High interindividual variability in urinary fosfomycin concentrations in healthy female volunteers

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ABSTRACT

Objectives

Fosfomycin is increasingly being prescribed for the treatment of uncomplicated urinary tract infections in an era of emerging drug resistance. Surprisingly, little is known of the urinary concentrations of fosfomycin and its interindividual variation after the standard single 3 gram oral dose. We aimed to gain more insight into urinary fosfomycin pharmacokinetics to evaluate its effectiveness.

Methods

Three grams of fosfomycin trometamol was administered to 40 healthy female volunteers with an estimated mean glomerular filtration rate of > 90 mL/min/1.73m^2. Urine samples were collected from every urination during 48 hours, and then twice daily for up to 7 days. Time, volume and pH were recorded. Concentrations were quantified with UPLC-MS/MS. Effectiveness was evaluated based on urinary concentrations and the target MIC of *E. coli*, the most common uropathogen.

Results

A high interindividual variability was found. Peak concentration was 1982.0 ± 1257.4 mg/L, urinary half-life 12.4 ± 5.7 hours and excretion rate over 48 hours 29.9 ± 7.1 mg/h. Recovery was 44.5 ± 12.6% after 48 h and 47.0 ± 10.4% after 7 days. Concentrations remained above the EUCAST breakpoint of 32 mg/L in 100% of the volunteers over the first 24 h, 67.5% for 48 h and 30% for 72 h. A high urinary output was associated with low urinary concentrations and consequently reduced time > MIC, $AUC_{0\text{-}7days}$/MIC and C_{max}/MIC values.

Conclusions

Considerable interindividual variability observed in the pharmacokinetics of fosfomycin signifies a risk for inadequate drug exposure in a significant proportion of the population. The current dosing regimen should therefore be reevaluated.

INTRODUCTION

Uncomplicated urinary tract infections (UTIs) are the most common bacterial infections among otherwise healthy, premenopausal, non-pregnant women (1). In most cases, these infections are caused by *Escherichia coli* (*E.coli*), but an increased prevalence of infections caused by extended-spectrum beta-lactamase (ESBL) producing *Enterobacteriaceae* and multi drug resistant (MDR) pathogens has been observed, which is a concerning development (2–4).

Oral fosfomycin is gaining more attention as an alternative or even a first line treatment due to the increased incidence of UTIs caused by ESBL-producing or MDR pathogens (2, 5, 6). Clinical studies have demonstrated the efficacy of fosfomycin in the treatment of lower UTI caused by resistant (ESBL-producing) *E. coli* (7, 8). However, only 70 – 85% of the treatments with fosfomycin result in a clinical success (9). One of reasons of treatment failure might be inadequate urinary concentrations and/or a large interindividual variation.

Despite fosfomycin having been used clinically for decades, little is known about its pharmacokinetic (PK) and pharmacodynamic (PD) characteristics. A few small pharmacokinetics studies have been conducted, however none inferred a relationship between urinary fosfomycin concentrations and the effectiveness of the treatment (10–13). Furthermore, no concentrations were measured beyond 72 hours (h) in order to fully describe the elimination process. This is an important limitation since the time-course of urinary drug concentrations directly influence the uropathogen kill-rate and thereby the efficacy of the antibiotic treatment (14). Knowledge of these concentrations (PK) serves as the base of therapy optimization and the prevention of the emergence of resistance (15, 16).

This study aimed to gain more insight into the population distribution of urinary concentrations of fosfomycin to evaluate the effectiveness of the standard treatment based on the expected uropathogen fosfomycin minimal inhibitory concentrations (MIC) .

METHODS

Study design and drug administration

The study was designed as a single center, open label, single dose study in the home setting. Volunteers received a single oral dose of 3 grams of fosfomycin trometamol (*Monuril®, Zambon Nederland B.V., Amersfoort, the Netherlands*). Fosfomycin was administered under supervision during the first visit with a standardized volume of 250 mL water to rule out drug non-adherence. Urine was collected during one week after

fosfomycin administration. No restrictions were placed on food or fluid intake prior to fosfomycin administration or during the study week.

The study was approved by the ethical committee of the Erasmus Medical Center (MEC-2016-121) and registered with EudraCT (2015-005700-28).

Study population

Written informed consent was obtained from all volunteers prior to participation. Inclusion criteria were (1) female, (2) age ≥ 18 years and (3) healthy. Health status was assessed by taking the medical history and an interview, and was confirmed during the first visit before fosfomycin administration by a general blood test. To that purpose, two capillary blood samples of ~0.5 mL each were taken from a finger. Besides creatinine (50-90 μmol/L) also electrolytes and blood counts were checked.

Exclusion criteria included menstruation during the sampling week; known severe renal impairment (defined as eGFR < 30 mL/min1.73m^2); co-medication with any antimicrobial agent within 1 month prior or with metoclopramide; history of intolerance/allergy to fosfomycin; pregnancy or lactation.

Sample collection

Urine samples were self-collected at home from every urination during the initial 48 h, and then twice daily up until 7 days after fosfomycin administration. Urine was collected in a 1000 mL measuring cup, subsequently 1 mL was transferred to a tube (1.5 mL safe-lock, Eppendorf) and immediately stored in a freezer (≈-20°C). A portable cooling box was provided to keep the samples cool when the volunteer was not at home. The volume and time of the urination were recorded in a schedule. Volunteers measured pH of each sample with a dipstick (pH-range 0-14, Boom BV, Meppel, the Netherlands). After one week, all collected samples were delivered to the researchers and stored at -80°C until analysis. Stability of the samples at 18°C, -20°C, and -80°C was confirmed during the method validation (17).

Quantification of fosfomycin in urine

Fosfomycin concentrations in urine were assayed using a validated ultra performance liquid chromatography tandem mass spectrometric (UPLC-MS/MS) method as described in detail elsewhere (17). Samples expected to fall outside the validated concentration range (0.75 to 375 mg/L) were diluted with drug free urine as described before (17).

Pharmacokinetic analysis

Urinary concentrations from each volunteer were plotted against time after administration in a semi-logarithmic graph, from which the maximum concentration ($C_{max,}$ mg/L) and corresponding time (T_{max}, h) were established. The mean population urinary con-

centrations with standard deviation (SD) were plotted against time. The concentration elimination half-life ($T_{1/2}$) was estimated from the individual concentration-time graphs. The fosfomycin excretion (in mg) was calculated by multiplying the urinary fosfomycin concentrations by the volume of urine collected for each urination and calculated for specific time intervals. The cumulative recovery (%) was expressed as percentage of the fosfomycin dose. The urinary output (mL) was defined as the total volume of the produced urine per time interval. Fosfomycin excretion rate (mg/h) was calculated over time periods of 12 h, 24 h and 48 h and calculated from the total amount fosfomycin excreted (mg) divided by the time interval (h).

The influence of the following volunteer characteristics: urinary output, number of urinations, estimated glomerular filtration rate (eGFR), BMI, urinary pH, time/type of the last meal prior to fosfomycin administration and fluid intake on the PK parameters (C_{max}, T_{max}, $T_{1/2}$, excretion and recovery) was explored to explain the interindividual pharmacokinetic variability (IIV). The CKD-EPI equation was applied to estimate eGFR using the mean value of the two capillary creatinine measurements (18).

Pharmacodynamic analysis

PK/PD indices were calculated using GraphPad Prism 7.01 based on individual concentration-time graphs and MICs of 0.5 – 128 mg/L. This range was chosen based on MICs of possible uropathogens (European Committee on Antimicrobial Susceptibility Testing; EUCAST) (19). Effectiveness was defined as the ability to reach adequate concentrations in urine using different measures of PK/PD targets as presented for the EUCAST fosfomycin trometamol clinical breakpoints in the EUCAST rationale document (20).

Safety assessment

Safety evaluations included the collection of volunteer-reported adverse events (AEs) and serious AEs.

RESULTS

Study population

Forty volunteers participated in the study meeting all inclusion criteria. All completed the full sampling week. Their characteristics are presented in table 1. Three cases of diarrhea, two cases of abdominal pain, one case of headache, and one case of dizziness were reported. No serious AEs were reported.

Table 1: Volunteer characteristics and pharmacokinetic parameters presented as population mean and standard deviation (SD).

Characteristics		Mean	SD
Age	(years)	24.3	7.9
Height	(cm)	170.0	6.4
Weight	(kg)	64.1	8.4
BMI		22.1	2.4
eGFR	(mL/min/1.73m^2)*	112.9	72-133**
Pharmacokinetic parameter			
C_{max}	(mg/L)	1982.0	1257.4
T_{max}	(h)	7.5	4.2
$T_{1/2}$	(h)	12.4	5.7

*reported as > 90 mL/min/1.
**range

Sample collection

A total of 891 urine samples with a mean of 22.3 (± 2.9) samples per volunteer were collected. The number of collected samples was dependent of the individual urination rhythm. The pH of the samples was comparable between the volunteers (pH of 5.5 (± 0.5)).

Pharmacokinetic analysis

The mean concentrations for the time intervals are demonstrated in figure 1. As demonstrated in table 1, a high IIV was observed for all PK parameters. A log-linear relationship (R^2=0.95) was found between mean urinary concentration and time after

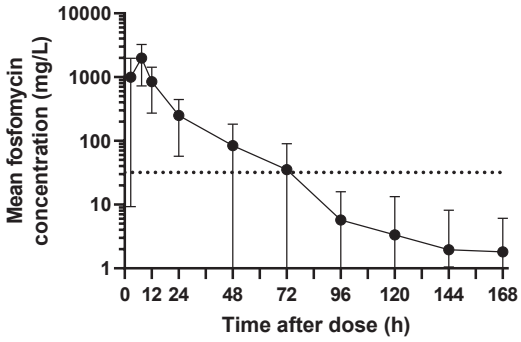

Figure 1: Mean urinary fosfomycin concentration – time curve
Mean concentration-time curve with on the vertical axis the urinary fosfomycin concentration on a log scale and the time after the fosfomycin dose on the horizontal axis. The variability is presented as the SD (vertical bars). The dotted line represents the clinical breakpoint of 32 mg/L for susceptible Enterobacteriacea according to the EUCAST.

dose. The C_{max} obtained in the 2-4 h; 4-6 h; 6-8 h; 8-10 h; 10-12 h and > 12 h time intervals in respectively 23.1%; 23.1%; 20.5%; 7.7%; 7.7% and 17.9% of the volunteers. Urinary concentrations remained above the EUCAST breakpoint of 32 mg/L (dotted line in figure 1) in 100% of the volunteers for 24 h, in 67.5% for 48 h and in 30% for 72 h. Fosfomycin was still detectable (C_{7days}=1.8mg/L) after 7 days in 18% of the volunteers.

The cumulative recovery over 7 days is demonstrated in figure 2. An average of 47.0% (± 10.4%) was excreted over 7 days of which 44.5% (± 12.6%) was excreted over the initial 48 h. In fact, 90% of the excretion occurred within the initial 32 h, 95% within 42 h and 99% within 60 h. Most fosfomycin (36.1%) was excreted during the first 6 h. Table 2 presents an overview of the excretion results. The range of urinary output was similar for day 1 and day 2 (Supplementary data 1).

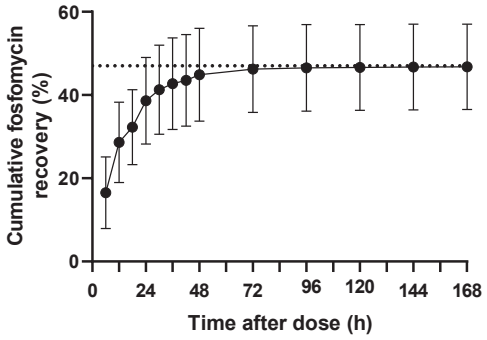

Figure 2: Mean cumulative fosfomycin recovery – time curve
Mean and SD (vertical bars) of the cumulative fosfomycin recovery (%) for the specific time intervals. The recovery reaches a plateau of 47.0% which represents the dotted line.

Table 2: Summary of the excretion parameters presented as population means and SD during the first 48 h after fosfomycin administration

Time interval	Excretion		Number of samples		Excretion rate		Recovery	
(h)	(mL)				(mg/h)		(%)	
0-12	1035	(501)	3.7	(1.3)	71.6	(24.1)	28.6	(9.7)
12-24	802	(451)	2.5	(1.1)	25.0	(12.5)	9.6	(5.0)
24-48	1866	(814)	6.0	(1.8)	7.8	(4.0)	6.3	(3.2)

Volunteers with a high urinary output over 48 h (6386 mL) out of a mean of 13 samples, had a higher recovery (56.9%) and a lower C_{max} (1051.0 mg/L) compared to the mean population (3702 mL; 12 urine samples; 44.5% recovery; C_{max} of 1982.0 mg/L). The recovery was found to be lower (43.4%) and C_{max} was high (3206.8 mg/L) in volunteers with a lower urinary output (1850 mL) out of 10 samples. No relationship

was found between neither the eGFR and the excretion rate nor between one of the other volunteer characteristics and the PK parameters.

Pharmacodynamic analysis

The mean values and ranges of the PK/PD indices are demonstrated in figure 3. An exponential relationship was found between the T>MIC and the MIC values (R^2=0.97; figure 3a). Concentrations exceeded 32 mg/L for 60 h with a wide range from 33.6 h to 111.0 h. Strains with MIC < 16 mg/L would be exposed to concentrations exceeding this concentration for at least 36 h (dotted line). Figure 3b demonstrates that $AUC_{0\text{-}7days}$/MIC values exceed the EUCAST breakpoint value of 3994 for bacteriostasis (dotted

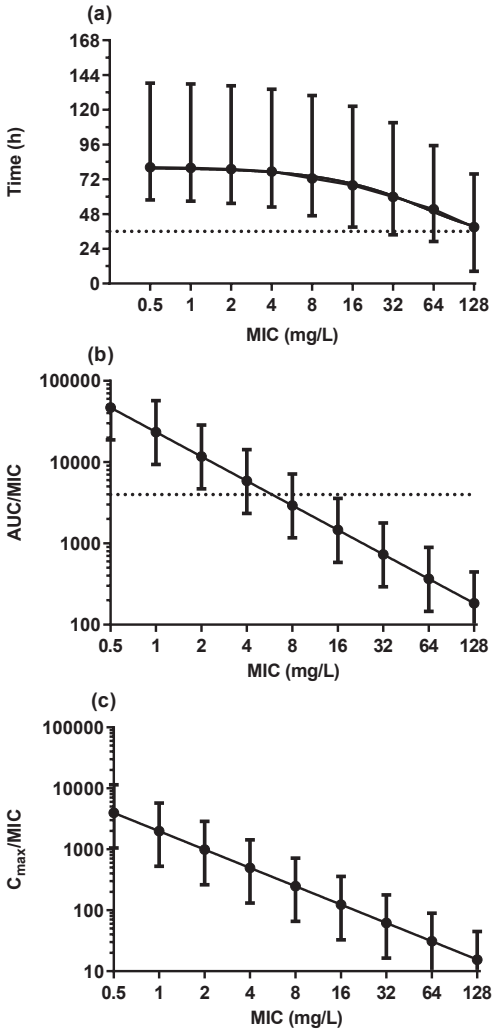

Figure 3: Mean PK/PD index values for *E. coli* MICs

Mean and range (vertical bars) of the T>MIC **(3a)**, $AUC_{0\text{-}7days}$/MIC **(3b)** and C_{max}/MIC **(3c)** for all MICs with the MICs on the horizontal axis and the three different PK/PD indices on the vertical axis. Both axes have logarithmic scale. The dotted line in figure 3a represents the 36 h time point and the dotted line in figure 3b represents the EUCAST AUC/MIC value for bacteriostasis.

line) only for strains with MIC < 2 mg/L (20). Given the observed high IIV in urinary concentrations, effective killing of strains with MICs of 4-8 mg/L is questionable. Strains with MICs of > 16 mg/L are never exposed to concentrations exceeding the MIC so effective killing would be unlikely. When considering the peak concentration, strains with MICs of < 32 mg/L would achieve a minimal average C_{max}/MIC value of 61.9 (16.4-179.1). This is demonstrated in figure 3c.

DISCUSSION

This study provides a full perspective of the urinary PK profile of fosfomycin and its interindividual variability during both the absorption and elimination phases after a single oral dose of 3 grams. PK parameters were calculated based on urinary concentrations of 40 volunteers from 7 days.

The urinary output and C_{max} appeared to be correlated. High urinary output and number of urinations were associated with a lower C_{max} and a higher recovery compared to volunteers with a low urinary output and number of urinations over 48 h. This supports the importance of informing patients on the need to administer fosfomycin after emptying the bladder as stated in the product information in order to minimize the urge to urinate so that C_{max} values could be tripled (21).

C_{max} values in reported studies are comparable with our findings, but T_{max} values were found to be somewhat lower (≈ 4 h) (10, 11, 22–25). Urinary concentrations were followed between 8 h and 72 h in 4-13 volunteers in these studies. This resulted in recovery values ranging from 25% (over 8 h) to 51% (over 48 h).

The presence of the high IIV is our most important finding. This variability might be a reason for the treatment failures in 15 – 30% of the patients (9). It also causes uncertainties in the prediction of the PK/PD indices and therefore in the ability to evaluate the effectiveness of the treatment. Effectiveness was evaluated based on the clinical breakpoint for *Enterobacteriacea* (S) according to the EUCAST (≤ 32 mg/L (20)). The 36 h time point was chosen based on the therapeutic concentration as stated in the product information of fosfomycin (21). Based on these two numbers and the T>MIC as PK/PD index, it was concluded that fosfomycin treatment should be effective for strains with MIC values up to 16 mg/L. The EUCAST clinical breakpoint for *Enterobacteriaceae* bacteriostasis in urine of 3994 was chosen to evaluate the therapy based on the $AUC_{0\text{-}7days}$/MIC value as PK/PD index (20). Recent observations confirm this value (26). When taking the IIV into account, only strains with MICs ≤2 mg/L are treatable with the current therapy. C_{max}/MIC, with breakpoint value 32 mg/L, was also calculated to give a complete view of the PD. Of note, the clinical breakpoints from EUCAST are based

on limited evidence since urinary data for fosfomycin are sparse which is important to keep in mind when interpreting the PD related results (20).

Urinary concentrations were followed during 7 days. This offered the opportunity to study the complete course of both absorption and elimination phases. We have shown that this was of added value since fosfomycin excretion was still not fully completed after 7 days in 18% of the volunteers. This is a strength of this study since previous studies reported PK parameters based on samples obtained after maximum 72 h (10, 11, 22–25). The high number of 40 volunteers strengthens the results of our study. Since the volunteers all collected the samples based on their own urinary rhythm, variation exists in the time points on the horizontal axis in figure 1. This can be seen as a limitation, but we consider this as a strength since it reflects the real world situation.

Although volunteers were instructed to make notes of a possible missed urine sample, we cannot exclude the possibility that one or more volunteers did not report such an event. This could have led to results that are somewhat biased regarding recovery and urinary output results.

Another limitation of our study was that the group of volunteers was relatively homogeneous, impeding exploration of the influence of covariates such as GFR or food intake on the PK parameters. This will be different in the patient population were more variability in these characteristics can be expected. The influence of the urination frequency is important if our results are translated to the clinical situation. A frequent and strong urge to urinate resulting in a high amount of small urine portions is one of the effects of an UTI. Using standard PK equations, the effect of increased urinary frequency can be simulated in a mathematical model. This demonstrates that increased urinary frequency will only slightly increase the C_{max} and shorten the T_{max}, while only decreasing the AUC (which represents total drug exposure in the bladder) by less than 5% (27). These negligible changes in PK parameters will therefore not alter the conclusions regarding the effectiveness of fosfomycin treatment in this clinical scenario. When fosfomycin is administered to an elderly patient with renal impairment the elimination half-life could be longer. However, the reported half-life values are comparable with what is found in the elderly, indicating that the influence of renal impairment falls within the high variation of which we reported (13).

E.coli, the most common uropathogen, is rarely associated with micro-organism induced changes in urinary pH so we consider the influence of pH differences due to infection negligible small (28). On the contrary, pH can influence the PD effect of the treatment, but this was not within the scope of this research.

Our data can serve as a base for in vitro models to investigate the influence of the distribution of urinary concentrations on the killing-rate of pathogens. Hereby, the relevant PK/PD index and the corresponding breakpoints can be found in order to optimize patient outcomes and minimize the emergence of resistance for fosfomycin.

In conclusion, this is the first study in a large cohort monitoring urinary fosfomycin concentrations during one week. This provides more insight into the full PK profile and the effectiveness of the current treatment of UTIs in the population of healthy females. The high IIV and/or inadequate drug exposure can be an explanation for the observed treatment failures in part of the patient population.

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Transparency declarations

All authors have no conflicts of interest to disclose.

Supplementary data

Figure S1 demonstrates the distribution of the volume of urine during the first and second day of the sample collection week of the volunteers. This figure is available as Supplementary data.

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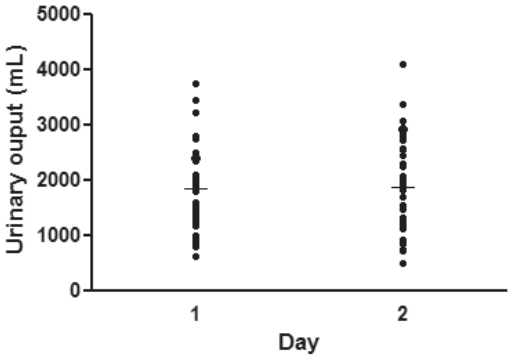

Figure S1: Distribution of the urinary output during day 1 and day 2

Scatterplot of the urinary output during day 1 and day 2 from all 40 volunteers. The mean values of each day (–) are 1836 mL on day 1 and 1866 mL on day 2. These values are not significantly different ($p>0.05$ in Wilcoxon matched pairs test).