A semi-physiological model for moxifloxacin pharmacokinetics accounting for the effect of co-administered drugs and genetic polymorphisms

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Background and Objectives

Moxifloxacin (MOXI) is currently recommended for the treatment of MDR-TB

It could potentially reduce the time to culture conversion in patients with drug susceptible TB

Objective: To the pharmacokinetics (PK) of moxifloxacin and identified the effect of selected covariates on PK parameters

Methods

Blood samples were collected from 58 South African tuberculosis patients recruited in the PK sub study of the IMPRESS study.

IMPRESS investigated superiority of substituting MOXI for ethambutol

Patients received 400 mg of MOXI:

- Daily with rifampicin and isoniazid for 6 months and pyrazinamide for 2 months
- A single dose around 1 month after the end of TB treatment

HIV+ patients received ART, mostly Efavirenz-based

Plasma samples were collected prior to drug dose and at 2.5, 6 and 24 h post dose

PK sampling was done at months 1 and/or 2, at month 6 and ~4 weeks after the completion of TB treatment following a single dose of moxifloxacin.

Model building:

- NONMEM 7.3 (FOCE-I),
- Pirana,
- PSN,
- Xpose

Table 1 Patient info

Covariate	Median (range)
Sex	M = 41(71%) / F = 17 (29%)
Age (years)	38 (20 to 60)
Weight (kg)	58 (44 to 105)
Fat-free mass (kg)	47 (32 to 63)

Results

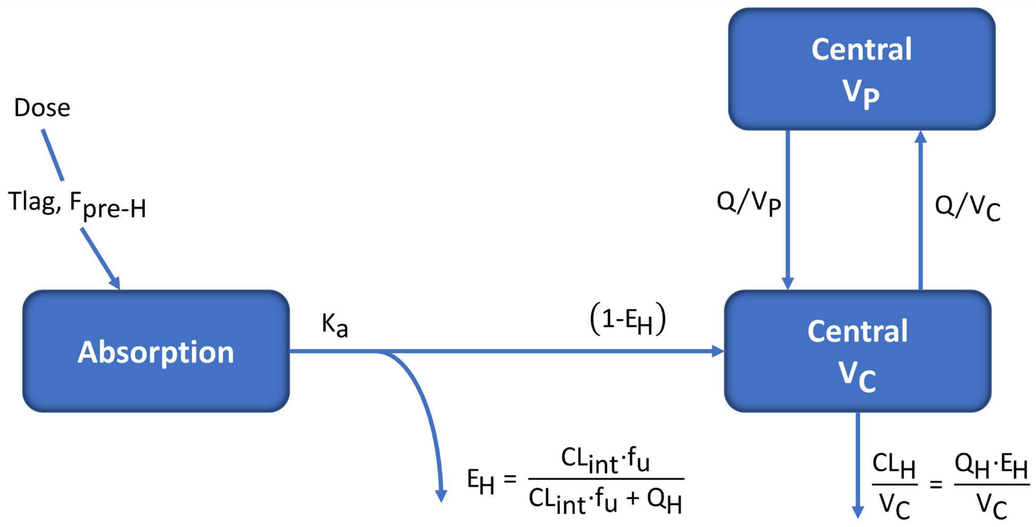

Figure 1 Structural model

The best model was a two-compartment disposition model, with first-order lagged absorption and drug elimination through a semi-mechanistic model to capture liver first-pass effect

For a typical individual in the dataset, volume of liver was fixed to 1 L , hepatic plasma flow (Q_H) 50 L/h and free fraction of moxifloxacin (f_u) at 50%.

Table 2 Final parameter estimates (2.5th and 97.5th bootstrap percentiles)

Parameter	Estimate	BSV/ BOV+
CL_{int} [L/h]	50 (45; 56)	12.1 (2.6; 16.7) 12.2 (4.6; 18.9)+
V_C [L]	127 (109; 137)	8.6 (0.5; 13.5)
Q [L/h]	2.1 (1.6; 4.5)	
V_P [L]	31 (22; 51)	
F_{pre-H}	1 FIXED	35.6 (28.2; 42.1)+
Alag [h]	0.55 (0.45; 0.73)	
Ka [/h]	2.8 (1.2; 3.5)	93.2 (0.9; 122)+
Covariates		
Single dose on Cl_{int} (%)	-28.9 (-36.5; -21.9)	
Single dose on F_{pre-H} (%)	-22.4 (-32.4; -11.6)	
Efavirenz based ART on CL_{int} (%)	+42.9 (32.6; 56.1)	
Single dose scaling on BOV-F_{pre-H}	0.62 (0.41; 0.85)	
Unobserved doses scaling on BOV-F_{pre-H}	2.48 (1.73; 3.75)	
TA 5/6 repeats for rs8175347 on Cl_{int} (%)	-20.6 (-29.3; -13.6)	
Residual Unexplained Variability		
Proportional error	17.4 (12.3; 21.2)	
Additive error	0.011 (0.004; 0.017)	

CL and V parameters reported for patient with FFM of 47 kg

Table 3 Typical values for exposure to moxifloxacin

MOXI SCENARIO	ON RIFAMPICIN	ON EFAVIRENZ	TA 5/6 REPEAT FOR rs8175347	AUC (mg·h/L)
Steady-state	Yes	Yes	Yes	15.2
Steady-state	Yes	Yes	No	12.1
Steady-state	Yes	No	Yes	21.7
Steady-state	Yes	No	No	17.2
Single dose	No	Yes	Yes	16.6
Single dose	No	Yes	No	13.2
Single dose	No	No	Yes	23.7
Single dose	No	No	No	18.8

Allometric scaling [1] was applied to all clearance and volume parameters (including the liver) to account for body size using **fat-free mass**.

Priors were included on Ka and ALAG to using parameter estimates reported by Zvada et al. [2]

The model identified the effect on exposure of

- **rifampicin** co-administration or MOXI administration at **steady-state** vs. single dose
- **Efavirenz** co-administration
- TA 5/5 repeat for **rs8175347** genotype

Extraction ratio (E_H) was highest (40%) in patients that were administered efavirenz based ART and did not have TA 5/6 repeat for rs8175347 during the 6 months of rifampicin based antituberculosis treatment

Preliminary analysis showed that patients who have AC and AA genotypes for rs3755319 had increased clearance but the effect was not supported in the final model

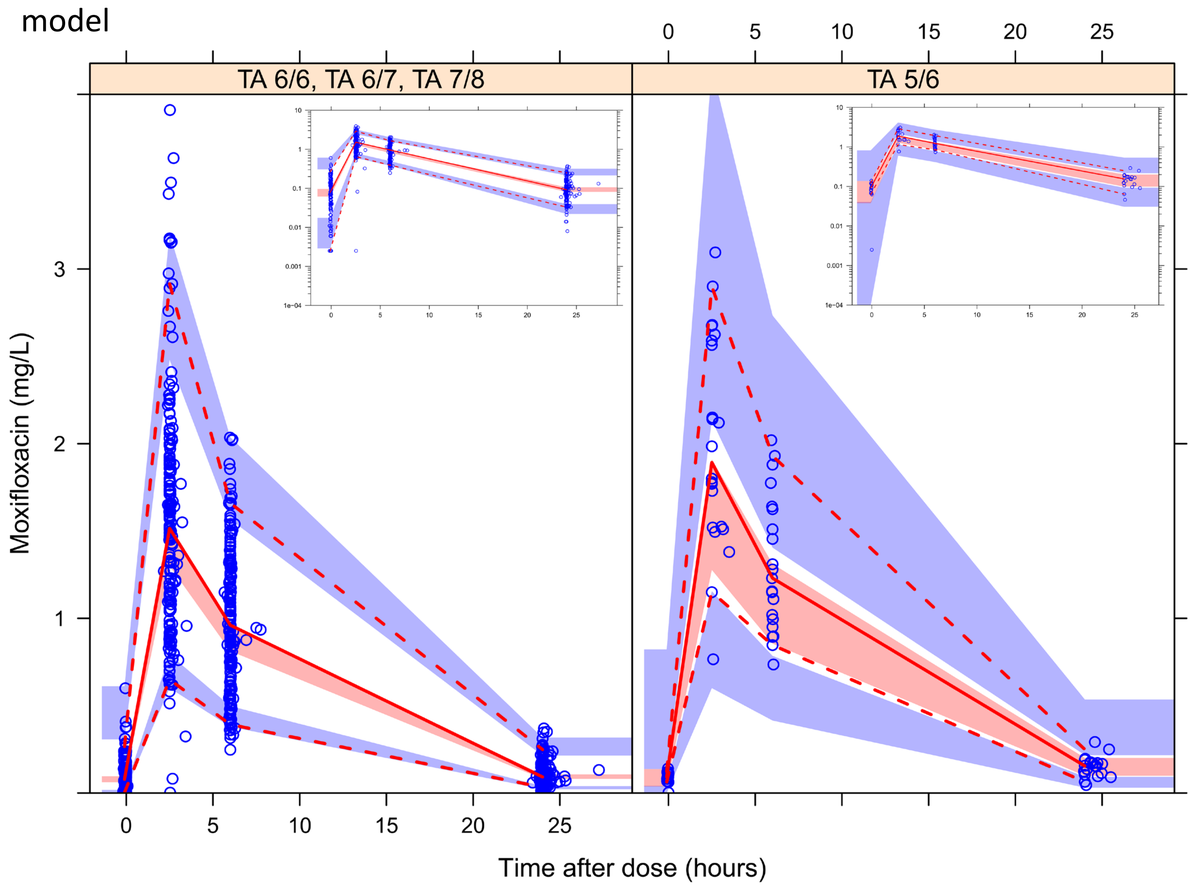

Figure 3 Visual predictive check stratified by TA repeats for rs8175347

Conclusions

A semi-mechanistic model with hepatic extraction described the data adequately.

We quantified the effect of EFV co-administration and single dose vs. steady state (or RIF co-administration), and TA repeats for rs8175347 had limited effect on exposure.

Clinical significance of the effects found warrants further investigation on the proportion of patients attaining therapeutic exposure at the currently recommended dose of 400 mg.

FFM was found to be a better descriptor of body size than total body weight as in other PK studies for antituberculosis drugs [3,4].

References

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