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

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Background

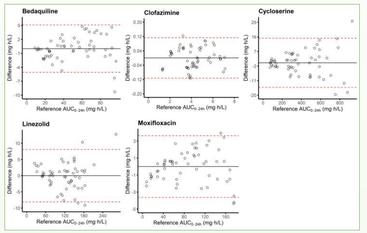
- China is simultaneously confronted with a high burden of multidrug-resistant tuberculosis (MDR-TB) and type II diabetes mellitus (T2DM). [1-3]
- Nevertheless, there remains unknown how the status of T2DM and glucose control affect the pharmacology for most of the second-line drugs against MDR-TB.
- 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.

Method

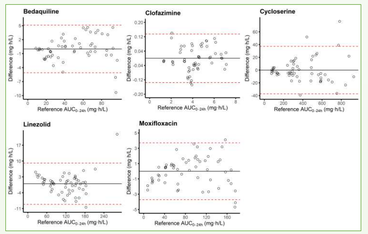
- A prospective multi-central pharmacokinetics study of bedaquiline, clofazimine, cycloserine, linezolid, and moxifloxacin was conducted in China between June 2016 to June 2019.
- The study subjects were bacteriological-diagnosed MDR-TB patients with T2DM diagnosed at least 1 year before. T2DM diagnosis 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 (R^2) was selected.
- The recommended dosage at different MIC levels were evaluated by probability of target attainment (PTA) analysis with Monte Carlo simulation.

Result

- 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). The bodyweight affected the Vd and the clearance of cycloserine(%CV=77.46,%CV=64.74).
- For detecting five drugs simultaneously, the best two-point (0 and 6 h, $R^2 > 0.99$) and three-point (0, 2 and 6 h, $R^2 > 0.98$) strategies within 6 hours were developed for both methods. Sampling at 2 h (all $R_{MLR}^2 > 0.95$) was the best strategy within 2 hours. (Figure 1.)
- The reported threshold values for linezolid, bedaquiline, and moxifloxacin are 119, 118, and 53. Simulations showed the WHO-recommended regimens of linezolid (600 mg daily) and moxifloxacin (400 mg daily) achieved > 90%PTA below MICs of 1.00 and 0.25 mg/L. Bedaquiline regimen (400 mg daily for 14 days, then 200 mg thrice weekly) fail to attain a PTA of 90% at the MIC of 0.06 mg/L. (Figure 2.)



(A)



(B)

Figure 1. Bland-Altman Plot consistency evaluation of limited sampling strategy based on multiple linear regression (A:0 and 6 h, B:0 , 2 and 6 h)

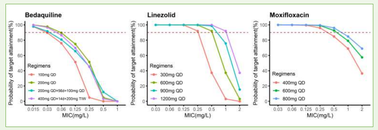


Figure 2. The probability of target attainment against varying minimal inhibitory concentrations for linezolid, bedaquiline and moxifloxacin.

Conclusion

- 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 sampling at 2 h can be applied in outpatients.
- Moreover, dosing adjustments are necessary for high drug resistance.

Reference

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Further Information

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