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Pharmacokinetics of fosfomycin in patients with prophylactic treatment for recurrent *Escherichia coli* urinary tract infection

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Objectives: To evaluate the pharmacokinetics and clinical effectiveness of IV and oral fosfomycin treatment in patients with recurrent urinary tract infection (rUTI) with *Escherichia coli*.

Patients and methods: Patients with rUTI treated with 3 g of oral fosfomycin every 72 h for at least 14 days were included in a prospective open-label single-centre study. Serum samples were taken after oral and IV administration of fosfomycin. Urine was collected for 24 h on 3 consecutive days. Fosfomycin concentrations in serum and urine were analysed using validated LC–MS/MS. Pharmacokinetics were evaluated using a population model. EudraCT number 2018-000616-25.

Results: Twelve patients were included, of whom nine were also administered IV 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 2.13 h, respectively. Geometric mean urine concentrations on Days 1, 2 and 3 were above an MIC of 8 mg/L after both oral and IV 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 UTI symptoms decreased after fosfomycin dosing (by 3.1 points, 95% CI = −0.7 to 7.0, $P = 0.10$).

Conclusions: Oral fosfomycin at 3 g every 72 h provides plasma and urine concentrations of fosfomycin above the MIC for *E. coli*. This pharmacokinetic model can be used to develop optimal dosing regimens of fosfomycin in patients with UTI.

Introduction

Urinary tract infections (UTIs) are common and associated with a considerable burden of hospital admissions and associated healthcare costs.[1] Management of patients with recurrent UTIs (rUTIs) is challenging, particularly given the increasing prevalence of antimicrobial resistance.[2,3] 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.[4]

Fosfomycin is considered the first choice of treatment for UTI because of its favourable side effect pattern compared with other antibiotics.[4] Fosfomycin was discovered in 1969 and has sustained activity against several MDR 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 MDR 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 IV for the treatment of various infections.[4,11–19] Most of these studies lack accurate measurements of fosfomycin levels, especially in

the lower range of clinically relevant concentrations. The recent development of LC–MS/MS to measure fosfomycin levels in serum and urine now allows an accurate analysis of fosfomycin in serum and urine of patients.[20,21]

The aim of the present study was to evaluate the pharmacokinetics and clinical effectiveness of IV and oral fosfomycin treatment in patients with *Escherichia coli* rUTI.

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-centre study including patients with rUTI, defined as at least three UTIs per year or two during the last 6 months.[4] Inclusion criteria were: age ≥18 years; treatment of rUTI with 3 g of oral fosfomycin every 72 h for at least 14 days as indicated by the treating physician; ability to communicate in Dutch; and written informed consent. Exclusion criteria were: renal insufficiency [estimated glomerular filtration rate (eGFR) <30 mL/min/1.73 m^2]; known allergy for fosfomycin; pregnancy or breast feeding; active malignancy; loss or donation of ≥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, 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 min IV infusion. Sampling of blood and urine was performed around a planned dose of 3 g of oral fosfomycin and, optionally, when an oral dose was replaced by the equivalent IV dose.

Blood samples were collected pre-dose and after oral (at t = 30, 60, 90, 120, 180, 240, 300 and 360 min) and IV (at t = 10, 20, 30, 60, 90, 120, 180, 240, 300 and 360 min) fosfomycin administration in plain serum tubes. After collection, samples were centrifuged at 3500 rpm at room temperature and serum was transferred to a storage tube and frozen at −80°C until analysis. Urine was collected for 24 h on 3 consecutive days, starting at the time of administration of fosfomycin. Total 24 h 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 LC–MS/MS method.[21] Analysis of the samples was performed at the Department of Pharmacy, Erasmus MC, Rotterdam, The Netherlands. The upper and lower limits of quantification were 375 and 0.75 mg/L, respectively, for both matrices. Results above the upper limit of quantification were diluted and re-analysed.

Pharmacokinetic analysis

Population pharmacokinetic modelling using non-linear 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-compartment models with linear and non-linear elimination were developed using physiological parameterization, e.g. absolute clearance, absolute volumes of distribution and absolute bioavailability. 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 BMI. 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 equivalent to P = 0.05), standard goodness-of-fit plots (including visual predictive check of 1000 simulations), relative 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 h was calculated by multiplying the volume of urine and the urinary fosfomycin concentration. Serum fosfomycin levels are 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 6 weeks before and after having started fosfomycin treatment for rUTI. A questionnaire based on the Acute Cystitis Symptom Score was used, consisting of a four-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 gastrointestinal complaints, paraesthesias, rash or itching, headache and tiredness. Quality of life was assessed on a scale of 1 (worst) to 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 fosfomycin treatment in months was retrieved from the patients' medical records.

Results

Patient characteristics

In total, three men and nine women with rUTI on stable oral fosfomycin treatment were included. Nine participants (three men and six women) also received an IV 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/1.73 m^2 (63–103). All participants had a urine culture with *E. coli* as the causative microorganism of rUTI. Detailed patient characteristics are listed in Table 1. Individual serum concentrations after 3 g of fosfomycin (oral and IV) are displayed in Figure S1 (available as Supplementary data at *JAC* Online).

Table 1. Patient characteristics

Patient	Sex	Age (years)	BMI (kg/m^2)	eGFR (mL/min/ 1.73 m^2)	Urological history and comorbidities	Duration on fosfomycin treatment (months)	Uropathogen	UTIs per year before treatment	UTIs per year caused by different microorganisms while using fosfomycin	Urinary culture during treatment
1	female	63	27.0	103	pelvic prolapse, gastro-oesophageal reflux disease, epilepsy	5	*E. coli*	9	2	negative
2	female	68	27.4	83	atrial fibrillation, breast cancer, nitrofurantoin pneumonitis	13	*E. coli*	12	2	negative
3	female	69	27.4	95	acromegaly, breast cancer, hypertension	11	*E. coli*	10	0	negative
4	female	63	27.9	92	colorectal cancer, T2DM	2	*E. coli*	12	2	negative
5	male	75	28.7	63	TUR-prostate, neurogenic bladder, CIC, coronary artery disease, sleep apnoea syndrome	75	*E. coli*	8	2	negative
6	female	75	28.7	78	urgency urinary incontinence, T2DM, hypertension, aortic aneurysm	6	*E. coli*	9	0	negative
7	female	74	25.2	66	breast cancer, uterus carcinoma, proctocolitis, carotid artery disease	2	*E. coli*	10	0	negative
8	male	57	28.0	83	CBP, sleep apnoea syndrome	7	*E. coli*	NA	0	negative
9	male	76	26.3	85	CBP with prostate stones, TUR-prostate, hypertension	2	*E. coli*	NA	NA	positive
10	female	75	19.7	83	pelvic prolapse, stress urinary incontinence, iCVA	3	*E. coli*, *Klebsiella pneumoniae*	12	8	positive
11	female	49	26.1	76	hypospadias repair, nephrectomy because of chronic pyelonephritis with renal stones	8	*E. coli*	12	0	negative
12	female	44	28.4	97	none	1	*E. coli*	12	0	negative

CBP, chronic bacterial prostatitis; CIC, clean intermittent catheterization; iCVA, ischaemic cerebrovascular accident; NA, not assessable; T2DM, type 2 diabetes mellitus; TUR, transurethral resection.

Pharmacokinetic analysis

Serum pharmacokinetics

Initial data fitting started using a two-compartment 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 versus time, but caused structural bias and overparameterization (condition number >100 000), so model development was continued with a two-compartment 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 minimization and a proportional error structure resulting in a significantly 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

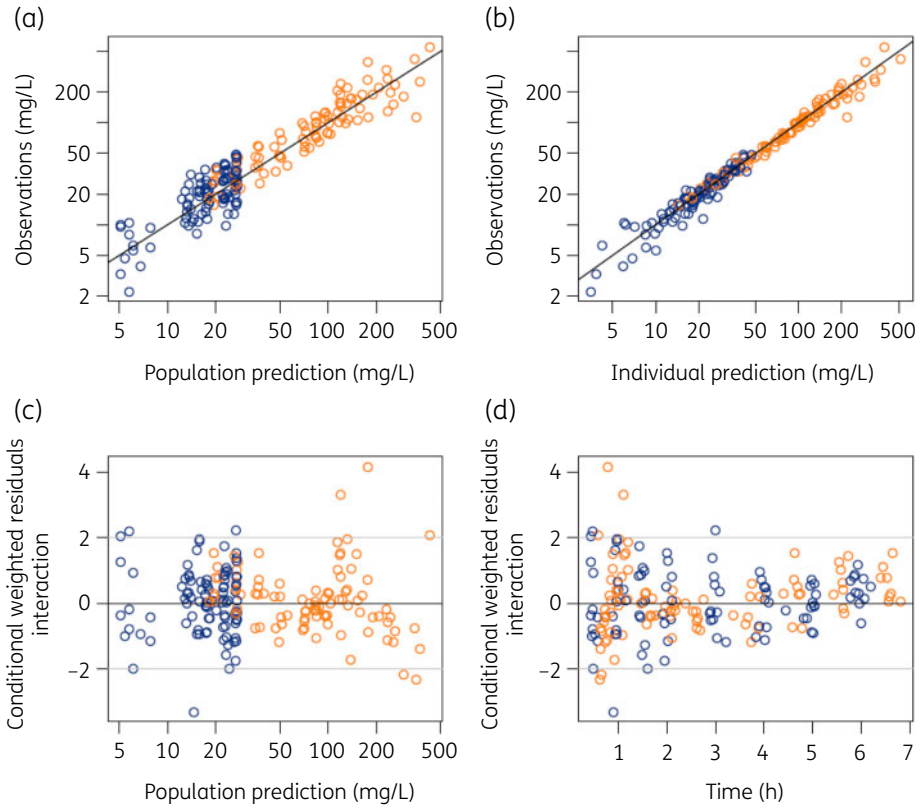

Figure 1. Goodness-of-fit plots of the fosfomycin pharmacokinetic model with serum data after oral (blue) and IV (orange) administration. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Table 2. Population pharmacokinetic parameter and numerical diagnostics

Pharmacokinetic parameter	Parameter estimate (RSE%)	Interindividual variation 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)	
Proportional error (ω^2)	residual error (shrinkage%) = 0.025 (7.34)	
Additive error (ω^2)	residual error (shrinkage%) = 3.43 (7.44)	

conditional weighted residuals with interaction showed no bias over the range of population predictions (Figure 1c), but a slight underprediction for the late timepoints (Figure 1d). The parameter estimates of the population pharmacokinetic model are displayed in Table 2. All parameters were estimated with reasonable precision as all RSEs were below 30%. Between-subject variability was relatively low for clearance, central volume of distribution and bioavailability (with %CV of 25.5%, 22.7% and 40.2%, respectively). The condition number was 50.9, which is well below the threshold of overparameterization. The shrinkages of the empirical Bayes estimates that characterize the interindividual variability and the residual error were well below 20%. The visual predictive check 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

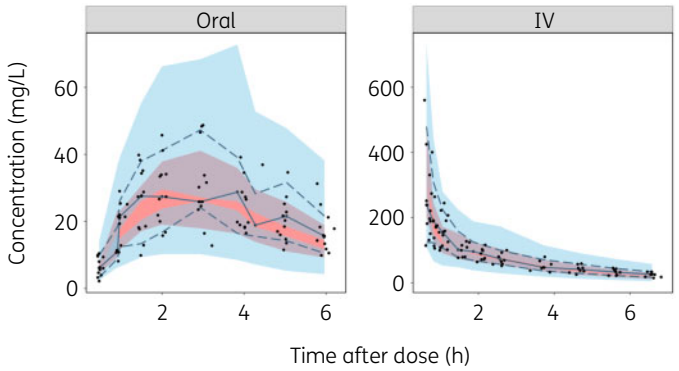

Figure 2. Visual predictive check for the fosfomycin pharmacokinetic model after oral and IV administration. Continuous and broken lines represent the observed 10th, 50th and 90th percentiles for all observations and the shaded areas represent the 95% CI for the 10th, 50th and 90th percentiles of the model predictions. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

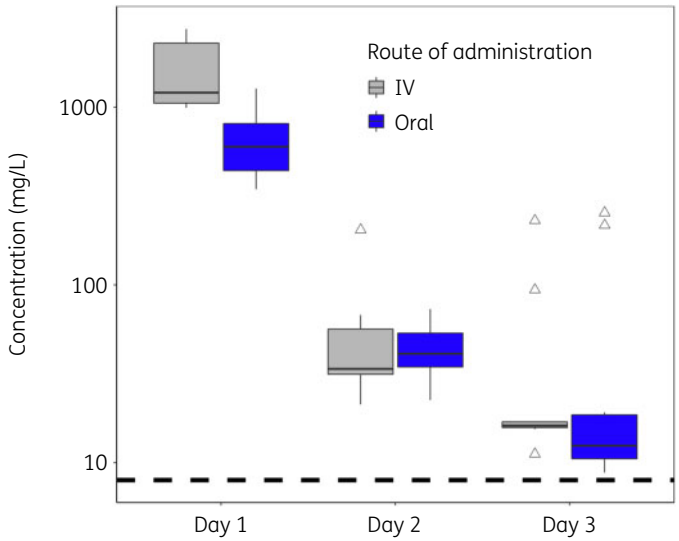

Figure 3. Urine fosfomycin concentrations after IV and oral administration of 3 g of fosfomycin. The broken line represents the MIC for *E. coli* (i.e. 8 mg/L). Outliers are depicted as triangles. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

concentrations are within the 95% 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, 41.41±17.1 and 20.5±45.60 mg/L, respectively. After IV administration these concentrations were 1512.17±788.27, 43.55±43.62 mg/L and 25.37±45.65 mg/L, respectively. The mean ± SD total amount of renally excreted fosfomycin was 1.21±0.37 g after oral intake and 2.96±0.52 g after IV administration.

Clinical effectiveness

Eleven participants completed the questionnaire (92%). The average score of UTI symptoms decreased after fosfomycin dosing (by 3.1 points, 95% CI = −0.7 to 7.0, $P = 0.10$). Quality of life improved by 2.3 points (95% CI = 3.4–1.2, $P = 0.001$). Most reported side effects were gastrointestinal complaints ($n = 8$), tiredness ($n = 8$) and headache ($n = 7$). The details of the questionnaire are provided in Table S1.

Discussion

In this study, we evaluated the pharmacokinetics and clinical effectiveness of IV and oral fosfomycin treatment in patients with rUTI with *E. coli*. The two-compartment pharmacokinetic model accurately described the individual serum fosfomycin concentration–time profiles after oral and IV administration. The total volume of distribution at steady-state (central and peripheral volumes of distribution) was approximately 9.5 L, which is comparable to previously reported literature (range = 9.8–30.2 L).[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 h).[16,17,28–31,33–35] This indicates that our pharmacokinetic model resulted in physiologically plausible parameter estimates. The estimated bioavailability was 18% (95% CI = 11.5%–23.7%), which is markedly lower than previously reported bioavailability estimations (range = 33%–58%).[16,17,27,33] All previously reported bioavailability estimations were measured in a healthy population, whereas our population is older and has more comorbidities, like diabetes mellitus ($n = 2$). Diabetes mellitus may reduce resorption as has been shown for rifampicin.[36] Furthermore, the use of other medication may be another explanation for the difference in bioavailability, e.g. bioavailability of fosfomycin is lowered by co-administration of metoclopramide. Notable is the total amount of renally excreted fosfomycin that we found (1.21 g) 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 bioavailability 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 were fitted to a two-compartment model where a three-compartment 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-compartment model, the model was clearly overparameterized, which indicates that the data do not allow identification of a three-compartmental model. A three-compartment 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 h), urine concentrations remained

relatively high, even after 72 h. This supports the suggestion from the model development process that a three-compartment 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 and hence a prolonged serum exposure and prolonged accumulation of fosfomycin in urine.

Urine fosfomycin concentrations during 24 h ranged from 300 to 1500 mg/L, which is considerably higher than serum exposure (AUC_{0-6} 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.[37] In our study, oral and IV administration of 3 g of fosfomycin resulted in average urine fosfomycin concentrations high enough to induce an antibacterial effect based on the MIC for *E. coli* (i.e. 8 mg/L).[38] Debate is ongoing about whether, in non-tissue invasive UTIs like cystitis, urine concentrations could be used as a marker for efficacy or whether pharmacokinetic/pharmacodynamic indexes for plasma should be used.[39] Based on a recent study using intravesical gentamicin for rUTI, it could be argued that antibiotic urine levels are the dominator of its effect as this strategy was highly effective, while no gentamicin in plasma could be detected.[40]

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-favourable' kinetics, e.g. its relatively short half-life, which would cause the time at which concentrations are above the MIC to be relatively short.[41] In this study, serum concentrations remained above the epidemiological cut-off value for *E. coli* (an MIC of fosfomycin of 8 mg/L) for approximately 10 h after oral administration of 3 g of fosfomycin.[38] This would suggest that, for MDR uropathogenic Enterobacterales with a relatively low MIC, 3 g of 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 an MIC of fosfomycin $\leq$4 mg/L.

In this study we dosed fosfomycin tromethamine at 3 g every 72 h. Rudenko and Dorofeyev[42] 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 at 3 g every 10 days. Based on the study of Rudenko and Dorofeyev,[42] guidelines recommend dosing fosfomycin at 3 g every 10 days for prophylactic purposes.[4] This dosing regimen with a prolonged interval will result in low fosfomycin levels and might induce resistance. Higher concentrations of fosfomycin *in vitro* could decrease resistance development.[43] In this respect a more intensified dosing regimen would be justified. The results of a non-inferiority trial of Costantini *et al.*[12] provide support for an intensified dosing regimen, as 3 g of fosfomycin every 7 days showed non-inferiority to prulifloxacin in female patients with rUTI. However, it is unknown if any unwanted effects occur with an intensified regimen, such as changes in intestinal microbiome, more side effects or development of resistance. It should be noted that high interindividual urinary fosfomycin concentrations were observed in healthy individuals, which makes it difficult to establish a suitable endpoint for effective concentrations and ultimately to choose the most optimal dosing regimen for rUTI.[44]

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

It should be noted that our patient cohort was relatively small and heterogeneous and had rUTI with varying underlying causes. In addition, all participants had fairly good renal function and normal BMI. Previously, creatinine clearance and bodyweight have been identified as covariates that explained part of the interindividual variability for clearance and volume of distribution, respectively.[13] In our data these covariates, unexpectedly, could not be identified. This may be caused by the limited number of subjects and the little variance of renal function in our dataset. Secondly, for the MIC for *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 provide proof that oral fosfomycin provides adequate plasma and urine concentrations of fosfomycin for *E. coli* based on the MIC. Given the growing concern of MDR in rUTI and the limited amount of treatment alternatives, our study argues that 3 g of fosfomycin every 72 h can be an effective oral prophylaxis regimen in patients with *E. coli* rUTIs. Based on the pharmacokinetic model, additional clinical and dosing studies can be developed to evaluate optimal dosing of fosfomycin in patients with UTI.

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Transparency declarations

None to declare.

Author contributions

C.v.N. and S.G.K. conceived the idea for the study. S.G.K., A.C.D., E.B.W., I.M.C.K., J.B., J.S. and C.v.N. contributed to the design of the study. S.G.K., C.v.N. and A.C.D. collected the data. J.S. performed the model development. S.G.K., A.C.D., C.v.N. and J.S. analysed the data and wrote the manuscript. E.B.W., I.M.C.K. and J.B. reviewed the manuscript. All authors approved the final version of the manuscript.

Supplementary data

Figure S1 and Table S1 are available as Supplementary data at *JAC* Online.

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