Population PK of Isoniazid in South African Adults.

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Background and Objectives

Isoniazid, together with rifampicin, forms the backbone of 1st line anti-tubercular treatment.

Isoniazid metabolism is highly dependent on genetic polymorphisms of N-acetyltranferase 2 [1].

The objective was to develop a population PK model of isoniazid.

Methods

61 South African HIV-infected subjects with TB.

Fixed dose combination of rifampicin, isoniazid, pyrazinamide, & ethambutol, WHO weight-based dosing recommendations [2].

Intensive PK sampling on 4 occasions: on day 1, 8, 15, & 29 of treatment.

Data below limit of quantification (LOQ) →M6 method [3] + add err LOQ/2.

Table 1. *Patients details*

Covariate	Median and IQR
Sex	28 M, 33 F
Age (y)	32 (27 - 37)
Body Weight (kg)	55.2 (50.0 - 62.4)
Body Height (m)	1.59 (1.54 - 1.68)
Body Mass Index (kg/m^2)	21.8 (19.1 – 24.6)
Fat Free Mass (kg)	42.2 (35.2 - 47.3)

Results

Isoniazid PK was described by

- Two-compartment disposition
- First-order elimination
- Absorption through transit compartments [4]
- Fat Free Mass (FFM) allometric scaling volumes and clearances.

Parameter values (in Table 2):

- Large BOV in absorption and bioavailability, BSV in bioavailability
- Initially BSV-CL 50%+ → Mixture model + BSV-CL 20%
- 2 subpopulations: fast (28.1 L/h) & slow (60.7 L/h) metabolisers
- Fast metabolisers also have lower bioavailability (-27%)
- Higher bioavailability in patients receiving more tablets.

Table 2. *Parameter estimates, along with precision as %RSE, in brackets. Values for CL/F, V/F, Q/F, and V_2/F are scaled to a FFM of 42.2 kg.*

Parameter	Typical Value	BSV	BOV
CL/F [L/h]	Slow: 28.1 (9.8%), Fast: 60.7 (8.9%)	18.7% (16.6%)	
V/F [L]	90.8 (12%)		
Ka [h^{-1}]	2.06 (11.3%)		67.5% (7.6%)
MTT [h]	0.555 (7.9%)		45.8% (11.6%)
NN (transit)	39.6 (34.6%)		
Q/F [L/h]	17.1 (21.2%)		
V_2/F [L]	33.4 (12.2)		
F	Slow: 1 (FIX), Fast: 0.728 (7.3%)	31.2% (18.9%)	23.8% (7.6%)
% Slow metab.	44.8% (19.4%)	**F if dose=375 mg**	+46.5% (53.8%)
Error	Add: 0.0235 (9.7%) Prop: 18.7% (3.3%)	**Error for BLQ data**	Add: 0.04 (FIX)

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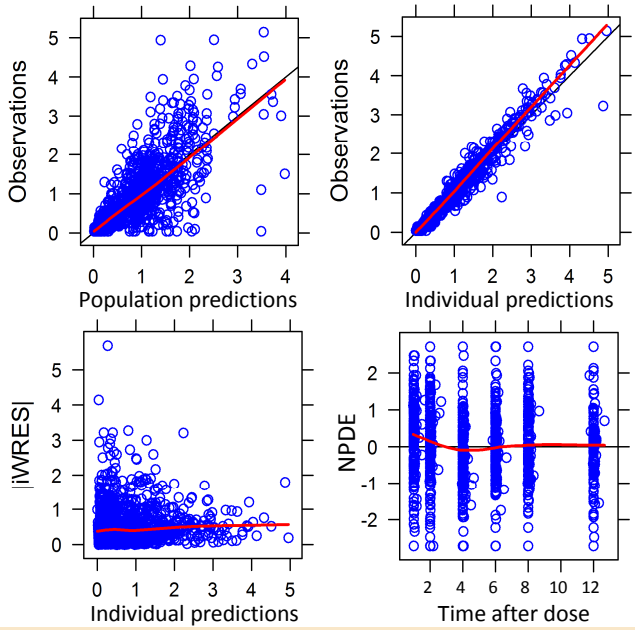

Figure 2. *Goodness of fit plots*

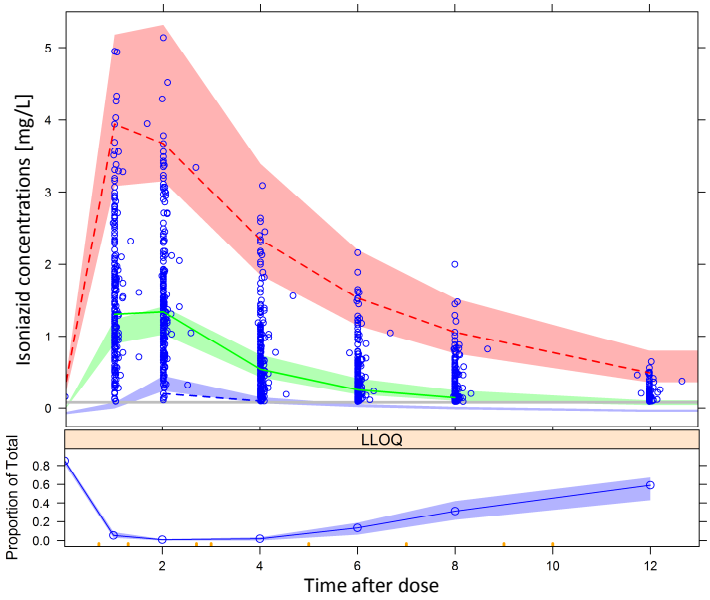

Figure 2. *VPC for the concentration data (upper) and the proportion of data below limit of quantification (lower panel). Dashed and solid lines are observed data for different percentiles, while shaded areas are the corresponding model predictions.*

Conclusions

A mixture with 2 subpopulations could separate fast and slow metabolisers.

Isoniazid has trimodal elimination [1], but a more complicated mixture model was not supported by the data.

Fast metabolisers also have lower bioavailability, possibly due to a larger extent of first-pass metabolism.

The increase in bioavailability with higher doses may indicate saturation of first-pass metabolism.

References and Acknowledgements

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