Anti-tuberculosis Drug Dynamics: From Blood to Lesions to Single Cells

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Abstract
To predict body concentrations of drugs, in particular at the site of their effect, physiologically based pharmacokinetic (PBPK) models simulate the fate of a substance through major tissues and organs. In the case of pulmonary tuberculosis (TB), the complexity of the pathology calls for a specialized version of PBPK modeling, taking into account multiple sub-compartments in the infected lung. Distribution studies with several TB drug classes have shown that small molecules do not penetrate evenly into distinct niches such as inflamed lung, pleural fluid, cellular granulomas, necrotic foci, cavity wall and caseum. Even within a class where compounds exhibit comparable physicochemical properties, the extent of penetration in lung and lesion compartments often follows different patterns for each drug. Imaging studies have consistently revealed poor diffusion of drug series through the caseum of granulomas and cavities, a site that hosts persisting bacilli which survive chemotherapy. In vitro studies of drug uptake in non-replicating Mycobacterium tuberculosis have also demonstrated that intracellular concentrations of anti-TB agents such as the fluoroquinolones, rifamycins, and linezolid are significantly lower in non-replicating than in growing bacilli. Differential drug distribution and uptake may contribute to the observation that cavitary TB disease is associated with lower cure rates than non-cavitary TB. The rising combination of moxifloxacin, pyrazinamide, and PA-824 currently in clinical trials against drug-sensitive and multi-drug resistant TB appears to provide coverage of the major lesion compartments in which Mtb bacilli reside. Improved control of the TB pandemic will come from drug combinations that achieve complementary distribution across inflamed lung tissues and lesion compartments, while minimizing local monotherapy to prevent the emergence of drug resistance.

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