Pharmacokinetics and dose response of three different anti-TB drugs in rat (balb/c) infection model of tuberculosis

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Abstract

Introduction: Robust and physiologically relevant infection models are required to investigate pharmacokinetic-pharmacodynamic (PK/PD) correlations for anti-tuberculosis agents at preclinical discovery.

Material and methods: This study has validated an inhalation-based rat infection model of tuberculosis (TB) harboring mycobacteria in a replicating state that is suitable for investigating pharmacokinetics and drug action of anti-tubercular agents. A reproducible and actively replicating lung infection was established in Wistar rats by inhalation of a series of graded inocula of Mycobacterium tuberculosis (MTB). Following an initial instillation of \( \log_{10} 10 \) CFU/lung, MTB grew logarithmically for the first 3 weeks, and then entered into a chronic phase with no net increase in pulmonary bacterial loads. Dose response of front-line anti-TB drugs was investigated following pharmacokinetic measurements in the plasma of infected rats.

Results: Rifampicin, Isoniazid, and pyrazinamide dosed per orally exhibited bactericidal and good dose response with maximal effect of 6.77, 3.55, and 5.90 \( \log_{10} 10 \) CFU reductions in the lungs, respectively. In contrast, ethambutol was merely bacteriostatic with 5.90 \( \log_{10} 10 \) CFU/lung reduction and did not reduce the bacterial burden beyond the initial bacterial loads present at the beginning of treatment in spite of high blood ethambutol levels. Rat infection model with actively replicating bacilli provides a physiologically distinct and pharmacologically relevant model that can be exploited to distinguish investigational compounds into bacteriostatic or bactericidal scaffolds.

Conclusions: The present study proposes that this rat infection model – although it needs more drug substance – can be used in early discovery settings to investigate the pharmacology of novel anti-tubercular agents for the treatment of active pulmonary tuberculosis.

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