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Population pharmacokinetics of oral fosfomycin calcium in healthy women

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Background: Fosfomycin is an antibiotic extensively used to treat uncomplicated urinary tract infections in women, and it is available in different salts and formulations. The European Medicines Agency (EMA) recommends further studies to characterize the pharmacokinetics of fosfomycin calcium for oral administration and to justify its dosage recommendation.

Objectives: A population pharmacokinetic model of fosfomycin calcium was developed after oral administration to healthy women.

Methods: A clinical trial (a randomized, open-label, bioavailability study of single and multiple doses of 1000 mg capsules, single dose of 500 mg capsule and single dose of 250 mg/5 mL suspension of oral fosfomycin calcium under fasted conditions in healthy women volunteers, Code: PD7522.22, EudraCT: 2020-001664-28) was carried out at the Clinical Trial Unit, Araba University Hospital (Vitoria-Gasteiz, Spain). Twenty-four healthy women were included in the study, and plasma samples were collected at different times over a period of 24 h. The concentration–time data of fosfomycin in plasma were modelled by a population approach using a nonlinear mixed-effects modelling implemented by NONMEM 7.4 (ICON Clinical Research LLC, North Wales, PA, USA).

Results: The pharmacokinetics of fosfomycin was best described by a two-compartment model. Creatinine clearance and body weight were identified as covariates for fosfomycin clearance and volume of distribution, respectively.

Conclusions: This study provides relevant information on the pharmacokinetic profile of fosfomycin in women after oral administration as calcium salt. This population model may be very useful for establishing dosage recommendations of fosfomycin calcium to treat urinary tract infections in women.

Introduction

Fosfomycin was first isolated from *Streptomyces* spp. cultures in Spain in 1969,[1] although it is currently produced using a synthetic process. It is a low-molecular weight (138 g/mol), highly polar phosphonic acid derivative (cis-1,2-epoxypropyl phosphonic acid) that represents its own class of antibiotics. Fosfomycin has a broad-spectrum antimicrobial activity, which shows bactericidal activity against various Gram-negative and Gram-positive bacteria. It is particularly active against *Escherichia coli* and some other Enterobacterales. It also shows good activity against *Staphylococcus aureus*, including MRSA and most coagulase-negative staphylococci. It is less active against *Enterococcus* spp. and *Pseudomonas aeruginosa*.

Oral fosfomycin is available in different formulations (fosfomycin trometamol granules, fosfomycin calcium hard gelatine

capsules or powder for oral suspension), which are indicated to treat uncomplicated urinary tract infections (UTIs) in women and female adolescents. UTIs are one of the most common types of infections worldwide after respiratory and gastrointestinal tract infections[2,3] and affect women of all ages. Approximately 60% of adult women will experience at least one UTI in their lifetime.[4,5] They are one of the most common indications for which antimicrobials are prescribed[6,7] since they may be properly managed with oral antibiotics in most cases.[8]

Fosfomycin exhibits extensive penetration into many tissues and is well tolerated, but there are differences in absorption between the available fosfomycin salts: a higher bioavailability has been observed for the trometamol derivative (37%–44%), while the calcium salt has a bioavailability of 20%–30%.[9] In addition, whilst the pharmacokinetics of fosfomycin trometamol is well described, there is little information on the calcium salt. Therefore, the data on the recommended doses of fosfomycin trometamol are not applicable to fosfomycin calcium, and existing information regarding safety and efficacy of fosfomycin trometamol cannot be extrapolated directly to fosfomycin calcium, so a clear distinction in the clinical usefulness of both formulations is needed. In fact, the European Medicines Agency (EMA) states that data which justify the labelled dosage recommendation for fosfomycin calcium (500–1000 mg every 8 h) are not available, and further studies are required.[10]

Based on the assumption that additional studies are needed to further evaluate the pharmacokinetics of fosfomycin calcium, the objective of this study was to develop a population pharmacokinetic (PK) model for fosfomycin in healthy women after the oral administration of the calcium salt. The degree of interindividual variability (IIV) of the model parameters was estimated, as well as the subject characteristics responsible for IIV. The impact of using different pharmaceutical formulations on the plasma concentration versus time profiles was also evaluated.

Materials and methods

Study design and setting

This was an open-label, randomized, crossover study of single and multiple doses of fosfomycin calcium administered to healthy women volunteers under fasted conditions carried out at the Clinical Trial Unit, Araba University Hospital (Vitoria-Gasteiz, Spain). The study was conducted after the approval from the Basque Country Ethics Committee, Vitoria-Gasteiz. The Spanish Agency of Medicines and Healthcare Products (AEMPS) authorization was also obtained (Code: PD7522.22, EudraCT: 2020-001664-28). The study was carried out in accordance with both national and international regulations (ICH Guidelines) applicable to clinical trials. Written informed consent was obtained from each subject. No relevant changes after trial commencement occurred.

Participants

Twenty-four healthy women were selected from the database of volunteers from the Clinical Trials Unit located at Araba University Hospital. A formal statistical sample size calculation was not carried out since the main objective of this study was to develop a population PK model for fosfomycin after oral administration of the calcium salt.

Volunteers were eligible for inclusion in the study if the following inclusion criteria were met: (1) healthy women; (2) age between 18 and 55 years inclusive; (3) body mass index (BMI) of 18.5 to 30 kg/m^2; (4) no evidence of significant organic or psychiatric disease based on history, physical examination and additional tests; (5) clinical laboratory values (red blood cell count, haemoglobin, haematocrit, serum and urine glucose, cholesterol, triglycerides, urea, serum creatinine, bilirubin, transaminases, alkaline phosphatase and urine protein, among others) within normal limits; (6) negative test result for hepatitis B and C virus and human immunodeficiency virus; (7) normal electrocardiogram and vital signs; (8) using effective contraceptive method; and (9) capability to communicate effectively and to provide written informed consent.

Participants who met any of the following exclusion criteria were not enrolled in the study: (1) history of allergy or hypersensitivity to drugs and/or excipients; (2) smoker; (3) positive for drugs of abuse at each experimental visit; (4) usage of any prescribed medication, over-the-counter (OTC) medicinal products and/or herbal products during the last 14 days preceding the treatment dosing or when the elimination half-life does not ensure their disappearance from the body in time; (5) breastfeeding and/or pregnancy; (6) major surgery during the previous six months; (7) blood donation in the 12 weeks prior to the commencement of the trial; and (8) participation in another clinical trial during the two months prior to the trial.

Drug administration and dosing

Healthy women received the following test treatments: i) single dose of 500 mg fosfomycin (Fosfocina® 500 mg capsule); ii) single dose of 1000 mg fosfomycin (2 Fosfocina® 500 mg capsules); iii) single dose of 1000 mg fosfomycin (20 mL of Fosfocina® suspension); and iv) multiple doses of 1000 mg (two capsules of Fosfocina® 500 mg/8 h for 3 days). All subjects received all treatments according to a randomized sequence (Tables S1 and S2, available as Supplementary data at *JAC* Online), with a wash-out period exceeding 1 week. Randomization was carried out by using the software MAS v2.1 (GlaxoSmithKline). All formulations were provided by Laboratorios ERN S.A., Barcelona, Spain.

The fosfomycin capsules were administered with 200 mL of water in fasting conditions. During the housing days, a standardized diet was provided to each subject. In all cases, water was restricted for at least 1 h before dosing until 1 h after dosing (except for 200 mL of drinking water administered during dosing). At all other times, drinking water was provided *ad libitum*.

Data collection and drug assay

Blood samples (6 mL) were collected at 13 time-points (baseline or predose and 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 6, 8, 12 and 24 h post-administration) from each subject at each experimental period. When women received the multiple-dose regimen, samples were collected after the last dose. Blood samples were centrifuged at 2000*g* for 10 min at 2°C to 8°C within 30 min after sample collection. The resulting plasma was stored in a freezer at a temperature of −20°C at the clinical site. Later, all samples were stored at −80°C until analysis.

The samples were sent to Kymos Pharma Services, S.L. (Cerdanyola del Vallès, Spain) for blinded analysis. The concentrations of fosfomycin in plasma samples were determined according to a validated high-performance liquid chromatography–mass spectrometry (HPLC–MS/MS) method. Agilent 1100 HPLC system coupled to a mass spectrometer API-4000 Sciex equipped with a TurbolonSpray ion source was used. Linearity was demonstrated from 50 ng/mL (lower limit of quantification) to 50 000 ng/mL (upper limit of quantification). Inter-day and intra-day precision (expressed as coefficient of variation) of the lower limit of quantification was <10%, and inter-day and intra-day accuracies (expressed as relative error) of the lower limit of quantification were <12%. Inter-day and intra-day precision of the quality controls (150–1500–25 000–40 000 ng/mL) was <8%, and inter-day and intra-day accuracies of the quality controls were <10%. Fosfomycin recovery was 72.47%, 75.93% and 83.94% for 150, 1500 and 40 000 ng/mL, respectively.

Population PK modelling

From plasma concentrations of fosfomycin, nonlinear mixed-effects modelling was implemented by NONMEM 7.4 (ICON Clinical Research LLC, North Wales, PA, USA) to estimate fosfomycin PK population parameters using first-order conditional estimation method with interaction (FOCE INTER). Pirana v. 3.0.0 software was used to organize the model-building and evaluation process. A systematic model building approach was followed to determine the structural base model. Afterwards, the best-fit statistical error model was selected, followed by the development of a covariate model and the subsequent model evaluation.

During the model building and according to previously published studies,[11–14] one and two compartment models with first-order absorption and linear elimination were explored as base PK models. Mean population PK variables, IIV and residual error were assessed in the model. IIV, tested for all the structural parameters, was estimated assuming a log-normal distribution of the parameter values in the population. Interoccasion variability (IOV) was evaluated using exponential models for the ratio of clearance to bioavailability (CL/F), the ratio of central volume of distribution to bioavailability (V1/F) and the absorption rate constant (KA) to assess differences in individual parameters across study occasions. Residual variability was explored according to additive, proportional and combined (additive + proportional) error models.

Different variables were explored as potential covariates that may explain the IIV and support a better fit. Age, body weight, creatinine clearance (CL_{CR}), total plasma proteins and transaminase levels (GOT, GPT and GGT) were evaluated for inclusion in the model as continuous covariates. The continuous covariates were all centered to the median value. The formulation type (capsule or suspension) was evaluated as a categorical covariate. The selection of covariates was carried out using a stepwise covariate model-building procedure (SCM tool in PsN 5.0.0). During the forward inclusion and backward deletion, covariates were considered statistically significant if $P<0.05$ (decrease in objective function value >3.84 for 1 degree of freedom) and $P<0.01$ (decrease in objective function value >6.63 for 1 degree of freedom), respectively.

The development, selection and evaluation of the model were based on both statistical and graphical methods. A decrease in the value of the objective function given by NONMEM (approximately equal to $-2\times$Log (Likelihood), −2LL) of 3.84 points between two nested candidate models was considered an improvement in the model performance statistically significant at $\alpha=0.05$. Other selection criteria were the plausibility of the estimated parameters, reduced variance of IIV and residual errors, as well as the goodness-of-fit (GOF) plots. The η- and ε-shrinkage were calculated to determine the reliability of empirical Bayes estimates (EBE) and the power to identify model misspecification in the goodness-of-fit diagnostics.[15] When shrinkage was greater than 20%, the diagnoses based on EBEs were not considered to be informative,[16] and other graphical methods, such as the diagnostic plots based on the normalized prediction distribution errors (npde), were considered.

The predictive performance of the final model was evaluated using a prediction-corrected visual predictive check (pcVPC).[17] The pcVPC was performed with 200 sets of concentration values simulated from the final population PK model. The model was evaluated by comparing the median and 5th and 95th percentiles of the observed concentration–time profile of selected subgroups of subjects in the analysis data set, with the corresponding 90% prediction intervals. Moreover, bootstrapping (Bootstrap tool in PsN 5.0.0) was conducted by running 1000 datasets generated by random sampling in order to assess the robustness of the final model. Non-parametric medians and 95% (2.5th and 97.5th percentiles) confidence intervals (CIs) of pharmacokinetic parameters were obtained and compared with final model estimates.

Using the same dosing regimens administered to volunteers, 2000 subjects with different body weights (55, 64 and 90 kg) and CL_{CR} (80, 108 and 150 mL/min) were simulated to evaluate the impact of the covariates on the PK of fosfomycin calcium by estimating CL/F and V1/F values for each group of virtual women. Body weight and CL_{CR} values were selected considering the range of real values of the women included in the study (55, 64 and 90 kg and 80, 108 and 150 mL/min, respectively).

Results

Demographics, clinical characteristics and sample collection

Twenty-four healthy volunteer women were included in the study. Demographic and laboratory characteristics of the participants are described in Table 1. A total of 13 blood samples for each individual period or phase were withdrawn, and 1124 concentration–time data points were available for population PK model building. For the multiple-dose regimen, two subjects did not complete the dosing schedule properly, and other two did not complete the sampling schedule; therefore, these four patients were excluded for this sequence. Moreover, the concentration of the pre-dose sample in one subject receiving multiple doses was interpreted as analytical error and this concentration value was not considered for the pharmacokinetic study.

Figure 1 shows the plasma concentration–time profiles (normal scale and log scale) of fosfomycin after administration as single (*n*: 24) or multiple dose (*n*: 20). All of them were used for PK modelling. As expected, maximum drug concentration (Cmax) varied depending on the dose level administered. Thus, Cmax ranged from 1.1 to 5.2 mg/L with 500 mg capsules, from 1.2 to 7.0 mg/L with 1000 mg capsules, from 2.5 to 9.5 mg/L with 1000 mg suspension and from 4.3 to 12.3 mg/L with the multiple-dose regimen (1000 mg q8h, 3 days). Regardless of the group, the time to reach Cmax (tmax) ranged from 1 to 4.5 h.

Population pharmacokinetic model development and evaluation

Base model

Considering the population PK model diagnostic criteria previously described, the two-compartment model with first order

Table 1. Demographic data of study participants

Characteristic	Mean	Median	SD	Min	Max
Age (years)	32	32	9	19	49
Weight (kg)	65.1	64.3	9.6	51.7	94.8
BMI (kg/m^2)	23.9	23.9	2.5	20.0	29.9
SCr (mg/dL)	0.77	0.77	0.07	0.64	0.92
CL_{CR} (mL/min)[a]	109.4	108.0	20.7	82.9	158.4
GOT (U/L)	18	17	5	13	34
GPT (U/L	16	13	11	6	54
GGT (U/L)	16	14	7	9	40
Total proteins (g/dL)	7.0	7.0	0	6.3	7.6

BMI, body mass index; CL_{CR}, creatinine clearance; GOT, aspartate aminotransferase; GPT, alanine aminotransferase; GGT, gamma-glutamyl transferase; Min, minimum value; Max, maximum value; SCr, serum creatinine; SD, standard deviation.
[a]Estimated by the Cockcroft–Gault equation.

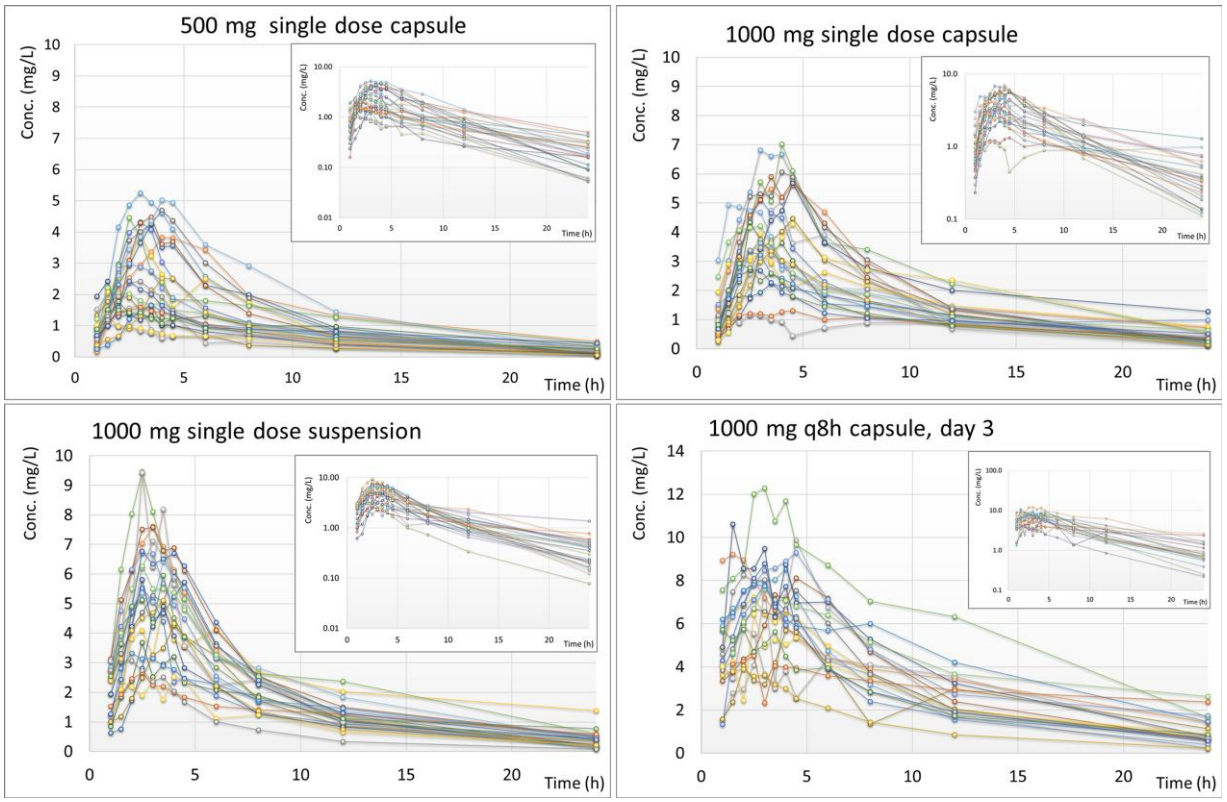

Figure 1. Plasma concentration versus time curves of fosfomycin after the administration of each formulation to women: single dose of 500 mg capsule, single dose of 1000 mg capsule. single dose of 1000 mg suspension and multiple doses of 1000 mg capsules of fosfomycin calcium. In the right upper corner, log scale concentrations. Conc: drug concentration. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

absorption and elimination improved the fit with respect to the one-compartment disposition model. The inclusion of an absorption lag time (TLAG) significantly improved the fitting. The interindividual variability (IIV) was explored on all pharmacokinetic parameters of the model and was described by a log-normal variance model. IIV was identified for CL/F, V1/F, KA and TLAG.

Exponential modelling of IOV was included for CL/F and V1/F. Overall, the inclusion of IOV reduced the IIV on CL/F and V1/F from 22.7% to 20.4% and from 42.5% to 32.1%, respectively, and it was maintained in the model.

Covariate selection and final model

The dosage form (capsules versus suspension) had a significant effect on fosfomycin KA and on TLAG. Body weight and CL_{CR} were also identified as covariates for V1/F and CL/F, respectively. The final population pharmacokinetic model is presented in Table 2, including the model estimates, shrinkage values and the results derived from 919 successful bootstrap runs. Condition number was 8.08, demonstrating no model instability. According to the model, the typical value for V1/F, inter-compartmental clearance (Q/F) and steady-state volume of distribution (Vss/F) are 24.4 L, 4.04 L/h and 144.9 L, respectively. The estimated CL/F value for a woman with CL_{CR} of 108 mL/min is 23.7 L/h. KA was higher with the suspension than with the capsules, and TLAG was shorter with the suspension than with the capsule.

RSE (%) and bootstrap results showed that the parameters were accurately estimated. The npde and CWRES were used to evaluate the selected model because η- and ε-shrinkage exceeded 25%. GOF plots obtained with the final model (Figure 2) showed no trend in CWRES or NPDE over time or predicted concentrations of the drug, respectively. The pcVPC showed that the model adequately predicted the observed data presented in Figure 3, where most of the observations were within the prediction intervals of the model.

In order to explore the impact of the covariates on the PK of fosfomycin, CL/F and V1/F were computed after simulating different cohorts of women (body weight of 55, 65 or 90 kg, and CL_{CR} of 80, 108 or 150 mL/min) receiving single-dose 1000 mg capsule, 1000 mg capsule q8h, single-dose 500 mg capsule or single-dose 1000 mg suspension. Table 3 displays a summary of the main results to analyse the influence of the main covariates on drug distribution and elimination. As it can be seen, V1/F is affected to a great extent by the body weight, increasing from 26.1 ± 19.3 L in women of 55 kg to 42.7 ± 31.7 L if the body weight is 90 kg. Moreover, CL/F increases when the CL_{CR} increases from 21.5 ± 8.5 L/h in women with CL_{CR} of 80 mL/min to 32.8 ± 12.9 L/h in those with CL_{CR} of 150 mL/min.

Table 2. Final population parameter estimated of fosfomycin with the bootstrap results

Parameter	Estimate		RSE (%)	Shrinkage (%)	Bootstrap [median (2.5th–97.5th percentile)]
CL/F (L/h) = θ_{CL}*$e^{(\theta CLCR*(CLCR-108))}$	θ_{CL}	23.7	5	—	23.1 (20.5–25.6)
	θ_{CLCR}	0.0060	38	—	0.0062 (0.0017–0.0107)
V1/F (L) = θ_{V1}*(BW/64)	θ_{V1}	24.4	14	—	24.9 (18.9–32.5)
Q/F (L/h) = θ_{Q}	θ_{Q}	4.04	24	—	4.40 (2.56–6.53)
Vss/F = (V1*(1 + θ_{V2}))	θ_{V2}	4.94	38	—	5.13 (3.14–16.21)
KA (capsules) = θ_{KA1}	θ_{KA1}	0.15	10	—	0.15 (0.12–0.19)
KA (suspension) = θ_{KA1}x θ_{KA2}	θ_{KA2}	1.17	9	—	1.15 (0.98–1.42)
	KA (suspension) = 0.18				
TLAG (capsules) = θ_{TLAG1}	θ_{TLAG1}	0.84	2	—	0.84 (0.81–0.86)
TLAG (suspension) = θ_{TLAG1}xθ_{TLAG2}	θ_{TLAG2}	0.84	5	—	0.83 (0.73–0.91)
	TLAG (suspension) = 0.70				
IIV on CL/F (%)		15.7	27	η_{sh} = 34	15.7 (6.3–22.6)
IIV on V1/F (%)		29.4	47	η_{sh} = 43	30.8 (10.5–51.6)
IIV on KA (%)		32.7	18	η_{sh} = 6.0	32.8 (21.0–44.2)
IIV on TLAG (%)		4.8	34	η_{sh} = 44	5.1 (2.1–7.5)
IOV on CL/F (%)		34.6	10		33.8 (27.8–39.4)
IOV on V1/F (%)		66.7	14		63.9 (43.2–83.3)
RE additive (mg/L)		0.209	17	ε_{sh} = 8	0.201 (0.128–0.309)
RE proportional (%)		0.199	8		0.198 (0.159–0.229)

BW, body weight; CL/F, apparent total body clearance of the drug from plasma; CL_{CR}, creatinine clearance; IIV, interindividual variability; KA, absorption rate constant; Q/F, intercompartmental clearance; RE, residual error; RSE, relative standard error; TLAG, lag time; V1/F, volume of distribution of the central compartment; Vss/F, volume of distribution at steady state; η, deviation between the typical estimate of the parameter and the individual-predicted estimate, corresponds to the IIV; ηsh, shrinkage value for a parameter; εsh, shrinkage value for the residual error.

Discussion

The information available on the pharmacokinetic characteristics of fosfomycin calcium is scarce.[13,18] To the best of our knowledge, this is the first study reporting a population model to describe the pharmacokinetics of fosfomycin after oral administration of the calcium salt. As expected, fosfomycin plasma concentrations measured in our study were lower than those obtained after the administration of the trometamol derivative. According to our results, data concentrations were best supported by a two-compartment model in accordance with other studies with intravenously administered sodium fosfomycin and oral fosfomycin trometamol.[14,19]

The population pharmacokinetic parameters estimated with our model compare well to those reported in previous studies.[14,20] The mean values of fosfomycin Vss/F (144.94 L) and CL/F (23.7 L/h) in the women were similar to those obtained by Wenzler *et al.*[20] after oral administration of fosfomycin trometamol to healthy subjects. They reported a mean V/F of 138.6 ± 57.4 and 147 ± 67.6 L on Days 1 and 5, respectively, after the administration of 3 g every day and a mean CL/F of 22.2 and 20.4 L/h on Days 1 and 5, respectively. Goto *et al.* carried out in 1981 a study to characterize the pharmacokinetics of fosfomycin in Japanese healthy subjects after intravenous and oral (calcium salt) administration.[13] These authors reported Vss values for intravenous administration of 0.32 and 0.36 L/kg for single dose of 20 and 40 mg/kg, respectively. For oral administration of the same dose levels, the mean volume of distribution values were 0.52 and 1.04 L/kg, respectively. They detected discrepancies in the volume of distribution when comparing intravenous and oral administration and between doses, and they concluded that the pharmacokinetic model used in the oral study might be too simple for analysing the concentration profile after oral administration. The distribution volume of fosfomycin is comparable to the total extracellular body water,[21] which is explained by the low molecular weight (182 g/mol), that may facilitate penetration across capillary pores, low plasma protein binding and high hydrophilicity.

Our PK model identified the following covariates: creatinine clearance in CL/F, body weight in V1/F and formulation (capsule or suspension) in absorption parameters (KA and TLAG). Fosfomycin does not undergo metabolism, and it is excreted unchanged in the urine, with less than 0.5% eliminated by the biliary route,[22] which justifies the inclusion of CL_{CR} as a covariate on CL in the final model. Although all participants had normal renal function (CL_{CR} estimated by the Cockcroft–Gault equation ranged from 82.88 to 158.43 mL/min), the CL_{CR} value conditioned the total CL to the extent that CL/F is more than 50% higher in a woman with CL_{CR} of 150 mL/min than in one with a CL_{CR} of 80 mL/min. One study[18] evaluated the pharmacokinetics of fosfomycin tromethamine and calcium in young and elderly subjects, and significant differences were found in fosfomycin clearance between young and elderly subjects with both salts, which may be explained by differences in the CL_{CR} of both groups (127 and 77.9 mL/min, respectively). A recently published population PK model of IV fosfomycin also

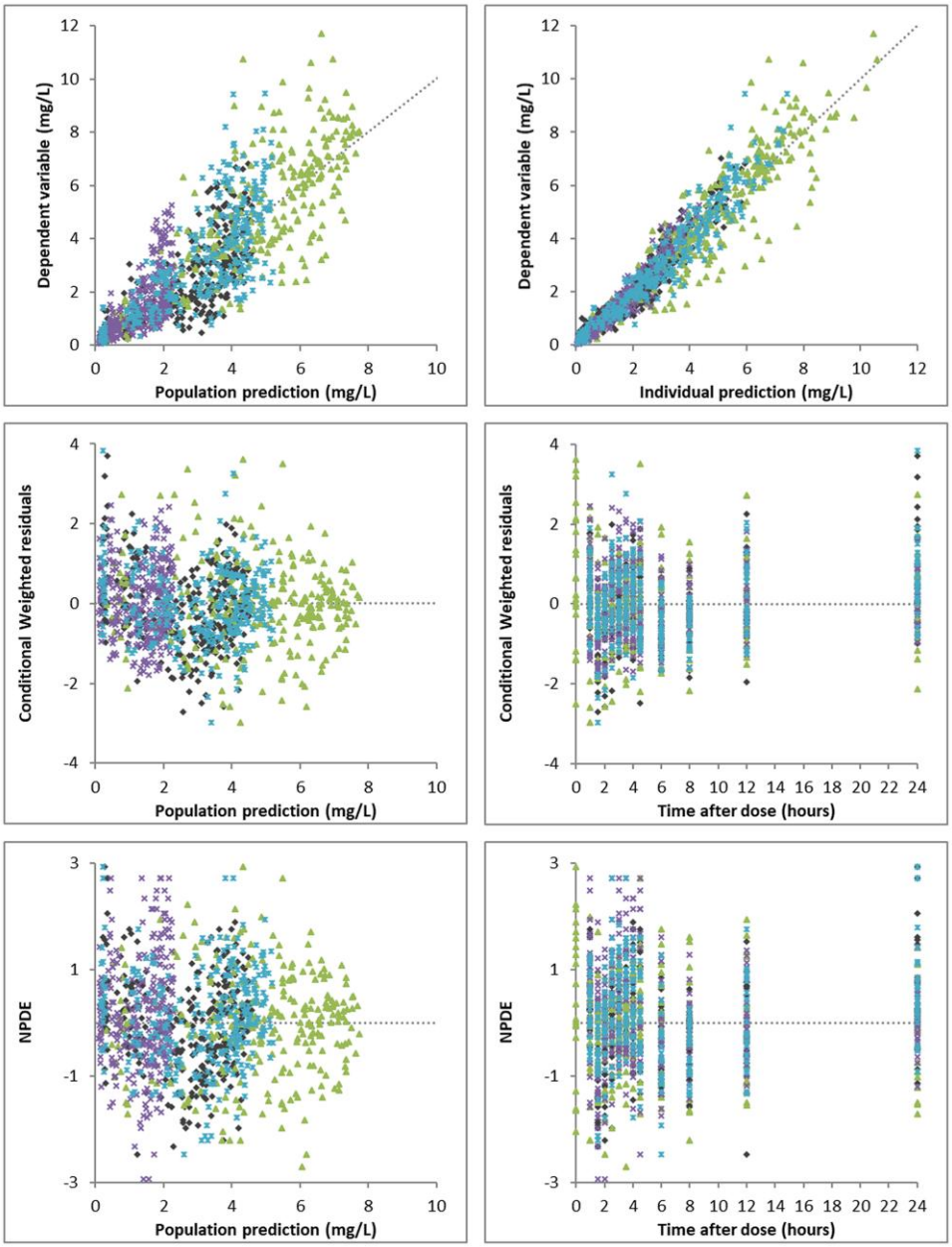

Figure 2. Goodness of fit plots of the final model: population predicted versus the observed fosfomycin concentrations, individual predicted versus observed fosfomycin concentrations, conditional weighted residuals versus population prediction and versus time and normalized prediction distribution errors (NPDE) versus population predicted concentration and versus time. Purple cross: single dose of 500 mg capsule; black diamond: single dose of 1000 mg capsule; green triangle: multiple doses of 1000 mg capsules; blue cross: single dose of 1000 mg suspension. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

identified creatinine clearance as a covariate for CL, and they also recommend adjusting dosing regimens to renal function.[23]

The body weight significantly affected V1/F. This result also reported for other hydrophilic drugs, such as gentamycin,[24] and questioned the common assumption that only limited changes in volume of distribution are to be expected for hydrophilic drugs; that is, lipophilicity alone seems to be a poor predictor of how volume of distribution changes with increasing body weight, as it has been shown in recent reviews.[25,26]

As expected, disposition parameters (volume of distribution and plasma clearance) are not affected by the formulation. However, in our study, fosfomycin given as a suspension showed higher KA and lower TLAG than when given as capsules, although differences are not expected to be clinically relevant.[27–29]

Since fosfomycin is used for the treatment of UTIs, its effectiveness is best correlated to urine drug concentrations rather than plasma levels. In order to assess the effectiveness of fosfomycin calcium, urine samples from the volunteer women were

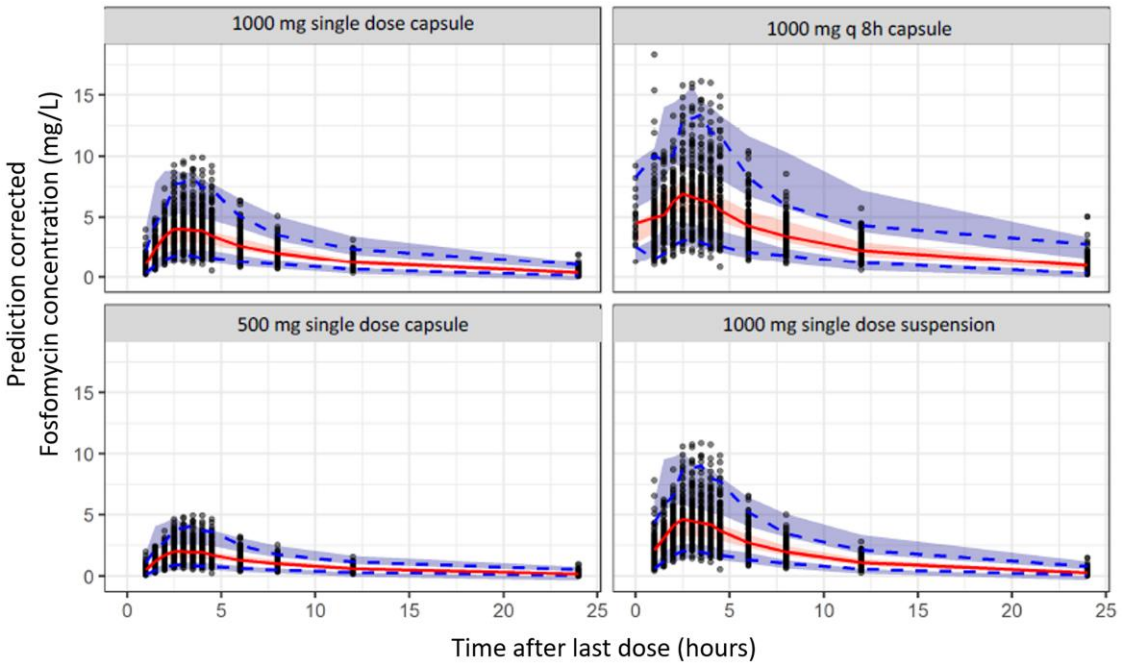

Figure 3. Prediction-corrected visual predictive check of the final model. The dots represent the prediction-corrected concentrations (mg/L). The lines represent the 5th, 50th and 95th percentiles of the observations. Simulation-based 90% prediction intervals for the median and the 5th and 90th percentiles are displayed by pink and blue shading, respectively. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

Table 3. Estimated PK parameters in simulated cohorts of women with different body weights (BW) and creatinine clearances (CL_{CR})

V1/F (L)	BW 55 kg	BW 64 kg	BW 90 kg
Mean (SD)	26.1 (19.3)	30.5 (22.5)	42.7 (31.7)
Median	20.8	24.1	33.7
P		<0.05	<0.05
CL/F (L/h)	CL_{CR} 80 mL/min	CL_{CR} 108 mL/min	CL_{CR} 150 mL/min
Mean (SD)	21.5 (8.5)	25.5 (10.1)	32.8 (12.9)
Median	19.8	23.7	40.5
P		<0.05	<0.05

CL/F, apparent total body clearance of the drug from plasma; V1/F, volume of distribution of the central compartment; SD, standard deviation.

also collected, and a pharmacokinetic/pharmacodynamic (PK/PD) analysis by Monte Carlo simulation was reported.[27] Considering fosfomycin urinary concentrations and the susceptibility profile of *Escherichia coli* (the main bacteria involved in UTIs), the PK/PD analysis revealed that oral fosfomycin calcium at a dose level of 1000 mg every 8 h provides urine concentrations sufficient to attain the established PK/PD target for the treatment of UTIs in women.

The major limitation of this study is that healthy women were included instead of women with UTI. However, significant PK differences are not expected between healthy women and women with uncomplicated UTI, which includes acute, sporadic or recurrent lower (uncomplicated cystitis) and/or upper (uncomplicated pyelonephritis) UTI.[30,31] Another limitation is that in our study, only healthy young women were included, and women with renal failure or obese (BMI ≥ 30 kg/m^2) were excluded. Considering that CL_{CR} and body weight were identified as significant covariates on fosfomycin pharmacokinetics, caution should be exercised when extrapolating results to those subpopulations since dose adjustment might be needed.

Conclusions

In conclusion, this study provides relevant information on the pharmacokinetic profile of fosfomycin in women after oral administration as calcium salt. A two-compartment model best described the plasma concentration time profile, and CL_{CR} and body weight have been identified as important determinants for CL and distribution

volume of the central compartment, respectively. This population model may be very useful for establishing dosage recommendations of fosfomycin calcium to treat UTIs in women.

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Transparency declarations

All authors declare they have no conflict of interest. The funders had no role in the design of the study, in the collection, analyses, or interpretation of data, in the writing of the manuscript or in the decision to publish the results. A.I., A.A.L., and A.R.G. wrote the manuscript; A.I., Z.A., M.C. and A.R.G. designed the research; A.I., Z.A., M.C. and A.R.G. performed the research; and A.I., A.A.L., M.A.S., A.P.R., A.C.B., and A.R.G. analysed the data. All the authors reviewed the manuscript critically and approved the final version to be published.

Supplementary data

Tables S1 and S2 are available as Supplementary data at *JAC* Online.

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