Population pharmacokinetic modelling of pyrazinamide in plasma and cerebrospinal fluid from HIV-associated tuberculosis meningitis adults

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Background and objectives

Tuberculosis meningitis (TBM) is a devastating manifestation of infection by *Mycobacterium tuberculosis* bacilli and is associated with severe morbidity and high mortality, especially in individuals with HIV. [1]

Pyrazinamide is an antimicrobial agent used in the standard first-line anti-TB treatment regimen, including for TBM. Pyrazinamide achieves excellent brain concentrations in animal models and may have an important role in TBM therapy. [2]

Although well-studied in patients with pulmonary TB, plasma pharmacokinetics (PK) and cerebrospinal fluid (CSF) penetration of pyrazinamide in TBM still requires further research.

Objective: to describe the plasma and CSF pharmacokinetics of pyrazinamide in adults with HIV-associated TBM.

Methods

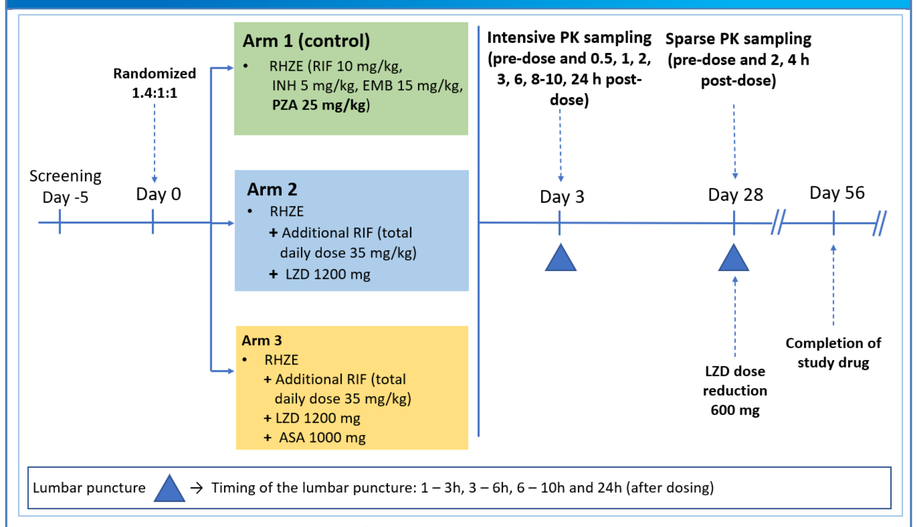

Figure 1. Study protocol. RIF: rifampicin; INH: isoniazid; EMB: ethambutol, PZA: pyrazinamide, LZD: linezolid; ASA: aspirin

This PK study was nested in LASER-TBM, a phase 2a, randomized and multicentre clinical trial carried out among HIV-positive adults with newly diagnosed TBM in South Africa.[3]

Plasma pyrazinamide concentrations were assayed using LC-MS/MS. Samples below limit of quantification (0.2 mg/L) were imputed as LLOQ/2, following the M6 method.[4]

The PK analysis was performed using FOCE-I in NONMEM v7.5.1. The CSF concentrations were linked to the central compartment using a hypothetical effect compartment, which estimates the plasma-to-CSF equilibrium half-life and the CSF-to-plasma partition coefficient.

Results

Table 1. Participants characteristics

Characteristic	Median (Min - Max)
Age (years)	39 (25 – 78)
Weight (kg)	60.0 (30.0 – 107)
Height (m)	1.6 (1.4 – 1.8)
Fat-free mass (kg)	45.2 (30.3 – 59.4)
	n (%)
Male/Female	27 (55) / 22 (45)
HIV positive	49 (100 %)
On ART/Naïve ART/Previous ART	15 (31 %) / 20 (41 %) / 14 (28 %)
African/Caucasian/Coloured	41 (84 %) / 2 (4 %) / 6 (12 %)

ART: Antiretroviral treatment

A total of 414 plasma and 44 CSF concentrations were available from 49 participants for the PK analysis. Only one (2.27%) CSF and 5 (1.2%) plasma observations were below the LLOQ.

Plasma pharmacokinetics of pyrazinamide was best described by a one-compartment model with first-order elimination and transit compartments absorption (Figure 2).

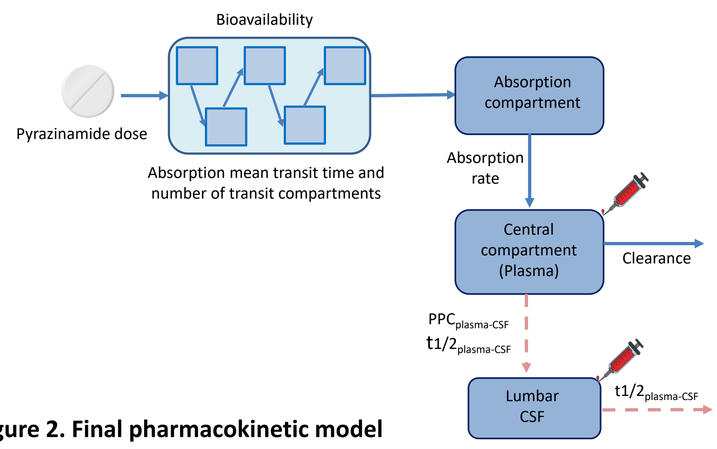

Figure 2. Final pharmacokinetic model

Results

- Fat-free mass was better predictor of body size effect on disposition parameters than weight.
- Clearance was larger by 30% on day 28 compared with day 3 of study.
- No statistically significant differences were observed between the intervention arms receiving the high dose of rifampicin. (with and without aspirin) and the one receiving the standard regimen.

Table 2. Final parameter estimates

Parameter	Typical value	95% CI[a]	Variability (%)	95% CI[a]
Clearance (L/h)[b]	4.19	3.86 – 4.45	Between subject: 18.5	16.2 – 26.2
Volume of distribution (L)[b]	45.0	43.4 – 46.6		
Absorption constant rate (1/h)	2.50	2.29 – 2.68	Between occasion: 87.3	81.7 – 108
Mean transit time (h)	0.294	0.184 – 0.380	Between occasion: 102	85.3 - 134
Number of transit compartments (n)	4.25	3.76 – 4.88		
Bioavailability	1 FIXED	-	Between occasion: 15.8	11.5 – 17.8
Scaling BOV for unobserved dose (-fold change)[c]	2.51	2.32 – 2.91		
Increased clearance on day 28 (%)	+30.0	23.8 – 37.3		
Proportional error (%)	8.30	7.25 – 9.08		
Additive error (mg/L)[d]	0.04 FIXED	-		
Plasma-to-CSF equilibrium half-life, $t_{1/2\ plasma\text{-}CSF}$ (h)	0.66	0.43 – 0.90		
Maximal pseudo-partition coefficient to CSF, PPC_{max} (.)	1.05	0.99 – 1.09		
Proportional error CSF (%)	11.4	9.04 – 16.1		
Additive error CSF (mg/L)[d]	0.04 FIXED	-		

[a] 95% confidence intervals (CI) were obtained using sampling-importance resampling (SIR).
[b] Allometrically scaled; typical values reported for typical median individual with 45 kg fat-free mass.
[c] A change in the variability for absorption parameters was estimated for the doses before the sampling visit and the pre-dose observation, representing the uncertainty of dosing times from the previous days.
[d] The estimate of the additive component of the error was not significantly different from its lower boundary of 20% of LLOQ, so it was fixed to this value.

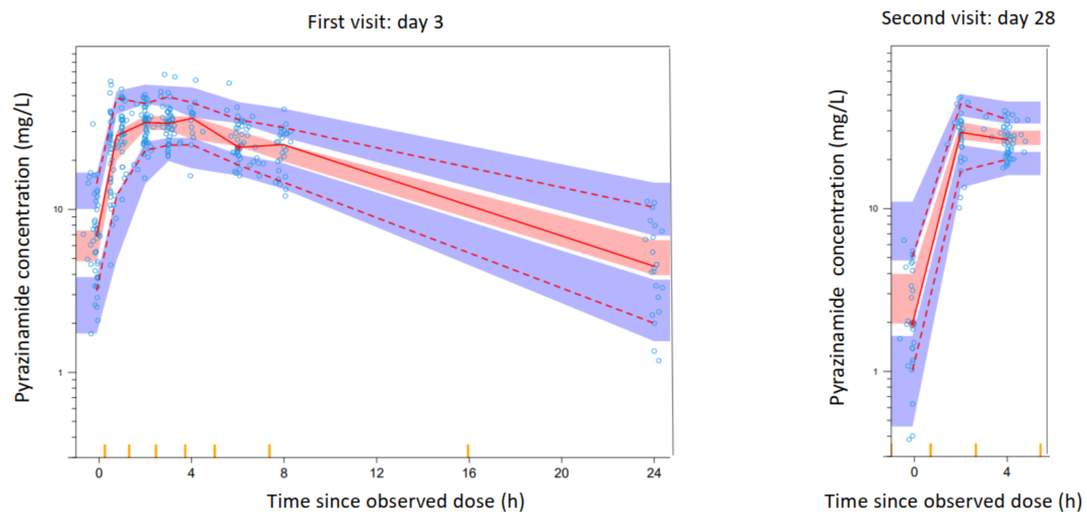

Figure 3. Visual Predictive Check (log scale) of the final model. The solid and dashed lines are the 5th, 50th, and 95th percentiles of the observed data (blue circles), while the shaded areas represent the 95% confidence intervals for the same percentiles of the model predictions.

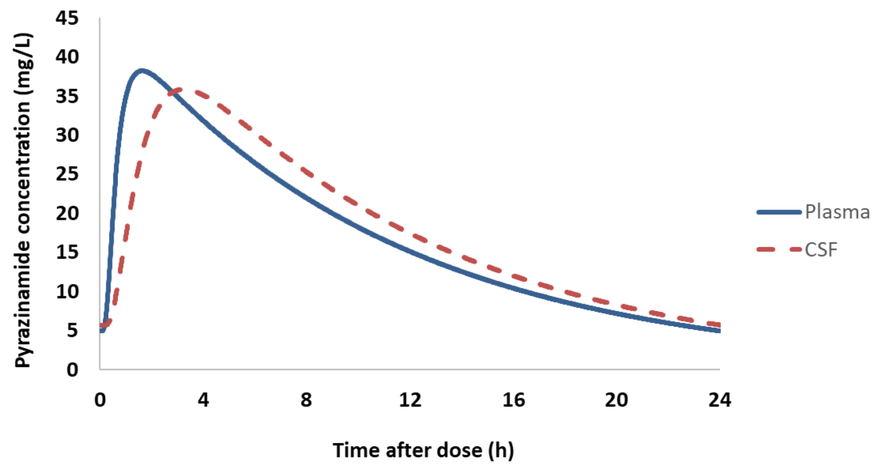

Figure 4. Simulated typical concentration-time profiles for plasma and cerebrospinal fluid (CSF).

Conclusions

We developed a model describing the pharmacokinetics of pyrazinamide in plasma and CSF in adults with TBM. Our model confirms that pyrazinamide quickly reaches the CSF and achieves concentrations similar to plasma, supporting further efficacy evaluations in TBM. Our results on plasma PK are in line with previous reports in pulmonary TB patients. Consistently with Chirehwa *et al*.[5], we observed an increase in pyrazinamide clearance over treatment duration. The reasons for this are unclear, but possible explanations are induction of drug-metabolising enzymes by rifampicin, or the recovery of clearance processes with treatment.

References

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