Population Pharmacokinetics of Isoniazid in Children with Pulmonary Tuberculosis

SP Zvada[1], USH Simonsson[2], P Denti[1], PR Donald[3], HS Schaaf[3], PJ Smith[1], HM McIlleron[1]

[1]University of Cape Town, Department of Medicine, Division of Clinical Pharmacology, South Africa
[2]Uppsala University, Department of Pharmaceutical Biosciences, Uppsala, Sweden
[3]Department of Paediatrics and Child Health, Faculty of Health Sciences, University of Stellenbosch, and Tygerberg Children's Hospital

Email: simbarashe.zvada@uct.ac.za; s imba.zvada@gmail.com

Background and Objectives

- Isoniazid is one of the most important first-line anti-TB drugs
- **Children are often neglected** during optimization of doses: daily doses (4-6 mg/kg) of Isoniazid derived from adult doses have been reported to be inadequate [1]
- The World Health Organisation's revised guidelines (2010) recommend a dose of 10-15 mg/kg/day in children across all weights [2]
- The aim of our study was to develop a model that describes population pharmacokinetics of isoniazid in children with tuberculosis and employ it to explore the adequacy of the new guidelines.

Methods

- Previously published data (summarized in Table 1) from 56 South African children hospitalized for treatment of tuberculosis were used to describe the population pharmacokinetics of isoniazid [3]
- Also rifampicin and pyrazinamide were part of the treatment, in a "pediatric" dispersible fixed dose combination

Table 1. *Demographic and clinical characteristics of study of the children*

Gender	29 males and 27 females
HIV status	22 Positive, 34 Negative
PK Sampling	1 and 4 months (at 0.75;1.5;3.0;4.0;6.0 hours after dose)
Acetylator Genotype	Slow (20), intermediate (24) ,fast (8), and unknown (8)
Age (yr) - median (IQR)	3.22 (1.58-5.38)
Weight (kg) - median (IQR)	12.5 (8.84 -17.2)

Results

- The pharmacokinetics of isoniazid was best described by a two-compartment model with first-order elimination and absorption
- Total body weight was included in the model through allometric scaling on oral clearance ($CL = CL_{std} \cdot (WT/12.5)^{0.75}$ and on apparent volume of distribution ($V = V_{std} \cdot (WT/12.5)$)
- Final parameter estimates are shown in Table 2, model validation was through inspection of goodness of fit plots (Figure 1) and visual predictive check (Figure 2)

Table 2. *Final parameter estimates for Isoniazid pharmacokinetics*

Parameter	Estimate (%RSE)	IIV (%RSE)	IOV (%RSE)
CL/F *slow acetylators* (L/hr/12.5kg)	4.55 (14.1)		-
CL/F intermediate acetylators (L/hr/12.5kg)	9.89 (8.9)	22.4 (20.7)	-
CL/F *fast acetylators* (L/hr/12.5kg)	14.8 (17.4)		-
V/F central (L/12.5kg)	13.0 (14.4)	23.8 (42.2)	
ka (hr^{-1})	1.54 (18.9)	-	44.9 (21.7)
Q /F (L/hr/12.5kg)	2.31 (14.7)	-	-
V3/F peripheral (L/12.5kg)	8.64 (78.5)	-	-
Oral bioavailability	1 FIX	-	39.1 (7.3)
Proportional Error (%)	25.4 (3.1)	-	-

- SIMULATION:
  - Using these values of CL, 10 mg/kg doses in accordance with the new WHO guidelines would achieve a median AUC_{INF} of 21.9, 12.6 and 8.3 mg•h/L in slow, intermediate and fast acetylators, respectively
  - These AUCs are low when compared to the value of 32.5 mg•h/L (interquartile range: 22.5-42.4 mg•h/L) obtained in an ethnically similar but adult population [4]

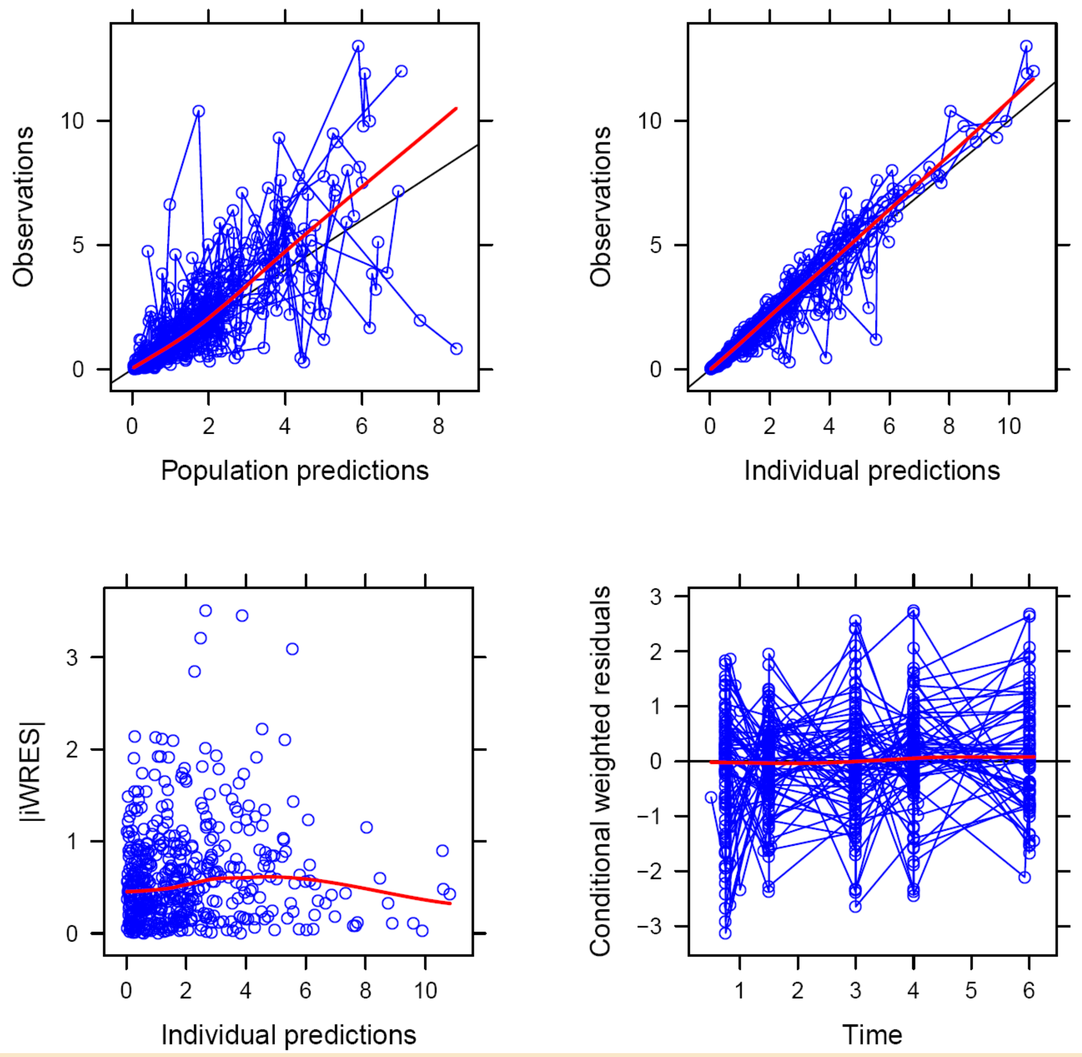

Figure 1. *Goodness of fit plots for the final Isoniazid model. The small open (blue in colour) circles are the observed concentration-time data points, the solid black line represent the scatter plot smoothing, and the solid red line is the line of best fit.*

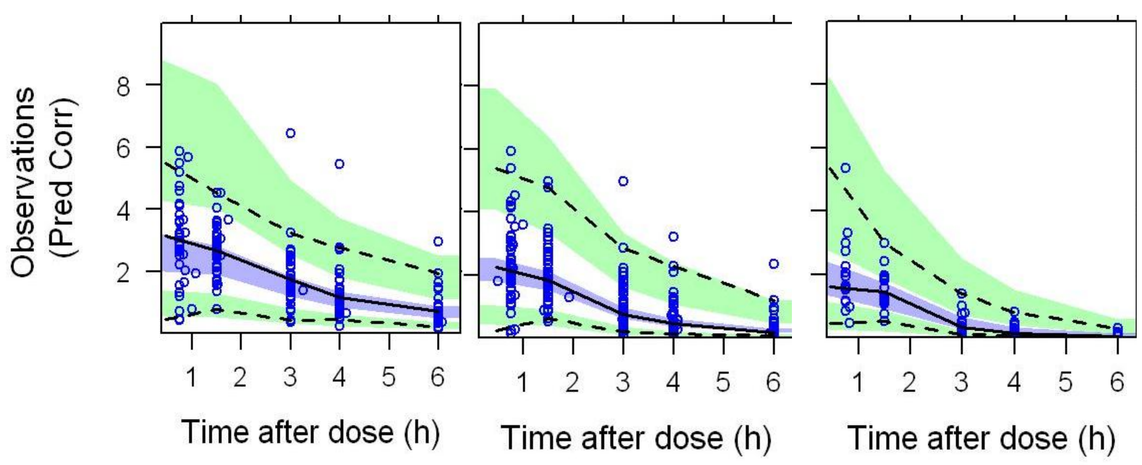

Figure 2. *Prediction corrected visual predictive check for the final isoniazid model stratified on genotype. The dashed and solid lines; lower, middle and upper are 5th, 50th, 95th percentiles of the observed data, respectively. The shaded areas around each percentile indicate the 95% confidence interval from model prediction. The small open circles are the observed concentration-time data points.*

Conclusions

- Our model adequately described the pharmacokinetics of isoniazid in children
- Our results suggests that even with the new target dose (WHO guidelines - 2010); **children, especially the fast acetylators, may be under-dosed compared to adults**.

Acknowledgements

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References

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