Population Pharmacokinetics of Levofloxacin in South African children.

Paolo Denti (1), Anthony Garcia-Prats (2), Heather Draper (2), H. Simon Schaaf (2), Lubbe Wiesner (1), Helen McIlleron (1), Anneke Hesseling (2)

[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, South Africa

email: paolo.denti@uct.ac.za

Background and Objectives

The fluoroquinolone levofloxacin is the levo-isomer of the racemic mixture ofloxacin and is widely used for treatment and prophylaxis of MDR-TB.

Limited information on its pharmacokinetics (PK) is available in children. The aim of this study was to characterise levofloxacin PK in paediatrics to optimise dosing.

Objective: describe levofloxacin PK in children, investigate the effect of weight, age, and dosing procedure (see below), and optimise future dosing regimens.

Methods

109 South African children enrolled in a study on MDR-TB treatment/prophylaxis.

Daily dose of levofloxacin **15- 20 mg/kg, exact dose** on the day of PK sampling.

Blood samples collected pre-dose, and at 1, 2, 4, 6 and 8 hr post-dose.

Smaller children received **crushed tablets**, often by **naso-gastric tube**.

NONMEM 7.3 with FOCE-I was used to interpret the PK data.

Table 1. Patient info

Covariate	Median (range) or count
Sex	M=56 F=53
Age (years)	2.1 (0.32-8.65)
Weight (kg)	12.4 (5.88-21.8)
Dose (mg)	212 (88.5-435)
Dose (mg/kg)	15 (10-21.4)
Administration procedure	Whole Tab=7 Crushed Tab=12 Naso-Gastr Tube + Crushed Tab=90
HIV status	P = 16 N = 93

The effect of body size was captured with allometric scaling [1], and other tested covariates were of age, HIV status, treatment vs. prophylaxis, and drug administration procedure.

Simulations from the final model were used to optimise doses across different weight bands, targeting piblished adult exposure [2].

Results

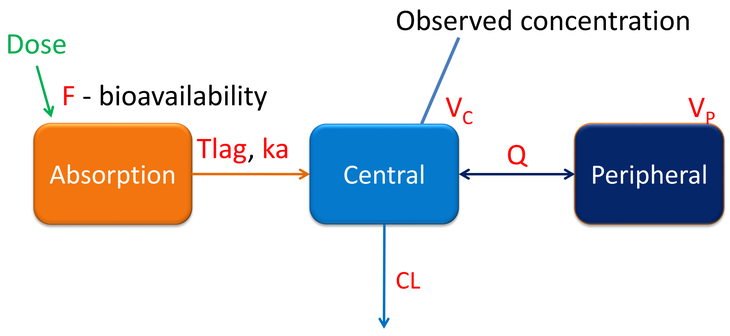

Figure 1. Structural model

2-compartment model
1st-order elimination and 1st-order absorption with lag time.

Increased BOV in F was included **to account for imprecise dosing information** for the days before the PK visit.

The use of **naso-gastric tube** increased the rate of absorption, **but no significant effect on bioavailability was** detected.

Maturation was found for CL and **HIV positive children** were found to have 16% **slower CL**.

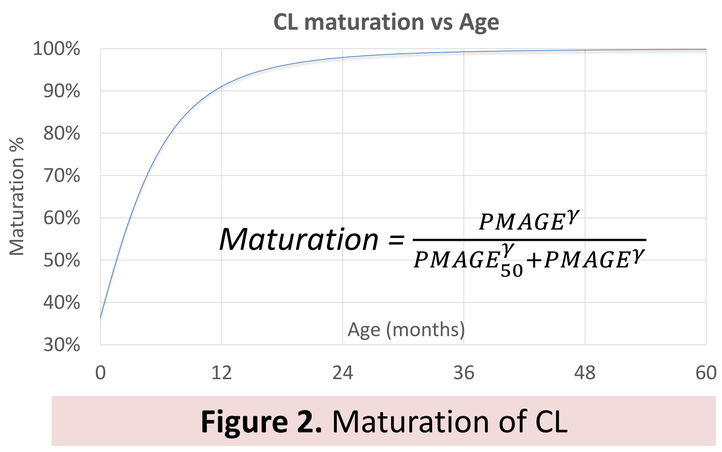

Figure 2. Maturation of CL

Table 2. Final parameter estimates (%RSE)

PK Parameter	Typical value	Variability
CL [L/h]	**HIV-:** 4.7 **HIV+:** 3.95 (-16%)	BSV: 15.2%
Vc [L]	19.2	
Q [L/h]	0.796	
Vp [L]	3.4	
Absorption Tlag [h]	**Normal dosing:** 0.242 **NGT:** 0.0347 (-86%)	BOV: 130.4%
ka (h^{-1})	1.61	BOV: 64.8%
F – bioavailability []	1 FIXED	BOV: 21.8%

CL includes effect of age and weight
Vc, Q, Vp include effect of weight
Values are for the typical child in the dataset: 2 years, 12 kg
Projected CL for 70 kg adult is: 12.1 L/h

Other parameters			
Extra BOV in F for Unobserved dose	4.48-fold		
Maturation at 50%	1.59 months after birth	**Shape factor for maturation**	3.39
Additive error (mg/ L)	0.016 (20% of LLOQ)	**Proportional error**	11.6%

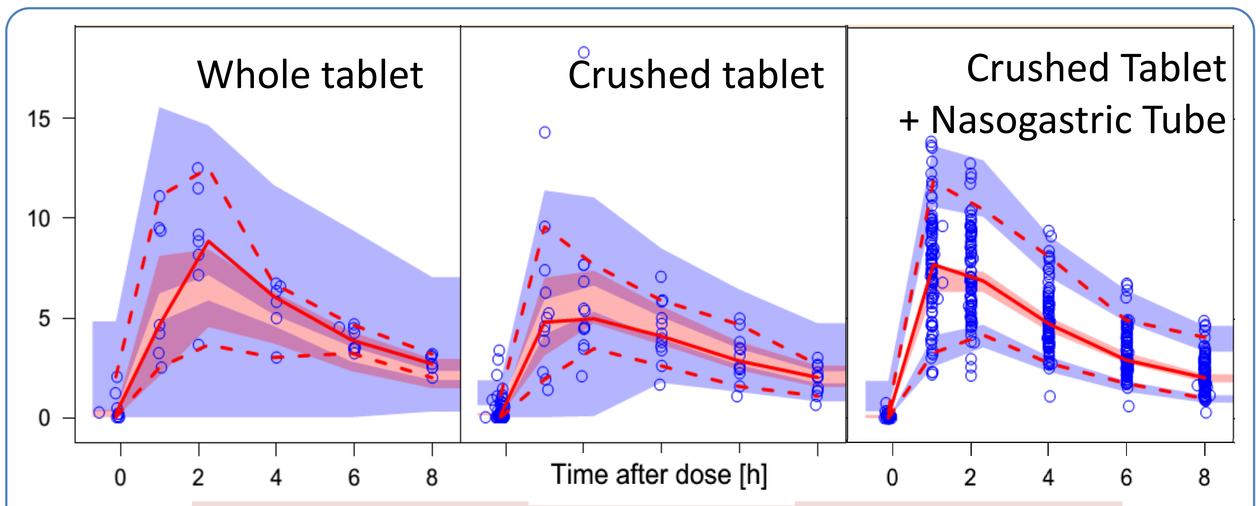

Figure 3. Visual predictive check, stratified by dosing procedure

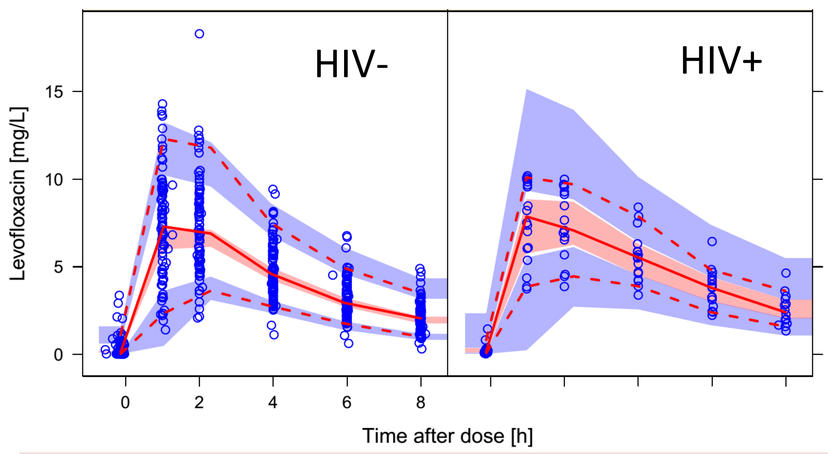

Figure 4. Visual predictive check, stratified by HIV status

Table 2. Model-derived dosing recommendations

Target exposure AUC of 131 h·mg/L (after 1000mg dose in adults) [2]								
Dose (mg)	200	300	400	600	800	1000	1200	1400
Weight band (kg)	<5	5 - 6	6 - 9	9 - 13	13 - 18	18 - 24	24 - 30	30 - 35

From >20 kg the values are extrapolated, and higher than the corresponding values in adults.

Model-derived suggested doses **targeting the same AUC may cause larger Cmax in smaller children (<1 years)**, raising toxicity concerns (Figure 5).

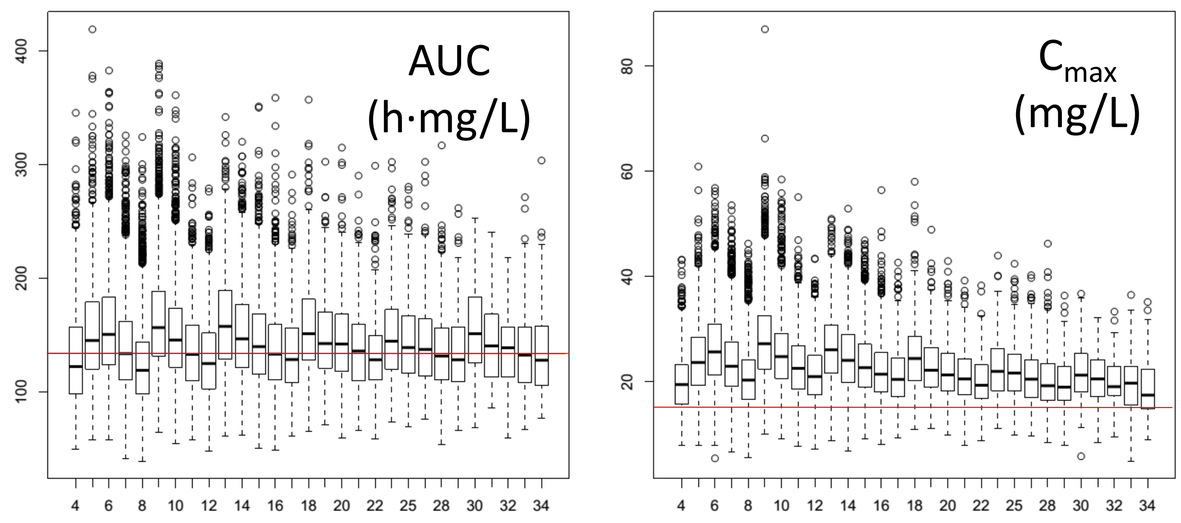

Figure 5. Simulated exposures (AUC and Cmax) with revised guidelines for different weights. Red lines are median values from [2]

Conclusions

Consistently with reports from other paediatric studies [3,4], children achieve levofloxacin exposures considerably lower than adults using the same mg/kg dose.

Only part of this difference could be explained by allometric scaling.

To achieve exposures similar to adults after 1000mg dose, the paediatric dose should be increased by up to 50 mg/kg, with smaller children receiving higher mg/kg doses, except very young children (<1 year old), who have immature clearance.

Dose optimization studies of levofloxacin are needed in children.

Slightly higher exposure in HIV positive children, of unlikely clinical significance, would need further investigation in other studies.

References

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