Isoniazid exposure among patients with tuberculosis and diabetes in Brazil

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BACKGROUND

- Tuberculosis (TB) and diabetes mellitus (DM) are major global health burdens[1,2]
- DM is associated with more severe TB disease, increased treatment failure rates, and higher mortality[3,4]
- Individuals with TB and uncontrolled DM were found to have a lower risk of TB-treatment related adverse drug reactions (TB-ADR)[5]
  - ➢ Individuals with glycated hemoglobin (HbA1c) levels of 11% had 83% reduction in risk of TB-ADR (compared to normal HbA1c levels)
- Hypothesis: lower TB-ADR risk due to lower TB drug levels

OBJECTIVE

- Correlate isoniazid (INH) local maximal concentrations with HbA1c levels

METHODS

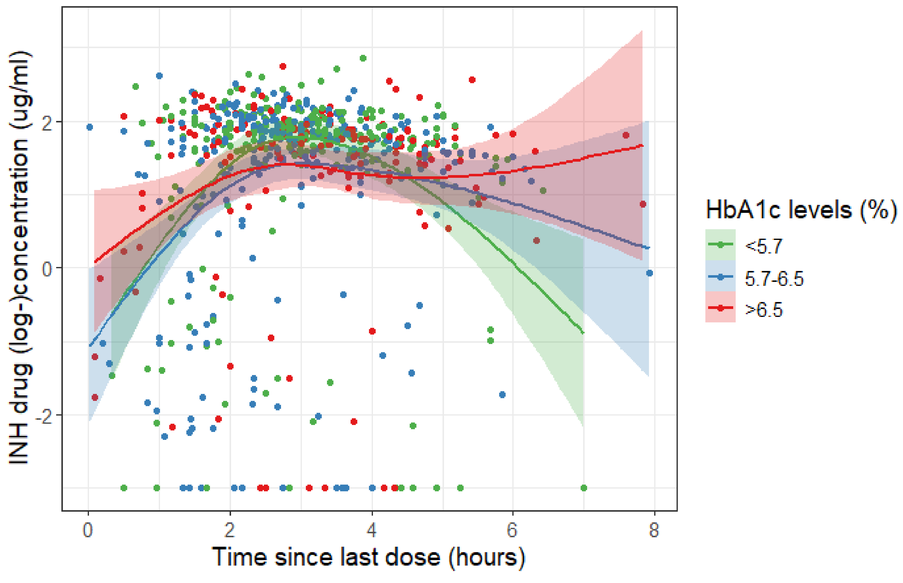
- Participants from a multicenter cohort study (5 sites)
  - ➢ Regional Prospective Observational Research in Tuberculosis (RePORT) Brazil[6] (enrollment: Jun-2015 until Jun-2019, 2-year follow-up)
- Eligibility: adults (≥18 years) with culture-confirmed, drug-susceptible, pulmonary TB, standard TB treatment (according to participant weight), with samples available within 8h of the previous TB dose, two timepoints (month 1, 2)
- HbA1c as continuous and categorical variable. HbA1c<5.7% was considered normal, HbA1c ≥5.7%-<6.5% was pre-DM, and HbA1c ≥6.5% was DM
- INH levels quantification: liquid chromatography-mass spectrometry (SCIEX6500 Qtrap, Redwood City, CA) and log-transformed (log-INH).
  - time since last dose in hours (self-reported)
- Endpoint: INH time-to-concentration curves according to HbA1c
  - Noncompartmental analysis
  - Spearman correlation, 5% sig. level
  - concentration was modelled as a function of time, using restricted cubic splines with 3 knots, HbA1c (linearly), and their interaction.
  - Area Under the Curve (AUC) calculated

RESULTS

- 657 samples available from the 379 participants
- Median baseline HbA1c 5.9 (Interquartile Range [IQR] 5.5-6.4)
- Median time since last dose 3 hours (IQR 2.1-3.9)
  - Normal 2.99h, Pre-DM 2.76h, DM 3.31h (p=0.03)
- 131 (34%) participants with normal HbA1c, 154 (41%) had pre-DM, and 94 (25%) had DM

Patients with TB and diabetes or pre-diabetes had higher INH exposure (AUC), but lower INH local maximal concentration than patients with TB with normoglycemia

Figure 1. INH Time-to-concentration curves according to HbA1c categories



Abbreviations: INH, isoniazid; HbA1c, glycated hemoglobin
Spearman correlation coefficient= -0.117 (p=0.003)
Thirty samples (9.4%) were below level of quantification (BLQ), set as half of the minimum level of quantification.

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RESULTS (Continued)

- HbA1c levels (continuous) *vs* log-INH: coefficient of -0.099 (p=0.01)
- HbA1c categories *vs* log-INH: coefficient **-0.117** (p=0.003) (**Figure 1**)
- **AUC=10.03ug*h/ml (DM),** AUC=7.57ug*h/ml (Pre-DM), AUC=7.02ug*h/ml (normal)

LIMITATIONS

- Factors such as *NAT2* acetylator profile, body mass index, sex, age may influence INH levels
- Data on directly observed therapy (DOT) were only whether it had been prescribed; 4 different types of DOT were used.

CONCLUSIONS

- Higher INH exposure among Pre- and DM participants
- Lower INH local maximal concentration as HbA1c increases
- Altered drug dynamics (absorption, distribution, or metabolism) could contribute to these lower levels

FUTURE DIRECTIONS

- PK/PD model being developed, with more covariates using compartmental analysis and non-linear mixed-effect model (Monolix®)
- Integrate/combine all four TB drugs (INH, rifampin, pyrazinamide, and ethambutol)

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