Drugs: clinical and preclinical pharmacology of drugs already marketed or used off-label for TB

Title: Pharmacokinetic Modelling of Rifampicin, Isoniazid, Pyrazinamide, Linezolid, and Rifabutin in CNS Tissues: A Rabbit Model Study of Tuberculosis Meningitis

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Introduction:

Tuberculosis meningitis (TBM), the severest form of *Mtb* infection, has high mortality and disability rates [1]. Current TBM treatments are derived from pulmonary TB protocols, without considering the protective barriers and the disease-induced physiological changes that influence drug penetration into the central nervous system (CNS). Monitoring drug concentrations in human CNS is challenging, necessitating the use of preclinical TBM models to better understand site of infection PK. This study investigates the PK of rifampicin (RIF), isoniazid (INH), pyrazinamide (PZA), linezolid (LZD) and rifabutin (RBT) in CNS tissues using a TBM rabbit model [2].

Methods:

A rabbit TBM model that emulates human TBM's neurological and immunopathological features was used [2]. Four separate experiments were conducted in rabbits that had reached a pre-defined neurological endpoint of TBM: RIF, INH and PZA co-administered, LZD, and RBT. Drugs were administered orally for 3 days at doses approximating human-equivalent exposures: 90 mg/kg or 120 mg/kg for RIF, 30 mg/kg for INH, 175 mg/kg for PZA, 90 mg/kg for LZD, and 15 mg/kg for RBT. Blood samples were collected pre-dose and at intervals up to 24 hours post-dose on days 1 and again on

day 3 up to necropsy time. Necropsies were performed at 2, 3-, 6-, 10-, and 24-hours post-dose to collect terminal plasma, cerebrospinal fluid (CSF), meninges, spinal cord, brain, and lung tissues samples. Drug concentrations were measured using liquid chromatography-mass spectrometry. The lower limits of quantification in tissues were 0.01 mg/L for RIF, INH, and LZD and 0.05 mg/L for PZA and RBT.

A plasma model was developed for each drug, with clearance and volume of distribution scaled by weight. Then the CSF and tissue concentrations were modelled using an "effect" compartment approach, estimating pseudo-partition coefficients (PPCs) and equilibration half-lives ($T_{1/2eq}$) for each compartment.

Results:

Data were obtained from 16 rabbits for RIF, 4 for INH and PZA, 13 for LZD, and 7 for RBT. Except for three PZA plasma samples, all drug levels were above the quantification limit. A one-compartment model with transit absorption and first-order elimination best described the PK of all drugs except for INH, which followed a two-compartment model. All drugs demonstrated good and rapid penetration into lung tissues (PPCs >0.65 and $T_{1/2eq}$ <1 hour). However, CNS penetration varied. INH and PZA had the most favourable CNS penetration, with PPCs ranging between 0.8–1, and 0.5–1, respectively, and $T_{1/2eq}$ ranges of 2–4 min, and 4–12 min, respectively. RBT also showed high PPCs (0.4–7), but slower equilibration (1.1–3.7 h). RIF had poor penetration (PPC: 0.07–0.3 and T1/2eq: 0.6–3 h), while LZD fell in between (PPC of 0.1–0.4 and $T_{1/2eq}$ of 0.5–1 h).

Conclusion:

This study successfully used a rabbit TBM model [2] to develop PK models for antitubercular drugs in CNS tissues. The PPC and $T_{1/2eq}$ values for CSF aligned with human data [3–5], suggesting that these preclinical models could predict human CNS drug levels. Despite sample size limitations, the study provides critical insights into drug penetration in CNS tissues, vital for optimising TBM treatment. Our work provides a rational starting point to establish CNS exposure targets for effective TBM therapy.

References:

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