



# Semi-mechanistic model for Isoniazid and Acetyl-isoniazid in a cohort of TB/HIV co-infected patients

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## Background and Objectives

Isoniazid (INH) is an essential component of 1<sup>st</sup> line anti-tuberculosis treatment and has excellent early bactericidal activity

INH metabolism primarily involves acetylation to Acetyl-INH (AcINH) by N-acetyltransferase-2 (NAT2), whose encoding genes are highly polymorphic

**Objective:** To describe pharmacokinetics (PK) of INH and Acetyl isoniazid (AcINH) among TB/HIV co-infected patients

## Methods

142 TB/HIV co-infected and treatment naïve patients recruited into a 3 treatment arm clinical trial in West Africa

**ARM1:** Efavirenz based ART started at 2 weeks after initiating TB treatment

**ARM2:** Standard TB treatment

**ARM3:** Standard TB treatment + high dose (15 mg/kg ) rifampicin

Patients received weight-adjusted daily dose of INH according to WHO

Blood samples collected at pre-dose, and at 2, 3, 6, and 10 hr post-dose

Samples available for analysis: 705 for INH & 370 for AcINH

**Table 1** Patient info

| Covariate           | Median (range)   |
|---------------------|------------------|
| Sex                 | M =63%           |
| Age (years)         | 38 (19 to 65)    |
| Weight (kg)         | 52 (34 to 92)    |
| Fat-free mass (kg)  | 43 (26 to 68)    |
| Dose (mg/kg FFM)    | 5.9 (4.4 to 8.1) |
| Dose (mg/kg weight) | 4.8 (3.3 to 6.1) |

### Model building:

- NONMEM 7.3 (FOCE-I),
- Pirana,
- PSN,
- Xpose

## Results

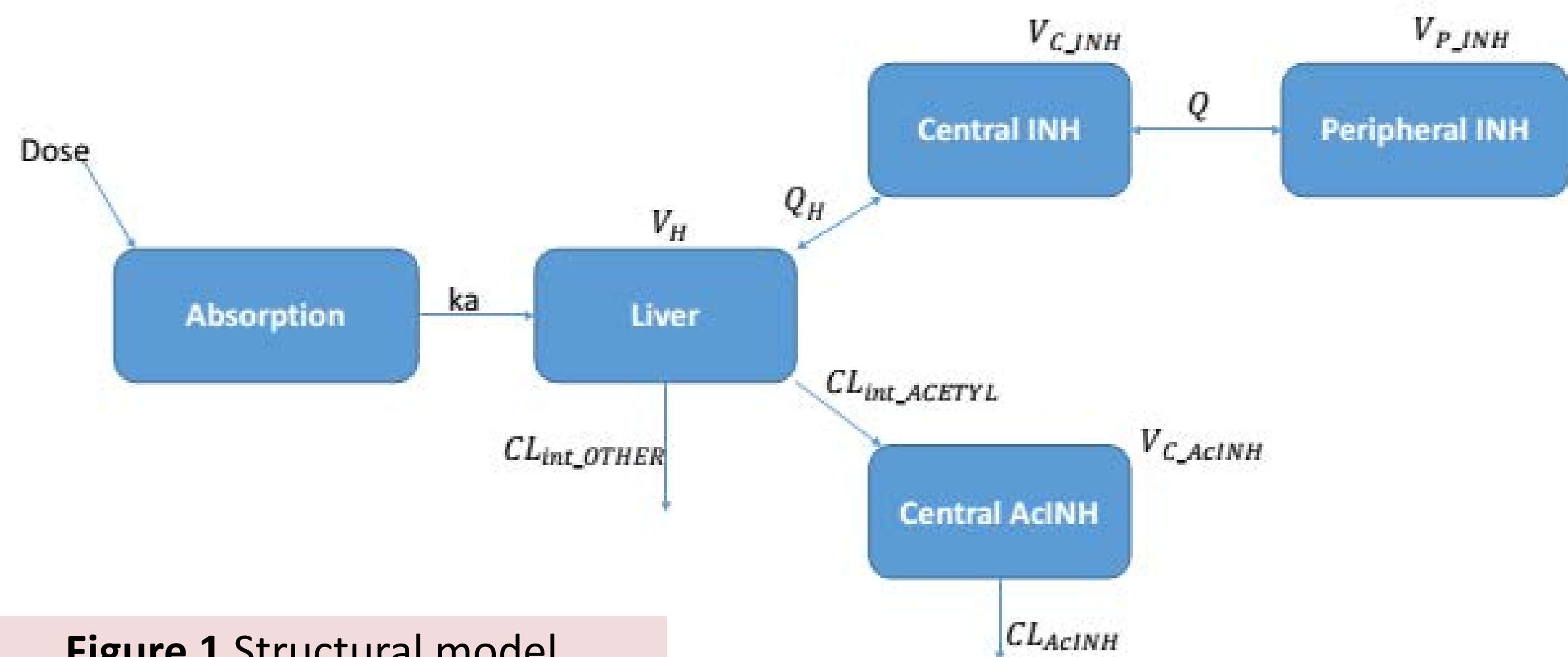


**Figure 1** Structural model

2-compartment model for INH & 1- compartment model for AcINH

**Well-stirred liver model** was used to describe both **hepatic clearance** and **first-pass metabolism** due to hepatic extraction  $E_H$

$$E_H = \frac{(CL_{int\_ACETYL} + CL_{int\_OTHER}) \cdot f_u}{(CL_{int\_ACETYL} + CL_{int\_OTHER}) \cdot f_u + Q_H} \quad CL_H = E_H \cdot Q_H$$

$CL_{int\_ACETYL}$  is intrinsic clearance responsible for acetylation while  $CL_{int\_OTHER}$  is responsible for other hepatic metabolic pathways

For a typical individual in the dataset, volume of liver ( $V_H$ ) was fixed to 1 L , hepatic plasma flow ( $Q_H$ ) 50 L/h and free fraction of isoniazid ( $f_u$ ) at 95%

**Table 2** Final parameter estimates (5<sup>th</sup> and 95<sup>th</sup> bootstrap percentiles)

| Parameter                                   | Estimate     | BSV/ BOV <sup>+</sup>               |
|---------------------------------------------|--------------|-------------------------------------|
| CL <sub>int_ACETYL</sub> [L/h]              | Fast<br>Slow | 31.6 (28.1; 36.0)<br>5.3 (4.5; 6.5) |
| CL <sub>int_OTHER</sub> [L/h]               |              | 28.3 (19.2; 35.6)                   |
| V <sub>C_INH</sub> [L]                      |              | 51.5 (49.1; 53.9)                   |
| ka [1/h]                                    |              | 1.8 (1.6; 2.2)                      |
| Bioavailability                             |              | 1 FIXED<br>+18.6 (12.6; 25.4)       |
| Q [L/h]                                     |              | 1.0 (0.5; 1.7)                      |
| V <sub>P_INH</sub> [L]                      |              | 6.5 (4.5;99.1)                      |
| ARM1 effect on CL <sub>int_ACETYL</sub> [%] |              | 34 (14.1; 73.2)                     |
| Batch effect on Bio [%]                     |              | -62 (-64.9; -58.2)                  |
| Proportion (fast) [%]                       |              | 50 (42.6; 57.5)                     |
| CL <sub>ACINH</sub> [L/h]                   |              | 6.1 (5.3; 7.0)                      |
| V <sub>C_ACINH</sub> [L]                    |              | 32.4 (28.4; 37.8)                   |
| Prop error_INH                              |              | 11.3 (9.7; 12.6)                    |
| Prop error_AcINH                            |              | 6.5 (5.0; 7.9)                      |

CL and V parameters reported for patient with FFM of 43 kg

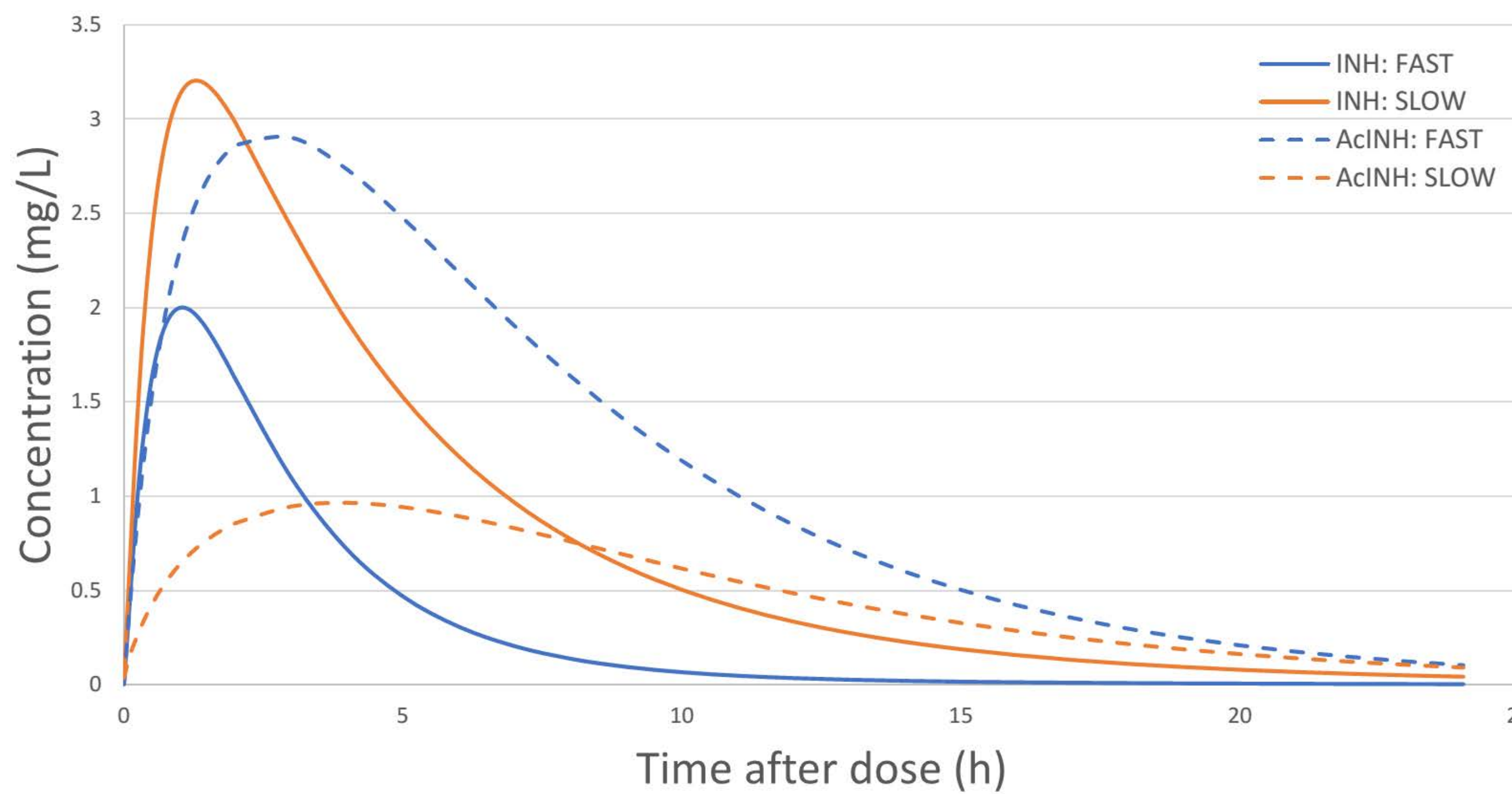


**Figure 2** Simulated concentrations for two different acetylator status

Typical patient on 300 mg dose of INH with 43 kg fat-free mass

**Allometric scaling** [1] was applied to all clearance and volume parameters (including the liver) to account for body size using **fat-free mass**.

A mixture with two subpopulations of **fast and slow acetylators** was supported

**Intrinsic CL via acetylation among fast acetylators** was 5-fold that of slow and approximately similar difference in  $E_H$  (35% vs. 8%)

**32% and 73% of INH is metabolised to AcINH** in slow and fast acetylators respectively

Patients who administered tablets from 2 of the batches had **lower bioavailability**

**Patients who started ART at 2 weeks** after TB treatment initiation had **34% higher clearance** of INH associated with acetylation

**Less than 10%** of the patients had Cmax were within the target range of 3 to 5 mg/L [4]

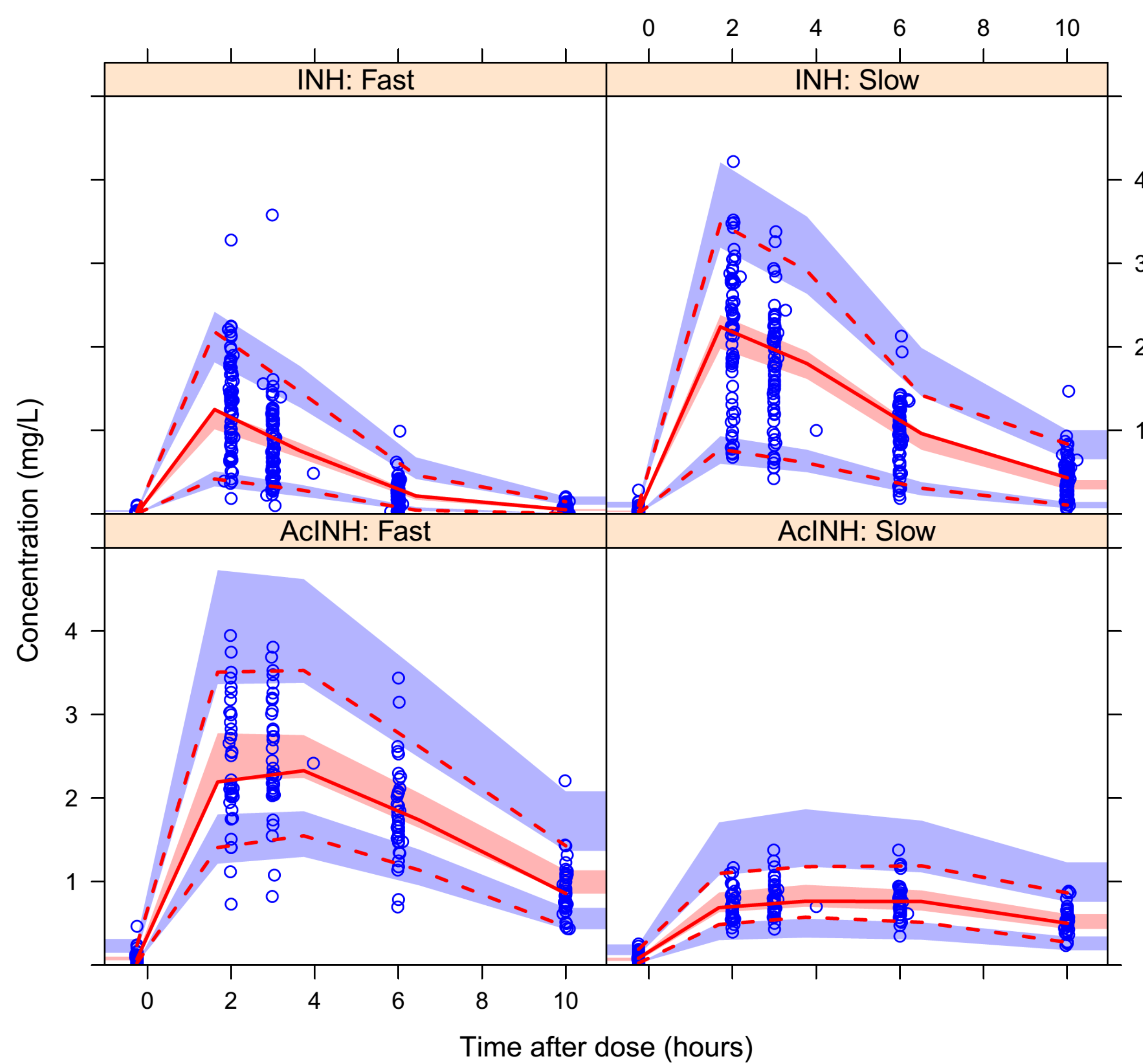


**Figure 3** Visual predictive check

## Conclusions

Model could separate acetylation (responsible for formation of AcINH) from other elimination pathways, and consistent with literature, quantified the difference in CL between fast and slow acetylators

Hepatic extraction associated acetylation was much higher among fast compared to slow acetylators

FFM was found to be a better descriptor of body size than total body weight as in other PK studies[2,3]

## References

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