Dynamic PET facilitated Compartmentalized Brain and Lung Tissue Antibiotic Exposures of Tuberculosis Drugs

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Tuberculous meningitis is the most serious form of tuberculosis (TB), affecting the young and immunocompromised. TB meningitis due to multidrug-resistant (MDR) strains is associated with high mortality (40-100%). Importantly, effective treatments for MDR TB meningitis are lacking, and the activity of the only approved MDR regimen for pulmonary TB (BPaL – bedaquiline, pretomanid, linezolid) is substantially inferior to the standard TB regimen in a mouse model of TB meningitis. We performed dynamic positron emission tomography (PET) using radioanalogs of antibiotics (^{18}F-pretomanid, ^{18}F-sutezolid, ^{18}F-linezolid and ^{76}Br-bedaquiline) active against MDR strains to measure multicompartmental exposures (area under the curve, AUC) in several mammalian species (mice, rabbits, humans). Each radioanalog is chemically identical to the parent antibiotic and the radioisotope is retained within the major metabolite. PET facilitated pharmacokinetic modeling predicted tissue exposures which were used to design optimized regimens. PET demonstrated discordant antibiotic exposure in lung and brain compartments in mouse and rabbit studies. While all antibiotics achieved high lung exposures ($AUC_{lung/plasma}$ ~1), only ^{18}F-pretomanid achieved high brain exposures. First-in-human ^{18}F-pretomanid PET studies (n = 8 subjects) also demonstrated high exposures in both lung and brain compartments. Pharmacokinetic modeling confirmed equivalence between animal and human PET studies and identified the human doses necessary to attain therapeutic brain exposures. Several pretomanid-based regimens demonstrated excellent bactericidal activity, substantially better than the BPaL regimen in the mouse model of TB meningitis. While addition of bedaquiline did not contribute to activity, addition of pyrazinamide significantly improved the activity of all regimens in the brain. In conclusion, bactericidal activity of antibiotics is substantially different in lung and brain compartments, due discordant tissue exposures. This has important implications for developing antibiotic treatments for TB meningitis. Imaging provides a clinically translatable platform to facilitate antibiotic drug development. These optimized antibiotic regimens should be evaluated in clinical studies for TB meningitis.