Population pharmacokinetics of levofloxacin in South African adults treated for rifampicin-resistant tuberculosis.

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Background and Objectives

Rifampicin-resistant tuberculosis (RR-TB) is a public health threat whose global incidence has increased by 3.1% between 2020 and 2021 [1].

South Africa is one of the 30 high-tuberculosis burden countries in the world with increasing cases of RR-TB [1].

Levofloxacin is a fluoroquinolone antibiotic recommended by the World Health Organization (WHO) as a group A drug for inclusion in RR-TB regimens [2].

Levofloxacin is mainly excreted unchanged in urine, and undergoes limited metabolism [3].

Data describing the pharmacokinetics of levofloxacin in RR-TB patients are limited.

Objective: We aimed to characterize the population pharmacokinetics of levofloxacin in South African adults treated for rifampicin-resistant tuberculosis.

Methods

BEAT Tuberculosis is a phase three randomized controlled trial comparing the efficacy and safety of a novel 6 month treatment regimen for RR-TB (study strategy) with the current 9-12 month South African standard of care regimen (control strategy).

TB patients ≥ 6 years of age with RR-TB, with or without resistance to isoniazid and/ or fluoroquinolones (FQs), were recruited from 2 study sites: Jose Pearson TB Hospital in Port Elizabeth and King Dinuzulu Hospital in Durban, South Africa.

The trial regimen (study strategy) consisted of bedaquiline, delamanid, clofazimine, linezolid and levofloxacin. Levofloxacin was subsequently stopped if FQ resistance was detected.

Participants were followed up for 76 weeks post treatment initiation.

A subset of adult participants ≥ 18 years of age were intensively sampled at Jose Pearson Hospital (0, 2, 4, 6, 8, 10 and 24 hours post-dose), after approximately four weeks of treatment.

We used NONMEM 7.5.1 (FOCE-I), PsN 5.3.1, Pirana 2.9.9 and R 4.2.2 to estimate the population pharmacokinetic parameters of levofloxacin.

We tested one- and two-compartments disposition models with and without lag and transit absorption compartments.

We explored the effect of HIV status and creatinine clearance on the population pharmacokinetics of levofloxacin.

Creatinine clearance was estimated using the Cockcroft-Gault formula.

Results

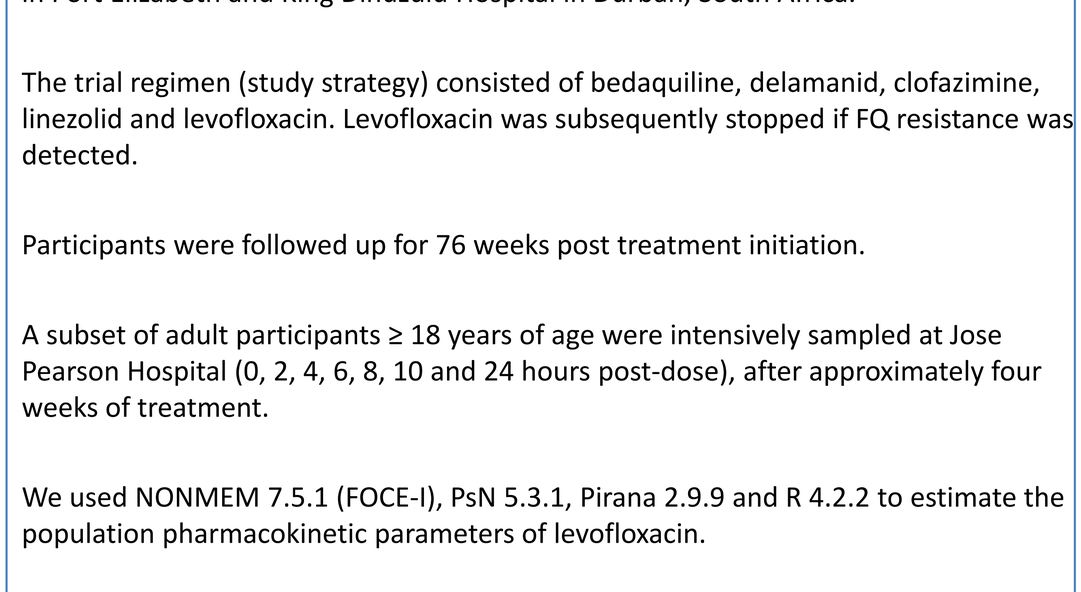

Figure 2: Participant characteristics of RR-TB patients treated with levofloxacin.
Disclaimer: The results reported here in the poster includes an additional 9 participants (enrolled later in the trial) that were not included in the participant number reported in the submitted abstract.

Allometric scaling was applied based on the median fat-free mass (FFM) value for clearance (CL) and volume of distribution (V) using the following equations:

$$CL = TVCL \cdot \left(\frac{FFM}{TVFFM}\right)^{0.75}$$

$$V = TVV \cdot \left(\frac{FFM}{TVFFM}\right)$$

Results

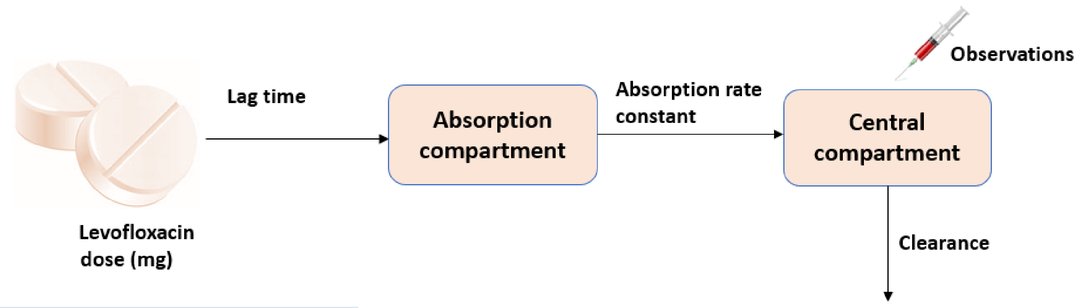

Figure 3. Levofloxacin model structure

Table 1. Final parameter estimates

Parameter	Typical value (95% CI)[b]	Variability as %CV (95% CI)[b]
Clearance (L/h)[a]	5.98 (5.40 – 6.55)	BSV: 19.9[c] (15.6 – 24.9)
Volume of distribution (L)[a]	93.9 (87.3 – 101)	
Absorption rate constant (1/h)	1.10 (0.783 – 1.54)	BOV: 69.8[c] (53.3 – 89.7)
Lag time (h)	1.09 (0.847 – 1.36)	BOV: 39.6[c] (26.7 – 51.3)
Bioavailability, *F*	1 (fixed)	BOV: 16.7[c] (12.9 – 21.0)
Proportional error (%)	7.98 (6.70 – 9.59)	
Additive error (mg/L)	0.233 (0.0906 – 0.381)	
Scaling of BOV in *F* for unobserved doses (fold)[d]	2.46 (1.56 – 3.71)	

[a]This parameter has been adjusted by allometric scaling, and the values reported here refer to a subject with a fat-free mass of 43.6 kg.

[b]The values in the parentheses are empirical 95% confidence interval (CI) computed from standard errors using Sampling Importance Resampling (SIR).

[c]The parameter variability was included either as between-subject variability (BSV) or between-occasion variability (BOV), assuming a lognormal distribution. BSV and BOV are reported here as the percent coefficient of variation (CV) calculated as %CV= √(ω^2) × 100, where ω^2 is the variance.

[d]This is a multiplicative factor increasing the BOV in bioavailability (*F*) for all predose concentrations, which follow an unobserved dose.

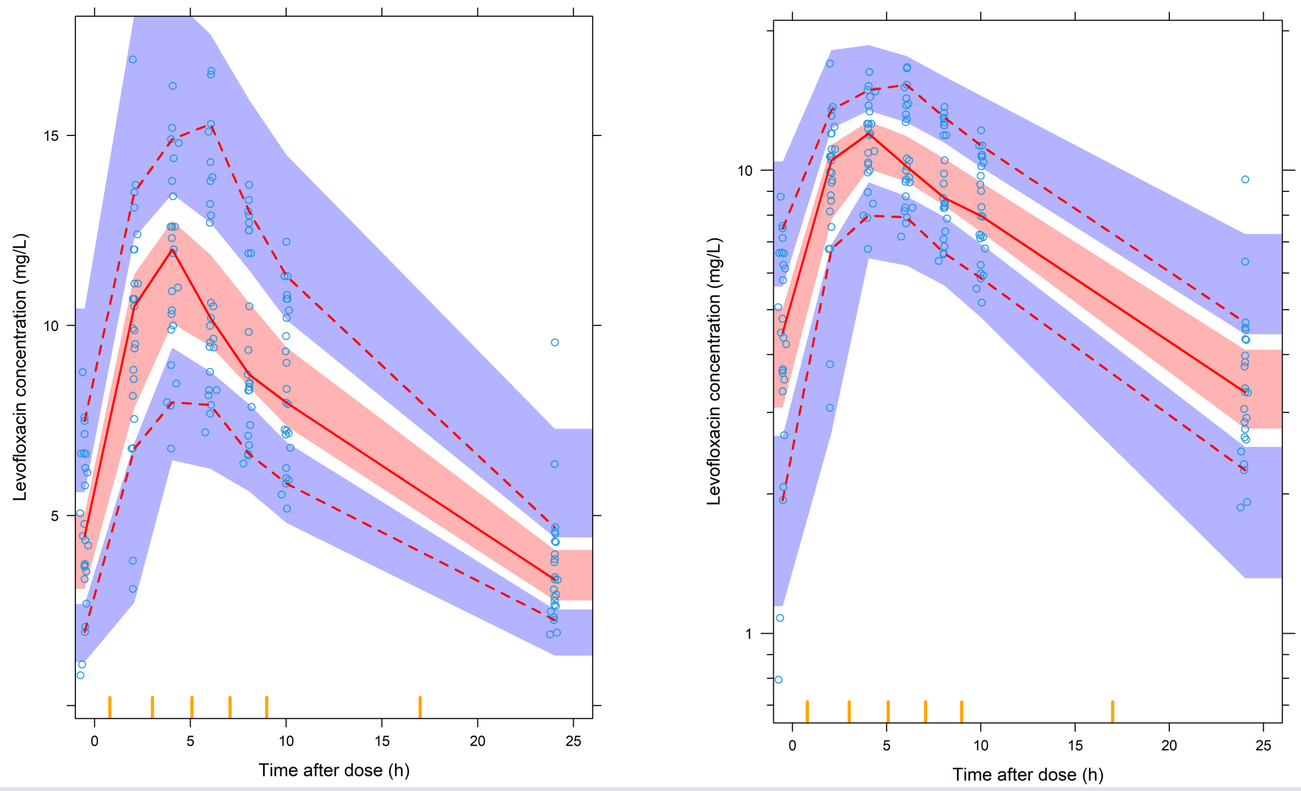

Figure 4. Visual Predictive Check of levofloxacin concentration versus time after dose in normal- and log-scale on the y-axis. The solid and dashed lines represent the 5th, 50th, and 95th percentiles of the observed data, while the shaded areas represent the model-predicted 95% confidence intervals for the same percentiles. The circles are the observed concentrations.

Conclusions

A one-compartment disposition model with first-order elimination and absorption with lag-time best described the data, which is consistent with a previous study [4].

Fat-free mass was a better body size descriptor for disposition parameters than total body weight.

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