Penetration of rifampin and rifapentine into diseased lung in the rabbit cavity pulmonary disease model of TB

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Background

- Rifampin (RIF) and rifapentine (RPT) are potent sterilizing drugs.

- In mouse models daily RPT can cure TB in 3 months.

- In clinical trials, substitution of 10 mg/kg of daily RIF with 10 mg/kg of daily RPT is not more efficacious; higher doses of RPT seem to improve microbiologic outcomes.

- There is little information about the penetration of rifamycins into infected areas in humans.

- The rabbit cavitary pulmonary TB model has human-like TB pathology (necrotic granulomas and cavities) and may provide some insights into drug distribution of anti-TB drugs in humans.
Rabbit cavitary model

Aerosol infection

8 rabbits

10^5 - 10^6 CFU/ml of Mtb H37Rv aerosol exposure

sacrifice and necropsy (week 17)

<table>
<thead>
<tr>
<th>baseline</th>
<th>week</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
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</table>

Bronchoscope infection

Injection of Mtb:H37Rv
1-0.3ml
10^5 - 10^7 CFU/ml

Cavitary lesion
Experimental design

Drug delivery:

[Diagram showing drug delivery process]

IV infusion

- RIF: 5mg/ml
- RPT: 10mg/ml
- In vehicle solution

Plasma

Uninvolved lung tissue (UI)

Tissue surrounding lesion (SL)

Cellular lesion (LE)

Cavitary lesion wall (CAW)

Caseum (CAC)

Homogenate

70% methanol

LC/MS

MALDI-MSI
Optimizing experimental conditions: healthy rabbits

**RIF in lung tissue**

**RPT in lung tissue**

**PK of RPT (30mg/kg) in plasma and lung tissue**

- **C**\textsubscript{max} : 27µg/ml (0.5h)
- AUC\textsubscript{0-15} : 100 µg*h/ml
- T\textsubscript{1/2} : 4.5h

**In human plasma PK of single dose of RPT (20mg/kg, oral administration)**

- **C**\textsubscript{max} : 25µg/ml (5h)
- AUC\textsubscript{0-12} : 403µg*h/ml
- T\textsubscript{1/2} : 25.9 h

Penetration of single dose of **RIF** (10mg/kg) by LC/MS: rabbits with TB disease

**Penetration of RIF in diseased lung**

- UI: uninvolved lung tissue
- SL: tissue surrounding lesion
- LE: cellular lesion
- CAC: caseum from necrotic lesion

**PK of RIF in plasma and diseased lung**

- $C_{\text{max}}$: 17µg/ml
- $AUC_{0-6}$: 40 µg*h/ml
- $T_{1/2}$: 2h

In human plasma PK of single dose (10mg/kg, oral administration)

- $C_{\text{max}}$: 10.5µg/ml
- $AUC_{0-12}$: 57.5 µg*h/ml
- $T_{1/2}$: 3h

Clin Pharmacol Ther. 2012 May; 91(5):

doi:10.1038/clpt.2011.323
MALDI-MSI and H&E staining of lung tissue: single dose of RIF

2h

3h

6h

Necrotic lesion

Cellular lesion

Necrotic lesion
Penetration of single dose of **RPT** (30mg/kg) by LC/MS: rabbits with TB disease

**Penetration of RPT in diseased lung**

- **UI**: uninvolved lung tissue
- **SL**: tissue surrounding lesion
- **LE**: cellular lesion
- **CAW**: cavitary lesion (wall)
- **CAC**: cavitary lesion (caseum)

**PK of RPT in plasma and diseased lung**

- **C**$_{\text{max}}$ : 50µg/ml
- **AUC**$_{0-6}$ : 175µg*h/ml
- **T ½**: 4.5h
MALDI-MSI and H&E Staining of lung tissue: single dose of RPT

2h

3h

6h

cellular lesion

cavitary lesion

cavitary lesion
Penetration of multiple-dose of **RIF** (10mg/kg) by LC/MS: rabbits with TB disease

**PK of RIF in plasma (M2h)**

<table>
<thead>
<tr>
<th>Concentration of RIF (ng/ml)</th>
<th>First dose (30min)</th>
<th>Second dose (4h)</th>
<th>Third dose (2h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>30min</td>
<td>5h</td>
</tr>
<tr>
<td></td>
<td>10000</td>
<td>20000</td>
<td>30000</td>
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</table>

**AUC** \(0\text{-}12.5\text{h}: 241\mu g\text{*h/ml} \)

**PK of RIF in plasma (M12h)**

<table>
<thead>
<tr>
<th>Concentration of RIF (ng/ml)</th>
<th>First dose (30min)</th>
<th>Second dose (4h)</th>
<th>Third dose (2h)</th>
<th>Forth dose (12h)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>30min</td>
<td>4h</td>
<td>30min</td>
</tr>
<tr>
<td></td>
<td>5000</td>
<td>45000</td>
<td>35000</td>
<td>25000</td>
</tr>
</tbody>
</table>

**AUC** \(0\text{-}26\text{h}: 431\mu g\text{*h/ml} \)

**Penetration of RIF in different compartments of TB disease**

<table>
<thead>
<tr>
<th>Concentration of RIF (ng/g)</th>
<th>M2h</th>
<th>M12h</th>
</tr>
</thead>
<tbody>
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</table>

In human plasma PK of multiple-dose (10mg/kg, oral administration, 14 days)

**C**\(_{\text{max}}\): 7.5\mu g/ml (5h)

**AUC** \(0\text{-}12\text{h}: 45.2\mu g\text{*h/ml} \)

**T ½**: 2.4 h


- **UI**: uninvolved lung tissue
- **SL**: tissue surrounding lesion
- **LE**: cellular lesion
- **CAW**: cavitary lesion (wall)
- **CAC**: cavitary lesion (caseum)
MALDI-MSI and H&E staining of lung tissue: multiple-dose of RIF

Uninvolved lung

Cavitary lesion (1)

Cavitary lesion (2)

Cellular lesion

Necrotic lesion
Penetration of multiple-dose of RPT (20mg/kg) by LC/MS: rabbits with TB disease

**PK of RPT in plasma (M2h)**

- **AUC** \(_{0-13}\): 494µg*·h/ml

**PK of RPT in plasma (M12h)**

- **AUC** \(_{0-23}\): 833µg*·h/ml

**Penetration of RPT in different compartments of TB disease**

- In human plasma PK of multiple-dose (20mg/kg, oral administration, 14 days)
  - \(C_{\text{max}}\): 34.1µg/ml (5h)
  - AUC \(_{0-12}\): 483 µg·h/ml
  - T \(\frac{1}{2}\): 16h

MALDI-MSI and H&E staining of lung tissue: multiple-dose of RPT

**M2h**
- Uninvolved lung
- Cavitary lesion (1)
- Cavitary lesion (2)

**M12h**
- Cellular lesion
- Necrotic lesion
Conclusions

• We have established the PK of IV RIF and IV RPT in rabbits; half-life of RPT is much shorter in rabbits than humans. Data can be used to determine human-equivalent dosing for subsequent single and multiple dose experiments.

• Penetration into granulomatous lesions was excellent for both RIF and RPT and drugs remained in this type of lesions longer than in healthy lung tissue.

• Penetration of RIF into caseum in necrotic or cavitary lesions was poor, but accumulation of RIF in caseum can be achieved by giving multiple-dose of RIF with longer exposure time, which is consistent with that in human necrotic caseum.

• RPT penetrated into caseum even poorer than RIF in comparison to their uninvolved lung tissue; multiple dosing with longer exposure time seemed not to improve penetration of RPT into caseum during the observation time, which remains to be confirmed in humans.

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