Limited sampling strategy and dose evaluation for second-line anti-tuberculosis drugs in patients with type II diabetes mellitus

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Background

China is simultaneously confronted with a high burden of multidrug-resistant tuberculosis (MDR-TB) and type II diabetes mellitus (T2DM). Nevertheless, there remains unknown how the status of T2DM and glucose control affect the pharmacology for most of the second-line drugs against MDR-TB. To fill the gap, this study aimed to develop population pharmacokinetics models for second-line TB drugs by rich sampling among TB patients with T2DM and evaluate the limited sampling strategies and dose adequacy.

Methods

A prospective multi-central pharmacokinetics study of bedaquiline, clofazimine, cycloserine, linezolid, and moxifloxacin was conducted in China between June 2016 to June 2019. The study subjects were bacteriological-diagnosed MDR-TB patients with T2DM diagnosed at least 1 year before. T2DM diagnosis was based on WHO criteria: random blood sugar 11.1 mmol/L, fasting blood sugar 7.0 mmol/L, or plasma glucose 11.1 mmol/L in OGTT for 2 hours. The blood samples were collected at pre-dose and at 5 to 9 specific time points after intake of anti-TB drugs after a two-week inpatient treatment. The plasma concentration was measured using a liquid chromatography-tandem mass spectrometry method. The population pharmacokinetics models were developed by nonlinear mixed effect analyses. For clinical feasibility, limited sampling strategies with a maximum of three samples were evaluated using the Bayesian approach and multiple linear regression, within 2 hours and 6 hours respectively. The strategy with the highest average adjusted determination coefficient (R2) was selected. The recommended dosage at different MIC levels were evaluated by probability of target attainment (PTA) analysis with Monte Carlo simulation.

Results

Totally 696 plasma samples were collected from 58 participants with T2DM. Two-compartment pharmacokinetic models described the concentration-time profile of clofazimine, and moxifloxacin well. A three-compartment model with dual zero-order absorption described bedaquiline well and a one-compartment model were chosen for cycloserine and linezolid. The covariate of hemoglobin affected the volume of distribution (Vd) and the clearance of moxifloxacin (%CV=35.71, %CV=49.61), bedaquiline (%CV=14.21, %CV=45.74), linezolid (%CV=24.87, %CV=43.05) and the clearance of clofazimine(%CV=26.93). For detecting five drugs simultaneously, the best two-point (0 and 6 h, R2 >0.99) and three-point (0, 2 and 6 h, R2 > 0.98) strategies within 6 hours were developed for both methods. Sampling at 2 h (all RMLR2 > 0.95) was the best strategy within 2 hours. The reported threshold values for linezolid, bedaquiline, and moxifloxacin are 119, 118, and 53. The recommended WHO dosage (600mg once daily and 400 mg daily) for linezolid and moxifloxacin resulted in PTA> 90% at breakpoints (1 and 0.25 mg/L). For linezolid, moxifloxacin and bedaquiline, all regimens resulted in PTA>90% at MICs 0.25, 0.25, and 0.03 mg/L.

Conclusions

We established the population pharmacokinetics models and LSSs for the five second-line drugs in Chinese MDR-TB patients with T2DM. Sampling at 0 ,2 and 6 h can be an accurate 3-point sampling strategy for inpatients while the 2-hour sampling strategy can be applied in outpatients. Moreover, dosage regimens recommended by WHO may be insufficient for T2DM patients with high levels of drug resistance.