Pharmacokinetics of levofloxacin during pregnancy and post-partum in persons living with HIV and without HIV and receiving treatment for rifampicin-resistant tuberculosis

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BACKGROUND

Fluoroquinolones are key for treatment of rifampicin-resistant tuberculosis (RR-TB) but are not recommended during pregnancy due to limited pharmacokinetic (PK) and safety data. We described the PK of levofloxacin during pregnancy and postpartum in persons living with or without HIV and receiving treatment for RR-TB in routine care.

Compared to the post-partum period, levofloxacin exposures among pregnant people treated for RR-TB appear to be lower in the second trimester but similar in the third trimester

METHODS

- Between 2017 and 2019, pregnant women receiving treatment with ≥ 2 second-line antituberculosis drugs in routine care were included.
- Participants enrolled in the second trimester (20-26 weeks gestation) or third trimester (30-38 weeks gestation) and had intensive PK sampling at least once during pregnancy and at 2-8 weeks post-partum.
- Levofloxacin doses were administered on site and samples were collected pre-dose and at 1, 2, 4, 6, 8 and 12 hours post-dose.
- Levofloxacin plasma concentrations were measured using high-performance liquid chromatography tandem mass spectrometry assay.
- Pharmacokinetic parameters were estimated using non-compartmental methods and compared (within participant) using geometric mean ratios (GMR) with 90% confidence intervals (CI); a CI between 0.8 and 1.25 suggests similar pharmacokinetics.

RESULTS

- Of 13 pregnant participants with RR-TB, eleven received levofloxacin (750 mg or 1000 mg daily) during pregnancy; eight (73%) continued treatment post-partum.
- Ten (91%) participants were enrolled at two sites in South Africa; one was from Tanzania.
- Median age was 31 years, IQR 25 - 33.5 years.
- Six (55%) participants were living with HIV.
- GMRs and CIs suggest similar exposure (AUC) in 3T versus PP (n=7), but lower AUC in 2T versus PP (n=4).

TABLE 1. PK parameters of levofloxacin during pregnancy and post-partum

Pharmacokinetic parameters	Second trimester (2T) (n = 6) Median [Q1, Q3]	Third trimester (3T) (n = 10) Median [Q1, Q3]	Post-partum (PP) (n = 8) Median [Q1, Q3]	2T vs PP (n = 4) GMR [90% CI]	3T vs PP (n = 7) GMR [90% CI]
C_{max} (µg/mL)	10.31 [9.33, 12.10]	10.55 [7.71, 11.00]	10.61 [8.20, 12.70]	0.86 [0.59, 1.25]	0.98 [0.85, 1.12]
C_{min} (µg/mL)	0.94 [0.85, 1.03]	1.45 [0.04, 1.59]	1.41 [0.16, 1.72]	0.72 [0.17, 3.00]	1.23 [0.24, 6.23]
AUC_{0-12} (µg*h/mL)	69.01 [60.12, 77.14]	77.64 [70.51, 85.05]	80.23 [71.80, 97.73]	0.75 [0.60, 0.95]	0.94 [0.81, 1.08]
$T_{1/2}$ (h)	6.28 [5.71, 6.64]	8.71 [5.95, 10.19]	8.17 [6.42, 9.30]	0.84 [0.73, 0.97]	1.11 [0.83, 1.50]
CL/F (litres/hr)	13.43 [12.03, 15.45]	12.88 [11.76, 14.18]	11.38 [9.96, 13.64]	1.33 [1.05, 1.67]	1.07 [0.93, 1.23]
Vd/F (litres)	108.92 [97.39, 159.31]	167.86 [114.44, 206.86]	134.96 [107.44, 198.01]	1.12 [0.86, 1.44]	1.16 [0.79, 1.72]

Cmax = maximum concentration; Cmin = minimum concentration; AUC = area under the curve; $T_{1/2}$ = half life; CL/F = clearance; Vd/F = volume of distribution; 2T = second trimester; Q1 = first quartile; Q3 = third quartile; 3T = third trimester; PP = post-partum; GMR = geometric mean ratio; CI = confidence interval.

CONCLUSIONS

- Levofloxacin plasma exposures over 12 hours were similar during the third trimester and post-partum periods.
- Additional safety analyses would further support the use of levofloxacin during pregnancy at current recommended doses.

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