Original Article

Microbiological Activity in Serum and Urine of Healthy Subjects Against Extended-Spectrum Beta-Lactamase (ESBL)-Producing *Escherichia coli* Compared between Original Brand and Generic Oral Fosfomycin Trometamol

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Objective: To determine the microbiological activity in serum and urine of healthy subjects against extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli* compared between original brand and generic oral fosfomycin trometamol.

Materials and Methods: This randomized crossover study was conducted at Siriraj Hospital. Fourteen healthy subjects with a mean age of 34.14 years received a single 3-gram dose of either original brand fosfomycin trometamol (Monurol®) or generic oral fosfomycin trometamol (Fosfomet®). After a 1-week washout, both groups were switched to the other medication and the process was repeated. Blood samples and urine samples were collected from each subject at baseline before drug administration, and then at 1, 2, 5, and 8 hours after taking the study drug. Another urine sample was collected on day 2 of the study. Inhibitory activity against ESBL-producing *E. coli* was evaluated by disk diffusion method, and bactericidal activity was evaluated by broth microdilution method.

Results: Inhibitory activity and bactericidal activity in serum and urine samples against ESBL-producing *E. coli* was highest between 2 and 5 hours after administration of the study drugs. Inhibitory and bactericidal activity in serum samples were both less and shorter than those observed in urine samples. Urine samples continued to demonstrate high inhibitory and bactericidal activity at 24 hours after drug administration. There were no significant differences in inhibitory or bactericidal activities in serum or urine samples when compared between administration of original brand fosfomycin trometamol (Monurol®) and administration of generic oral fosfomycin trometamol (Fosfomet®). Mild diarrhea was the only adverse event observed, and there was no significant difference in this side effect between groups.

Conclusion: Inhibitory activity, bactericidal activity, and rate of adverse events were all found to be comparable between original brand fosfomycin trometamol (Monurol®) and generic oral fosfomycin trometamol (Fosfomet®).

Keywords: Microbiological activity, Fosfomycin trometamol, Extended-spectrum beta-lactamase (ESBL)-producing *Escherichia coli*

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Escherichia coli is accounted for 80% of all causative bacterial species that cause uncomplicated lower urinary tract infection[1]. The prevalence of extended-spectrum beta-lactamase (ESBL)-producing *E. coli* colonization and infection has been increasing in both community-acquired and hospital-acquired settings in Thailand and worldwide[2-4]. ESBL-producing *E. coli* is usually resistant to cephalosporins and fluoroquinolones. Therefore, the antibiotics with activity against ESBL-producing *E. coli* are important for treatment of urinary tract infections. An oral antibiotic that is active against ESBL-producing *E. coli* is

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needed for therapy of urinary tract infections of mild to moderate severity in ambulatory patients.

Fosfomycin is a synthetic phosphonic acid derivative that inhibits cell wall synthesis at the initial step involving phosphoenolpyruvate synthetase[5]. Fosfomycin demonstrated good in vitro activity and effectiveness in clinical studies against common Gram-negative and Gram-positive uropathogens, including ESBL-producing isolates[6]. Fosfomycin trometamol, which is a stable salt of fosfomycin, is well absorbed after oral administration, and is excreted in unchanged form at a high concentration in urine[7]. Current guidelines from the Infectious Diseases Society of America (IDSA) and the European Society for Clinical Microbiology and Infectious Diseases (ESCMID) recommend oral fosfomycin trometamol as one of the first-line agents for treatment of acute uncomplicated lower urinary tract infection[8]. Many clinical trials reported comparable efficacy between fosfomycin trometamol and other first-line antibiotics for treatment of acute uncomplicated lower urinary tract infection[9,10]. Moreover, fosfomycin trometamol was reported to have achieved acceptable concentrations in prostate gland, which supports its use in patients with prostatitis[11]. Most adverse effects described for fosfomycin trometamol are usually mild and transient, including mild gastrointestinal disturbances[12].

The bioavailability of oral fosfomycin trometamol in adults is approximately 34% to 41%, and 54% to 65% of absorbed fosfomycin trometamol is detected in urine[13]. Following a single oral 5.61-gram dose of fosfomycin trometamol (equivalent to 3 grams of fosfomycin), pharmacokinetic studies showed that peak serum concentration (C_{max}) occurred in 4 hours with a mean elimination half-life of 5.7 hours in subjects with normal renal function[13]. Peak urinary concentrations reached approximately 4,000 ug/mL in 2 to 4 hours, and urinary half-life was 12.4 hours[14]. Fosfomycin trometamol demonstrated concentration-dependent killing and inhibition activity that was directly proportional to fosfomycin concentration[15]. The Clinical and Laboratory Standards Institute (CLSI) susceptibility breakpoints for fosfomycin trometamol currently only exist for urinary isolates of *E. coli* and *Enterococcus faecalis*, with minimum inhibitory concentration (MIC) breakpoint of 64 mg/L or less or inhibition zone diameter breakpoint of 16 mm or less considered as being susceptible[16].

In Thailand, original brand fosfomycin trometamol (Monurol®) is available as a 3-gram of fosfomycin sachet. The cost of original brand fosfomycin trometamol remains high. Recently, generic fosfomycin trometamol (Fosfomet®) has been approved by the Thailand Food and Drug Administration (FDA). However, this generic product is exempted from having its bioavailability study in comparison with the original brand product by the Thailand FDA since the formulation of oral fosfomycin trometamol is in powder form that is dissolved in water prior to oral administration. Therefore, an assessment of the activity of generic fosfomycin trometamol (Fosfomet®) against the targeted bacteria causing lower urinary tract infection including ESBL-producing *E. coli* should be performed. The aim of the present study was to determine the microbiological activity in serum and urine of healthy subjects against ESBL-producing *E. coli* compared between original brand and generic oral fosfomycin trometamol.

Materials and Methods

This randomized crossover study was approved by the Institutional Review Board of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand. All subjects provided written informed consent to participate in the present study. The study was conducted at the Clinical Trial Unit of the Faculty of Medicine Siriraj Hospital between November 2018 and January 2019.

Subjects and fosfomycin trometamol administration

Fourteen healthy subjects were enrolled in whom seven were males and seven were females. The mean age of subjects was 34.14 years (range 19 to 39). Seven subjects were randomly allocated to receive a single 3-gram dose of original brand fosfomycin trometamol (Monurol®), and the other seven subjects to receive a single 3-gram dose of generic oral fosfomycin trometamol (Fosfomet®) dissolved in 120 mL of water after breakfast. After a one-week wash-out period, the subjects who received original brand fosfomycin trometamol (Monurol®) were switched to generic fosfomycin trometamol (Fosfomet®), and the subjects who received generic fosfomycin trometamol (Fosfomet®) were switched to original brand fosfomycin trometamol (Monurol®).

Blood and urine sample collection

Blood sample (3 mL) and urine sample (5 mL) were collected from each subject at fasting state in the morning of the first study day. Blood sample (3 mL) and urine sample (5 mL) were collected from each subject at 1, 2, 5, and 8 hours after administration of the study medication. Another urine sample (5 mL)

was collected from each subject at 24 hours after the subject received the study drugs. The serum samples were separated from the collected blood samples. The serum samples and urine samples were stored at –70°C until the microbiological activity in the serum and urine samples was tested.

It was postulated that the mean inhibition zone diameter in disk immersed urine sample collected from the subject who received original brand fosfomycin trometamol (Monurol®) at 2 hours after the administration was 25 mm with the standard deviation of 2 mm. If the mean inhibition zone diameter in disk immersed urine sample collected from the subject who received fosfomycin trometamol (Fosfomet®) at 2 hours after the administration should not be less than 22 mm with type I error (one-sided) of 5%, at least seven subjects were needed.

Bacteria

The study bacterium was a urinary isolate of fosfomycin-susceptible ESBL-producing *E. coli*. Fosfomycin susceptibility was tested by disk diffusion method according to CLSI standard. Fosfomycin disk content is 200 µg with glucose-6-phosphate 50 µg per disk (Oxoid, UK). The inhibition zone diameter of study *E. coli* and *E. coli* ATCC 25922 was 34 mm and 30 mm, respectively. The quality control for the range of inhibition zone diameter of *E. coli* ATCC 25922 for fosfomycin disk is 22 to 30 mm[16].

Inhibitory activity in serum and urine samples by disk diffusion method

The study bacteria were prepared at the amount of 0.5 McFarland standard. The prepared bacteria were inoculated onto the surface of a Mueller-Hinton agar plate. Sterile blank disks were then placed on each agar plate, and 20 µL of the collected urine and serum samples was dropped on each blank disk. The inoculated agar plate with urine and serum sample-immersed disks was then incubated at 35°C for 16 to 18 hours, after which the inhibition zone around each immersed disk was measured.

Determination of bactericidal activity in serum and urine samples by broth microdilution method

Collected serum and the first urine samples were diluted in microdilution wells that contained cation-adjusted Mueller-Hinton broth (CA-MHB) to achieve the following dilution ratios: undiluted, 1:2, 1:4, 1:8, 1:16, 1:32, 1:64, 1:128, 1:256, and 1:512. The other urine samples, in addition to the first sample, were diluted to achieve dilution ratios of 1:5, 1:10, 1:20, 1:40, 1:80, 1:160, 1:320, 1:640, 1:1,280, and 1:2,560. Each sample was performed in duplicate. An equal volume of 50 µL of CA-MHB containing 10^6 CFU/mL of the study bacteria was inoculated into each microdilution well to achieve dilutions of 1:2, 1:4, 1:8, 1:16, 1:32, 1:64, 1:128, 1:256, 1:512, and 1:1,024 or 1:10, 1:20, 1:40, 1:80, 1:160, 1:320, 1:640, 1:1,280, 1:2,560, and 1:5,120. The microdilution plate was incubated at 35°C for 16 to 20 hours. All microdilution wells were then inspected for visible growth, and 20 µL of the content in each clear well was taken for subculture on brain heart infusion agar. Bactericidal activity was defined as the lowest titer of the content in the well that killed more than or equal to 99.95% of the inoculated bacteria.

Data analysis

Data relating to microbiological activity in serum and urine samples against ESBL-producing *E. coli* are described as median and range. Comparisons of those microbiological activity results between original brand fosfomycin trometamol (Monurol®) and generic oral fosfomycin trometamol (Fosfomet®) were performed using Wilcoxon signed ranks test. A p-value less than or equal to 0.05 was considered statistically significant.

Results

Inhibitory activity in serum and urine samples

The inhibitory activity in serum and urine samples collected from subjects before and after receiving a single dose (3 grams) of original brand fosfomycin trometamol (Monurol®) and a single dose of (3 grams) generic oral fosfomycin trometamol (Fosfomet®) against ESBL-producing *E. coli* as determined by disk diffusion method is shown in Table 1, Table 2, Figure 1, and Figure 2. No inhibition zone was detected in any of the disks immersed with serum or urine samples that were taken from subjects prior to administration of the study drugs. The inhibition zone in disks immersed with serum or urine samples was detected at 1 hour, and it was highest between 2 and 5 hours after administration of the study drugs. The inhibition zones of serum samples were less and shorter than those of urine samples. The urine samples collected at 24 hours after taking the study drugs still contained high inhibitory activity against ESBL-producing *E. coli*. There were no significant differences in the inhibition zone diameters of the serum and urine samples collected from subjects between after receiving a single dose (3 grams) of original brand fosfomycin trometamol (Monurol®) and after receiving generic

Table 1. Inhibition zone diameters in serum samples compared between original brand fosfomycin trometamol (Monurol®) and generic fosfomycin trometamol (Fosfomet®)

Time after study drug administration (hours)	Inhibition zone diameter (mm), Median (range)		p-value
	Monurol®	Fosfomet®	
0	6 (6 to 6)	6 (6 to 6)	1.00
1	6 (6 to 10)	6 (6 to 7)	0.41
2	8.5 (6 to 12)	9 (6 to 11)	0.61
5	8 (6 to 11)	8 (6 to 10)	0.66
8	6 (6 to 8)	6 (6 to 8)	0.79

A p<0.05 indicates statistical significance

Table 2. Inhibition zone diameters in urine samples compared between original brand fosfomycin trometamol (Monurol®) and generic fosfomycin trometamol (Fosfomet®)

Time after study drug administration (hours)	Inhibition zone diameter (mm), Median (range)		p-value
	Monurol®	Fosfomet®	
0	6 (6 to 6)	6 (6 to 6)	1.00
1	18 (10 to 27)	18 (12 to 27)	0.93
2	24.5 (20 to 33)	25 (19 to 33)	0.89
5	26 (22 to 32)	28 (18 to 32)	0.72
8	25 (16 to 30)	24.5 (18 to 31)	0.69
24	20 (8 to 27)	20 (8 to 28)	0.36

A p<0.05 indicates statistical significance

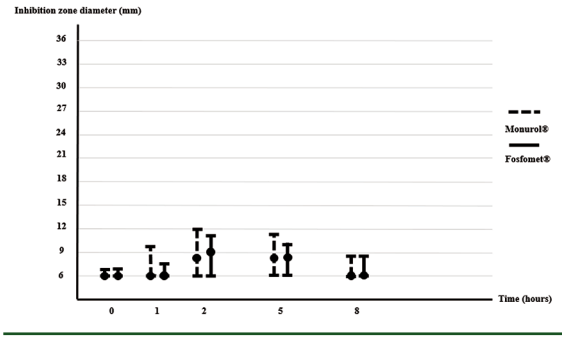

Figure 1. Inhibition zone diameters in serum samples compared between original brand fosfomycin trometamol (Monurol®) and generic fosfomycin trometamol (Fosfomet®).

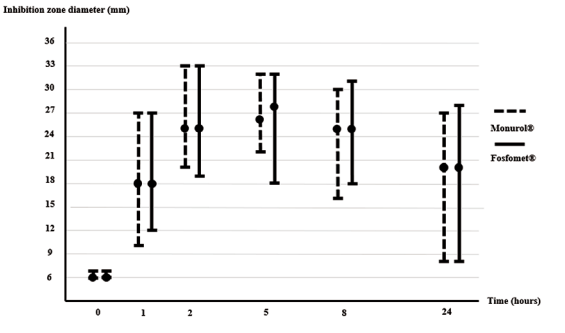

Figure 2. Inhibition zone diameters in urine samples compared between original brand fosfomycin trometamol (Monurol®) and generic fosfomycin trometamol (Fosfomet®).

oral fosfomycin trometamol (Fosfomet®) against ESBL-producing *E. coli* at all sample collection time points.

Bactericidal activity in serum and urine samples

The bactericidal activity in serum and urine samples collected from subjects before and after receiving a single dose (3 grams) of original brand fosfomycin trometamol (Monurol®) and a single dose (3 grams) of generic oral fosfomycin trometamol (Fosfomet®) against ESBL-producing *E. coli* as determined by broth microdilution method is shown in Table 3, Table 4, Figure 3, and Figure 4. No bactericidal activity or very low bactericidal activity was detected in all of the serum and urine samples that were taken from subjects prior to administration of the

Table 3. Bactericidal titers in serum samples compared between original brand fosfomycin trometamol (Monurol®) and generic fosfomycin trometamol (Fosfomet®)

Time after study drug administration (hours)	Bactericidal titer, Median (range)		p-value
	Monurol®	Fosfomet®	
0	<1:2 (<1:2 to 1:4)	<1:2 (<1:2 to 1:4)	0.41
1	1:4 (<1:2 to 1:8)	1:2 (<1:2 to 1:8)	0.26
2	1:8 (1:2 to 1:16)	1:8 (<1:2 to 1:16)	0.21
5	1:6 (1:2 to 1:16)	1:4 (1:4 to 1:16)	0.92
8	1:4 (<1:2 to 1:8)	1:4 (1:2 to 1:8)	0.58

A p<0.05 indicates statistical significance

Table 4. Bactericidal titers in urine samples compared between original brand fosfomycin trometamol (Monurol®) and generic fosfomycin trometamol (Fosfomet®)

Time after study drug administration (hours)	Bactericidal titer, Median (range)		p-value
	Monurol®	Fosfomet®	
0	<1:2 (<1:2 to <1:2)	<1:2 (<1:2 to <1:2)	1.00
1	1:40 (1:20 to 1:320)	1:80 (1:20 to 1:320)	0.57
2	1:480 (1:80 to 1:1280)	1:320 (1:80 to 1:1280)	0.47
5	1:640 (1:160 to 1:1280)	1:640 (1:80 to 1:2560)	0.87
8	1:320 (1:40 to 1:1280)	1:240 (1:80 to 1:1280)	0.59
24	1:80 (1:10 to 1:320)	1:120 (1:10 to 1:320)	0.47

A p<0.05 indicates statistical significance

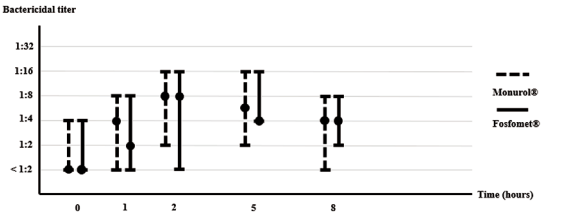

Figure 3. Bactericidal titers in serum samples compared between original brand fosfomycin trometamol (Monurol®) and generic fosfomycin trometamol (Fosfomet®).

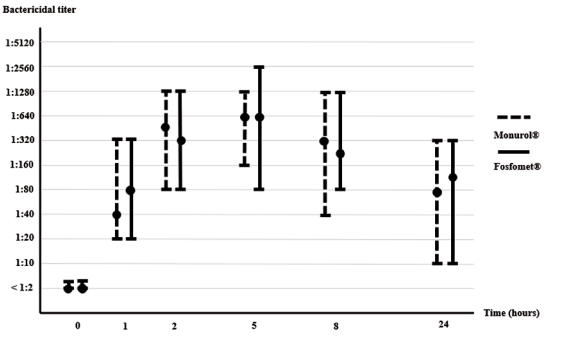

Figure 4. Bactericidal titers in urine samples compared between original brand fosfomycin trometamol (Monurol®) and generic fosfomycin trometamol (Fosfomet®).

study drugs. Bactericidal activity in serum and urine samples was detected at 1 hour, and it was highest between 2 and 5 hours after administration of the study drugs. The bactericidal activity in serum samples was less and shorter than those of the urine samples. Urine samples collected at 24 hours after administration of the study drugs continued to demonstrate high bactericidal activity against ESBL-producing *E. coli*. There were no significant differences in the bactericidal activity in serum and urine samples collected from subjects between after receiving a single dose (3 grams) of original brand fosfomycin trometamol (Monurol®) and after receiving generic oral fosfomycin trometamol (Fosfomet®) against ESBL-producing *E. coli* at all sample collection time points.

Adverse events

Six subjects who received original brand

fosfomycin trometamol (Monurol®) had mild diarrhea, and five subjects who received generic fosfomycin trometamol (Fosfomet®) had mild diarrhea.

Discussion

The procedures that were used in the present study to determine the microbiological equivalence of generic fosfomycin trometamol with that of original brand fosfomycin trometamol should be regarded as valid and reliable. A randomized crossover design was employed to eliminate any biological differences among subjects since all included subjects received both generic fosfomycin trometamol (Fosfomet®) and original brand fosfomycin trometamol (Monurol®). ESBL-producing *E. coli* was used as the test bacteria in the present study since the rational for using fosfomycin trometamol is to cover the common antibiotic-resistant bacteria that cause lower urinary tract infection. Disk diffusion and broth microdilution are the standard methods used for determination of inhibitory activity and bactericidal activity in biological samples, and each sample in the present study was tested in duplicate. The observed inhibitory activity and bactericidal activity in serum and urine samples of subjects after receiving fosfomycin trometamol confirmed the known pharmacokinetic property of this drug that the drug concentration is much lower in serum than in urine, and the concentration of fosfomycin was still high in urine at 24 hours after fosfomycin trometamol administration. The inhibitory activity and bactericidal activity in serum and urine samples of subjects compared between after receiving generic fosfomycin trometamol (Fosfomet®) and after receiving original brand fosfomycin trometamol (Monurol®) were not statistically significantly different ($p>0.05$). The differences in inhibitory activity and bactericidal activity in serum and urine samples of subjects compared between after receiving generic fosfomycin trometamol (Fosfomet®) and after receiving original brand fosfomycin trometamol (Monurol®) also had no clinical importance, because the maximum difference in inhibition zone diameter was 3 mm, and the maximum difference in bactericidal titer was 1-fold dilution. The adverse events experienced by subjects while receiving generic fosfomycin trometamol (Fosfomet®) were comparable to those experienced by subjects when taking original brand fosfomycin trometamol (Monurol®). It should be noted that mild diarrhea is a common side effect of fosfomycin trometamol, because it occurred in 36% to 43% of subjects who received a single dose (3 grams) of fosfomycin trometamol. Therefore, generic fosfomycin trometamol (Fosfomet®) can be used as an alternative to original brand fosfomycin trometamol (Monurol®) for treatment of lower urinary tract infection in clinical practice. The present study also demonstrated that in vivo microbiological activity study or microbiological equivalence study of the generic products of antibiotics is feasible and less expensive than bioequivalence study, and it should be performed for the generic antibiotics that their bioavailability data in comparison with the original antibiotics are exempted by the regulatory authority for drug registration.

Conclusion

Inhibitory activity, bactericidal activity, and rate of adverse events were all found to be comparable between the original brand fosfomycin trometamol (Monurol®) and the generic fosfomycin trometamol (Fosfomet®).

What is already known on this topic?

Original brand fosfomycin trometamol (Monurol®) has been used to treat uncomplicated lower urinary tract infection in Thai patients for a decade.

What this study adds?

Generic fosfomycin trometamol (Fosfomet®) was assessed for its in vivo microbiological activity against ESBL-producing *E. coli*. The results of this study revealed the microbiological activity of Fosfomet® against ESBL-producing *E. coli* to be comparable to that of original brand fosfomycin trometamol (Monurol®). In vivo microbiological activity study or microbiological equivalence study of generic antibiotics is feasible and less expensive than bioequivalence study. In vivo microbiological activity study or microbiological equivalence study of the generic products of antibiotics is feasible and less expensive than bioequivalence study, and it should be performed for the generic antibiotics that their bioavailability data in comparison with the original brand antibiotics are exempted by the Thailand FDA.

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Conflicts of interest

The authors declare no conflict of interest.

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