Rational use of antibiotics

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CHAPTER 10

PHARMACOKINETICS OF FOSFOMYCIN IN PATIENTS WITH PROPHYLACTIC TREATMENT FOR RECURRENT *E. COLI* URINARY TRACT INFECTION

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ABSTRACT

OBJECTIVES To evaluate pharmacokinetics and clinical effectiveness of intravenous and oral fosfomycin treatment in patients with recurrent urinary tract infection (RUTI) with *Escherichia coli*.

PATIENTS AND METHODS Patients with RUTI treated with oral fosfomycin 3 gram every 72 hours for at least 14 days were included in a prospective open label single-center study. Serum samples were taken after oral and intravenous administration of fosfomycin. Urine was collected for 24 hours at 3 consecutive days. Fosfomycin concentrations in serum and urine were analysed using a validated ultra performance chromatography tandem mass spectrometry. Pharmacokinetics were evaluated using a population model.

RESULTS Twelve patients were included, of whom nine also administered intravenous fosfomycin. Data were best described by a two-compartment model with linear elimination and a transit-absorption compartment. Median values for absolute bioavailability and serum half-life were 18% and 2.13h, respectively. Geometrical mean urine concentrations on day 1, 2 and 3 were above an MIC of 8 mg/L after both oral and intravenous administration. Quality of life reported on a scale of 1-10 increased from 5.1 to 7.4 (p=0.001). The average score of urinary tract infection symptoms decreased after fosfomycin dosing (3.1 points, 95% CI: -0.7 – 7.0, p=0.10).

CONCLUSIONS Oral fosfomycin provides urine levels of fosfomycin above MIC for *E. coli* and seems to improve symptoms. The pharmacokinetic model can be used to develop dosing regimes of fosfomycin in patients with *E. Coli* RUTI.

INTRODUCTION

Urinary tract infections are common and associated with a considerable burden of hospital admissions and associated healthcare costs.[1] Management of patients with recurrent urinary tract infections (RUTI) is challenging, particularly given the increasing prevalence of antimicrobial resistance.[2] Continuous antimicrobial prophylaxis is one of the strategies for the prevention of RUTI. The choice of antimicrobial should be based on patterns of resistance, tolerability, side effects, availability and costs. Commonly used agents for this purpose are fluoroquinolones, nitrofurantoin, trimethoprim-sulfamethoxazole and oral cephalosporins.[3]

Fosfomycin is considered the first choice of treatment for RUTI because of its favorable side effect pattern compared to other antibiotics.[4] Fosfomycin was discovered in 1969 and has sustained activity against several multidrug-resistant uropathogenic Enterobacteriaceae.[5-8] Fosfomycin has been considered to be less useful for the treatment of systemic infections, because of its rapid clearance after oral administration. However, increased and sustained urinary drug concentrations are observed after systemic administration.[9] Given the trend of increasing antimicrobial resistance, fosfomycin may be an appealing alternative for the treatment and prophylaxis of RUTI caused by multidrug-resistant uropathogens.[10]

What remains unclear is the optimal dosing regimen of fosfomycin treatment in patients with RUTI, despite the numerous studies that have reported the pharmacokinetic and pharmacodynamic characteristics of fosfomycin, especially when administered intravenously for the treatment of various infections.[3,11-19] Most of these studies lack accurate measurements of fosfomycin levels, especially in the lower range of clinically relevant concentrations. The recent development of liquid chromatography – mass spectrometry to measure fosfomycin levels in serum and urine now allow for an accurate analysis of fosfomycin in serum and urine of patients.[20,21]

The aim of the present study was to evaluate pharmacokinetics and clinical effectiveness of intravenous and oral fosfomycin treatment in patients with RUTI with *E. coli*.

PATIENTS AND METHODS

Ethics

The study was conducted at the Haga Teaching Hospital, The Hague, The Netherlands. The study protocol was approved by the Medical Ethics Committee of South-West Holland (protocol 18-050) and the Institutional Scientific Review Board of the Haga Teaching Hospital. This study was registered under EudraCT number 2018-000616-25. Written informed consent of all participants was obtained.

Study design and patients

This study was a prospective open label single-center study including patients with rUTI, defined as at least three UTIS per year or two during the last six months.[3] Inclusion criteria were: age ³ 18 years, treatment of rUTI with oral fosfomycin 3 gram every 72 hours for at least 14 days as instignated by the treating physician, ability to communicate in Dutch and written informed consent. Exclusion criteria were: renal insufficiency (estimated glomerulair filtration rate (eGFR) <30ml/min/1.73 m^2), known allergy for fosfomycin, pregnancy or breast feeding, active malignancy, loss or donation of ³ 500 ml of blood within 90 days prior to screening, participation in an investigational drug study within 90 days prior to day 1, use of metoclopramide, and any condition that might interfere with treatment compliance or study conduct (e.g., use of illicit drug, alcohol dependence).

Study procedures

Data on patient demographics (age and gender), medical history, medication use, height and weight and renal function (calculated using the CKD-EPI method) were collected at baseline. [22]

Fosfomycin tromethamine (5,63 g, Monuril®, Zambon S.p.A.) was used for the oral administration and fosfomycin disodium (3,96 g, Fomicyt®, Nordic Pharma BV) was administered in a 30 minutes intravenous infusion. Sampling of blood and urine was performed around a planned dose of 3 gram oral fosfomycin and, optionally, when an oral dose was replaced by the equivalent intravenous dose.

Blood samples were collected pre-dose and after oral (at t = 30, 60, 90, 120, 180, 240, 300, 360 minutes) and intravenous fosfomycin administration (at t = 10, 20, 30, 60, 90, 120, 180, 240, 300 and 360 minutes) in plain serum tubes. After collection, samples were centrifuged at 3500 rounds per minute at room temperature and serum was transferred to a storage tube and frozen at -80° C unil analysis. Urine was collected for 24 hours on 3 consecutive days, starting at the time of administration of fosfomycin. Total 24-hour urine volume was measured and an aliquot was frozen at -80° C until analysis.

Fosfomycin analysis

Fosfomycin concentrations in serum and urine were analysed using a validated ultra performance chromatography tandem mass spectrometry (LC-MS/MS) method.[21] Analysis of the samples was performed at the Department of Pharmacy, Erasmus University Medical Centre, Rotterdam, The Netherlands. The upper and lower limits of quantification (ULOQ and LLOQ) were 375 mg/L and 0.75mg/L for both matrices. Results above the ULOQ were diluted and re-analysed.

Pharmacokinetic analysis

Population pharmacokinetics modelling using nonlinear mixed-effects modelling methods was carried out based on serum fosfomycin concentration data using NONMEM 7.3.[23] Visual exploratory inspection of the data revealed multi-exponential decay in the individual serum fosfomycin concentration versus time profiles. Therefore, two- and three-compartmental models with linear and nonlinear elimination were developed using physiological parameterization, e.g., absolute clearances (CL), absolute volumes of distribution (V) and absolute bioavailability (F). Various absorption models with and without delay in absorption were explored. Mixed-effects models were evaluated using first-order conditional estimation with interaction (FOCEI) maximum likelihood estimation. Interindividual variability was assumed to be log-linear distributed and covariance between the estimated parameters was explored. Proportional, additive and combined residual error structures were tested. Potential covariate relationships between Bayesian post-hoc parameter estimates and individual covariate values were formally tested in the model if the Pearson correlation coefficient was >0.5. Potential covariates were age, sex, race, height, weight, serum creatinine concentrations and body mass index. Criteria for model selection and evaluation were based on numerical and graphical evaluation as described previously, using the minimum objective function value (MOFV, 3.84 points resembling p=0.05), standard goodness-of-fit plots (including Visual Predictive Check of 1000 simulations), residual standard error (RSE) of the population parameter estimates and the coefficient of variation (%CV).[24]

Urine fosfomycin concentrations were graphically represented by geometric boxplots. Renal excretion in 72 hours was calculated by multiplying the volume of urine and the urinary fosfomycin concentration. Serum fosfomycin levels were presented as individual plots.

Clinical effectiveness

After inclusion, each patient filled out a questionnaire with questions about symptoms of cystitis, quality of life and adverse events six weeks before and after having started fosfomycin treatment for rUTI. A questionnaire based on the Acute Cystitis Symptom Score was used, consisting of a 4-point scale indicating the severity of each symptom ranging from 0 (no symptom) to 3 (severe symptoms), with a maximum total score of 30 (most severe symptoms).[25] Questions on adverse events included gastro-intestinal compliants, paresthesias, rash or itching, headache and tiredness. Quality of life was assessed on scale of 1 (worst) till 10 (best). Paired t-tests were performed to compare symptoms of cystitis, quality of life and adverse events before and after fosfomycin treatment.

Information about known urinary cultures (routinely performed before and after start of fosfomycin treatment) and the total duration of fosfomycine treatment in months were retrieved from the patient's medical records.

RESULTS

Patients characteristics

In total, 3 men and 9 women with rUTI on stable oral fosfomycin treatment were included. Nine participants (3 men and 6 women) also received an intravenous fosfomycin dose. The median (range) demographics were: age 66 (44-76) years, BMI 26.8 (20.4-28.7) kg/m^2, weight 79.9 (57-97) kg, height 169.5 (153-186) cm and eGFR 83 ml/min/1.73m^2 (63-103). All participants had *E. Coli* as cause of rUTI. Detailed patient characteristics are listed in *table 1*.

Pharmacokinetic analysis

SERUM PHARMACOKINETICS

Initial data fitting started using a two-compartmental model structure with proportional residual error. The individual data after oral administration were best described by a transit compartment, as a standard lag time absorption model resulted in a higher MOFV (79 points).[26] Expanding the model to a three-compartment model reduced the bias in the conditional weighted residuals with interaction *vs.* time but caused structural bias and overparameterisation (condition number > 100000), so model development was continued with a two-compartmental model structure. A combined residual error structure proved most fit for purpose as the use of an additive residual error structure resulted in problems in the minimisation and a proportional error structure resulting in a significant higher MOFV (137 points). Interindividual variability was identified on the central volume of distribution, clearance and bioavailability. Additional sources for interindividual variability resulted in unacceptable levels of overparameterization (condition number > 1000). No covariates were identified that could explain variability.

In general, the pharmacokinetics of fosfomycin were adequately captured by the model. The central and individual trend of the data were well described as the population predictions (*figure 1A*) and individual predictions (*figure 1B*) closely followed the line of unity for both oral and iv fosfomycin data. The conditional weighted residuals with interaction showed no bias over the range of population predictions (*figure 1C*) but a slight underprediction for the late time points (*figure 1D*). The parameter estimates of the population pharmacokinetic model are displayed in *table 2*. All parameters were estimated with reasonable precision as all relative standard errors (RSEs) are below 30%. Between-subject variability was relatively low for V, CL and F (with CVs of 25.5%, 22.7% and 40.2%). The condition number was 50.9, which is well below the threshold of overparameterisation. The shrinkages of the empirical Bayes estimates that characterize the inter-individual variability and the residual error were well below 20%. The visual predictive check (VPC) is displayed in *figure 2*, which demonstrates that both the variability and the structural trend of the data are adequately captured by the model. The 10th, 50th and 90th percentiles of the observed serum-concentrations are within the 95% confidence intervals (CI) of the 10th, 50th and 90th percentiles of the model predicted serum-concentrations.

URINE PHARMACOKINETICS

Urine data are represented in *figure 3*. For 1, 2 and 3 days after oral fosfomycin dosing, the geometric mean (SD) urine concentrations were 622.3 (± 335.1), mg/L 41.41 (± 17.1) mg/L and 20.5 (± 45.60) mg/L. After intravenous administration these concentrations were 1512.17 (± 788.27) mg/L, 43.55 (± 43.62) mg/L and 25.37 (± 45.65) mg/L. Mean total amount renally excreted fosfomycin (SD) was 1.21 (± 0.37) gram after oral intake, and 2.96 (± 0,52) gram after intravenous administration.

Clinical effectiveness

Eleven participants completed the questionnairre (92%). The average score of urinary tract infection symptoms decreased after fosfomycin dosing (3.1 points, 95% CI: -0.7 – 7.0, p=0.10). Quality of life improved by 2.2 points (95% CI: 3.4 – 1.2, p=0.001). Most reported side effects were gastro-intestinal complaints (n=8), tiredness (n=8) and headache (n=7). The details of the questionnaire are provided in supplementary 1.

DISCUSSION

In this study, we evaluated pharmacokinetics and clinical effectiveness of intravenous and oral fosfomycin treatment in patients with rUTI with *E. coli*. The two-compartmental pharmacokinetic model accurately described the individual serum fosfomcyin concentration-time profiles after oral and intravenous administration. The total volume of distribution at steady state (central and peripheral volumes of distribution) was approximately 9.5 L, which is comparable to previous reported literature (range: 9.8-30.2L).[27-32] All model parameters were estimated with high accuracy and resulted in a half-life of 2.13 h which is also in line with previously reported values (range: 1.2-4.0 hours).[16,17,28-31,33-35] This indicates that our pharmacokinetic model resulted in physiological plausible parameter estimates. The estimated bioavailability was 18% (95% confidence interval: 11.5 -23.7%) which is markedly lower than earlier reported bioavailability estimations (range: 33-58%).[16,17,27,33] All previous reported bioavailabity estimations were measured in a healthy population whereas our populations is older and has more co-morbidities, like diabetes mellitus (n=2). Diabetes mellitus may reduce resorption as has been shown for rifampin and fluxcloxacillin.[36,37] Furthermore, the use of other medication may be another explanation for the difference in bioavailabilty, e.g. bioavailabilty of fosfomycin is lowered by co-administration of metoclopramide. Notable is the total amount renally excreted fosfomycin we found (1.21 gram) after oral intake, which is above the amount

absorbed and the calculated bioavailability. This could be explained by variation in measurement of fosfomycin concentration and urine volume or by underestimation of the bioavailability in our calculations. Further research is needed to explore the factors of decreased bioavailibity of fosfomycin.

In the pharmacokinetic model evaluation, it was shown that there is some bias in the conditional weighted residuals over time (*figure 1D*). This could be indicative of a suboptimal structural pharmacokinetic model, e.g., the data was fitted to a two-compartmental model where a three-compartmental model would be more appropriate. As a result, the pharmacokinetic model consequently estimates lower concentrations than observed at the latest sample times. When fitting a three compartmental model, the model was clearly overparameterized, which indicates that the data do not allow identification of a three-compartmental model. A three compartmental model would require the quantification of three distinct exponential declines. However, an already dense sampling strategy was applied. Therefore, it is suggested that the duration of serum sampling should be extended in future study designs. When using this pharmacokinetic model for simulations, the accumulation of drug, and thus also the renal clearance into urine, would be slightly underestimated. Despite the relatively short serum half-life (2.13 hours), urine concentrations remained relatively high, even after 72 hours. This supports the suggestion from the model development process that a three-compartmental model is more appropriate as this would lead to a third exponential decay representing the distribution into deeper tissues that results in a slower release into serum hence a prolonged serum exposure and prolonged accumulation of fosfomycin in urine.

Urine fosfomycin concentrations during 24 hours ranged from 300-1500 mg/L, which is considerably higher than serum exposure ($AUC_{0\text{-}6h}$ oral 22.0 mg·h/L and iv 85.2 mg·h/L). This was an expected finding as the urinary tract has a collective function, and the renal clearance of fosfomycin is high. In our study, oral and intravenous administration of 3 g fosfomycin resulted in average urine fosfomycin concentrations high enough to induce an antibacterial effect based on the the epidemiological cut-off value of *E. coli* (i.e., 8 mg/L).[38] However, individual urine concentrations are average values over a 24 hour period. Fosfomycin concentrations in the urinary tract are highly affected by the amount of urine that is produced and timing of urination, which makes it difficult to relate fosfomycin urine concentrations over a 24 hour period to clinical effectiveness.

Although fosfomycin seemed an effective treatment for rUTI in this study, its added value for the treatment of systemic infections has always been argued, due to its "less-favorable" kinetics, e.g., its relatively short half-life, which would render the time at which concentrations are above the MIC to be relatively short.[39] In this study, serum concentrations remained above the epidemiological cut-off value of *E. coli* (a minimum inhibitory concentration (MIC) of 8 mg/L fosfomycin) for approximately 10 hours after oral administration of 3 g fosfomycin.[38] This would suggest that for multidrug-resistant uropathogenic Enterobacterales with a relative low MIC, 3 g fosfomycin orally or slight increments in dose or dosing regimen could be effective for the treatment of systemic infections. The EUCAST MIC distribution data suggest that many urinary pathogens have an even lower MIC, e.g., half of *E. coli* isolates have a MIC of ≤4 mg/L fosfomycin.

In this study we dosed fosfomycin trometamol 3 gram every 72 hours. Rudenko *et al.* performed a similar study in patients with rUTIs and found a significant decrease of 2.8 UTIs per year after oral dosing of fosfomycin trometamol 3 g every 10 days.[40] Based on the study of Rudenko *et al.*, guidelines recommend to dose fosfomycin 3 g every 10 days for prophylactic purpose.[3] This dosing regime with a prolonged interfall will result in low fosfomycin levels and might induce resistance. Higher concentrations of fosfomycin *in vitro* could decrease resistance development.[41] In this respect a more intensified dosing regime would be justified. The results of a non-inferiority trial of Constanti *et al.* provide support for an intensified dosing regime, as 3 g of fosfomycin every 7 days showed non-inferiority to prulofloxacin in female patients with rUTI.[12] However, it is unknown if any unwanted effects occur with an intensified regime, such as changes in intestinal microbioma, more side effects or development of resistance. It should be noted that high interindividual urinary fosfomycin concentrations were observed in healthy individuals,[42] which makes it difficult to establish a suitable endpoint for effective concentrations, and ultimately to choose the most optimal dosing regime for rUTI.

Our study has several strengths. First of all, the patients in our study reflect real-life practice, which is different to previous studies using healthy and predominantly young individuals. Furthermore, in our this study most participants received both an oral and intravenous dose of fosfomycin (n=9). The dense sampling strategy allowed us to asses the pharmacokinetics accurately. Finally, this is the first study done after multiple doses of fosfomycin trometamol.

It should be noted that our patient cohort was relatively small and heterogenous with rUTIs with varying underlying causes. In addition, all participants had fairly good renal function and normal BMI. No interindividual variability as covariate of the demographic parameters was observed on the pharmacokinetics, though it is a small cohort. Secondly, for the MIC of the *E.coli,* we used the epidemiological cut-off value which may be not applicable to each individual patient. Finally, clinical effectiveness indicated by symptoms of UTI and quality of life was retrospectively assessed through questionnaires, rendering it subject to response bias.

Altogether, our data proof that oral fosfomycin provides adequate urine levels of fosfomycin for *E. coli* and seems to improve symptoms. Given the growing concern of multidrug resistancy in rUTI and the limited amount of treatment alternatives, our study argues that fosfomycin 3g every 72 hours can be an effective oral prophylaxis regimen in patients with *E.coli* rUTIs. Further clinical and dosing studies are now warranted to evaluate dosing regimes in patients with *E. Coli* rUTI.

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FIGURE 1 **Goodness-of fit plots of the fosfomycin pharmacokinetic model with serum data after oral (dark grey) and intravenous (light grey) administration.**

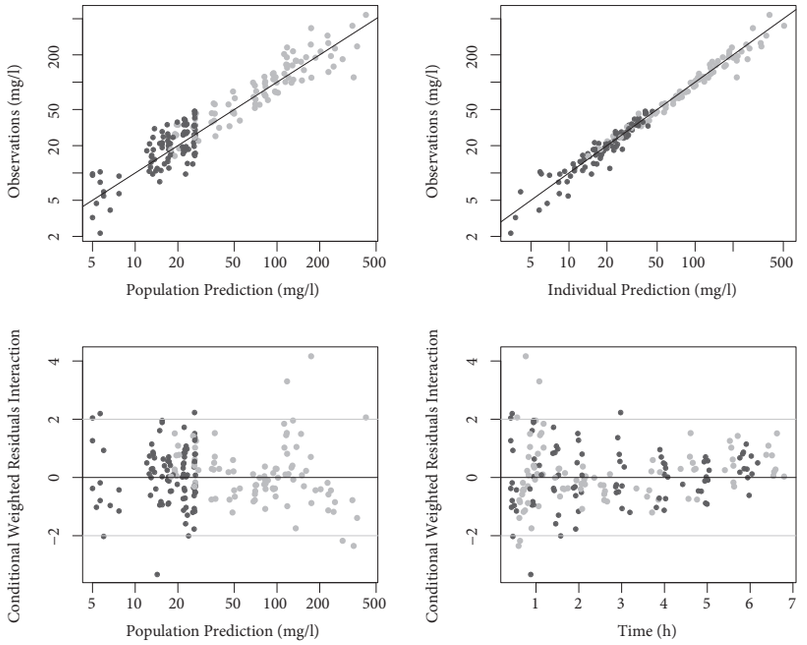

FIGURE 2 **Visual Predictive Check for the fosfomycin pharmacokinetic model after oral and intravenous administration. Solid and dashed lines represent the observed 10th, 50th and 90th percentiles for all observations, shaded area represents the 95% CI for the 10th, 50th and 90th percentiles of the model predictions.**

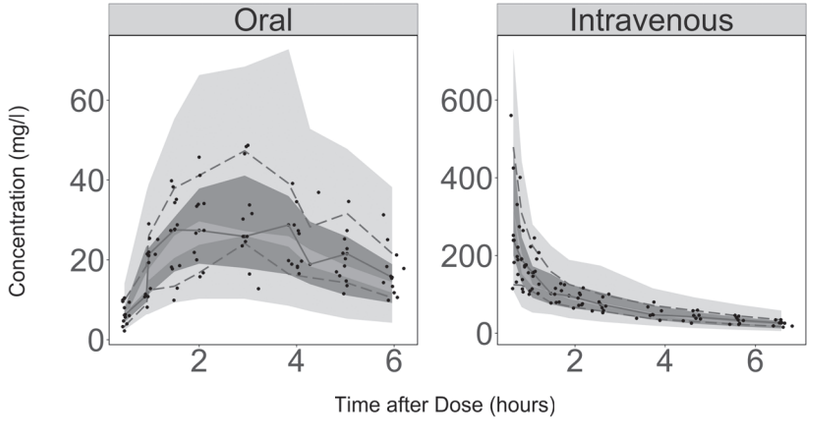

FIGURE 3 **Urine fosfomycin concentrations after intravenous and oral administration of 3 gram fosfomycin. The dotted line represents the MIC of 8 mg/L for *E. coli*. Outliers are depicted as triangles.**

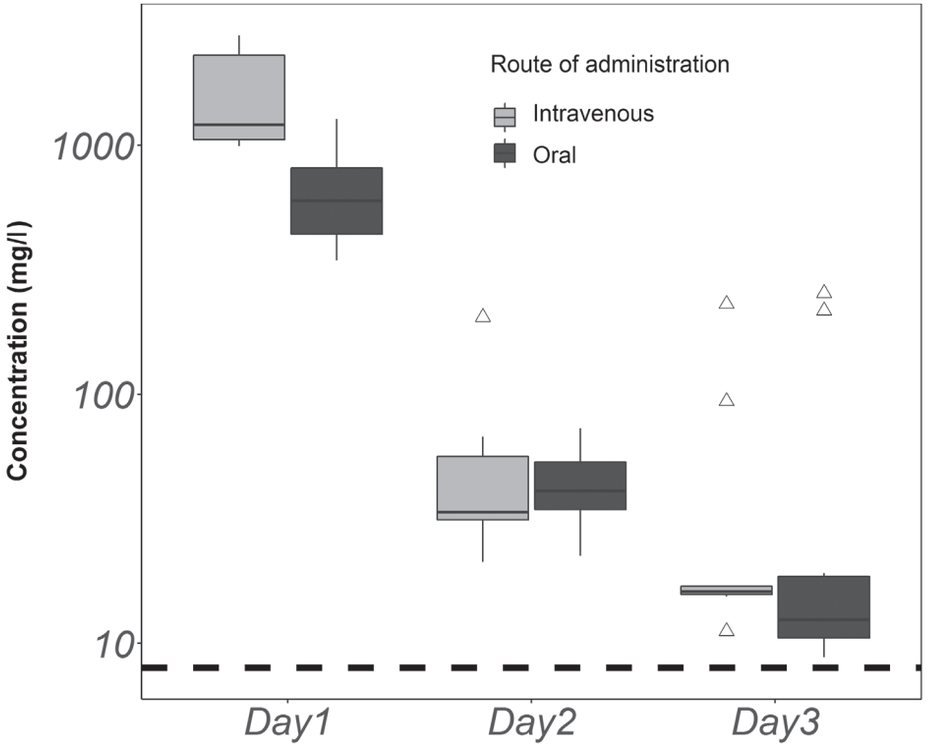

TABLE 1 Patients characteristics.

Patient	Sex	Age (year)	BMI (kg/m²)	eGFR (ml/min/1.73 m²)	Urologic history and co-morbidities	Duration on fosfomycin-treatment (months)	Uro-pathogen	UTIs per year before treatment	UTIs per year on treatment with different micro-organism	Urinary culture during treatment
1	F	63	27.0	103	Pelvic prolapse, Gastro-esophegal reflux disease, Epilepsia	5	*E. Coli*	9	2	negative
2	F	68	27.4	83	Atrial fibrillation, Breast cancer, Nitrofurantoin pneumonitis	13	*E. Coli*	12	2	negative
3	F	69	27.4	95	Acromegaly, Breast cancer, Hypertension	11	*E. Coli*	10	0	negative
4	F	63	27.9	92	Colorectal cancer, T2DM	2	*E. Coli*	12	2	negative
5	M	75	28.7	63	TUR-prostate, Neurogenic bladder, CIC, coronary artery disease, Sleep apnea syndrome	75	*E. Coli*	8	2	negative
6	F	75	28.7	78	Urgency urinary incontinence, T2DM, Hypertension, Aortic aneurysm	6	*E. Coli*	9	0	negative
7	F	74	25.2	66	Breast cancer, Uterus carcinoma, Proctocolitis, Carotic artery disease	2	*E. Coli*	10	0	negative
8	M	57	28.0	83	CBP, Sleep apnea syndrome	7	*E. Coli*	na	0	negative
9	M	76	26.3	85	CBP with prostate stones; TUR-prostate; hypertension	2	*E. Coli*	na	na	positive
10	F	75	19.7	83	Pelvic prolapse, Stress urinary incontinence, ICVA	3	*E. Coli* *Klebsiella pneumoniae*	12	8	positive
11	F	49	26.1	76	Hypospadias repair, Nephrectomy because of chronic pyelonephritis with renal stones	8	*E. Coli*	12	0	negative
12	F	44	28.4	97	None	1	*E. Coli*	12	0	negative

F: female, M: male, BMI: body mass index, eGFR: estimated glomerular filtration rate, CBP: chronic bacterial prostatitis, CIC: clean intermittent catherization, T2DM: type 2 diabetes mellitus, ICVA: ischemic cerebrovascular accident, na; not assessable.

TABLE 2 Population pharmacokinetic parameter and numerical diagnostics.

Pharmacokinetic parameter	Parameter estimate (RSE%)	IIV in %CV (shrinkage%)
Clearance (L/h)	5.05 (18.6)	25.5 (17.8)
Central volume of distribution (L)	1.32 (16.3)	22.7 (16.9)
Intercompartmental clearance (L/h)	6.31 (10.6)	
Peripheral Volume of distribution (L)	8.19 (7.7)	
Bioavailability (%)	18 (17.8)	40.2 (3.61)
Mean transit time (h)	1.72 (5.16)	
Number of transit compartments	0.60 (29.6)	
	Residual error (shrinkage%)	
Proportional error (ω2)	0.025 (7.34)	
Additive error (ω2)	3.43 (7.44)	

RSE: residual standard error, IIV: interindividual variation.

Supplementary

SUPPLEMENTARY 1 Details questionnaire.

	Frequency		Urgency		Incomplete bladder emptying		Suprapubic pain		Lower back pain		Hematuria	
Patient	B	A	B	A	B	A	B	A	B	A	B	A
1	3	1	2	0	0	0	2	0	1	0	1	0
2	1	1	0	0	2	2	1	1	0	0	3	3
3	2	1	0	0	0	0	1	1	0	0	1	1
5	1	1	1	1	3	3	0	0	0	0	2	2
6	1	1	2	2	0	0	1	1	0	0	0	1
7	2	1	2	2	1	1	0	0	0	0	0	0
8	3	1	3	3	2	2	1	1	0	0	0	0
9	3	3	3	2	3	2	1	0	0	0	0	0
10	0	0	0	0	0	0	2	2	0	0	3	3
11	1	1	1	1	3	3	2	2	0	1	3	3
12	1	0	2	1	1	0	2	0	1	0	1	0

B: before start treatment fosfomycin, A: after start treatment Fosfomycin.

	Dysuria		Fever		General dyscomfort		Impairment daily life		Total score		Quality of life	
Patient	B	A	B	A	B	A	B	A	B	A	B	A
1	2	1	0	0	2	0	2	0	15	2	4	7
2	0	1	0	0	0	1	1	1	8	10	5	9
3	0	0	0	0	0	0	0	0	4	3	4	8
5	2	2	1	1	1	1	0	0	11	11	8	8
6	1	1	0	0	1	0	0	0	6	6	7	7
7	2	0	1	0	2	1	2	1	12	6	4	7
8	0	0	0	0	1	1	1	1	11	9	7	8
9	1	1	1	0	2	1	2	1	16	10	3	7
10	0	0	0	0	0	0	0	0	5	5	4	7
11	1	3	1	1	1	1	2	3	15	19,5	5	5
12	1	0	1	0	2	0	2	0	14	1	5	8

B: before start treatment fosfomycin, A: after start treatment Fosfomycin.

SUPPLEMENTARY 2 **Individual serum concentrations after 3 gram fosfomycin oral and IV. The dark grey line represents patients data, the light grey line represents the predicted concentration based on the pharmacokinetic model.**