Challenges in modelling the pharmacokinetics of isoniazid in South African tuberculosis patients

Justin J Wilkins¹, Grant Langdon¹, Helen McIlleron¹, Goonaseelan Pillai², Peter J Smith¹ and Ulrika S H Simonsson³

(1) Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, South Africa
(2) Modelling & Simulation, Clinical Development & Medical Affairs, Novartis Pharmaceuticals AG, Basel, Switzerland
(3) Division of Pharmacokinetics and Drug Therapy, Department of Pharmaceutical Biosciences, Uppsala University, Sweden
Isoniazid (INH)

- Key part of first-line tuberculosis chemotherapy
- Rapidly and completely absorbed from the intestine
- Subject to first-pass effect
- Substantial presystemic metabolism occurs in intestinal mucosal cells
- Subject to metabolic polymorphism - trimodal
Patient Data

- 266 pulmonary tuberculosis (PTB) patients on first-line chemotherapy
- On treatment for 8-10 days prior to start of study
- 200-400 mg p.o. daily
- Samples for PK analysis were taken over between 1 and 6 weeks
Representative Individual Profiles

Dose: 300mg

INH Concentration (mg/L)

Day 4
Modelling Procedure

- 2-compartment model with first-order absorption & elimination

- Model assessment criteria
  - ΔOFV
  - GOF plots
  - Scientific plausibility
  - Precision & accuracy
Modelled using dual absorption compartments - fast and slow, characterized by absorption half-lives $H\lambda_{a,fast}$ and $H\lambda_{a,slow}$.

$F_{slow} = 1 - F_{fast}$

$H\lambda_{fast} = \Theta(3)$

$H\lambda_{slow} = \Theta(4) + H\lambda_1$
Other Aspects

- IOV/IIV characterization was a key objective
- 27 dosing occasions, IOV on 2 parameters - 56 ETA parameters needed

\[ (CL/F)_i = \theta_{CL/F} \cdot \exp \left( \eta_i^{CL/F} + \kappa_{ij}^{CL/F} \right) \]

Other Aspects

- Fast, intermediate and slow
- Data did not allow identification of intermediate group (indistinguishable from fast group)

$\text{MIX}$
$\text{NSPOP} = 2$
$P(1) = \text{THETA}(8)$
$P(2) = 1 - \text{THETA}(8)$

...
Other Aspects

- Several models tested to account for enterohepatic circulation (EHC)
- EHC models were unable to produce either a substantial ΔOFV or a successful covariance step
- No literature evidence
- GAM as implemented in Xpose used to identify potential covariate relations
- Screened using stepwise covariate modelling (SCM) method

\[
TV(\text{CL/F}) = \theta_{\text{CL/F}} \cdot \left[ 1 + \theta_{\text{WT}} \cdot (\text{WT} - \text{WT}_{\text{med}}) \right]
\]

\[
TV(\text{V/F}) = \theta_{\text{V/F}} + \theta_{\text{SEX}} \cdot \text{SEX}
\]
The Model

- Slow Absorption: $F_{\text{slow}} = 1 - F_{\text{fast}}$
- Fast Absorption: $F_{\text{fast}}$

Dose

Peripheral $V_2$

Central $V_1$

- $k_{12}$
- $k_{21}$
- $P_{CL}$

- $H_L_{a,\text{slow}}$
- $H_L_{a,\text{fast}}$

- $IIV$
- $IIV$
- $IIV$
- $IIV$
- $IOV$
- $IOV$

- $H_L$
- $CL/F$

- $F_{\text{slow}}$
- $F_{\text{fast}}$

- $Dose$

- $Sex$
- $Weight$
- $IIV$
- $IOV$

University of Cape Town
Goodness-of-Fit
# Goodness-of-Fit

<table>
<thead>
<tr>
<th>Time (h)</th>
<th>INH Concentration (mg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>DV</td>
</tr>
<tr>
<td>2</td>
<td>DV</td>
</tr>
<tr>
<td>4</td>
<td>DV</td>
</tr>
<tr>
<td>6</td>
<td>DV</td>
</tr>
<tr>
<td>8</td>
<td>DV</td>
</tr>
</tbody>
</table>

Goodness-of-Fit

- DV
- PRED
- IPRED

![Graphs showing INH concentration over time with DV, PRED, and IPRED lines.](image)

- DV
- PRED
- IPRED

![Graphs showing INH concentration over time with DV, PRED, and IPRED lines.](image)

- DV
- PRED
- IPRED

![Graphs showing INH concentration over time with DV, PRED, and IPRED lines.](image)

- DV
- PRED
- IPRED

![Graphs showing INH concentration over time with DV, PRED, and IPRED lines.](image)

- DV
- PRED
- IPRED
## Parameter Estimates

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>% RSE</th>
<th>IIV (IOV)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral clearance ($CL_{fast}/F, L.h^{-1}$)</td>
<td>10.4</td>
<td>2.90</td>
<td>0.156</td>
</tr>
<tr>
<td>Oral clearance ($CL_{slow}/F, L.h^{-1}$)</td>
<td>4.42</td>
<td>3.48</td>
<td>0.551</td>
</tr>
<tr>
<td>Ratio of fast acetylators to slow acetylators ($P_{CL}$)</td>
<td>0.225</td>
<td>14.9</td>
<td></td>
</tr>
<tr>
<td>Half-life of absorption for fast compartment ($HL_{a,fast}, h$)</td>
<td>0.518</td>
<td>4.15</td>
<td>0.551</td>
</tr>
<tr>
<td>Half-life of absorption for slow compartment ($HL_{a,slow}, h$)</td>
<td>5.78</td>
<td>5.55</td>
<td>1.09</td>
</tr>
<tr>
<td>Dose fraction, fast cpt ($F_{fast}$)</td>
<td>0.526</td>
<td>3.73</td>
<td></td>
</tr>
<tr>
<td>Apparent volume of distribution, central compartment ($V_1/F, L$)</td>
<td>6.86</td>
<td>9.31</td>
<td>0.268</td>
</tr>
<tr>
<td>Apparent volume of distribution, peripheral compartment ($V_2/F, L$)</td>
<td>13.0</td>
<td>Fixed</td>
<td></td>
</tr>
<tr>
<td>Intercompartmental rate constant ($k_{12}, h^{-1}$)</td>
<td>2.43</td>
<td>12.2</td>
<td></td>
</tr>
<tr>
<td>Intercompartmental rate constant ($k_{21}, h^{-1}$)</td>
<td>1.75</td>
<td>8.51</td>
<td></td>
</tr>
<tr>
<td>Residual Variability</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constant coefficient of variability</td>
<td>0.191</td>
<td>3.03</td>
<td></td>
</tr>
</tbody>
</table>
The Final Model

- Acetylator phenotype
- INH PK Model
- Enterohepatic circulation
- Complex absorption
- Covariate relations
- SCM

Parsimonious Model for INH PK
Aspects of this project were funded by the Medical Research Council of South Africa.

Grateful thanks to Jean van Dyk, Afia Fredericks and the patients and staff of D P Marais SANTA Centre and Brewelskloof Hospital for the input, support and cooperation they have lent this work.
Complex Absorption

Dose: 300mg

INH Concentration (mg/L)

Time (h)

Day 4

Univeristy of Cape Town
F2 = \text{THETA}(5) \quad ; \text{F for fast comp}
F3 = (1 - F2) \quad ; \text{F for slow comp}

HLA1 = \text{THETA}(3) * \text{EXP}(BSV + BOV)
; \text{abs half-life of fast abs comp}
HLA2 = \text{THETA}(4) * \text{EXP}(\text{ETA}(4)) + HLA1
; \text{abs half-life of slow abs comp}
K21 = 0.693/HLA1
K31 = 0.693/HLA2

...
Modelling Issues: IOV

...
$\text{OMEGA BLOCK(1) .04}$
$\text{OMEGA BLOCK(1) SAME}$
$\text{OMEGA BLOCK(1) SAME}$
...

$\text{PK}$
$\text{BSV = ETA(1)}$
$\text{BOV = ETA(5)}$
$\text{IF (OCC.EQ.2) BOV = ETA(6)}$
$\text{IF (OCC.EQ.3) BOV = ETA(7)}$
$\text{IF (OCC.EQ.4) BOV = ETA(8)}$
...
$\text{HLA1 = THETA(3) * EXP (BSV + BOV)}$
...

Modelling Issues: Acetylator Phenotype

$\text{MIX}$

\text{NSPOP} = 2

\begin{align*}
\text{P}(1) & = \text{THETA}(8) \\
\text{P}(2) & = 1 - \text{THETA}(8) \\
\end{align*}

\ldots

\begin{align*}
\text{Q1} & = 0 \\
\text{Q2} & = 0 \\
\end{align*}

\begin{align*}
\text{IF} \ (\text{MIXNUM.EQ.1}) & \text{ Q1} = 1 \\
\text{IF} \ (\text{MIXNUM.EQ.2}) & \text{ Q2} = 1 \\
\end{align*}

\begin{align*}
\text{CL1} & = \text{THETA}(1) \\
\text{CL2} & = \text{THETA}(9) \\
\end{align*}

\begin{align*}
\text{TVCL} & = ((\text{CL1} \times \text{Q1}) + (\text{CL2} \times \text{Q2})) \times (1 + \\
& \text{THETA}(11) \times (\text{WT-50})) \\
\end{align*}

\begin{align*}
\text{CL} & = \text{TVCL} \times \text{EXP (BSV2 + BOV2)} \\
\end{align*}

\ldots
$PROB INH FINAL
$DATA inh_dual_jun04.csv IGNORE=@
$INPUT ID IDNO=DROP OCCO=DROP DAY=DROP RATE=DROP
  TIME TT=DROP DV MDV AMT CMT EVID
  AGE SEX WT HT=DROP BMI=DROP
  RACE=DROP SMOK ALC PKG=DROP HIV
  HB=DROP HCT RBC=DROP MCV=DROP WBC=DROP
  AP=DROP ALT=DROP AST CRT=DROP
  TBIL=DROP UREA=DROP RIFP=DROP PZAP
  FDC DS=DROP
  LOC OCCD=DROP CLCR BSA=DROP OCC DRUG

$SUBROUTINE ADVAN6 TRANS1 TOL=5

$MODEL COMP = (CENT)
  COMP = (ABS1); fast abs comp
  COMP = (ABS2); slow abs comp
  COMP = (PERI)
  ...

$THETA (0, 4.6) ;1 CL1
$THETA (0, 21.2) ;2 V1
$THETA (0, 0.3) ;3 HLA1
$THETA (0, 6.1) ;4 HLA2
$THETA (0, .6, 1) ;5 F-fast
$THETA (0 FIX) ;6 ADD error
$THETA (0, 0.22) ;7 CCV error
$THETA (0, 0.23, 1) ;8 P1
$THETA (0, 11) ;9 CL2
$THETA 0.01 ;10 SEX on V1
$THETA 0.01 ;11 WT on CL
$THETA 13 FIX ;12 V2
$THETA (0, 2.5) ;13 K14
$THETA (0, 1.8) ;14 K41

$OMEGA .2 .3 .5 1.35

$OMEGA BLOCK(1) .04
$OMEGA BLOCK(1) SAME
$OMEGA BLOCK(1) SAME

...
$OMEGA BLOCK(1)$ SAME
$OMEGA BLOCK(1)$ SAME

$SIGMA$ 1 FIX
$ABBREVIATED$ DERIV2=NO

$MIX$

$NSPOP$ = 2
$P(1) = THETA(8)$
$P(2) = 1 - THETA(8)$

$PK$

$BSV = ETA(1)$
$BOV = ETA(5)$
$IF (OCC.EQ.2) BOV = ETA(6)$
$IF (OCC.EQ.3) BOV = ETA(7)$
$IF (OCC.EQ.4) BOV = ETA(8)$
$IF (OCC.EQ.5) BOV = ETA(9)$
$IF (OCC.EQ.6) BOV = ETA(10)$

$BSV2 = ETA(3)$
$BOV2 = ETA(32)$
$IF (OCC.EQ.2) BOV2 = ETA(33)$
$IF (OCC.EQ.3) BOV2 = ETA(34)$

$Q1 = 0$
$Q2 = 0$
$IF (MIXNUM.EQ.1) Q1 = 1$
$IF (MIXNUM.EQ.2) Q2 = 1$

$MXN=0$
$IF (MIXNUM.EQ.1) MXN=1$
$IF (MIXNUM.EQ.2) MXN=2$
Full Final Model

\[
\begin{align*}
\text{CL1} &= \text{THETA}(1) \quad ; \text{CL1} \\
\text{CL2} &= \text{THETA}(9) \quad ; \text{CL2} \\
\text{TVCL} &= ((\text{CL1} \times Q1) + (\text{CL2} \times Q2)) \times \\
& \quad (1 + \text{THETA}(11) \times (\text{WT} - 50)) \\
\text{CL} &= \text{TVCL} \times \text{EXP}(\text{BSV} + \text{BOV}) \\
\text{TVV1} &= \text{THETA}(2) + \text{THETA}(10) \times \text{SEX} \quad ; \text{V1} \\
\text{V1} &= \text{TVV1} \times \text{EXP}(\text{ETA}(2)) \quad ; \text{V1} \\
& \quad ; \text{abs half-life of fast abs comp} \\
\text{HLA1} &= \text{THETA}(3) \times \text{EXP}(\text{BSV2} + \text{BOV2}) \\
& \quad ; \text{abs half-life of slow abs comp} \\
\text{HLA2} &= \text{THETA}(4) \times \text{EXP}(\text{ETA}(4)) + \text{HLA1} \\
\text{K21} &= 0.693 / \text{HLA1} \\
\text{K31} &= 0.693 / \text{HLA2} \\
\text{V2} &= \text{THETA}(12) \\
\text{K14} &= \text{THETA}(13) \\
\text{K41} &= \text{THETA}(14) \\
\text{F2} &= \text{THETA}(5) \quad ; \text{F for fast abs} \\
\text{F3} &= (1 - \text{F2}) \quad ; \text{F for slow comp} \\
\text{S1} &= \text{V1} \\
\text{K10} &= \text{CL} / \text{V1} \\
\end{align*}
\]

...
Full Final Model

$EST POSTHOC NOABORT PRINT=10 MAXEVAL=9999
   MSFO=run526.msf SIGDIG=3

$COV PRINT=E MATRIX=S

$TABLE ID TIME IPRED IWRES ETA1 ETA2 ETA3 ETA4 ETA5 ETA6 ETA33 OCC AA1 AA2 AA3 AA4
   NOPRINT ONEHEADER FILE=sdtab526

$TABLE ID CL V1 HLA1 HLA2 F2 F3 K21 K31 K10 K14 K41 V2 MXN
   NOPRINT ONEHEADER FILE=patab526

$TABLE ID AGE WT HCT AST
   NOPRINT ONEHEADER FILE=cotab526

$TABLE ID SEX SMOK ALC HIV PZAP FDC LOC
   NOPRINT ONEHEADER FILE=catab526

$TABLE ID AUC CP
   NOPRINT ONEHEADER FILE=run526.fit

University of Cape Town