Model-based meta-analysis of rifampicin exposure and mortality in phase II tuberculosis meningitis trials

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Background

- Mortality of tuberculosis meningitis (TBM) often >40%
- Intensified rifampicin treatment → improved outcomes?
Objectives

To characterize population pharmacokinetics of high-dose rifampicin in plasma and cerebrospinal fluid (CSF)

Evaluate the relationship between individual exposures and mortality

Investigate the need for weight-banded dosing
### Data and methods

<table>
<thead>
<tr>
<th></th>
<th>Study 1</th>
<th>Study 2</th>
<th>Study 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rifampicin dose</strong></td>
<td>450 mg PO, 600 mg IV</td>
<td>750 or 900 mg PO, 600 mg IV</td>
<td>450, 900 or 1350 mg PO</td>
</tr>
<tr>
<td><strong>N subjects</strong></td>
<td>60</td>
<td>30</td>
<td>60</td>
</tr>
<tr>
<td><strong>PK sampling</strong></td>
<td>Plasma: rich, day 2±1 and 12±3 CSF: two single samples (3-9h)</td>
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<td><strong>Follow up (days)</strong></td>
<td>180</td>
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<td>180</td>
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- **PK**: Nonlinear mixed-effects models
- **Mortality**: Parametric time-to-event models
Plasma PK model in a nutshell

- Two disposition compartments
- Well-stirred liver model
- Saturable clearance
- Autoinduction

- Oral bioavailability 78% (CI<sub>95%</sub> 71-84)
- Volume of distribution 19% (CI<sub>95%</sub> 12-26) lower at late sampling days

Details: Chirehwa et al., AAC 2016; Svensson et al., CPT, 2018; Savic et al., CPT, 2015
CSF PK model

- 170 observations
- Half-life for distribution 2.1 h (CI$_{95\%}$ 1.3-2.9)
- Partition coefficient 5.5% (CI$_{95\%}$ 4.4-6.4)
  - Higher CSF protein \(\Rightarrow\) increased partition coefficient
6-month mortality

- **148** individuals, **58** died, **15** dropped out

- Exponentially declining hazard
  - Lower age
  - Higher baseline Glasgow Coma Scale score
  - Higher rifampicin plasma AUC$_{0-24h}$

Reduced hazard
Influence of rifampicin on mortality

- Plasma $\text{AUC}_{0-24\text{h}}$ (day 2±1)
  - Stronger than $C_{\text{max}}$ or CSF exposure
- Hill equation, maximal effect not estimable
- $\text{EC}_{50} = 211 \text{ mg/L}^*\text{h}$ (RSE 94%)
Influence of rifampicin on mortality

Age: 30 years
GCS score: 13

Rifampicin exposure mg/L*h (corresponding dose)
229 (1350mg po)
181 (900mg po)
125 (750mg po)
120 (600mg iv)
48.3 (450mg po)
Simulations flat dosing

- Virtual population: 10,000 African and Indonesian TBM patients

Very little effect of dose-individualization on total body weight!
Conclusions

- Higher rifampicin exposure → substantially decreased the risk of death
- Maximal effect not reached → 1350 mg or higher
- Little effect of weight-banding → not necessary

The optimal dose of rifampicin in treatment of TBM should be further investigated in phase III type trials:

HARVEST
Acknowledgments

• Patients and staff participating in the trials

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Radboudumc: Lindsey te Brake, Reinout van Crevel, Rob Aarnoutse

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Acknowledgments

Alva – 7 weeks tomorrow