Single-dose Fosfomycin Tromethamine for Treatment of Urinary Tract Infection in Hong Kong Women: a Preliminary Prospective Study

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Objective: To investigate the clinical efficacy and side-effect profile of a single 3-g dose of fosfomycin tromethamine in the treatment of Hong Kong women having uncomplicated urinary tract infections.
Methods: This was a prospective open-labeled uncontrolled study carried out in Gynaecology Outpatient Clinic, Department of Obstetrics and Gynaecology, Queen Elizabeth Hospital, Hong Kong. Adult women with clinical symptoms of urinary tract infections, confirmed by microscopy and culture (colony-forming unit, $>10^5$ /ml) of mid-stream urine specimens, were recruited.
Results: Of 44 subjects studied, 98% returned for follow-up. Forty-eight hours after treatment with fosfomycin, the bacterial eradication rate was 86% (38/44), 91% (20/22), 100% (4/4), and 60% (3/5) for all bacteria, *Escherichia coli* (non-ESBL–producing strains), *Escherichia coli* (ESBL-producing strains), and *Klebsiella*, respectively. However, 19% of the subjects experienced diarrhoea.
Conclusion: Our preliminary study suggests that a single dose of fosfomycin had a high bacterial eradication rate after 48 hours, compared to 1-week course of other antibiotics, but was associated with a high frequency of diarrhoea. Further studies using a larger sample size and longer follow-up are needed.

Introduction

The syndrome of uncomplicated urinary tract infection (UTI) in women is characterised by dysuria, frequency, and / or urgency in combination with pyuria and bacteriuria, in the absence of any known underlying renal or urological dysfunction or obstruction[1]. This definition has been approved by Food and Drug Administration in the United States. In the United Kingdom, the Royal College of Obstetricians and Gynaecologists revealed that almost 50% of women experience at least one UTI during their lifetime. One epidemiological study showed that up to 27% of women experience at least one culture-confirmed recurrence within 6 months of their initial infection[2]. If not treated adequately, UTI may progress to pyelonephritis, and more rarely to rupture of the kidney, septicaemia, and periurethral abscess[3-5].

In Hong Kong, the biological cure rate for a 1-week course of oral norfloxacin and cotrimoxazole to treat UTIs is around 97% and 83%, respectively[6]. The most common organism causing UTI in Hong Kong is *Escherichia coli*[7,8]. However, the emergence of antibiotic-resistant *E. coli* imposes significant limitations on the choice of treatment, particularly when used in outpatients. In one local study,

resistance of *E. coli* to antibiotics was demonstrated to be 61% for ampicillin, 41% for co-trimoxazole, 30% for sultamicillin (Unasyn; Pfizer, USA) and 30% for co-amoxiclav (Augmentin; GlaxoSmithKline, UK)[7]. In the Netherlands, one population survey demonstrated that the isolation rate of urinary ESBL (extended spectrum beta-lactamase) *E. coli* strains had increased from 0.1% to 1% (p<0.001) in 5 years[9].

The usual duration of traditional antibiotic therapy for the treatment of UTI is 7 to 10 days. A local study in 2005 demonstrated a compliance rate of 82% only for short 3-day antibiotic treatment courses[8]. It was therefore hypothesised that single-dose treatment might inevitably improve patient compliance for UTI treatment and reduce the emergence of antibiotic resistance.

Fosfomycin is an old drug, which was first discovered in Spain in 1969. Fosfomycin tromethamine is a highly water-soluble salt, which achieves reliably high bioavailability after oral administration[10-13]. It acts by inhibiting pyruvyl

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transferase, a cytoplasmic enzyme that catalyses the first step in the biosynthesis of peptidoglycans[14], and has a broad spectrum of activity against the most common Gram-positive and Gram-negative bacterial pathogens responsible for UTIs. Moreover, it has good distribution into tissues, achieving clinically relevant concentrations in serum, kidneys, the bladder wall, and other organs. For treatment of uncomplicated UTI, fosfomycin can be given as a single dose and thus avoids compliance problems.

Studies in the United States and Europe showed a better biological cure rate for 3-g single fosfomcin doses than after co-amoxiclav (85 vs 72%[15]), norfloxacin (94 vs 87%[16]), and nitrofurantoin (83 vs 76%[17]). Single-dose fosfomycin was associated with a high patient satisfaction rate and low frequency of side-effects (diarrhoea and nausea, 2% each) in a Caucasian population[15]. In German guidelines, it is recommended as first-line treatment for acute uncomplicated cystitis[16].

Since the spectrum of common causative organisms and their antibiotics resistance profiles are different depending on geographical area, the same effectiveness for fosfomycin cannot be assumed in the local population[7,17], especially as local data on its effectivenesss were lacking. Besides, fosfomycin is not available in Hong Kong public hospital settings. Therefore, the aim of this study was to determine the efficacy and side-effects of single-dose treatment for uncomplicated UTIs in Hong Kong women.

Methods

The study was designed as an open-label, uncontrolled study to investigate the clinical efficacy and side-effect profile of a single 3-g dose of fosfomycin tromethamine for the treatment of uncomplicated UTI in Hong Kong women.

The diagnosis of UTI was made based on clinical symptoms (urgency, dysuria, frequency) and the mid-stream urine sample yielding a significant bacterial count on culture (colony-forming unit, $>10^5$ /ml) and presence of white blood cells on microscopy. The sample size was estimated to be 44 (equivalence was defined as not more than 10% inferior to the biological cure rate by conventional antibiotics, assuming 85%[15], one-sided alpha=0.05, power=80%).

This study was approved by Research Ethics Committee (Queen Elizabeth Hospital) under Hospital Authority. All patients gave written informed consent, and all procedures were conducted in accordance with the Helsinki Declaration.

Women with confirmed UTI were recruited from the general Gynaecology outpatient clinic, Department of Obstetrics and Gynaecology of the Queen Elizabeth Hospital in the period between 1 January 2009 and 30 October 2009. Subjects were excluded if they had a history of urinary tract abnormality (including urinary tract stones or recurrent UTI history). Subjects were also excluded if they were pregnant, had a history of sensitivity to fosfomycin, or received antibiotic treatment by another medical practitioner within the last 4 weeks.

On the first visit, subjects were required to fill in a questionnaire providing information including demographic data, medical history, and concomitant medications (all treatments taken within the last month). Clinical symptoms including dysuria, urgency, and frequency were recorded in the questionnaire. After collecting the information, 1 sachet of fosfomycin (3 g) was dissolved in 150 ml water and drunk in front of the investigator, thus ensuring compliance.

The second (follow-up) visit was arranged 2 to 3 days after the first visit, and a second sample of clean mid-stream urine sample was collected for post-treatment urine microscopy and culture. The subject was also required to complete the second questionnaire to assess the symptoms of UTI. Besides, possible side-effects (diarrhoea, nausea, vomiting) were also recorded.

Successful urinary tract bacterial clearance could be mistakenly inferred due to very high antibiotic concentrations prevailing in the urine, as this might ensue 2 to 4 hours after taking fosfomycin (when plasma concentrations reached the peak)[13]. However, since the half-life of this antimicrobial's elimination is about 5.7 hours[13], at the second follow-up (48 hours after the first single dose) its plasma and urinary would be minimal and not likely to yield artifactual evidence of a cure.

Results

Demographics

In the period of 1 January 2009 to 30 October 2009, 44 subjects were recruited; one of whom defaulted the second visit. Thus, overall 98% of the subjects completed the study process. Their mean age was 48 years (standard deviation [SD], 13; range, 18-75 years). Among this group of subjects, 30 (68%) were pre-menopausal and 14 (32%) were post-menopausal; the defaulter was pre-menopausal.

Bacterial Characteristics in Mid-stream Urine Sample

Urine culture and sensitivity results of the first specimen yielded 48 strains of bacteria (some contained more than one bacterial strain). The most common pathogen was *E. coli* (including ESBL strains) which were identified in 26 (54%) of the specimens, followed by *Klebsiella* and group B *Streptococcus* (GBS) which were identified in five (10%) specimens. Other species included *Staphylococcus*, other coliform organisms, *Pseudomonas aeruginosa*, Enterococci and alpha haemolytic streptococcus (Table 1). The mean age of subjects infected with each bacterial stain was calculated, but the difference in mean ages did not reach statistical significance (p=0.8) using one-way analysis of variance.

Antibiotic susceptibility / resistance was determined by the microbiological laboratory according to the commonly used local antibiotics at Queen Elizabeth Hospital (Table 2).

Of the four ESBL strains of *E. coli* encountered, three (75%) were resistant to all oral antibiotics and only susceptible to intravenous agents like sulperazone, imipenem, and amikacin.

Treatment Efficacy

In this sample, 27 subjects presented with dysuria, giving a clinical improvement rate for dysuria of 86% after singe dose of fosfomycin. The two failed cases with persistent infection (patients 2 and 6; Table 3) could be regarded as biological and clinical treatment failures. In the remaining 25 cases, culture and microscopy of their post-treatment urine samples were all negative.

After further stratification, respective cure rates for *E. coli*, ESBL *E. coli*, and *Klebsiella* were 91%, 100%, and 60% (Table 4), there being no statistically significant difference in these cure rates (p=0.83).

Nevertheless, all three ESBL *E. coli* strains that were resistant to all oral antibiotics demonstrated biological and clinical course after single 3-g doses of fosfomycin.

After fosfomycin treatment, six subjects continued to have positive bacterial cultures and one subject had defaulted, which yielded a cure rate of 86%. Regarding these six subjects, four showed significant bacterial count ($>10^5$), in two the counts were insignificant (Table 3). The corrected success rate for bacterial eradication was 90%; persistence of the same bacterial strain was noted in three patients (patients 2, 4, and 6) indicating unsuccessful bacterial eradication. In patient 1, a different bacterial species was grown.

Side-effect Profile

The most common side-effect was diarrhoea, which occurred in eight (18%) of the subjects. Their mean age was 45 (SD, 11) years, which was similar to that in the overall sample. Other gastro-intestinal side-effects (nausea and vomiting) did not ensue, but two patients mentioned non-specific skin itchiness without a rash, but were not diagnosed to have allergy to fosfomycin. Side-effect profiles are shown in Table 5.

Discussion

Consistent with other Hong Kong reports[7], the present study demonstrated that *E. coli* is still the commonest causative organism for UTIs in women, followed by *Klebsiella*. In contrast to previous local studies[7,18], GBS was the third common causative organism.

Table 1. Stratified distribution of different bacterial species in subjects with uncomplicated urinary tract infection

Bacteria (n = 45)	No. of strains (%)	Median age (years)	Mean (standard deviation) age (years)
Escherichia coli	22 (46)	46	47 (15)
Escherichia coli (ESBL)	4 (8)	50	53 (53)
Group B *Streptococcus*	5 (10)	47	47 (3)
Klebsiella	5 (10)	49	49 (9)
Staphylococcus aureus	4 (8)	43	39 (20)
Alpha haemolytic streptococcus	3 (6)	45	62 (0)
Enterococci	3 (6)	44	57 (0)
Coliform organism	1 (2)	62	44 (12)
Pseudomonas aeruginosa	1 (2)	57	43 (12)

Table 2. Antibiotic resistance in *Escherichia coli, E. coli* (ESBL strain) and non–*E. coli* organisms

	No. (%)		
	E. coli (n = 22)	*E. coli* (ESBL strain) (n = 4)	Non–*E. coli* organisms (n = 19)
Ampicillin	18 (82)	4 (100)	7 (37) (5 *Klebsiella*, 1 Coliform, 1 *Proteus*)
Cotrimoxazole	9 (41)	1 (25)	2 (11) (1 *Proteus*, 1 *Klebsiella*)
Cefuroxime	1 (5)	4 (100)	0 (0)
Cefotaxime	0 (0)	3 (75)	0 (0)
Ceftazidime	1 (5)	2 (50)	0 (0)
Ciprofloxacin	3 (14)	1 (25)	2 (11) (1 Coliform, 1 *Klebsiella*)
Levofloxacin	2 (9)	0 (0)	0 (0)
Augmentin	4 (18)	1 (25)	1 (5) (*Klebsiella*)
Amikacin	0 (0)	0 (0)	Not done
Nitrofurantoin	Not done	Not done	0
Erythromycin	Not done	Not done	5 (26) (4 GBS[*], 1 *Enterococcus*)
Clindamycin	Not done	Not done	3 (16) (All GBS)
Gentamicin	8 (36)	1 (25)	2 (11) (1 Coliform, 1 *Klebsiella*)

Abbreviation: GBS = group B *Streptococcus*

Table 3. Stratified bacterial species on pre- and post-treatment mid-stream urine sample in failed treatment subjects[*]

Case No.	Pre-treatment		Post-treatment	
	Bacteria	Count (CFU/ml)	Bacteria	Count (CFU/ml)
1	*E. coli*	10^5	*Enterococcus species*	10^5
2	*E. coli*	10^5	*E. coli*	10^5
3	Alpha haemolytic streptococcus	10^5	*Acinetobacter* species	$<10^5$
4	*Klebsiella*	10^5	*Klebsiella*	10^5
5	*E. coli*	10^5	*Streptococcus aureus*	$<10^5$
6	*Klebsiella*, Coliform bacteria	10^5	*Klebsiella*	10^5

Abbreviations: CFU = colony-forming unit; *E. coli* = *Escherichia coli*

Table 4. Success rate of fosfomycin in eradicating *Escherichia coli* and *Klebsiella* (p=0.83)

Organism	No. of successful cases	Success rate
E. coli	20/22	91%
E. coli (ESBL)	4/4	100%
Klebsiella	2/5	60%

Table 5. Side-effect profiles of subjects after taking fosfomycin

Side-effects	No. (%)
Diarrhoea	8 (18%)
Nausea	0
Vomiting	0
Others (skin itchiness)	2 (5%)
Total	**10**

This finding is not surprising, as over the years the prevalence of GBS colonisation in the vagina has increased in Hong Kong women, albeit in a pregnancy[19,20]. Further investigations are required to assess the trend of GBS in causing uncomplicated UTIs.

This study demonstrated a bacterial eradication rate 48 to 72 hours after a single fosfomycin dose was 86%. In a study carried out by de Jong et al[18], they assessed their subjects on day 3 post-fosfomycin and reported a cure rate of 94% (31/33 cases). Similar cure rates were reported in other studies (84%, 85%, 93%) entailing longer periods (3-10 days)[21].

In the present study, there were four subjects with ESBL strains of *E. coli* grown from their urine samples. All enjoyed clinical and biological cures after one dose of fosfomycin, which is consistent with previous reports of high cure rates for ESBL-producing *E. coli* strains after fosfomycin treatment[22,23]. On the other hand, there was a 40% (2/5) failure rate for *Klebsiella*-infected patients in our series (Table 4). Possibly, this indicates a high fosfomycin resistance rate against *Klebsiella* among our patients, for which reason this antimicrobial may not be suitable for patients infected with this organism in our locality. However, such a high failure rate was not consistent with reports from Taiwan regarding the susceptability of *Klebsiella* pnemoniae to fosfomycin[24]. Further studies are required to better evaluate the effectiveness of fosfomycin treatment against *Klebsiella* UTIs.

A much higher rate of diarrhoea (19%) was found after fosfomycin treatment in the present study than the 2.4% reported in another study[25]. This could be due to intolerance to fosfomycin in our local population. Further studies using a larger sample size are required. Meanwhile fosfomycin treatment should be avoided in patients known to have had gastrointestinal side-effects following treatment with this drug.

High cost of this antibiotic is another important issue. A 1-week course of a traditional antibiotic like ampicillin or cotrimoxazole is about HK$6-7, and courses of nitrofurantoin are even cheaper (HK$2-3); one sachet of 3-g fosfomycin costs HK$35, which is similar to the cost of 500-mg cefuroxime axetil twice daily for 1 week used to treat UTIs.

If a patient has an uncomplicated UTI, the choice of antibiotics depends on several factors. They include: (a) individual risk and antibiotic pretreatment, (b) bacterial spectrum and antibiotic susceptibility, (c) demonstrated clinical efficacy of the antimicrobial, (d) epidemiological effects ('collateral damage'), and (e) adverse effects profile[16]. We recommend using conventional antibiotics (nitrofurantoin, cotrimoxazole, levofloxacin) based on susceptibility information. When patient's compliance is an issue, using a single-regimen fosfomycin is an alternative, because it achieves a high bacteria eradication rate. If no oral antibiotics is suitable based on the microbiological finding of drug resistance or patient allergic history, we suggest consideration of fosfomycin as it can avoid hospitalisation for a course of antibiotic treatment, but not if *Klebsiella* is the pathogen or in subjects with a bowel problem.

The small sample size of the present preliminary study was a limitation. Another limitation was the failure to perform fosfomycin sensitivity testing on the urinary pathogens. According to previous studies, the susceptibility of *E. coli* was high (94-99%)[17,26], though frequent use may accelerate widespread resistance[27]. Another drawback was the wide range of ages in our study patients. More importantly, we did not follow medium-term (7-10 days) and long-term (6 months) follow-ups. A study with a larger sample size, age stratification, and a longer follow-up may is needed. This study did not include pregnant women, though animal studies show that fosfomycin crosses the placenta, and clinical trials support its efficacy and safety for the treatment of bacteriuria in pregnancy[28,29].

Conclusion

Our preliminary study suggests that a single dose of fosfomycin induces a high bacterial eradication rate within 48 hours, compared to other antimicrobials taken for 1 week, but it is associated with a high frequency of diarrhoea.

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