Population PK of Isoniazid in South African TB patients

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Isoniazid

Isoniazid (INH) is a key drug used for the prevention and treatment of tuberculosis, with a strong early bactericidal activity.

It is acetylated in the liver and small intestine and its clearance is highly dependent on genetic polymorphisms of N-acetyltransferase 2 (NAT2), and trimodality has been previously reported [Parkin et al.].

A large of range of values has been reported for the pharmacokinetic parameters of isoniazid in different populations.

**Aim:** characterize INH PK in South Africans (from KwaZulu-Natal) using intensively sampled data
Dataset

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

- Isoniazid (together with rifampicin, pyrazinamide, ethambutol in a FDC) was given once daily in the morning. 5 days per week, but 10 patients were dosed 7 days per week.

- About half of the patients received ARVs (Lamivudine, Zidovudine and Efavirenz) from week 2

- **Doses** were adjusted **according to** body weight, **WHO guidelines**

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

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Median</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>28 M</td>
<td>33 F</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>
<tr>
<td>Age [years]</td>
<td>32</td>
<td>18 - 47</td>
</tr>
</tbody>
</table>

Presented at the 4th International Workshop on Clinical Pharmacology of TB Drugs, 16 September 2011, Chicago, IL, USA
Methods

The software NONMEM VII with FOCE-I was employed

Allometric scaling [Anderson and Holford] was used to adjust for body size:
  - total body weight and fat-free mass were tested

Large amount of data below limit of quantification (LOQ):
  - 23% including pre-dose samples, 19% excluding them
  - M6 method [Beal]
    - keep only first or last sample in a series
    - impute to LOQ/2
  - Additive error fixed to LOQ/2 for BLQ samples
  - A simulation showed good results applying this method
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**Structural Model**

- **Dose**
  - Bioavailability \((F)\)
  - Series of transit compartments [Savic et al.]
  - Meat Transit Time (MTT) + Number of Trans Cmpts (NN)
  - 39.6

- **Absorption Cmpt**
  - \(F_{\text{Slow}} = 1\)
  - \(F_{\text{Fast}} = 0.729\)
  - BSV 31.2%
  - BOV 23.8%
  - 0.555 h
  - BOV 45.8%

- **Central Cmpt**
  - CL/V
  - V = 91.0 L

- **Peripheral Cmpt**
  - Q = 17.1 L/h
  - \(V_p = 33.5\) L

- **CL/V**
  - CL_{Slow} = 28.3 L/h
  - CL_{Fast} = 60.9 L/h
  - BSV 18.7%
  - BOV 67.5%

- \(2.07\) h^{-1}
Visual Predictive Check

Isoniazid concentrations [mg/L]

% of BLQ

Time after dose

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## Parameter values

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Typical Value</th>
<th>BSV</th>
<th>BOV</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CL/F [L/h]</strong></td>
<td><strong>Slow: 28.3 (12%)</strong>&lt;br&gt;Fast: 60.9 (11%)</td>
<td>18.7% (17%)</td>
<td></td>
</tr>
<tr>
<td><strong>V/F [L]</strong></td>
<td>91.0 (14%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ka [h⁻¹]</strong></td>
<td>2.07 (12%)</td>
<td>67.5% (8%)</td>
<td></td>
</tr>
<tr>
<td><strong>MTT [h]</strong></td>
<td>0.555 (8%)</td>
<td>45.8% (13%)</td>
<td></td>
</tr>
<tr>
<td><strong>NN (transit)</strong></td>
<td>39.6 (32%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Q/F [L/h]</strong></td>
<td>17.1 (25%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Vₚ/F [L]</strong></td>
<td>33.5 (15%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>F (bioavailability)</strong></td>
<td><strong>Slow: 1 (FIX)</strong>&lt;br&gt;Fast: 0.729 (12%)</td>
<td>31.2% (19%)</td>
<td>23.8% (8%)</td>
</tr>
<tr>
<td>% Slow metab.</td>
<td>44.9% (20%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Error</strong></td>
<td>Add: 0.0235 (9%)&lt;br&gt;Prop: 18.7% (3%)</td>
<td></td>
<td>Error for BLQ data Add: 0.04 (FIX)</td>
</tr>
</tbody>
</table>

CL, Q, V and V₃ are reported for a 42.2 kg fat-free-mass subject, which proved the best predictor.
# Discussion

Previously reported PK parameter values:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>CL &amp; Q (L/h)</th>
<th>V &amp; $V_p$ (L)</th>
<th>Metabolizers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wilkins et al. (NONMEM)</td>
<td>235 South African TB patients (parameter values for 70kg WT)</td>
<td>$CL_{Slow}$: 9.70  $CL_{Fast}$: 21.6  $Q$: 3.34</td>
<td>$V$: 57.7  $V_p$: 1730</td>
<td>Slow: 86.8%  Fast: 13.2%  Mixture model</td>
</tr>
<tr>
<td>Peloquin et al. (IT2B results)</td>
<td>24 male Caucasian healthy subjects (med WT 77kg)</td>
<td>$CL_{Slow}$: 14.5  $CL_{Fast}$: 50.0 Only 1 cmpt</td>
<td>$V_{Slow}$: 67  $V_{Fast}$: 90 Only 1 cmpt</td>
<td>Slow: 66.6%  Fast: 33.3% t½ &lt; or &gt; 2 h</td>
</tr>
<tr>
<td>Kinzig-Schippers et al. (NONMEM)</td>
<td>18 Caucasian healthy subjects (med WT 74kg)</td>
<td>$CL_{Slow}$: 10.0  $CL_{Inter}$: 19.2  $CL_{Fast}$: 28.4  $Q$: 44.3</td>
<td>$V$: 22.1  $V_p$: 35.2</td>
<td>Slow: 72.2%  Inter: 11.1%  Fast: 16.6%</td>
</tr>
</tbody>
</table>

Previously reported frequencies for acetylation status:

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Frequencies</th>
</tr>
</thead>
<tbody>
<tr>
<td>Loktionov et al.</td>
<td>101 Black S. African (NW province)</td>
<td>Slow: 39.6% - Fast: 60.4%</td>
</tr>
<tr>
<td>Parkin et al.</td>
<td>60 Mixed Race S. African (W. Cape)</td>
<td>Slow: 35% - Inter: 45% - Fast: 20%</td>
</tr>
<tr>
<td>Shaaf et al.</td>
<td>64 Black S. African (W. Cape)</td>
<td>Slow: 39.0% - Inter: 37.5% - Fast: 23.4%</td>
</tr>
</tbody>
</table>
Conclusions

• CL was characterized by a mixture of faster and slower metabolizers
  • Slow 28 L/h
  • Fast 61 L/h

• Faster metabolizers also have lower bioavailability (73% of slower metab.), possibly due to higher first-pass metabolism

• The highest dose of INH in our dataset (375mg) has higher bioavailability, possibly due to saturation of first-pass metabolism

• Limitation: No actual data on acetylator status or metabolite concentration

• Future plans
  • Measurement of INH metabolite to characterize phenotype
  • Genotyping of patients
Acknowledgments

• The patients participating in the studies

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• All my colleagues in the pharmacometrics lab at the UCT Division of Clinical Pharmacology