Model based evaluation of higher doses of rifampicin using a semi-mechanistic model incorporating auto-induction and saturation of hepatic extraction

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Rifampicin is the backbone of 1st line TB treatment

Recent reports suggest increasing the current dose (Boeree et al. 2015)

Metabolism by arylacetamide deacetylase (AADAC)
• a liver esterase (Nakajima et al. 2011)

Auto-induction:
• potent inducer of PXR-mediated pathways, increases its own clearance (and that of other drugs).
• auto-induction has been reported to take about a week (Smythe et al. 2013)

Dose-exposure non-linearity:
• seemingly saturation of metabolism (Acocella, 1978)
Changes in rifampicin exposure

Rifampicin exposure by weight-band (# of tablets), and day of treatment (McIlneron et al. 2012) Patients with lower weight and men were found to have lower exposure.
Aims

To quantify rifampicin auto-induction
  • Progression (how long?)
  • Extent (how much?)

To explain the exposure differences between weight-bands, and sex

To characterise dose-exposure non linearity
  • Hepatic extraction (saturation?)

To explore change in rifampicin exposure when doses are increased beyond the currently recommended dose of 10 mg/kg (range 8-12 mg/kg)
Data and Methods

61 South African, HIV+, TB patients (33 females and 28 males)

RIF + INH + PZA + ETH given as FDC once daily in the morning (mostly 5 days per week, 10 patients on 7 days p. w.)

Samples were taken on day 0, 7, 14, and 28 at 0, 1, 2, 4, 6, 8, 12 hours after dose

Doses adjusted according to body weight:

<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>&lt;37.9</th>
<th>38-54.9</th>
<th>55-69.9</th>
<th>&gt;70</th>
</tr>
</thead>
<tbody>
<tr>
<td># Tablets</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>RIF (mg)</td>
<td>300</td>
<td>450</td>
<td>600</td>
<td>750</td>
</tr>
</tbody>
</table>

Data analysed with NONMEM VII and FOCE-I
Structural Model

Hepatic extraction was described using a well-stirred liver model with saturation characterised using Michaelis-Menten kinetics (Gordi et al. 2005).

Changes in the PK parameters due to auto-induction were investigated.

Allometric scaling to adjust CL & V parameters for body size, using different size predictors.
Saturable Hepatic Metabolism

Well-stirred liver model:
Hepatic extraction \( (E_H) \) depends on:
- hepatic plasma flow \( (Q_H) \)
- enzymatic activity \( (CL_{int}) \)
- protein binding \( (f_u) \)

\[
E_H = \frac{CL_{int} \cdot f_u}{CL_{int} \cdot f_u + Q_H}
\]

\[
CL_H = Q_H \cdot E_H
\]

\( CL_{int} \) was saturable, depending on hepatic concentration \( (C_H) \)

\[
CL_{int} = \frac{CL_{int,max} \cdot K_m}{C_H + K_m}
\]

Parameter values were fixed
\( f_u = 20\% \quad Q_H = 50 \text{ L/h} \quad V_H = 1 \text{ L} \)
Auto-induction

Maximal Intrinsic CL vs days on treatment

\[ CL_{int,max} = CL_{int,max}^0 + (CL_{int,max}^{SS} - CL_{int,max}^0) \cdot \left( 1 - e^{-\left( \frac{\ln(2)}{t_{1/2\,ind}} \right) \cdot t} \right) \]
Individual $\text{CL}_{\text{int}}$ and $V$ of the central compartment were scaled using each subject’s fat-free body mass (FFM). Same for $Q_H$ and $V_H$.

Some women in the largest weight-band had FFM and thus $\text{CL}_{\text{int}}$ no larger than much smaller patients...

Relatively over-dosed.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical Value (90% CI)</th>
<th>BSV(%) (90% CI)</th>
<th>BOV(%) (90% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$CL^0_{int,max}$ [L/h]</td>
<td>93.2 (83.7-108)</td>
<td>22.5 (19.1-26.1)</td>
<td>21.9 (18.3-25.7)</td>
</tr>
<tr>
<td>$CL^{SS}_{int,max}$ [L/h]</td>
<td>176 (159-210)</td>
<td>22.5 (19.1-26.1)</td>
<td>21.9 (18.3-25.7)</td>
</tr>
<tr>
<td>$t_{1/2ind}$ [days]</td>
<td>4.5 (4.1-4.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$K_m$ [mg/L]</td>
<td>3.35 (3.00-3.56)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$V$ [L]</td>
<td>50.1 (47.7-52.8)</td>
<td>14.2 (11.5-16.2)</td>
<td></td>
</tr>
<tr>
<td>Pre-Hepatic Bioavailability</td>
<td>1 FIXED</td>
<td></td>
<td>11.0 (9.6-13.6)</td>
</tr>
<tr>
<td>$K_a$ [h$^{-1}$]</td>
<td>1.96 (1.7-2.2)</td>
<td></td>
<td>81.2 (72.2-88.4)</td>
</tr>
<tr>
<td>MTT (Abs Mean Transit Time) [h]</td>
<td>0.71 (0.67-0.78)</td>
<td></td>
<td>62.7 (57.0-75.4)</td>
</tr>
<tr>
<td>NN (Number of trans cmpts)</td>
<td>19.3 (18.1-22.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportional error (%)</td>
<td>10.8 (10.0-128)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Additive error [mg/L]</td>
<td>0.064 (0.059-0.07)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CL and V allometrically scaled and reported for the typical fat-free-mass subject (42.2 kg) 90% CI obtained using non-parametric bootstrap
Rifampicin PK - Results

Weight/dose effect

Dose-exposure non-proportionality
Rifampicin PK - Results

**Figure 2.** Distribution of exposure to rifampin (AUC, 0–24 h) at Day 14 in the various rifampin dosing groups. The reference line mimics a linear relationship. AUC = area under the plasma concentration–time curve; $C_{\text{max}}$ = peak plasma concentration.

Panacea Trial - Boeree et al. 2015
Rifampicin PK - Results

When rescaling to the average exposures in Panacea at 10 mg/kg...

**Relative change in SS AUC\textsubscript{0-24} from 10 mg/kg dose**

- AUC\textsubscript{0-24} (Simulated exposure)
- Panacea Trial
- AUC\textsubscript{0-24} (Linear dose exposure)

**Relative change in C\textsubscript{max} from 10 mg/kg dose**

- C\textsubscript{max} (Simulated exposure)
- Panacea Trial
- C\textsubscript{max} (Linear dose exposure)
Conclusions

Rifampicin PK was characterised using a well-stirred liver model with saturable metabolism, following Michaelis-Menten kinetics.

We quantified rifampicin auto-induction: progression and extent

- Maximum intrinsic clearance almost doubled (1.9 fold) from first dose to steady state (93 to 176)
- 50% effect is reached in 4.5 days, full induction (~97%) about three weeks

The best size predictor for CL is fat-free mass, which should be used to optimise dose instead of total body weight.

The predictions from the model closely mirror recent reports of high-dose rifampicin PK.

Further study is necessary to investigate the effect of dose administered on duration and extent of auto-induction.
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Maxwell Chirehwa
References


Backup Slides
Fat free mass (FFM) was estimated from height (HT) and weight (WT) and sex using the formula:

\[
FFM = \frac{\text{WHS}_{\text{max}} \cdot HT^2 \cdot WT}{\text{WHS}_{50} \cdot HT^2 + WT}
\]

\text{WHS}_{\text{max}} \text{ is } 42.92 \text{ kg/m}^2 \text{ and } \text{WHS}_{50} \text{ is } 30.93 \text{ kg/m}^2 \text{ in men, and } 37.99 \text{ kg/m}^2 \text{ and } 35.98 \text{ kg/m}^2, \text{ in women.}
Allometric scaling

Individual $CL_{int_i}$ and $V_i$ of the central compartment were scaled using each subject’s fat-free body mass (FFM). Similarly $Q_{H_i}$ and $V_{H_i}$

$$CL_{int_i} = CL_{int\_ref} \cdot \left( \frac{FFM_i}{FFM_{ref}} \right)^{0.75}$$

$$Q_{H_i} = Q_{H\_ref} \cdot \left( \frac{FFM_i}{FFM_{ref}} \right)^{0.75}$$

$$V_i = V_{ref} \cdot \left( \frac{FFM_i}{FFM_{ref}} \right)^{1}$$

$$V_{H_i} = V_{H\_ref} \cdot \left( \frac{FFM_i}{FFM_{ref}} \right)^{1}$$