Population pharmacokinetics of rifampicin in South African tuberculosis patients and the influence of drug transporter polymorphisms

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Introduction

• In 2008, 9-10 million new cases of tuberculosis (TB) with 2 million deaths (WHO, 2009)

• **Rifampicin** is key drug in treatment of TB

• Antimycobacterial effect and resistance depend on rifampicin concentration (Gumbo et al, 2007)

• Previous studies have shown highly variable rifampicin plasma concentrations (Wilkins et al, 2008)
AIM

• To describe the population pharmacokinetics of rifampicin in TB patients on standard treatment and investigate factors affecting interindividual variability
Methods

**Study Participants**
- 57 patients with pulmonary TB in Western Cape
- 21 patients were sampled on a second occasion
- 3-8 plasma samples at steady state (437 observations)

**Drug plasma concentration determination**
- LC-MS-MS

**Pharmacokinetic Analysis**
- Population non-linear mixed effects modeling using NONMEM VII

**Genotyping**
- Real-time PCR using fluorescent probes for allelic discrimination
- Genes included ABCB1, PXR, CAR, SLCO1B1
RESULTS

Allele frequencies in study population

- **SLCO1B1**
- **ABCB1**
- **PXR**
- **CAR**

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Rifampicin Pharmacokinetic Model

**DOSE**

- $F = 1$ for wild type
- $F = 0.82$ for SLCO1B1 rs4149032 heterozygotes
- $F = 0.72$ for homozygotes

**MTT**

- $MTT = 1.6\text{h}$ for males
- $MTT = 2.1\text{h}$ for females
- 27% shorter MTT with increasing dose

**CENTRAL COMPT**

- $V = 44\text{L/70kg}$ for males
- $V = 31\text{L/70kg}$ for females

**CL**

- $CL = 11\text{ L/h/70kg}$

$Ka = 1.1/\text{h}$
Visual Predictive Check
Observations vs. Time (Run 0)

- **Observations**
- **Median of observations**
- **5th and 95th percentiles of observations**
- **Model predicted confidence interval for corresponding percentile**
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Simulated Cmax before and after dose adjustment

Cmax mg/L

Wild type
Carrier dose 1
Carrier dose 2
Simulated AUC before and after dose adjustment

AUC$_{(0-\infty)}$ mg.h/L

Wild type  Carrier dose 1  Carrier dose 2
• Study underpowered to detect effect of ABCB1, CAR and PXR genotypes
• Higher doses shortened MTT
• 463C>A, rs11045819 has recently been reported to decrease rifampicin AUC (Weiner et al, 2010), but this allele was rare in our study population
Conclusion

• The SLCO1B1 rs4149032 polymorphism exists at a high frequency and results in a decrease in bioavailability of rifampicin of up to 30%
• Further studies in a larger population are required to confirm these findings
Acknowledgements

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<table>
<thead>
<tr>
<th>Parameter</th>
<th>Estimate (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL/F L/h/70kg</td>
<td>11 (10-12)</td>
</tr>
<tr>
<td>V/F L/70kg</td>
<td>50 (44-52)</td>
</tr>
<tr>
<td>$k_a$ /h</td>
<td>1.1 (0.9-1.3)</td>
</tr>
<tr>
<td>MTT h</td>
<td>1.6 (1.4-1.8)</td>
</tr>
<tr>
<td>Effect of female sex on V/F %</td>
<td>-30 (25-34)</td>
</tr>
<tr>
<td>Effect of female sex on MTT %</td>
<td>-30 (25-34)</td>
</tr>
<tr>
<td>Effect of $SLCO1B1$ rs41490932 on F1 in heterozygotes %</td>
<td>-18 (17-20)</td>
</tr>
<tr>
<td>Effect of $SLCO1B1$ rs41490932 on F1 in mutants %</td>
<td>-28 (21-30)</td>
</tr>
<tr>
<td>Effect of dose on MTT %</td>
<td>-27 (24-35)</td>
</tr>
<tr>
<td>BSV in F1 %</td>
<td>15 (12-16)</td>
</tr>
<tr>
<td>BSV in CL %</td>
<td>20 (18-29)</td>
</tr>
<tr>
<td>BSV in MTT %</td>
<td>52 (48-72)</td>
</tr>
<tr>
<td>Correlation between BSV in CL and MTT</td>
<td>0.86 (0.82-0.90)</td>
</tr>
<tr>
<td>WSV in F1 %</td>
<td>21 (16-22)</td>
</tr>
<tr>
<td>WSV in CL %</td>
<td>32 (30-48)</td>
</tr>
<tr>
<td>WSV in V %</td>
<td>29 (24-37)</td>
</tr>
<tr>
<td>WSV in MTT %</td>
<td>59 (47-63)</td>
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<tr>
<td>Correlation between WSV in V and MTT</td>
<td>-0.40 (-0.33 -0.74)</td>
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</tbody>
</table>