Pharmacokinetics and dose optimization strategies of para-aminosalicylic acid in children with rifampicin-resistant tuberculosis.

Louvina E. van der Laan[1,2], Anthony J. Garcia-Prats[2], H. Simon Schaaf[2], Maxwell Chirehwa[1], Jana L. Winckler[2], Jun Mao[1], Heather R. Draper[2], Lubbe Wiesner[1], Jennifer Norman[1], Helen McIlleron[1], Peter Donald[2], Anneke C. Hesseling[2*], Paolo Denti[1*] (* joint senior authors)

[1] Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, South Africa.

[2]Desmond Tutu TB Centre, Department of Paediatrics and Child Health, Faculty of Medicine and Health Sciences, Stellenbosch University, Cape Town, South Africa.

Email: vdlaan@sun.ac.za

Background and Objectives

Para-aminosalicylic acid (PAS) is a **WHO-recommended drug** (Group C) for rifampicin-resistant tuberculosis (RR-TB) treatment. Prevention of resistance in companion RR-TB drugs by PAS is dosage related and at **higher concentrations**, PAS may exhibit significant **bactericidal activity** in addition to its bacteriostatic properties. PAS is mainly (~ 80%) renally eliminated.

The **optimal dosing of PAS in children is uncertain**.

We describe the pharmacokinetics of the widely available **slow-release PAS formulation** in children treated for RR-TB, to identify any important covariates and to identify optimal drug dosing in children through simulations.

Methods

Data

- 27 children from South-Africa on at least 2 weeks of a PAS-containing individualized RR-TB regimen, dosed at 150-200 mg/kg in two divided doses.
- PAS slow-release granule formulation by PASER was used.
- Blood samples taken pre-dose and at 1, 2, 4, 8 and 11 h post PAS dose.

Assays

- Liquid-liquid extraction method using ethyl acetate, followed by LC-MS/MS detection. LLOQ was 0.391 mg/L.

Model

- NONMEM 7.4.4 with FOCE-I was used to develop the population PK model.
- PsN, Pirana and Xpose were used in the model building process for data exploration, visualization and creation of diagnostics.
- Allometric scaling was used to account for the effect of body size (using either total body weight or fat-free mass) and age was tested using a sigmoid Emax maturation model(1).
- Model-based simulations evaluated current 2019 WHO weight-band doses (200-300 mg/kg/day given as a once- or twice-daily dose) against the adult pharmacokinetic target of 50-100 mg/L for peak concentrations.

Results

Model

- PAS followed one-compartment kinetics with first-order elimination and transit-compartment absorption.
- The model detected a large inter-occasion variability (IOV) in bioavailability.
- Allometric scaling using body weight was included as a standard for paediatric populations (1), although the model showed no significant improvement after its inclusion (same using fat-free mass).
- Maturation parameters could not be robustly identified, as of the 10 (37%) children below 2 years of age, only 2 were below 1 year of age. Bayesian priors based on previously reported renal function (2), with 20% uncertainty, were therefore included in the model to improve simulation estimates in younger children.
- Increased PAS clearance was observed in both pharmacokinetic profiles from the only patient receiving efavirenz; this was retained in the model, as this interaction was previously reported in adults(3).
- No effect of renal function, sex, ethnicity, nutritional status, HIV status, other antiretrovirals (lamivudine, abacavir, lopinavir/ritonavir) or other RR-TB drugs was detected.

Table 2: Parameter estimates of the final model

Parameters	Typical value (95% CI)	BSV*/BOV** % (95% CI)
CL (L/h)*a*	9.15 (6.97, 11.7)	34.2* (21.8, 46.8)
Effect of efavirenz on CL in a single child (%)	+162 (+32, +351)	
V_C (L)*a*	38.7 (27.9, 53.5)	
MTT*b*	4.41 (3.81, 4.92)	34.2** (26.4, 45.6)
NN ( )*b*	16.3 (10.2, 25.3)	
F ( )	1- fixed	65.1** (48.2, 86.2)
Additive error (mg/L)*c*	0.0782 - fixed	
Proportional error (%)	34.2 (28.7, 41.1)	

a Reported for a child with a median weight of 13.3 kg. *b* Bayesian prior (ref 2). *c* Fixed to improve model stability.

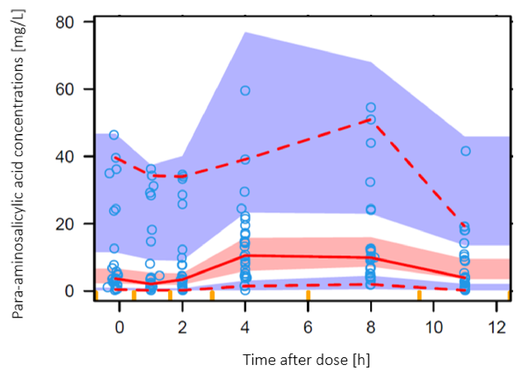


Figure 1. Visual predictive check. Lines represent the 5th, 50th, and 95th percentiles of the observed data, shaded areas are the model-predicted 95% confidence intervals for the same percentiles. Observed data are displayed as blue circles.

Table 1: Patient characteristics, n (%) or median) (IQR)

Characteristics	Children (n=27)
Age	3.87 (1.78-5.23)
Males	16 (59.3)
Weight (kg)	13.3 (10.9-17.0)
Black race	14 (51.9)
Z-score <-2*a*	
Weight-for-age	5 (18.5)
Length-for-age	10 (37.0)
No (%) HIV-positive	4 (14.8)
Creatinine (µmol/L)	26 (20.5-31.5)
Antiretroviral treatment (n=4)	
LPV/RTV-based regimen	3 (75)
EFV-based regimen	1 (25)
Antituberculosis treatment	
Terizidone	27 (100)
Pyrazinamide	25 (92.6)
High-dose isoniazid	25 (92.6)
Ethambutol	21 (77.8)
Ethionamide	21 (77.8)
Amikacin	15 (55.6)
Clofazimine	11 (40.7)
Levofloxacin	10 (37.0)
Linezolid	10 (37.0)
Moxifloxacin	9 (33.3)
Capreomycin	6 (22.2)
Ofloxacin	3 (11.1)
Amoxicillin-clavulanic acid	2 (7.41)
Delamanid	1 (3.70)

a Weight- and height-for-age Z-scores of <-2 include underweight/stunted to severely underweight/stunted participants.

Simulations

- Target peak concentrations (50-100 mg/L) were achieved **only** in children receiving PAS at the **higher WHO dose** range of 300 mg/kg in a **once-daily** dose.
- Children should be dosed at the **higher range** of current WHO-recommended PAS doses and in a **once-daily** dose to optimize treatment.

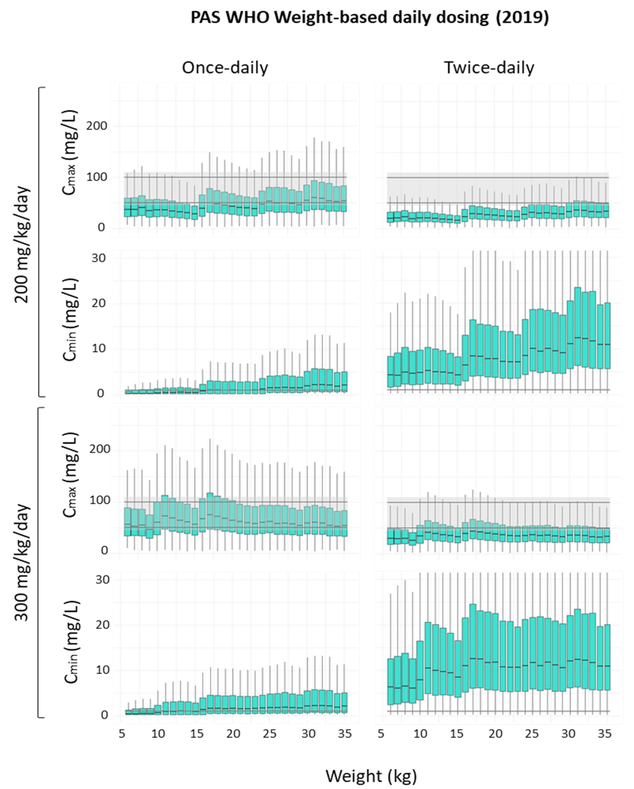


Figure 2. Simulated peak (Cmax) and minimum (Cmin) concentrations of PAS vs. weight in children receiving either the current WHO-recommended dose of 200mg/kg/day (upper panel), or 300 mg/kg/day (lower panel) given as either a once- (left panel) or twice-daily (right panel) dose. The dark-grey bands represents the desired (50- 100 mg/L), and the minimum (1 mg/L) adult target (± 10%).

Conclusions

- A transit compartment adequately describes absorption for the slow-release PAS formulation.
- **A once-daily dose of PAS at the higher end of the current WHO dose range of 300 mg/kg/day is recommended in children treated for RR-TB.**

References

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