

Effect of pregnancy on population pharmacokinetics of levofloxacin in South African adults with rifampicin-resistant tuberculosis.

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Background: Levofloxacin is a Group A WHO drug, recommended as a priority inclusion in treatment regimens for rifampicin-resistant tuberculosis (RR-TB). Pregnancy affects several drug clearance mechanisms and may affect drug concentrations, including levofloxacin. We aimed to characterize the pharmacokinetics of levofloxacin in patients with RR-TB and evaluate the effect of pregnancy.

Methods: We pooled data from two studies in South Africa, where participants received a minimum of five drugs including levofloxacin administered once daily at 750 or 1000 mg, depending on individual body weight. Blood samples were drawn pre-dose, 2-, 4-, 6-, 8-, 10-, and 24-hours post-dose. We used liquid chromatography tandem mass spectrometry assays to measure levofloxacin concentrations. In pregnant women, sampling was performed in the third trimester and at approximately 6-weeks postpartum. Data was analysed using non-linear mixed effects modelling.

Results: A total of 319 plasma samples were available from 47 participants, with a median (range) age of 32 (19-51) years, weight of 58 (37-98) kg, and serum creatinine of 58 (25-110) $\mu\text{mol/L}$. Out of 33 female participants included, 21 (64%) were pregnant, of whom 14 (67%) contributed matched antepartum and postpartum profiles. A one-compartment disposition model with first-order elimination and absorption with transit compartments best described the data. The typical values of clearance and volume of distribution, which were best allometrically scaled using fat-free mass (FFM), were 6.06 L/h and 85.9 L, respectively. After adjusting for both the effect of body size and serum creatinine, pregnancy was found to further increase levofloxacin clearance by 38.1%.

Conclusions: Pregnancy significantly increases the clearance of levofloxacin. Further studies should investigate whether this decrease in levofloxacin exposure during pregnancy warrants a dose adjustment.