta lactamase, only 71.3% were sensitive to nitrofurantoin.[11] In our study, 18.6% (34/183) of the cases infected by E.coli were

resistant to NF. This high resistance rate would be even higher if beta lactamase producing microorganisms were isolated.

Fosfomycin has become available in Turkey with this decade although it has been used in European conuntries for decades. Evaluation of fosfomycin tromethamine treatment for uncomplicated lower UTI in pregnant women is difficult. Between late 1980's and early 2000's, there are a few number of studies concerning single dose FT treatment; and in published studies, there are large variations both in the number of patients and in study drugs. studies comparing single dose fosfomycin treatment with conventional 5 or 7-day treatment of variable antibiotics in pregnant women who were diagnosed to have uncomplicated UTI have reported similar cure rates. In a randomised, multicenter trial by N.Ragni et al, covering 365 pregnant patients who have lower UTI and treated either by single dose FT or 7-day course of pipemidic acid, the microbiological cure rate was found to be 94.4 and 86.5% respectively.[12] And in another multicenter study by Minassian et al which compared single dose FT therapy and 5-day course of trimethoprim in the treatment of acute cyctitis in 547 women, microbiological cure rate achieved was 83.3% for the trimethoprim treated group and 83.0% for the FT treated group.[13] Also in another study by S.Krcmery et al,[14] clinical cure and bacteriological eradication rate of the uropathogens was similar for single dose FT and 3-day course of oral ceftibuten (95.2% versus 90.0% respectively).

In a recent meta-analysis including twenty seven trials, only five of them involved pregnant patients[15] No difference was found in the comprehensive analysis regarding all comparators combined but relevant data provided from trials involving pregnant patients was insufficient. In our study, relatively large number of patients were involved and all were pregnant. In contrast to other studies which found no difference between single dose fosfomycin or conventional 5 or 7-day treatment of variable antibiotics, our results demonstrated a significantly increased cure rate by FT use.

In the ARESC (Antimicrobial Resistance Epidemiological Survey on Cystitis) study which included 4264 female patients, fosfomycin was found to be one of the most active drugs against E.coli[16] with a cure rate of 98.1%. In our study, also, the sensitivity of E.coli to FT was found to be 95% (189/199).

Conclusion

The treatment of acut lower UTI in pregnant women is essential because it can lead to a largely preventable condition, acute pyelonephritis. In accordance with previously published studies single dose or short course treatment with an appropriate drug should be recommended for treatment of these patients and the drug to be used preferably should be an FDA category 'B' drug.

Fosfomycin tromethamine has all these characteristics and proven to preserved its in vivo activity which make it an effective, safe, single dose treatment choice in the management of uncomplicated lower UTI in pregnant women.

Further studies are needed to show its activity in complicated urinary tract infections.

Gebelerde Komplike Olmayan Üriner Sistem Enfeksiyonunun Tedavisi: Tek Doz Fosfomycin Tromethamine vs. Multipl Doz Nitrofurantoin

AMAÇ: Komplike olmayan alt üriner sistem enfeksiyonu olan gebe kadınlarda tek doz fosfomisin tromethamine (FT) tedavisinin yararının değerlendirilmesi

GEREÇ VE YÖNTEM: Bu çalışmada, semptomatik, komplike olmayan alt üriner sistem enfeksiyonu ispatlanmış 421 gebe kadın rastgele tek doz FT(Monurol®, Zambon Group S.p.A, Milan-ITALY)(n=217) ve 7 gün süreli nitrofurantoin (n=204) tedavi gruplarına ayrıldı.İdrar kültürü tedaviden 15 gün sonra negatif ise tedavinin yararlı olduğu bulundu.

BULGULAR: FT ile tedavi edilen 205(%94.5) hastada ve nitrofurantoin ile tedavi edilen 164 (%80.4) hastada mikrobiyolojik kür elde edildi ($p<0.05$).Patojen mikroorganizmalar baskın olarak E.coli (199 FT ve 183 NF grupta) takiben Klebsiella (18 FT and 21 NF grupta) idi.

SONUÇ: Gebe kadınlarda akut alt ÜSE tedavisi gereklidir.FT gebe kadınlarda komplike olmayan alt ÜSE yönetiminde yararlı, güvenli, tek doz tedavi seçimidir.

Anahtar Kelimeler: İdrar yolu enfeksiyonu, Gebelik, Fosfomisin tomehamine, Nitrofurantoin

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