

Original article

Single Dose Fosfomycin Trometamol Versus 5 Day Amoxicillin-Clavulanate Regimen For Treatment of Symptomatic Urinary Tract Infections in Pregnant Women

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ÖZET

Gebelerdeki semptomatik üriner sistem enfeksiyonlarında tek doz fosfomycin-trometamol ile 5 gün amoxicillin-clavulanate tedavilerinin karşılaştırılması

Giriş: Üriner sistem enfeksiyonları (ÜSE) doğum kliniklerine en sık başvuru nedenlerinden birisidir. Gebelikte meydana gelen çeşitli anatomik ve hormonal değişiklikler ÜSE'nin artışına neden olmaktadır. ÜSE tedavi edilmediğinde ciddi obstetrik komplikasyonlarla ilişkilidir. Bu çalışmada gebe kadınlardaki idrar yolu enfeksiyonlarında tek doz fosfomisin trometamol ile 5 gün amoksisillin-clavulanate tedavi etkinlikleri karşılaştırıldı.

Materyal ve Metot: İdrar kültürü pozitif akut sistit tanısı alan 50 gebe kadın randomize iki gruba ayrılarak fosfomycin ve amoxicillin-clavulanate ile tedavi edildi. Tedavi sonrası 7. ve 30. günler klinik ve mikrobiyolojik sonuçlar değerlendirildi.

Bulgular: Kısa süreli takiplerde kür oranı fosfomycin grubunda %88 iken, Amoxicillin grubunda %92 olarak bulundu. Fark istatistiksel olarak anlamsızdı ($p>0,005$). İki grup arasında 1 aylık takiplerde de kür oranlarının benzer olduğu görüldü. Yani klinik özellikleri benzer olan iki grupta da tedavi sonrası mikrobiyolojik kür oranları aynı idi.

Tartışma: ÜSE olan gebe kadınlarda tek doz fosfomycin tedavisi daha kolay uygulanabilir, daha ucuz ve daha iyi tolere edilebilen bir alternatiftir.

Anahtar Kelimeler: Gebelik; idrar yolu enfeksiyonu; fosfomycin

ABSTRACT

Introduction: Urinary tract infections (UTIs) are a common cause of admission in obstetrical wards. Several anatomical and hormonal changes in pregnant women lead to the increased risk of developing UTIs. Untreated UTIs can lead to serious obstetric complications. Antimicrobial agents considered safe and effective in pregnancy are nitrofurantoin, β lactam antibiotics including both penicillins and cephalosporins and fosfomycin trometamol. This study evaluated the clinical and microbiological efficiency of a single dose therapy of fosfomycin trometamol compared with 5-day treatment with amoxicillin-clavulanate for UTIs in pregnant women.

Material and Method: Fifty pregnant women, suffering from acute uncomplicated cystitis with positive urinary culture were randomly assigned to two groups: 25 were treated with fosfomycin and 25 with amoxicillin-clavulanate. Each patient was monitored clinically and microbiologically at day 7. and 30. Clinical characteristics of both treatment groups were similar.

Results: At the short follow-up clinical cure was achieved in 22 women (88%) in the fosfomycin trometamol treatment group and 23 women (92%) in the amoxicillin-clavulanate group. The difference is not significant ($p>0.005$). At the 1-month follow-up microbiological cure rates were same.

Discussion: Single dose of fosfomycin trometamol could be the treatment of choice due to its simpler administration, lower cost and better compliance in pregnant women with UTIs.

Key Words: Pregnancy; urinary tract infections; fosfomycin

INTRODUCTION

Urinary tract infections (UTIs) are a common cause of admission in obstetrical wards. It has been reported among 20% of the pregnant women¹.

Symptomatic UTI occurs in 17.9% of pregnancies, while asymptomatic bacteriuria has been reported in 13.0% of pregnant women².

Several anatomical and hormonal changes in pregnant women lead to ureteral dilatation and urinary stasis, which contribute to the increased risk of developing UTIs. Untreated UTIs can lead to serious obstetric complications, poor maternal and perinatal outcomes, such as pyelonephritis, low-birth-weight infants, premature delivery, and, occasionally, stillbirth; therefore, screening of pregnant women for UTI can minimize these UTI associated complications and prompt treatment of symptomatic UTIs and asymptomatic bacteriuria is warranted in pregnant women³. Escherichia coli is the primary urinary tract pathogen accounting for

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75%-90% of uncomplicated UTI isolates. Other uropathogens include *Staphylococcus saprophyticus* in 5%-10% episodes and *Klebsiella pneumoniae*, *Proteus mirabilis* and Group B *Streptococci* in less than 5%⁴. Drug use in pregnancy may have unpredictable effects.

Antimicrobial agents considered safe and effective in pregnancy are nitrofurantoin, β lactam antibiotics including both penicillins and cephalosporins and fosfomycin trometamol⁵.

This study evaluated the clinical and microbiological efficiency of a single dose therapy of fosfomycin trometamol compared with 5-day treatment with amoxicillin-clavulanate for uncomplicated lower urinary tract infections in pregnant women.

MATERIAL AND METHOD

This was a randomised prospective study in which the efficacy of two antibiotic regimens was compared in the treatment of symptomatic UTI during pregnancy. Between May, 2007 and April 2008 fifty-nine pregnant women with complaints of lower UTI were assessed for inclusion in the present prospective. Nine pregnant women were excluded because of negative initial urine cultures and initial resistance to one of the antibiotic agents.

Fifty pregnant women, suffering from acute uncomplicated cystitis with positive urinary culture who had not been treated with antibiotic agents in the previous 4 weeks, were randomly assigned to two groups: 25 were treated with fosfomycin and 25 with amoxicillin-clavulanate. The diagnosis of uncomplicated cystitis was based upon clinical symptoms of dysuria, frequency and urgency of urination and a positive urinary culture yielding $\geq 10^5$ colony-forming units [cfu] per mL of a microorganism sensitive to both fosfomycin trometamol and amoxicillin-clavulanate. Excluded from the study were women with known anatomic or functional renal abnormalities, patients with diabetes mellitus, and women with known allergy to amoxicillin-clavulanate.

Clean voided midstream urine was collected and cultered. All isolates were identified by standard procedures and tested for susceptibility to antimicrobial drugs by the Kirby-Bauer method.

Informed consent was obtained from each patient. Data on previous urinary tract infections, duration of symptoms of the previous episode, relation to sexual activity were obtained.

Patients were randomly assigned by a computer to nonblind treatment with either a single 3 gram dose of fosfomycin trometamol (Monurol; Bilim Pharmaceuticals, Istanbul, Turkey) or 5 day

therapy of two daily doses of 625 mg of amoxicillin-clavulanate (Augmentin; GlaxoSmithKline, Istanbul, Turkey). Each patient was monitored clinically and microbiologically at day 7 and 30. The presense of the same microorganism at day 7 (short follow-up) was considered a failure.

Recurrence was defined as a positive culture with the same pathogen after a previous negative culture. Adverse reactions were recorded at the day 7 follow up by spesifically asking about any symptoms that might have been related to drug treatment, such as gastrointestinal disturbances, fever and rash, etc.

SPSS version 10.0 (SPSS, Chicago, IL, USA) was used to perform statistical analyses. Non-parametric analyses were performed with Kruskal-Wallis and χ^2 tests, variance analyses were performed with analysis of variance, and Tukey HSD test was used for post-hoc analyses. $P < 0.05$ was considered to be statistically significant.

RESULTS

A total of 59 women were initially recruited for the study, of whom 5 were excluded because of negative initial urine cultures and 4 were excluded because of initial resistance to one of the antibiotic agents. 25 women recieved fosfomycin trometamol and 25 recieved amoxicillin-clavulanate. All 50 women completed the follow-up period. Clinical characteristics of both treatment groups were similar ($P > 0.05$) (Table 1).

Table 1. Clinical Characteristics

Characteristic	Fosfomycin Trometamol	Amoxicillin-Clavulanate
Total number of subjects	25	25
Age	25-34	27-35
Duration of symptoms (day)	3.2	4.1
No of subjects with first episode/ No with recurrent episode	18/7	16/9

At the short follow-up (day 7) clinical cure was achieved in 22 women (88%) in the fosfomycin trometamol treatment group and 23 women (92%) in the amoxicillin-clavulanate group. The difference is not significant ($p > 0.005$) (Table 2).

At the 1-month follow-up (Table 2), 20 women (80%) in the fosfomycin trometamol group and 22 women (88%) in the amoxicillin-clavulanate group were free of symptoms. The difference is not significant. Microbiological cure rates were same ($P > 0.05$).

Table 2. Clinical and Microbiological Responses

Outcome	Fosfomycin Trometamol (n=25)	Amoxicillin-Clavulanate (n=25)
Clinical Cure		
7-day follow-up	22 (88%)	23 (92%)
1-month follow-up	20 (80%)	22 (88%)
Microbiological Cure		
7-day follow-up	22 (88%)	23 (92%)
1-month follow-up	20 (80%)	22 (88%)

DISCUSSION

The advantages of single dose therapies for uncomplicated urinary tract infections in women are numerous, resulting in better compliance, fewer side effects, significant reduction of drug costs. In most of studies, the rate of cure is higher with single dose treatments than with 3. day or 5._day regimens⁶⁻¹¹. In 2007, Bayrak et al.¹² compared, a single dose of fosfomycin and 5-day course of cefuroxim, for the treatment of uncomplicated lower urinary tract infections in the second trimester of pregnancy, and found no differences between two groups. Therapeutic success was achieved in 93,2% for the women treated with fosfomycin versus 95% for those treated with cefuroxim.

In 2009, Estebanez et al.¹³ compared a regimen of a single dose of fosfomycin with the standard regiment of a 7 day course of amoxicillin-clavulanate in the treatment of asymptomatic

bacteriuria during pregnancy. The patients were a randomly assigned in two groups: 56 women were treated with amoxicillin–clavulanate and 53 patients with fosfomycin.

When two groups were compared, a single dose fosfomycin was found to be as effective as the standard course of treatment.

It is well recognized today that 3 day regimens are as effective as 7 day regimens, with fewer side effects and a lower cost¹. These advantages can be enhanced by single dose therapy, but more frequent relapses have been reported with several drugs^{14,15}. 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 pregnant women¹⁶.

The spectrum of activity of fosfomycin appears to cover all the common pathogens of uncomplicated urinary tract infections. Fosfomycin trometamol achieves high urinary tract concentrations with a prolonged antibacterial activity in the urine of up to 48 hours.

Based on our results, treatment with a single dose of fosfomycin may be said to be as effective as the 5-day course of 500 mg of amoxicillin–clavulanate. Single dose of fosfomycin trometamol could be the treatment of choice due to its simpler administration, lower cost and better compliance.

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