Background and Objectives

- Rifampicin is the mainstay of 1st line tuberculosis (TB) treatment
- Rifampicin, which is hepatically cleared, induces its own metabolism (auto-induction) and undergoes extensive first-pass metabolism [1]
- The onset and extent of auto-induction have not been adequately described
- Saturation of hepatic extraction of rifampicin at higher doses has been reported [2] and characterising the process becomes important if the dose of rifampicin is to be increased

Objectives
1. To describe rifampicin PK among TB patients accounting for auto-induction of clearance and saturation of hepatic extraction using a population model
2. Explore changes in exposure when dose is increased beyond currently recommended level

Methods

Data:
- 61 (33 females) HIV/TB co-infected and treatment naive patients from South Africa commenced weight-adjusted doses (10 mg/kg on week days; 10 patients received treatment every day of TB treatment as part of TB treatment.
- Blood samples were collected pre-dose, and at 1, 2, 4, 6, 8 and 12 hours post dose on each PK sampling day i.e. day 0, 7, 14 & 28
- Demographic data of 870 TB patients from South Africa & West Africa were used to simulate higher doses of rifampicin

Table 1. Characteristics of 61 patients with HIV/TB

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>32</td>
<td>18–47</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>55.2</td>
<td>34.4–98.7</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.59</td>
<td>1.41–1.81</td>
</tr>
<tr>
<td>Fat free mass (kg)</td>
<td>42.2</td>
<td>28.0-57.6</td>
</tr>
</tbody>
</table>

Table 2: Final parameter estimates (5th and 95th percentile)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical Value</th>
<th>5th percentile</th>
<th>95th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_L max (L/h)</td>
<td>93.2 (82.4-106)</td>
<td>22.5 (19.5-28.7)</td>
<td>21.9 (18.4-26.2)</td>
</tr>
<tr>
<td>V (L)</td>
<td>50.1 (48.3-52.9)</td>
<td>14.2 (11.7-16.6)</td>
<td></td>
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<tr>
<td>E (p-hepatic)</td>
<td>1 FIX</td>
<td>11.0 (9.9-15.3)</td>
<td></td>
</tr>
<tr>
<td>KA (L/h)</td>
<td>1.96 (1.70-2.11)</td>
<td>81.2 (75.6-88.5)</td>
<td></td>
</tr>
<tr>
<td>MTT (h)</td>
<td>0.71 (0.67-0.81)</td>
<td>62.7 (57.4-76.6)</td>
<td></td>
</tr>
<tr>
<td>NN</td>
<td>19.3 (18.5-21.9)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>C_L max (L/h)</td>
<td>176 (156-202)</td>
<td>22.5 (19.5-28.7)</td>
<td>21.9 (18.4-26.2)</td>
</tr>
<tr>
<td>t1/2 (days)</td>
<td>4.5 (4.0-4.8)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Km (mg/L)</td>
<td>3.35 (3.0-3.6)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Add err (mg/L)</td>
<td>0.06 (0.06-0.07)</td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Prop err (%)</td>
<td>10.8 (10.3-12.2)</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Methods

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

Maximum intrinsic clearance of rifampicin almost doubled from first dose to steady state (Table 2) with an induction half-life of 4.5 days

Intrinsic clearance was saturable and followed Michaelis-Menten kinetics

Incorporating saturation of hepatic extraction explained the higher bioavailability among patients receiving 5 tablets and the correlation between absorption and bioavailability: fast absorption was correlated with high bioavailability

Simulations show that higher 24 post-dose concentrations will be detected if dose is increased to 30 or 35 mg/kg compared to current dose

Non-linear increase in exposure measured by AUC or Cmax was observed when dose was increased beyond the currently recommended (Figure 2)

Results

Model structure is in Figure 1 and final parameter estimates in Table 2

Figure 1: Structure of the model

A well-stirred liver model was used to describe both hepatic clearance and first-pass metabolism due to hepatic extraction (C_L)

\[ E = \frac{C_{int} \cdot Q_L}{C_{int} + Q_L \cdot \frac{f}{1 + f} \cdot Q_L} \]

For a typical individual, volume of liver (V_L) was fixed to 1 L, hepatic plasma flow (Q_L) 50 L/h and free fraction of rifampicin (f) at 20% C_L is the concentration of rifampicin in the liver that drives intrinsic clearance (C_L int)

Allometric scaling was applied to all clearance and volumes parameters, including liver compartment to account for body size using fat free mass (FFM) [4]

Auto-induction of rifampicin was characterised using an exponential maturation on C_L int from day 0 to steady-state with an induction half-life (t1/2)

\[ C_L_{int, max} = C_L_{int, max}^{0} + \left( C_L_{int, max}^{0} - C_L_{int, max}^{*} \right) \left( 1 - e^{-\frac{t}{t_{1/2}}} \right) \]

Figure 2: Iframicin exposures at different dose

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Conclusions

Model predicts that increasing the dose of rifampicin result in a more than proportional increase in exposure, similar to recent report on high dose rifampicin [5]

Auto-induction of rifampicin clearance is almost complete after 3 weeks of treatment initiation

With the currently recommended dose of rifampicin, the model predicts saturation of hepatic extraction and larger exposures in patients with higher weight (and proportionally lower FFM), as previously observed [6]

The potential for increased toxicity with the nonlinear increase in rifampicin exposures warrants thorough investigation

More work is needed to investigate whether higher rifampicin doses may lead to more pronounced induction

References


*Numbers in bracket are the 5th and 95th percentiles of the distribution of simulated AUCs

Figure 2: Maximum intrinsic clearance of rifampicin almost doubled from first dose to steady state (Table 2) with an induction half-life of 4.5 days

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