Comparison of Fosfomycin Trometamol

by Tarmono Tarmono

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COMPARISON OF FOSFOMYCIN TROMETAMOL WITH CIPROFLOXACIN FOR UNCOMPLICATED UTI DUE TO E. COLI IN WOMEN

[1]Budiono, Heri; [1]Hardjowijoto, Sunaryo; [1]Djojodimedjo, Tarmono; [1]Soebadi, Doddy M; [2]Widodo, Agung Dwi Wahyu; [3]Budiono.

[1]Department of Urology, Faculty of Medicine/AirlanggaUniversity, Soetomo General Hospital, Surabaya.
[2]Department of Microbiology, Faculty of Medicine/Airlangga University, Soetomo General Hospital, Surabaya.
[3]Department of Public Health, Faculty of Medicine/AirlanggaUniversity, Soetomo General Hospital, Surabaya.

ABSTRACT

Objectives: *To compare clinical therapeutic effects (frequency, dysuria, and pyuria), microbiology, pharmacokinetic index Cmax/MIC of Fosfomycin trometamol single dose with Ciprofloxacin 2 x 500 mg for 5 days in the treatment of uncomplicated urinary tract stone (UTI) in women due to Escherichia coli (E. coli).* ***Materials & Methods:*** *We performed an experimental observational design from February until July 2013. Twenty two women with uncomplicated UTI due to E. coli underwent clinical and microbiological examination. Pharmacokinetic index (Cmax/MIC) is examined. Patients were divided into 2 group, Ciprofloxacin 2 x 500 mg for 5 days and Fosfomycin trometamol single dose. Repeat clinical and microbiological evaluation is performed after 7 days therapy. Statistical analysis use Chi-square test, paired T-test, and independent T-test.* ***Results:*** *In the treatment of uncomplicated UTI in women, Fosfomycin trometamol single dose therapy provides clinical cure (dysuria 81.2%, p = 0.338, frequency 90.9%, p = 0.004, pyuria 90.9%, p = 0.009) better than Ciprofloxacin 2 x 500 mg 5 days. Fosfomycin trometamol single dose therapy also provides bacteriological eradication (100%) better than Ciprofloxacin 2 x 500 mg 5 days (p = 0.035). Fosfomycin trometamol single dose had a higher pharmacokinetic index (Cmax/MIC) compared to Ciprofloxacin 2 x 500 mg (p = 0.035).* ***Conclusion:*** *Fosfomycin trometamol single dose therapy is superior to Ciprofloxacin 2 x 500 mg 5 days in the treatment of uncomplicated UTI in women.*

Keywords: *Therapeutic effect, fosfomycin trometamol, ciprofloxacin, uncomplicated UTI, Escherichia coli.*

ABSTRAK

Tujuan: *Untuk membandingkan efek terapi secara klinis (frekuensi, disuria, dan pyuria), mikrobiologi, dan indeks farmakokinetika Cmax/MIC terapi Fosfomisin trometamol 3 g dosis tunggal dengan Siprofloksasin 2 x 500 mg selama 5 hari dalam pengobatan infeksi saluran kemih (ISK) tanpa komplikasi pada wanita karena Escherichia coli (E. coli).* ***Bahan & cara:*** *Penelitian bersifat analitik eksperimental observasional dari Februari sampai Juli 2013. Dari 22 pasien wanita dengan ISK tanpa komplikasi karena E. coli dilakukan pemeriksaan klinis, mikrobiologi, dan farmakokinetik kemudian secara acak dibagi dalam 2 kelompok terapi yaitu Siprofloksasin 2 x 500 mg selama 5 hari dan Fosfomisin Trometamol dosis tunggal. Dievaluasi ulang pada hari ke-7 terapi. Hasil dianalisa dengan menggunakan uji Chi-Square, uji T-berpasangan, dan uji T-independen.* ***Hasil:*** *Dalam pengobatan ISK tanpa komplikasi pada wanita, terapi Fosfomisin trometamol dosis tunggal memberikan kesembuhan secara klinis (disuria 81.2%, p = 0.64, frekuensi 90.9%, p = 0.004, pyuria 90.9%, p = 0.009) lebih baik dari Siprofloksasin 2 x 500 mg 5 hari. Terapi Fosfomisin Trometamol dosis tunggal memberikan kesembuhan secara bakteriologis (100%) lebih baik dari Siprofloksasin 2 x 500 mg 5 hari (p = 0.035). Fosfomisin Trometamol dosis tunggal mempunyai Indeks Farmakokinetika (Cmax/MIC) lebih tinggi dari Siprofloksasin 2 x 500 mg (p = 0.035).* ***Simpulan:*** *Terapi Fosfomisin Trometamol dosis tunggal lebih unggul dibandingkan Siprofloksasin 2 x 500 mg 5 hari pada pengobatan ISK tanpa komplikasi.*

Kata kunci: *Efek terapi, Fosfomisin Trometamol, Siprofloksasin, ISK, Escherichia coli.*

Correspondence: Budiono, Heri; c/o: Department of Urology, Faculty of Medicine/Airlangga University, Soetomo General Hospital Surabaya. Jl. Mayjen. Prof. Dr. Moestopo 6-8 Surabaya 60286. Office: 031-5501318, Fax: 031-5024971. Mobile phone: 081 331258499. Email: heri.bud@yahoo.co.id.

INTRODUCTION

Urinary tract infection (UTI) is an inflammatory response of the urothelium to bacterial invasion marked with laboratory findings of pyuria and significant bacteriuria.[1,2] The clinical manifestations of UTI are irritating symptoms such as dysuria and frequency, which is accompanied by pyuria.[2-4] As the gold standard examination of UTI is urine culture with significant values obtained when the bacteria colonies > 105 CFU/ml.[2,4]

UTI is estimated to cause more than 7 million cases of UTI world wide.[1,5] Incidence of UTI in women is higher than men, approximately 20-30% of adult women had experience done or more UTIs, most between the ages of 20-40 years.[1,6] Based on data from 10 main diseases in Urology Outpatient Clinic Soetomo General Hospital Surabaya in 2012, UTI ranks 4th with 814 patient visits (5.46%).[7] Escherichia coli (E. coli) is a common bacteria that cause UTI. Another cause of UTI are bacteria Proteus sp, Klebsiella pneumoniae, Enterobacter faecalis, and Staphylococcus saprophyticus.[3,8]

Management of uncomplicated UTI is a short-termoral antibiotics for 3 to 5 days.[7] One of the antibiotics that is often used is Ciprofloxacin, the derivative of the quinolone carboxylic acid, which has antibacterial activity of gram positive and gram negative. Factors lead to wide availability of a cheap ciprofloxacin greatly increases its use, resulting in irrational usage and resistance to ciprofloxacin.[9]

In 1997, Fosfomycin trometamol is found, can be administered orally as single dose. This medication is an option because when given in a 3 g single dose, invitro activity for betalactam resistant gram-negative is high and minimal prevalence of resistance. It has been suggested as a first-line agent in the European Association of Urology guidelines.[10,11] Fosfomycin not only kill cells but also has the ability to disrupt biofilms of E. Coli. This may contribute to accelerated healing time.[12] Side effects that may occur in the use of this drug is diarrhea 10.4%, headache 10.3%, and nausea 5.2%.[13]

Dosage and interval of antibiotics should be based on pharmacokinetic and pharmacodynamic parameters. There is a fundamental relationship between the pharmacokinetics with a pharmacological response. Ratio of pharmacokinetic/pharmacodynamic measures is very beneficial for the potential efficacy of a antibiotic.[14]

Therapeutic response in uncomplicated UTI correlates well with concentration of drug in the urine and minimal inhibitory concentration. Peaktiter of bacteriostatic activity is measured as pharmacological index of Cmax/MIC (Cmax = Maximum Concentration of drug in the urine, MIC = Minimum Inhibitory Concentration). Mathew E. Levinson said for Concentration Dependent Antibiotic required index Cmax/MIC more than [10,15]

OBJECTIVE

To compare clinical therapeutic effects (frequency, dysuria, and pyuria), microbiology, Cmax/MIC of Fosfomycin trometamol 3 g single dose with Ciprofloxacin 2 x 500 mg for 5 days in the treatment of uncomplicated UTI in women due to Escherichia coli (E. coli).

MATERIAL & METHOD

This is an experimental analytic observational study from February until July 2013. Twenty-two female patients with uncomplicated UTI who fulfilled the inclusion criteria, were randomly allocated into 2 treatment groups, receiving Ciprofloxacin 2 x 500 mg for 5 days and a single dose of Fosfomycin trometamol. Patients with culture results other than E. coli is excluded.

Follow upon day 7 of therapy include clinical outcomes (dysuria, frequency, and pyuria), and microbiology results (urine culture). Maximum concentration of the drug in urine is measured by High Performance Liquid Chromatography (HPLC). Bacterial culture results in MIC (Minimum Inhibitory Concentration). Pharmacokinetics specified index Cmax/MIC was determined. Results were analyzed using Chi-Square test, Paired T-test, and Independent T-test.

RESULTS

Twenty two samples fulfilled the inclusion criteria, all patients had normal hemoglobin levels, normal blood leukocytes, normal serum creatinine, and the results of radiological examination with normal urinary tract anatomy. Distribution of most patients in group Ciprofloxacin at 21-30, 41-50, and 51-60 years, were respectively 27.3%, with range between 22-61 years, and Fosfomycin trometamol group at age 41-50 years of 45.5% with range between 38-62 years. There was no statistical difference in age between the 2 treatment groups (p = 0.46). Data normality test was performed with Kolmogorov-Smirnov One Sample test.

From 11 patients enrolled in Ciprofloxacin group, 4 patients (36.4%) complained of persistent dysuria while 7 patients (63.6%) had no dysuria after day 7 of therapy. While among 11 patients in Fosfomycin group, 2 patients (18.2%) had dysuria and 9 patients (81.2%) no dysuria after day 7 of therapy. With Chi-square test for independent group Ciprofloxacin 2 x 500 mg for 5 days and a single dose Fosfomycin trometamol 3 g performed equally in eliminating complaints of dysuria (p = 0.635).

Table 1. Dysuria in both of therapeutic groups.

	Dysuria		Total
	Persistent	Disappeared	
Ciprofloxacin	4	7	11
Fosfomycin	2	9	11
Total	6	16	22

Among 11 patients whom Ciprofloxacin 2 x 500 mg for 5 days treatment, 6 patients (54.5%) had persistent frequency and 5 patients (45.5%) reported frequency disappeared after day 7 of therapy. Paired T-test obtained with Ciprofloxacin 2 x 500 mg for 5 days did not eliminate complaints of frequency (p = 0.093). Among 11 patients 3 g single-dose Fosfomycin trometamol treatment, 1 patient (9.1%) remained frequency and 10 patients (90.9%) frequencies disappeared after day 7 of therapy. Obtained with Paired T-test 3 g single dose Fosfomycin trometamol eliminate complaints of frequency (p = 0.000).

By Chi-Square test, 3 g single-dose Fosfomycin trometamol eliminated complaints of urinary frequency better than Ciprofloxacin 2 x 500 mg for 5 days (p = 0.022).

Table 2. Complaints of frequency, both of therapeutic group.

	Dysuria		Total
	Remained	Disappeared	
Ciprofloxacin	6	5	11
Fosfomycin	1	10	11
Total	7	15	22

By Independent T-test, comparing the improvement of frequency (delta) both of therapeutic group, 3 g single dose Fosfomycin trometamol improved complaints of frequency better than 2 x 500 mg Ciprofloxacin for 5 days (p = 0.004).

Table 3. Improvement of frequency (delta) both of group therapy.

Delta Frequency	Mean	SD	p
Ciprofloxacin	1.00	1.8	0.004
Fosfomycin	3.55	1.9	

Among 11 patients whom Ciprofloxacin 2 x 500 mg for 5 days treatment, 4 patients (36.4%) remained pyuria and 7 patients (63.6%) pyuria disappeared after day 7 of therapy. With paired T-test Ciprofloxacin 2 x 500 mg for 5 days to eliminate pyuria (p = 0.002).

Table 4. Leucocyturia before treatment and day-7 of therapy (Ciprofloxacin 2 x 500 mg group).

Leucocytes	Mean	SD	p
Pre therapy	15.9	15.6	0.002
Day-7 therapy	8.5	3.5	

Among 11 patients who received 3 g single-dose Fosfomycin trometamol treatment, 1 patient (9.1%) remained pyuria and 10 patients (90.9%) pyuria disappeared after day 7 of therapy. With paired T-test 3 g single dose Fosfomycin trometamol could eliminate pyuria (p = 0.003).

Table 5. Leucocyturia before treatment and day 7 therapy (3 g single dose Fosfomycin trometamol group)

Leucocytes	Mean	SD	p
Before treatment	38.27	31.6	0.003
Day-7 therapy	6.55	5.6	

With T-test for independent group improvement of urine leukocytes (delta) between the 2 therapeutic groups obtained 3 g single dose Fosfomycin trometamol improved pyuria better than 2 x 500 mg Ciprofloxacin for 5 days (p = 0.009).

Among 11 patients whom Ciprofloxacin 2 x 500 mg 5 days treatment, 5 patients (45.5%) had positive urine culture and 6 patients (54.5%) were sterile day 7 of therapy. Among 11 patients allocated 3 g single dose Fosfomycin trometamol treatment all sterile urine culture on day 7 of therapy. With Chi-Square test for independent group obtained 3 g single

dose Fosfomycin trometamol provided better bacteriological cure than Ciprofloxacin 2 x 500 mg for 5 days (p = 0.035).

Table 6. Urine culture day 7 of therapy.

	Urine culture		Total
	Sterile	Positive	
Ciprofloxacin	6	5	11
Fosfomycin	11	0	11
Total	17	5	22

Among 11 patients Ciprofloxacin 2 x 500 mg 5 days treatment, 5 patients (45.5%) had index Cmax/MIC < 10 and 6 patients (54.5%) had index Cmax/MIC > 10. While among 11 patients 3 g single dose Fosfomycin trometamol treatment all have index Cmax/MIC > 10. By Chi-Square test, 3 g single dose Fosfomycin trometamol have better index Cmax/MIC than Ciprofloxacin 2 x 500 mg (p = 0.035).

Table 7. Cmax/MIC index both of therapeutic group.

	Cmax/MIC indcx		Total
	< 10	> 10	
Ciprofloxacin	5	6	11
Fosfomycin	0	11	11
Total	5	17	22

DISCUSSION

This study demonstrated that therapy with 3 g single dose Fosfomycin trometamol had better clinical cure than Ciprofloxacin 2 x 500 mg for 5 days (81.2% dysuria, 90.9% frequency, and 90.9% pyuria). Onsimilar research Nurgul Ceran et al, reported clinical cure in the treatment group 3 g single dose Fosfomycin trometamol was 82.3% and in Ciprofloxacin group 81%.[16] While Omer Bozkurt et al, from the Urology Hospital Ankara Turkey had clinical cure at 3 g single dose Fosfomycin trometamol group is 94%, and 96% in the Ciprofloxacin group.[17]

Actually, the main treatment goal of uncomplicated UTI is bacterial eradication and avoiding recurrence caused by relapse and re-infection. Bacteriuria is expected to be eliminated within 24 hours, whereas the clinical symptoms will still be settled within a few days. Approximately 20% of patients will experience prolonged clinical symptoms.[18] Thus, faster treatment will eradicate bacteria more quickly and eliminate clinical symptoms.

Successful treatment can be monitored clinically with the decline or disappearance of clinical symptoms after treatment.[10] Successful treatment in uncomplicated UTI is determined by the effectiveness of antibiotics used. Fosfomycin has a bactericidal effect is better because it works by inhibiting the early stages of bacterial wall synthesis while Ciprofloxacin works by inhibiting DNA synthesis by inhibiting the enzyme DNA gyrase and to poisomerase IV.

Fosfomycin not only kills bacteria but also have the ability to destruct bacterial biofilms. Fosfomycin also destroy bacteria fimbriae there by disrupting bacterial adhesion. Moreover, Fosfomycin make bacteria susceptible to polymorphonuclear cells. All this led to improved survival time in therapy with Fosfomycin.[10] While Ciprofloxacin was also included in the class of bactericidal antibiotics, but concentration dependent, so its bactericidal activity increases with increasing concentrations. Where as increasing concentrations of Ciprofloxacin in the urine is not as good compared to blood.[12]

By Chi-Square test group proven 3 g single-dose Fosfomycin trometamol therapy get better bacteriological cure compared Ciprofloxacin 2 x 500 mg for 5 days (p = 0.035).

On similar research, Nurgul Ceran et al, get a bacteriological cure in the treatment group 3 g single dose Fosfomycin trometamol is 83.1% and 78.4% in the Ciprofloxacin group.[16] In the Microbiology Clinic Soetomo General Hospital Surabaya, Ciprofloxacin have a sensitivity to the E. coli of 45%.[12] In Sanglah General Hospital Denpasar, sensitivity in E. coli were cultured from urine showed sensitivity to Ciprofloxacin only in 27%.[19] Juniastuti et al, conducted a study of isolates from the middle portion urine or urinary catheter in Soetomo General Hospital and receive sensitivity of E. coli to Ciprofloxacin of 44.6%.[20] While the research conducted by Jesus Oteo et al, on 231 samples of E. coli get Fosfomycin sensitivity was 90.9% and resistance to Fosfomycin was 9.1%.[21]

Side effects may occur with the use of Ciprofloxacin and Fosfomycin trometamol are the same, such as: nausea, dizziness, and diare.[10] In this study only found one patient who experienced drug side effects, in the 3 g single dose Fosfomycin trometamol group. This side effects is mild diarrhea which resolved without treatment after 1 day.

Ratio of pharmacokinetic/pharmacodynamic is very beneficial predictors for the potential efficacy of antibiotics.[14] In UTI case, response to therapy correlates well with the concentration of the drug in urine and minimal inhibitory concentrations were found in the urine. Peak concentration of bacteriostatic activity is measured in Pharmacological Index Cmax/MIC. Barger A et al, stated that the ratio Cmax/MIC more than 8 will get clinical and bacteriological cure.[22] But Levinson ME said for group required antibiotic concentration dependent index Cmax/MIC more than 10.[23]

In this study, the index Cmax/MIC Fosfomycin trometamol 100% more than 10, better than Ciprofloxacin 2 x 500 with a 54.5% above 10 (p = 0.035). This is appropriate because the bacteriological cure single-dose Fosfomycin trometamol group was also better than Ciprofloxacin 2 x 500 mg.

CONCLUSION

Fosfomycin trometamol single dose therapy is superior to Ciprofloxacin 2 x 500 mg 5 days in the treatment of uncomplicated UTI in women.

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