USING MODEL-BASED SIMULATIONS TO ALIGN MOUSE ANTIBIOTIC EXPOSURE WITH HUMAN CLINICAL EFFICACY FOR EXPLORATION OF COMBINATION THERAPY IN TUBERCULOSIS

Amarinder Singh[1], Ilham Alshiraihi[1], Sarah E. Maloney[2], Anthony J. Hickey[2], Mercedes Gonzalez-Juarrero[3], Bernd Meibohm[1]*

[1]Department of Pharmaceutical Sciences, College of Pharmacy, University of Tennessee Health Science Center, Memphis, Tennessee, USA 38163.

[2]Discovery Science and Technology, RTI International, RTP, Durham, North Carolina, USA 27709.

[3]Mycobacteria Research Laboratories, Department of Microbiology, Immunology and Pathology, Colorado State University, Fort Collins, Colorado, USA. 80525

Abstract

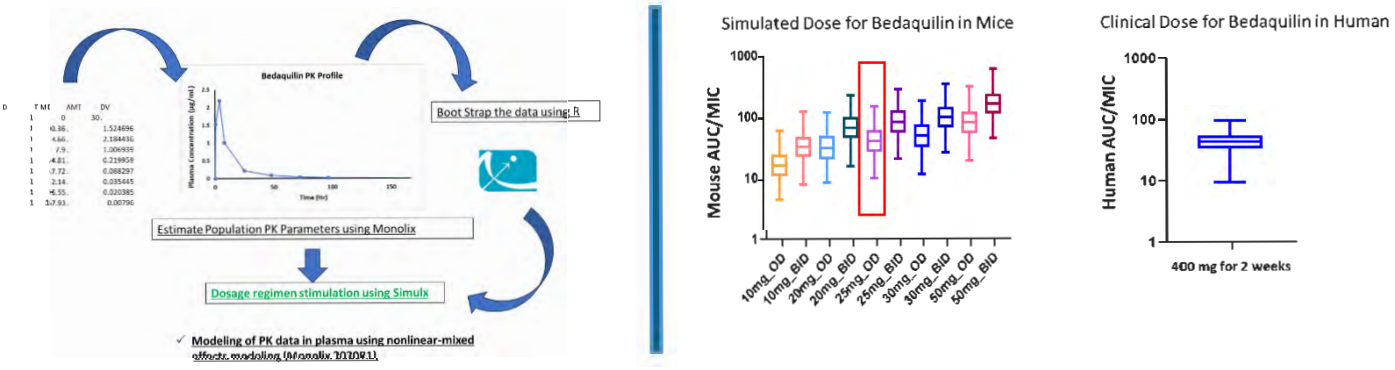
Preclinical experiments frequently utilize well-established drugs to evaluate various combination therapies and assess early efficacy, for example in tuberculosis therapy. Historically, the doses administered to animals in these studies are often selected based on literature values or arbitrary estimates, which may not accurately reflect the drug's clinical efficacy. To address this issue, we employed a modeling and simulation (M&S) based approach to precisely determine appropriate dosing regimens for pre-clinical species, leveraging pharmacokinetic (PK) data from existing literature and advanced simulation tools.

We began by extracting detailed mouse PK profiles for bedaquiline from the literature[1], using bootstrap techniques to include interindividual variability. Using the Monolix software suite, we created nonlinear mixed-effects models that captured the drug's behavior in mice. Simulx was then employed to conduct simulations across various dosing regimens (ranging from 10 mg/kg to 50 mg/kg) to explore their impact on drug exposure (AUC).

Our simulations aimed to determine a dosing regimen for mice that would replicate the pharmacokinetic profile observed in humans, specifically targeting an area under the curve for free drug (fAUC) which is a well-known efficacy index of bedaquiline in tuberculosis therapy.

The simulated fAUC/MIC values were compared with human clinical efficacy data to identify the optimal dose for mice. 25-30 mg/kg oral dose once daily was selected based on its ability to achieve an AUC/MIC value that aligns with human efficacious fAUC/MIC value[2], ensuring that preclinical dosing would provide clinically relevant exposure. The plasma protein binding between mice and humans was found to be the same in the literature which helps in simplifying the translation process. However, it is important to note that our model did not account for the formation of M2 and M3 metabolites in mice, contributing approximately 30% to the efficacy observed in humans. This omission represents a potential area for future refinement.

In conclusion, our study highlights a model-based approach to translate human clinical doses to preclinical mouse doses through exposure matching. Thus, leveraging detailed PK data and sophisticated simulation techniques, enhances the relevance of preclinical studies, facilitating more effective evaluation of combination therapies and potentially improving the translation of research findings from mice to humans.



Workflow from the extraction of PK data from literature to final simulation dose regimen comparison of bedaquiline in mice and clinically efficacious dose in humans.

Reference:

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2. Tawanda Gumbo, Iñigo Angulo-Barturen, Santiago Ferrer-Bazaga, Pharmacokinetic-Pharmacodynamic and Dose-Response Relationships of Antituberculosis Drugs: Recommendations and Standards for Industry and Academia, *The Journal of Infectious Diseases*, Volume 211, Issue suppl_3, June 2015, Pages S96–S106, https://doi.org/10.1093/infdis/jiu610