The pharmacokinetics of fosfomycin in urine

Evaluation of the effectiveness of the treatment of uncomplicated urinary tract infections based on urinary concentrations

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Fosfomycin background

- Urinary tract infections (UTIs) are the most common bacterial infections among otherwise healthy, nonpregnant women.\footnote{Araj GF et al. Leban. Med. J. 2012}
- Antimicrobial resistance is increasing among uropathogens.\footnote{Naber KG et al. Eur Urol. 2008}
- Oral fosfomycin remains one of the most effective antibiotics in the treatment of UTIs.
- Surprisingly, little is known about the pharmacokinetics (PK) of fosfomycin in urine.

The **FUEL** study was born!

(Fosfomycin Urine concentrations in hEalthy voLunteers)
Aim of the FUEL study

An evaluation of the effectiveness of the current treatment of uncomplicated urinary tract infections with fosfomycin

Measuring fosfomycin concentrations in urine during 7 days in healthy volunteers
after a single, oral dose of 3 grams

April 2016: Approval of ethical committee
July 2016: First volunteer was included
Sept 2016: End of inclusion
- study design (1)

3 grams fosfomycin

x 40

Date
Time
Volume
pH

0-48h EVERY
48h – 7 days 2x daily

1 mL
– study design (2)

Timepoints

Concentrations

Wijma, RA et al. 2017 (paper submitted)
The following **PK parameters** were calculated:

- Maximum concentration (mg/L) $C_{\text{max}}$
- Time to $C_{\text{max}}$ (h) $T_{\text{max}}$
- Concentration half-life (h) $T_{1/2}$
- Fosfomycin clearance (mg/h) $CL_{\text{fos}}$
- Recovery (%)

The following **PK/PD indices** were calculated:

- $T>MIC$: Time > Minimal Inhibitory Concentration [1]
- $AUC/MIC$: Area Under the Concentration-time curve / MIC [1]

[1]. MICs of the most common uropathogen, *E.coli*
Demographics & Sample collection

Demographics of the 40 healthy, female volunteers:

- **Age:** 24.3 ± 7.9 years
- **Length:** 170 ± 6.4 cm
- **BMI:** 22.1 ± 2.4
- **eGFR:** 119.7 ± 24.0 mL/min

Sample collection:

- **891 samples** were collected
- Mean number of samples for each volunteer: **22 (± 3)**
- Mean **pH** of all samples: **5.5 (± 0.5)**
Example of a concentration-time curve ($n=1$)

- $C_{\text{max}} = 4376 \text{ mg/L}$
- $T_{\text{max}} = 9.6 \text{ h}$
Mean concentrations over time \((n=40)\)

- \(C_{\text{max}} = 1982.0\ \text{mg/L}\)
- \(T_{1/2} \approx 12\ \text{h}\)
- \(T_{\text{max}} = 7.5\ \text{h}\)
- \(C_7\ \text{days} = 1.8\ \text{mg/L}\)
Mean concentrations over time ($n=40$) - with variance

- High interindividual variability (IIV) in urinary concentrations
  - $C_{\text{max}}$: 525-4414 mg/L
  - First sample < 0.75 mg/L: for some volunteers already after 48h and for some after > 168h

Mean concentration (mg/L) vs. Time after dose (h)
Mean cumulative recovery \((n=40)\) – with variance

Recovery\(_{48h}\) = 44.5% (26.2% - 65.1%)

Recovery\(_{7\text{days}}\) = 47.0% (26.4% - 67.1%)
T>MIC for all MICs \((n=40)\)

- All strains with MIC 0.5 - 64 mg/L are covered for at least \(48\) hours
- Only strains with MIC of \(128\) mg/L are not covered during the first \(48\) hours
T>MIC for all MICs \((n=40)\) – **with variance**

- **All strains with MIC 0.5 - 64 mg/L** are covered for at least 48 hours.
- **Only strains with MIC of 128 mg/L** are not covered during the first 48 hours.
- **But this conclusion is incorrect** if the variance is taken into account.

These strains could also have T>MIC of less than 48 hours so only MICs 0.5-4 mg/L are covered.
AUC$_{7\text{days}}$/MIC for all MICs ($n=40$) – with variance

- **MIC 0.5 - 2 mg/L:** Covered
- **MIC 4 – 8 mg/L:** Uncertain due to high variability in urinary concentrations
- **MIC 16 - 128 mg/L:** Not covered

[1]. fAUC/MIC for bacteriostasis in urine (3994) conform "Rationale for the EUCAST clinical breakpoints, version 1.0"
Conclusions

- Concentration over time:
  - Large variability is present in healthy volunteers with normal renal function, BMI, and urinary pH ($C_{\text{max}}$ 525 - 4414 mg/L)

- Excretion:
  - Recovery over 48 h (44.5%) ≈ Recovery over 7 days (47.0%)

- PK/PD index:
  - Time > MIC: Only MICs of 0.5 – 4 mg/L are covered during 48 h
  - AUC / MIC: MIC’s of 0.5 – 2 mg/L are covered for bacteriostasis
  - Difficult to evaluate effectiveness due to large variability
Acknowledgements

- Funding and support
  - This project was supported by the European Commission FP7 AIDA project (Preserving old antibiotics for the future, Health-F3-2011-278348)

- Volunteers
  - For participation

- Team lab hospital pharmacy Erasmus MC
  - Technical support with the LC-MS/MS method

- Johan Mouton, Birgit Koch and Teun van Gelder
  - For the support and guidance
Overview PK parameters and PK/PD indices

<table>
<thead>
<tr>
<th>PK parameter</th>
<th>Population mean</th>
<th>SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$</td>
<td>(mg/L)</td>
<td>1982.0</td>
</tr>
<tr>
<td>$T_{\text{max}}$</td>
<td>(h)</td>
<td>7.5</td>
</tr>
<tr>
<td>$T_{1/2}$</td>
<td>(h)</td>
<td>12.4</td>
</tr>
<tr>
<td>Recovery 0-7 days</td>
<td>(%)</td>
<td>47.0</td>
</tr>
<tr>
<td>Recovery 0-48 h</td>
<td>(%)</td>
<td>44.5</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PK/PD index</th>
<th>Population mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>$T &gt; \text{MIC}_{32 \text{ mg/L}}$</td>
<td>(h)</td>
<td>60</td>
</tr>
<tr>
<td>$\text{AUC}_{7\text{days}}/\text{MIC}$</td>
<td>MICs</td>
<td>0.5-2.0 mg/L covered</td>
</tr>
</tbody>
</table>

* ECOFF E.coli (32 mg/L) conform EUCAST

- $T_{\text{max}}$ was found to be higher compared to literature (< 4h)
- Large variability between subjects for all parameters/indices