CYP3A Induction by Rifampin and Rifapentine: Which Drug and Dose Does it Best?


4th International Workshop on Clinical Pharmacology of Tuberculosis Drugs
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CYP3A Induction by Rifamycins

• Rifamycins are potent inducers of cytochrome P450 enzymes, including CYP3A

• Human hepatocyte experiments have suggested that rifampin (RIF) is a stronger inducer than rifapentine (RPT) or rifabutin

• Understanding the relationship between rifamycin dose and magnitude of CYP3A induction will be informative for potential drug interactions
MDZ as a Probe Drug

- Midazolam is a short-acting benzodiazepine
- Metabolized by hydroxylation to 1-OH-MDZ, mediated almost exclusively by CYP3A
- Oral MDZ given with a drug of interest can be used to evaluate the effect of that drug on overall (liver + gut) CYP3A activity
- **We evaluated the effect of RPT dose on CYP3A activity using oral midazolam (MDZ) as a probe drug and RIF at standard dose as a comparator**
TBTC Study 29B Design

- Healthy volunteers were enrolled in Tuberculosis Trials Consortium Study 29B
  - RPT 5, 10, 15, or 20 mg/kg or RIF 10 mg/kg (n=6 per cohort), daily for 14 days (days 2-15)
  - Two single oral doses of 15 mg of MDZ, alone (day 1) and co-administered with RPT or RIF (day 15)
TBTC Study 29B PK Sampling

• Blood samples for PK analysis were collected prior to dose and at 0.5, 1, 2, 4, 5, 8, 12 and 24 hours post-dose
  – Plasma concentrations determined by
    • HPLC/MS procedure at the University of North Carolina (MDZ and 1-OH-MDZ)
    • LCMS procedure at Johns Hopkins University (RPT, desRPT, RIF and desRIF)
  – PK parameters calculated using standard noncompartmental methods using WinNonlin v 6.1
MDZ and 1-OH-MDZ Log Concentration v. Time Curves

Mean (SE) log-transformed plasma midazolam or 1-OH-midazolam concentrations versus time after a single dose of oral midazolam 15 mg delivered alone (●) or co-administered with rifampin (10 mg/kg daily (■)) or rifapentine (5, 10, 15, or 20 mg/kg daily (△)) at steady state.
Decrease in MDZ and 1-OH-MDZ AUC\textsubscript{0-12}

- Comparing RPT dose cohorts, no difference by dose
  - MDZ: ANOVA p-value=0.89
  - 1-OH-MDZ: ANOVA p-value=0.30

- Comparing RIF to all RPT cohorts, no statistically significant difference
  - MDZ: t-test p-value=0.11
  - 1-OH-MDZ: t-test p-value=0.24
Increase in MDZ Clearance

- Comparing RPT dose cohorts, no difference by dose
  - ANOVA p-value=0.73
- Comparing RIF to all RPT cohort, significant difference
  - t-test p-value=0.05
Decrease in MDZ and 1-OH-MDZ $C_{\text{MAX}}$

- Comparing RPT dose cohorts, no difference by dose
  - MDZ: ANOVA p-value=0.77
  - 1-OH-MDZ: ANOVA p-value=0.18

- Comparing RIF to all RPT cohort, no statistically significant difference
  - MDZ: t-test p-value=0.24
  - 1-OH-MDZ: t-test p-value=0.22
Median (IQR) RIF and RPT multiple dose PK Parameters

<table>
<thead>
<tr>
<th></th>
<th>RIF 10 mg/kg (n=6)</th>
<th>RPT 5mg/kg (n=5)</th>
<th>RPT 10mg/kg (n=5)</th>
<th>RPT 15mg/kg (n=6)</th>
<th>RPT 20mg/kg (n=6)</th>
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<tbody>
<tr>
<td><em><em>AUC</em> (µg</em>h/ml)**</td>
<td>45 (26-54)</td>
<td>218 (142-251)</td>
<td>330 (284-340)</td>
<td>560 (401-735)</td>
<td>483 (414-546)</td>
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<tr>
<td>Metabolite <em><em>AUC</em> (µg</em>h/ml)**</td>
<td>5.4 (2-6)</td>
<td>148 (70-148)</td>
<td>194 (178-202)</td>
<td>476 (264-890)</td>
<td>318 (223-461)</td>
</tr>
<tr>
<td><strong>C_MAX (µg/ml)</strong></td>
<td>7.5 (5-10)</td>
<td>15.7 (13-18)</td>
<td>21.7 (21-22)</td>
<td>35.9 (25-39)</td>
<td>34.1 (30-43)</td>
</tr>
<tr>
<td>Metabolite <strong>C_MAX (µg/ml)</strong></td>
<td>0.9 (0.5-1)</td>
<td>8.7 (5-9)</td>
<td>10.5 (10-12)</td>
<td>23.6 (15-40)</td>
<td>19.9 (14-30)</td>
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<tr>
<td><strong>C_AVG</strong> (µM)</td>
<td>2.3 (1.3-2.7)</td>
<td>10.3 (6.8-12)</td>
<td>15.7 (13-16)</td>
<td>26.6 (19-35)</td>
<td>23.0 (20-26)</td>
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</table>

*AUC for RPT is AUC_{0-24}, AUC for RIF is AUC_{0-12}

**C_{AVG} = AUC/24 hour dosing interval

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Conclusions

• Though RIF is a more potent CYP3A inducer than RPT on a µM scale, at clinically relevant doses, RPT is a stronger inducer of CYP3A than RIF.

• There was no evidence of a dose-response relationship between RPT dose and CYP3A induction at the doses tested.

• Recommendations for dose adjustments based upon RIF drug-drug interaction studies may not be readily extrapolated to RPT.
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