Optimal timing of oral fosfomycin administration for pre-prostate biopsy prophylaxis

Nathaniel J. Rhodes1,2, Bradley J. Gardiner3, Michael N. Neely4,5, M. Lindsay Grayson3,6, Andrew G. Ellis6,7, Nathan Lawrentschuk6,9, Albert G. Frauman6,7, Kelly M. Maxwell10, Teresa R. Zembower11 and Marc H. Scheetz1,2*

1Department of Pharmacy Practice, Midwestern University, Chicago College of Pharmacy, Downers Grove, IL, USA; 2Department of Pharmacy, Northwestern Memorial Hospital, Chicago, IL, USA; 3Department of Infectious Diseases, Austin Health, Heidelberg, Victoria, Australia; 4Laboratory of Applied Pharmacokinetics and Bioinformatics, Saban Research Institute, Children's Hospital Los Angeles, Los Angeles, CA, USA; 5Keck School of Medicine, University of Southern California, Los Angeles, CA, USA; 6Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia; 7Department of Clinical Pharmacology, Austin Health, Heidelberg, Victoria, Australia; 8Department of Surgery, Urology Unit, University of Melbourne, Melbourne, Victoria, Australia; 9Olivia Newton-John Cancer Research Institute, Austin Health, Heidelberg, Victoria, Australia; 10Department of Urology, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA; 11Division of Infectious Diseases, Feinberg School of Medicine, Northwestern University, Chicago, IL, USA

*Corresponding author. Tel: +1-630-515-6116; Fax: +1-630-515-6958; E-mail: mscheetz@nm.org

Received 14 January 2015; returned 1 February 2015; revised 21 February 2015; accepted 23 February 2015

Objectives: As the optimal administration time for fosfomycin peri-procedural prophylaxis is unclear, we sought to determine optimal administration times for fosfomycin peri-procedural prophylaxis.

Methods: Plasma, peripheral zone and transition zone fosfomycin concentrations were obtained from 26 subjects undergoing transurethral resection of the prostate (TURP), following a single oral dose of 3 g of fosfomycin. Population pharmacokinetic modelling was completed with the Nonparametric Adaptive Grid (NPAG) algorithm (Pmetrics package for R), with a four-compartment model. Plasma and tissue concentrations were simulated during the first 24 h post-dose, comparing these with EUCAST susceptibility breakpoints for Escherichia coli, a common uropathogen.

Results: Non-compartmental-determined pharmacokinetic values in our population were similar to those reported in the package insert. Predicted plasma concentrations rapidly increased after the first hour, giving more than 90% population coverage for organisms with an MIC \( \leq 4 \) mg/L over the first 12 h post-dose. Organisms with higher MICs fared much worse, with organisms at the EUCAST breakpoint being covered for <10% of the population at any time. Transitional zone prostate concentrations exceeded 4 mg/L for 90% of the population between hours 1 and 9. Peripheral zone prostate concentrations were much lower and only exceeded 4 mg/L for 70% of the population between hours 1 and 4.

Conclusions: Until more precise plasma and tissue data are available, we recommend that fosfomycin prophylaxis be given 1–4 h prior to prostate biopsy. We do not recommend fosfomycin prophylaxis for subjects with known organisms with MICs >4 mg/L.

Keywords: Drug administration schedule, prostate, pharmacokinetics

Introduction

Pre-procedural antimicrobial prophylaxis remains a standard of care for urological surgery in order to reduce the risk of infectious complications. The American Urological Association and the European Association of Urology recommend prophylactic antimicrobials prior to transrectal ultrasound-guided prostatic biopsy (TRUSP), with an oral fluoroquinolone-based or sulfamethoxazole/trimethoprim-based regimen, usually 1–2 h prior to biopsy.1,2 However, many of the Gram-negative Enterobacteriaceae responsible for urological and prostatic infections are increasingly resistant to such traditional prophylactic agents.3–6 This has led to renewed interest in older agents such as fosfomycin for procedural prophylaxis as well as alternative treatment for urological infections.7–9 Both the efficacy of fosfomycin in preventing infections after TRUSP and the achievable concentrations in prostatic tissue after oral administration have been described previously.7,8 However, previous studies have not addressed the optimal timing.
of fosfomycin administration prior to prostate biopsy. We assessed competing population pharmacokinetic models of fosfomycin after oral administration in order to define the optimal administration timing to provide effective plasma and tissue concentrations against likely pathogens. To aid in this investigation, we utilized available data from adult men undergoing transurethral resection of the prostate (TURP) who received preoperative fosfomycin to allow extrapolation to TRUSP prophylaxis in a pilot study.

Methods

Sample procurement

A total of 26 men undergoing TURP for benign prostatic hyperplasia received a single oral dose of 3 g of fosfomycin for surgical antibiotic prophylaxis between December 2010 and June 2011, as previously described. This study of fosfomycin penetrance was chosen due to its ability to provide sufficient samples of both peripheral zone and transition zone prostate tissue in quantities that allow meaningful pharmacological interpretation in the context of multiple urological procedures. Following the prophylactic dose, samples of plasma and prostate tissue (transition zone and peripheral zone) were obtained between 6 and 18 h after drug administration and assayed for fosfomycin with LC–tandem MS; all specimens were collected, stored and handled as previously described. Plasma samples were obtained at times convenient for subjects relative to the TURP procedure, peri-operative restrictions on oral intake and other procedures undertaken. With the aid of transrectal ultrasound, specific sampling of prostate tissue from the transition zone (typically the first surgical swipe, immediately adjacent to the prostate capsule) and the peripheral zone (typically the last surgical swipe, immediately adjacent to the prostate capsule) was achieved. Care was taken at the time of sample collection to ensure specimen contamination with blood and urine was kept to a minimum.

Population model building

The Nonparametric Adaptive Grid (NPAG) algorithm within the Pmetrics package for R (Los Angeles, CA, USA) was utilized for all model fitting. Multiple compartment models were built and tested to simultaneously model drug input and output as plasma and prostate concentrations (i.e. transition zone and peripheral zone). As all samples were obtained beyond the upper known T_max of 2 h, we fixed the absorption parameter estimate at 0.1 h^{-1} to reduce the variability in parameter estimates immediately after oral ingestion. Mass transit between compartments was fitted using differential equations. Assay error (standard deviation (SD)) was accounted for using an error polynomial as a function of the measured concentration, Y (i.e. SD = C_0 + C_1 Y + C_2 Y^2 + C_3 Y^3), with inputs of 1.15, 0.015, 0 and 0 to incorporate the lowest measured concentrations and a known coefficient of variation of 1.5% from the plasma assay. The inverse of the estimated assay variance (SD^{-2}) was used as the first estimate for weighting in the pharmacokinetic modelling. Final weighting was accomplished using lambda, an additive observation variance model to capture process noise (i.e. error = (SD^2 + lambda)^{-1}). The best-fit model was determined by the rule of parsimony and the lowest Akaiki's information criterion (AIC) score. Median Bayesian posterior parameter estimates for each patient were used for calculations of predicted fosfomycin concentrations. Goodness of fit was assessed by regression with an observed – predicted plot, coefficients of determination and log-likelihood values. Predictive performance evaluation was based on bias and imprecision of the population and individual prediction models. Mean weighted prediction error and bias-adjusted mean weighted squared prediction error defined bias and imprecision, respectively.

Simulations and probability of target attainment

For simulations, we used a semi-parametric sampling method available in Pmetrics rather than a normal or log-normal distribution, to best capture any deviances from normality. The final model consisted of 20 support points, and each point was a set of model parameter values and the probability of these values to predict observed fosfomycin concentrations in the population. Each support point then served as the mean for a multivariate normal distribution, weighted by the probability of the point, with covariance equal to the covariance matrix of the full model divided by the number of points (i.e. 20). The semi-parametric sampling from this
weighted, multivariate, multimodal normal distribution generated a novel population of 1000 parameter sets.

From each of the 1000 sets of simulated parameters, concentration–time profiles were created for 3 g of fosfomycin given orally once. Predicted concentrations were generated every half-hour for the first 24 h of therapy. The percentage of simulated regimens in which the plasma and prostate concentrations exceeded the MIC₅₀ (4 mg/L), the MIC₉₀ (16 mg/L) and the EUCAST MIC breakpoint (32 mg/L) for E. coli was calculated for each hour post-dose. Optimal timing of fosfomycin administration was assessed by evaluating the difference in time from oral administration until plasma and prostate concentrations fell below an MIC value of 4, 16 and 32 mg/L for 90% of the simulated population.

The study was approved by the Institutional Review Board at Midwestern University (Downers Grove, IL, USA) and the Human Research Ethics Committee at Austin Health (Victoria, Australia). All participants provided informed consent.

Results
Among the 26 males assessed, the following mean (±SD) parameters were noted: age, 68 ± 9 years; body weight, 86.2 ± 13 kg; and estimated glomerular filtration rate, 67 ± 12 mL/min/1.73 m². Three subjects did not contribute peripheral zone concentrations due to anatomical or specimen quantity limitations. The peripheral and transition zones were sampled on average 10 ± 3 min (mean ± SD) apart. Predicted plasma, transition zone prostate and peripheral zone prostate concentration–time curves for fosfomycin for the 26 subjects are shown in Figure 2, while the population-weighted parameter value distributions (mean, SD and median) identified using the NPAG fitting algorithm within Pmetrics are shown in Table 1. The non-compartmental estimates of the population pharmacokinetic parameters are shown in Table 2. The median (IQR) predicted plasma maximal concentration was 18.59 mg/L (10.94–20.69 mg/L), the median (IQR) predicted T_max was 2.8 h (2.1–3.0 h) and the median (IQR) predicted total clearance was 12.7 L/h (10.6–20.1 L/h).

Since a four-compartment model provided the best fit for the data, it was used for all simulations. Observed-versus-predicted plots for the four-compartment model were generated for plasma (Figure S1, available as Supplementary data at JAC Online), transition zone (Figure S2) and peripheral zone (Figure S3) concentrations. The r² for the plasma prediction was 0.993 for the posterior Bayesian prediction and 0.281 for the population predictive model (Figure S1). The AIC for the four-compartment model was 200.9. Bias and imprecision for observed versus predicted plasma concentrations were, respectively, −2.261 mg/L and 17.7 mg²/L² for the population model and −0.0519 mg/L and 0.2435 mg²/L² for the individual Bayesian posterior model. The 20 calculated support points and the covariance matrix in the lower triangular form are shown in Tables S1 and S2, respectively.

Optimal timing for oral administration was evaluated using simulated concentration–time profiles. The results of the simulated exposures using the above four-compartment model are shown in Figure 3. Predicted plasma concentrations rapidly increased after the first hour post-dose. However, plasma concentrations failed to exceed the EUCAST MIC breakpoint for E. coli susceptibility (i.e. 32 mg/L) for the entire 24 h period among >90% of the population, with up to 9.6% of the population exceeding the EUCAST breakpoint between 3.4 and 3.6 h post-administration (Figure 3a). At the EUCAST MIC₅₀, up to 59.7% of the population achieved plasma concentrations exceeding 16 mg/L between 2.6 and 2.8 h post-administration. At the EUCAST MIC₉₀, 100% of the population achieved plasma concentrations exceeding 4 mg/L by 0.8 h post-administration, with ≥90% of the population maintaining concentrations above 4 mg/L up to 12.2 h post-administration. Median (IQR) fosfomycin concentrations in plasma at time = 1, 2 and 3 h post-administration were predicted to be 13.4 mg/L (8.33–16.7 mg/L), 16.9 mg/L (10.4–20.5 mg/L) and 17.4 mg/L (11.0–21.2 mg/L), respectively.

Concentrations of fosfomycin in transition zone prostate tissue failed to exceed the EUCAST breakpoint for E. coli susceptibility in >90% of the population for the entire 24 h period, with up to 1.4% of the population exceeding the EUCAST breakpoint at 3.4 h post-administration. At the EUCAST MIC₅₀, 27.7% of the population achieved transition zone concentrations exceeding 16 µg/g between 4 and 4.4 h post-administration. At the EUCAST MIC₉₀,
Timing of fosfomycin for biopsy prophylaxis

Table 1. Post-Bayesian compartmental population pharmacokinetic parameter estimates for fosfomycin after oral administration

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Model estimates</th>
<th>Package insert</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>SD</td>
</tr>
<tr>
<td>( K_{12} )</td>
<td>rate constant after oral administration (fixed at 0.1 h(^{-1})); ( K_{13} ), rate transfer constant between central compartment and transition zone (per hour); ( K_{14} ), rate transfer constant between central compartment and peripheral compartment (per hour); ( K_{24} ), rate transfer constant between peripheral zone and central compartment (per hour); ( K_{32} ), rate transfer constant between peripheral zone and prostate (per hour); ( K_{30} ), elimination rate constant between central compartment (per hour); ( V_2 ), volume of distribution for central compartment (L); ( V_3 ), volume of distribution for peripheral zone (L); ( V_4 ), volume of distribution for peripheral zone prostate (L).</td>
<td></td>
</tr>
<tr>
<td>( K_{23} )</td>
<td>5.811</td>
<td>3.419</td>
</tr>
<tr>
<td>( K_{32} )</td>
<td>4.201</td>
<td>1.963</td>
</tr>
<tr>
<td>( K_{24} )</td>
<td>4.299</td>
<td>2.989</td>
</tr>
<tr>
<td>( K_{30} )</td>
<td>7.115</td>
<td>1.883</td>
</tr>
<tr>
<td>( K_{30} )</td>
<td>2.854</td>
<td>0.882</td>
</tr>
<tr>
<td>( V_2 )</td>
<td>5.865</td>
<td>3.340</td>
</tr>
<tr>
<td>( V_3 )</td>
<td>10.938</td>
<td>5.016</td>
</tr>
<tr>
<td>( V_4 )</td>
<td>7.065</td>
<td>2.484</td>
</tr>
</tbody>
</table>

\( K_{12} \), absorption rate constant after oral administration; \( K_{13} \), rate transfer constant between central compartment and transition zone (per hour); \( K_{14} \), rate transfer constant between central compartment and peripheral compartment (per hour); \( K_{24} \), rate transfer constant between peripheral zone and central compartment (per hour); \( K_{30} \), elimination rate constant between central compartment (per hour); \( V_2 \), volume of distribution for central compartment (L); \( V_3 \), volume of distribution for peripheral zone prostate (L). 

Table 2. Plasma non-compartmental population pharmacokinetic parameter estimates for fosfomycin after oral administration derived from Bayesian posterior individual time-concentration fosfomycin profiles

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Model estimates</th>
<th>Package insert</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>mean</td>
<td>SD</td>
</tr>
<tr>
<td>( C_{\text{max}} ) (mg/L)</td>
<td>17.909</td>
<td>8.027</td>
</tr>
<tr>
<td>( CL ) (L/h)</td>
<td>15.016</td>
<td>7.050</td>
</tr>
<tr>
<td>( K_{el} ) (1/h)</td>
<td>0.098</td>
<td>0.004</td>
</tr>
<tr>
<td>( V ) (L)</td>
<td>169.409</td>
<td>79.285</td>
</tr>
<tr>
<td>( T_{\text{max}} ) (h)</td>
<td>2.700</td>
<td>1.045</td>
</tr>
<tr>
<td>( t_{1/2} ) (h)</td>
<td>7.059</td>
<td>0.313</td>
</tr>
<tr>
<td>( \text{AUC} ) (mg·h/L)</td>
<td>236.507</td>
<td>121.758</td>
</tr>
</tbody>
</table>
| \( \text{AUC}_{\text{0-\infty}} \) (mg·h/L) | 247.044 | 128.722 | 2071 | 20 April 2019

Discussion

We believe this is the first pilot pharmacokinetic study to model the optimal dosing schedule for fosfomycin when used as single-dose prophylaxis prior to prostatic surgery. Our findings indicate that 3 g of fosfomycin in most likely to achieve adequate plasma and prostatic concentrations for highly susceptible organisms (MIC ≤ 4 mg/L) when surgery is performed between 1 and 4 h post-dose. Our interim recommendation is to wait at least 1 h after fosfomycin is administered to initiate surgery. This recommendation is based on: (i) predicted concentrations from our model; and (ii) uncertainty with the earliest concentrations in the model (due to constraints in sampling). When organisms are at the EUCAST MIC\(_{90}\) (i.e. 16 mg/L), moderate activity existed in the plasma between hours 1 and 5; prostatic concentrations were predicted to be insufficient for the vast majority of patients with organisms with an MIC of 16 mg/L. Few very patients will attain therapeutic concentrations of fosfomycin in the plasma or prostate when organisms have MICs ≥ 32 mg/L. In the setting of MICs ≥ 32 mg/L, TRUSP prophylaxis with fosfomycin is not predicted to be effective, and alternative agents should be pursued.

Previous studies of other agents and some guidelines suggest prophylaxis administration up to 3 h prior to biopsy. However, our recommendation of administration between hours 1 and 4 prior to surgery is slightly different from this recommendation. Our analysis suggests that attaining therapeutic concentrations in the prostate may be delayed and blunted compared with plasma. Therefore, we recommend administration of prophylaxis between hours 1 and 4. Additionally our results demonstrate that activity may be minimal at MICs well below the EUCAST breakpoint. Thus, oral fosfomycin may not be an optimal agent against some pathogens (such as highly resistant or MDR organisms with elevated fosfomycin MICs), particularly if maintaining prostatic concentrations above the MIC is important for the prevention of septic complications. Unlike previous authors who studied the prostatic pharmacokinetics of fluoroquinolones, the last dose being received ~1–5 h before analysis, our study population had therapeutic drug monitoring performed a median of 10 h after fosfomycin administration (ranging between 7 and 17.8 h). Since serially sampling prostatic tissue is difficult, our study was limited to tissue at a single timepoint for each patient. Nevertheless, adequate pharmacokinetic variation in our cohort allowed reasonable parameter estimation and simulation. Non-compartmental analyses of concentrations among our study subjects revealed maximum fosfomycin plasma concentrations and half-lives, reported as mean ± SD, of 17.9 ± 8.0 mg/L and 7.1 ± 0.3 h, respectively. The package insert describes a maximal plasma concentration of 26.1 ± 9.1 mg/L and a half-life of 5.7 ± 2.8 h after oral administration. Thus, our sample subjects demonstrated similar pharmacokinetics to subjects reported in the package insert.
Our study has limitations. Firstly, since very few prostate concentrations were obtained early after the dose, we are unable to make robust assessments of predicted inter-prostate transfer of fosfomycin soon after the dose was administered. Secondly, since subjects in our pilot pharmacokinetic cohort underwent TURP, which provides an approximation of prostatic concentrations, rather than TRUSP, we cannot be sure our findings are entirely generalizable to TRUSP prophylaxis—but they represent the most accurate and informative data currently available on this topic. Thirdly, though all subjects sampled in our pilot pharmacokinetic cohort had benign prostatic hyperplasia and not cancer or concurrent infection, the homogeneity of sample specimens according to diagnosis makes our model conservative. Future studies should evaluate whether patients with greater levels of inflammation achieve greater prostatic concentrations. Fourth, the prostate is a vascular tissue and as such some of the detectable fosfomycin in the prostate samples may represent fosfomycin within small blood vessels within the prostate rather than the prostate tissue itself. However, to the extent possible, care was taken to prevent prostate specimen contamination and the difference in observed concentrations in prostatic specimens compared with blood supports the absence of any systematic contamination. Additionally, peripheral zone prostatic concentrations may have been underestimated in our TURP-based model as this prostatic area is difficult to adequately sample in TURP. Future studies confirming prostatic concentrations via TRUSP are needed. Notably, our modelling was based on the predicted plasma concentrations required to achieve the EUCAST breakpoints for *E. coli* rather than those suggested by the CLSI (MIC 64 mg/L), since these latter breakpoints are defined solely for urinary infections. Clearly, local rates of fosfomycin susceptibility among potential pathogens may influence efficacy.

![Figure 3. Probability of fosfomycin concentrations exceeding the MIC at each hour indicated in (a) plasma, (b) transition zone prostate and (c) peripheral zone prostate. MIC\textsubscript{50}, 50th percentile MIC within the EUCAST database for *E. coli*; MIC\textsubscript{90}, 90th percentile MIC within the EUCAST database for *E. coli*.](https://academic.oup.com/jac/article-abstract/70/7/2068/776503)
In conclusion, given the increasing resistance of common pathogens to currently available antibiotics, our population modelling of fosfomycin concentrations in plasma and prostate has potentially important clinical implications for the use of this ‘forgotten’ agent. Based on our data, optimal concentrations are likely to require oral dosing 1–4 h prior to prostate procedures—an issue which may have implications for patients who require anaesthesia where a period of pre-operative fasting is often required. Further studies are necessary to better characterize plasma and prostatic fosfomycin concentrations following single and repeated oral dosing.

Acknowledgements

Portions of this paper were presented as a poster at the Fifty-fourth Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington, DC, 2014 (A-944).

We would like to acknowledge the following individuals who assisted with the original study of fosfomycin: Dr Andrew A. Mahony, MBBS, FRACP; Dr Damien M. Bolton, MD; MBBS, BA, FRACS, FRCS; and Mr Philip T. Zeglinski, BSc (Hons).

Funding

This study was carried out as part of our routine work.

Transparency declarations

None to declare.

Supplementary data

Tables S1 and S2 and Figures S1 to S3 are available as Supplementary data at JAC Online (http://jac.oxfordjournals.org/).

References


