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Population Pharmacokinetics of Levofloxacin and Moxifloxacin, and the Probability of Target Attainment in Ethiopian Patients with Multi-Drug Resistant Tuberculosis

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Abstract : The fluoroquinolones (FQs) are used off-label for the treatment of multidrug-resistant tuberculosis (MDR-TB), and for evaluation in shortening the duration of drug-susceptible TB in recently prioritized regimens. Within the class, levofloxacin (LFX) and moxifloxacin (MXF) play a substantial role in ensuring success in treatment outcomes. However, sub-therapeutic plasma concentrations of either LFX or MXF may drive unfavorable treatment outcomes. To the best of our knowledge, the pharmacokinetics of LFX and MXF in Ethiopian patients with MDR-TB have not yet been investigated. Therefore, the aim of this study was to develop a population pharmacokinetic (PopPK) model of levofloxacin (LFX) and moxifloxacin (MXF) and assess the percent probability of target attainment (PTA) as defined by the ratio of the area under the plasma concentration-time curve over 24-h (AUC0-24) and the in vitro minimum inhibitory concentration (MIC) (AUC0-24/MIC) in Ethiopian MDR-TB patients. Steady-state plasma was collected from 39 MDR-TB patients enrolled in the programmatic treatment course and the drug concentrations were determined using optimized liquid chromatography-tandem mass spectrometry. In addition, the in vitro MIC of the patients' pretreatment clinical isolates was determined. PopPK and simulations were run at various doses, and PK parameters were estimated. The effect of covariates on the PK parameters and the PTA for maximum mycobacterial kill and resistance prevention was also investigated. LFX and MXF both fit in a one-compartment model with adjustments. The apparent volume of distribution (V) and clearance (CL) of LFX were influenced by serum creatinine (Scr), whereas the absorption constant (Ka) and V of MXF were influenced by Scr and BMI, respectively. The PTA for LFX maximal mycobacterial kill at the critical MIC of 0.5 mg/L was 29%, 62%, and 95% with the simulated 750 mg, 1000 mg, and 1500 mg doses, respectively, whereas the PTA for resistance prevention at 1500 mg was only 4.8%, with none of the lower doses achieving this target. At the critical MIC of 0.25 mg/L, there was no difference in the PTA (94.4%) for maximum bacterial kill among the simulated doses of MXF (600 mg, 800 mg, and 1000 mg), but the PTA for resistance prevention improved proportionately with dose. Standard LFX and MXF doses may not provide adequate drug exposure. LFX PopPK is more predictable for maximum mycobacterial kill, whereas MXF's resistance prevention target increases with dose. Scr and BMI are likely to be important covariates in dose optimization or therapeutic drug monitoring (TDM) studies in Ethiopian patients.

Keywords : population PK, PTA, moxifloxacin, levofloxacin, MDR-TB patients, ethiopia
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