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CLOFAZIMINE DRUG LEVELS AND CARDIAC TOXICITY IN CHILDREN WITH RIFAMPICIN-RESISTANT TB



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BACKGROUND

World Health Organization (WHO) reported 132,222 new cases with rifampin-resistant tuberculosis (RR-TB) globally in 2020. Clofazimine (CFZ) is routinely recommended for RR-TB treatment, but no pharmacokinetic (PK) and limited safety data are available in children.

We aimed to characterize CFZ PK and its effect on QT prolongation in children with RR-TB.

METHODS

- An observational cohort study of South African children <18 years old treated for RR-TB.
- CFZ 100mg gel caps, dosed based on weight, were used.
- CFZ was given orally once daily (≥20 kg), or every 2nd day (10-20 kg), or Monday, Wednesday, and Friday or after every third day (<10 kg).
- PK sampling and electrocardiograms (ECG) were done pre-dose and at 1-, 4- and 10-hours post-dose.
- CFZ PK and QTcF (Fridericia method) interval data were analyzed and modelled in NONMEM.

Table 1. CFZ PK and ECG information

Variable	Value
PK samples (n=54)	
Total number of PK samples	370
Occasion 1 (n=54)	214
Occasion 2 (n=34)	136
Occasion 3 (n=5)	20
ECG measures (n=54) in children with PK data	
Total number of ECG measurements	1156
Occasion 1 (n=54)	629
Occasion 2 (n=39)	455
Occasion 3 (n=6)	72

RESULTS

54 (0.5 – 15.6 years) children

- 36 (65%) ≤ 5 years of age
- 5 (9.3%) HIV-positive

6 (2 mild, 4 moderate) events with QTcF > 450 ms

- The use of moxifloxacin on top of clofazimine increased pre-dose QTcF by 7%, but the effect was not significant.
- Pre-dose QTcF was associated with age, with 4ms increase per year of age after 3.35 years.

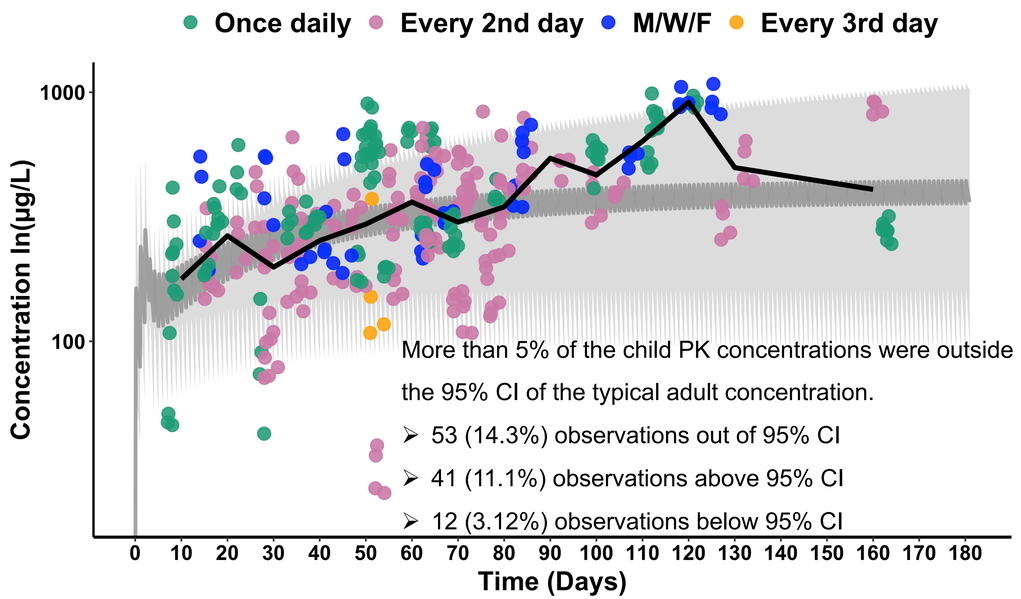

Figure 1. *Pharmacokinetic profile for children and simulated adult profile for six months of treatment. Solid circle represent child observed concentrations over time at unique sampling occasions. Black solid line is a mean child concentration; Gray solid line simulated adult concentration. Shaded area is the 95% confidence interval of the simulated adult concentration. Adult concentration data came from a phase 2A trial in South African adults who received 100mg daily dose(data not published). M/W/F, Monday/Wednesday/Friday*

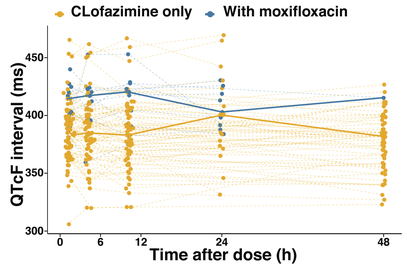

Figure 2. *QTcF profiles in children treated with clofazimine for rifampicin-resistant tuberculosis. The bold line (orange = clofazimine only; blue= with moxifloxacin) is the population median. QTcF = QT interval corrected by Fridericia formula.*

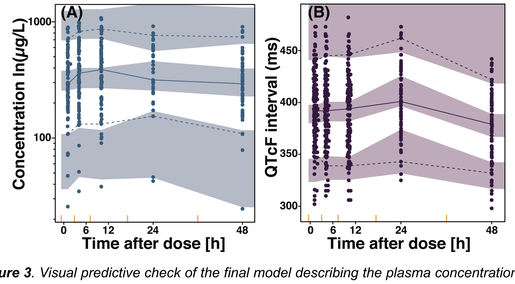

Figure 3. *Visual predictive check of the final model describing the plasma concentration of clofazimine (panel A) and QTcF interval (panel B) versus time. Closed circles are the observed data points; solid and dashed lines are the 50th, 5th, and 95th percentiles of the observed data; shaded areas are the simulated (n=1000) 95% confidence interval for the same percentile. QTcF = QT interval corrected by Fridericia formula.*

Table 2. Population pharmacokinetic and QTcF parameter estimates

Parameter	Value (% RSE), [95% CI]	IIV/BOV* %CV [d] (%RSE), [95% CI]
Pharmacokinetic model		
CL/F [a] (L/h)	5.22 (14), [3.8 , 6.8]	74.7% (22), [34 , 115]
V/F [b] (L)	2820 (12), [2220 , 4110]	
Ka (1/h)	0.928 (46), [0.4 , 4.5]	
Residual error, proportional (%)	16.5 (17), [10.2 , 20.8]	
Residual error, additive (µg/L)	24.4 (59), [0.2 , 45.4]	
Bioavailability	1[#]	35.2% (18), [22 , 54]*
Effect of age on V/F	0.307 (1.9), [0.2 , 0.3]	
Effect of HIV on CL/F (%)	1.88 (45.2), [0.3 , 5.0]	
QTcF model [c]		
Baseline (ms)	352 (2.0), [336 , 363]	5.2% (23.3), [3.2 , 8.4]
Slope (ms/h)	0.072 (24), [0.05 , 0.1]	52.7% (23.3), [23 , 79.3]*
Residual error, additive (ms)	15.9 (5.2), [14.4 , 17.5]	
Effect of age on baseline	0.010 (19.5), [0.01 , 0.01]	

[a] $CL/F = \theta_{pop} \cdot (1 + \theta_{HIV})$
[b] $V/F = \theta_{pop} \cdot (1 + \theta_{age} \cdot (age - 3.35\ years))$
[c] $QTcF = Baseline \cdot (1 + \theta_{age} \cdot (age - 3.35\ years)) + Slope \cdot C_p + \varepsilon$
[#] Biovailability is fixed to 1.
**Between occasion variability (intra-individual variability).*
CL/F: apparent clearance; V/F: apparent volume of distribution; Ka: absorption rate constant; θ_{pop}: population estimate; θ_{HIV}: effect of HIV positive status on CL/F; θ_{age}: effect of age on V/F and baseline QTcF, centered at the population median of 3.35 years; Cp: concentration of clofazimine in plasma; QTcF: QT-interval corrected by Fridericia formula; RSE: relative standard error; 95% CI: 95% confidence interval based on nonparametric bootstrap (n=1000)

CONCLUSIONS

- Our study found higher clearance in HIV-positive children, but due to the small sample size this needs further evaluation.
- Allometric scaling, the pillar defining weight-banded dosing approach for children was not supported by our data.
- More studies and quantification of developmental pharmacology are needed to support weight-based dosing of CFZ in children.
- CFZ concentration was directly associated with QTcF prolongation.
- This is the first study reporting CFZ PK/toxicodynamic in children, and the findings of this study provide an important basis for further evaluation.

ADDITIONAL KEY INFORMATION

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Conflict of interest

All authors declare no conflict of interest.

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