Title: Pharmacokinetic analysis of isoniazid and dexamethasone in adults with tuberculosis meningitis

Author: Jose Miguel Calderin (1), Sean Wasserman (2, 3), Juan Eduardo Resendiz-Galvan (1), Noha Abdelgawad (1), Angharad Davis (3, 5, 6), Cari Stek (3), Lubbe Wiesner (1), Robert J. Wilkinson (3, 4, 5, 7), Paolo Denti (1)

Institution: (1) Division of Clinical Pharmacology, Department of Medicine, University of Cape Town, South Africa. (2) Institute for Infection and Immunity, St George's University of London, United Kingdom. (3) Centre for Infectious Diseases Research in Africa, Institute of Infectious Disease and Molecular Medicine, and Department of Medicine, University of Cape Town, South Africa. (4) Division of Infectious Diseases and HIV Medicine, Department of Medicine, University of Cape Town, South Africa. (5) The Francis Crick Institute, London NW1 1AT, United Kingdom. (6) Faculty of Life Sciences, University College London, WC1E 6BT, United Kingdom. (7) Department of Infectious Diseases, Imperial College London W12 0NN, United Kingdom

Introduction:

Tuberculosis meningitis (TBM) is a severe TB form causing inflammation of the meninges. WHO recommends the same antibiotic treatment for TBM as for pulmonary TB, including isoniazid, without complete knowledge of drug penetration into the central nervous system, which may be limiting. Adjunctive dexamethasone is recommended to manage inflammation, but its exposure is likely reduced by rifampicin, a potent CYP3A4 inducer. We described the pharmacokinetics of isoniazid and dexamethasone co-administered with standard or high rifampicin doses in TBM patients and assessed isoniazid penetration into cerebrospinal fluid (CSF).

Methods:

This pharmacokinetic study was part of the LASER-TBM trial to assess intensified antituberculosis therapy in HIV-associated TBM adults. Participants were randomized into one of three arms. Arm 1 received a standard TB regimen ($R_{10mg/kg}$HZE). Arms 2 and 3 received $R_{35mg/kg}$HZE and linezolid, with or without aspirin. All arms received oral isoniazid at 5 mg/kg/day and dexamethasone, starting at 0.4 mg/kg/day with a weekly reduction of

0.1 mg/kg. Intensive and sparse blood sampling was performed on day 3 and day 28 after study enrolment, respectively. One CSF sample was collected during each visit. All samples were analysed using LC-MS/MS. Isoniazid concentrations were measured in all samples, while dexamethasone concentrations were measured in plasma samples collected on day 3. Data were analysed using nonlinear mixed-effects modelling, with separate models developed for each drug. The isoniazid CSF concentrations were modelled by implementing an effect compartment linked to the central compartment, estimating the plasma-CSF equilibration half-life ($t1/2_{plasma\text{-}CSF}$) and the CSF-plasma pseudo-partition coefficient ($PPC_{CSF\text{-}plasma}$).

Results:

In total, 414 isoniazid plasma and 44 CSF concentrations, along with 263 dexamethasone concentrations from 49 participants, were analyzed. The study population had a median (1st – 3rd quartile range) age of 39 (34 – 45) years, weight of 60 (54 – 74) kg, and fat-free mass (FFM) of 45 (39 – 51) kg. Fifteen participants (31%) were on antiretroviral treatment (ART), including 5 (11%) on a lopinavir/ritonavir-based regimen.

Isoniazid pharmacokinetics followed a two-compartment model with first-order absorption and elimination. The NAT2 phenotype had a strong effect on the isoniazid pharmacokinetic variability. The typical values of oral clearance, scaled allometrically using FFM, were 14.6, 32.2, and 64.7 L/h for slow, intermediate, and rapid acetylators, respectively. CSF concentrations equilibrated with plasma with a $t1/2_{plasma\text{-}CSF}$ of 3.8 h and a $PPC_{CSF\text{-}plasma}$ of 1.04, a value that indicates the relative exposure of isoniazid in CSF compared to plasma at steady state.

Dexamethasone pharmacokinetics was best described by a one-compartment model with first-order absorption and elimination. Typical clearance and volume of distribution, best allometrically scaled using FFM, were 132 L/h and 27.5 L, respectively. Co-administration of lopinavir/ritonavir-based ART was associated with a 91.3% reduction in dexamethasone clearance.

No statistically significant differences were observed for either isoniazid or dexamethasone between the standard- and high-dose rifampicin groups.

Conclusions:

Isoniazid achieves CSF exposure similar to plasma, data that is reassuring in the context of TBM. Higher dexamethasone clearance compared to previous monotherapy reports was observed, likely due to rifampicin-induced CYP3A4 activity, suggesting that dexamethasone dose adjustments may be beneficial for TBM patients receiving rifampicin.