Which data are necessary to build a WB-PBPK model that accurately predicts exposure in the lung? A case study using ethambutol for tuberculosis treatment

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BACKGROUND. Characterising exposure profiles in different organs is a key feature of Whole-Body Physiologically–Based Pharmacokinetic (WB-PBPK) models. However, it remains unclear which data are needed to enable accurate predictions. To investigate this issue, ethambutol (EMB), a drug used for pulmonary tuberculosis treatment, was used as paradigm drug . The work aimed: 1) to develop a WB-PBPK model to predict EMB lung concentration and, 2) to evaluate the predictive performance of the WB-PBPK framework both for prospective evaluation of molecules in *first-in-human* and in *poor data* scenarios, and for a retrospective analysis in *rich data* scenarios.

METHODS. The predictive performance of the PBPK framework was evaluated based on ***what-if*** scenarios, in which data were added progressively into model development, starting from in vitro and animal experiments, up to human clinical trials.

	First in human → only in simulation		Poor data scenarios → parameter estimation		Rich data scenario → parameter estimation
Rodgers and Rowland distribution model was adopted	**In vitro experiments: LogP and microsomal activity**	**Animal experiments: Monkey renal clearance**	**Human data: plasma concentration following IV administration [1]**	**Human data: urine following IV admi-nistration [1]**	**Human data: plasma concentration following oral administration [2]**
Scenario 1	X				
Scenario 2	X	X			
Scenario 3 with subscenarios	X	X	X		
Scenario 4	X		X	X	
Scenario 5	X		X	X	X
Scenario 6	Population predictions				

PK-Sim® PBPK modeling & simulation

Plasma data were simulated *via* the SimulX function of the R package mlxR, according to the models reported in [1,2]. The observed amount excreted in urine was used [1].

Model was parameterised on mean data following the first EMB dose (IV: 15mg/kg, oral: 800, 1000, 1200 mg). Parameters were estimated *via* the Monte Carlo-based method implemented in the PK-Sim [3] estimation toolbox. Typical subjects with adequate biometrics and demographics were used. Only one distribution model, identified on IV plasma and urinary data was used (i.e., Rowland and Rodgers distribution model [4,5]). Since EMB PK was linear, in scenarios 1-4 the predictive performances were evaluated based on the 800 mg dose level only.

WB-PBPK PREDICTIVE PERFORMANCE EVALUATION CRITERIA

- <u>In scenarios 1-4</u> the PBPK model-predicted and the observed AUC were compared *via* fold-change (predicted/observed). AUC variations within 2 fold were considered reasonably accurate.
- <u>In scenario 5</u> the model-predicted drug levels in plasma and in the lung at steady state were compared to the observed plasma and Alveolar Cells (AC) EMB concentrations following oral administration of 15mg/kg [6].
- <u>In scenario 6</u> the observed and predicted plasma concentration profiles at first dose and at steady state were compared considering populations instead of mean data.

REFERENCES.

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[4] T. Rodgers et al. (2005). Physiologically based pharmacokinetic modeling 1: predicting the tissue distribution of moderate-to-strong bases . J Pharm Sci. 94(6): 1259-1276.
[5] T. Rodgers et al. (2006) Physiologically based pharmacokinetic modeling 2: predicting the tissue distribution of acids, very weak bases, neutrals and zwitterions. J Pharm Sci. 95(6): 1238-1257.
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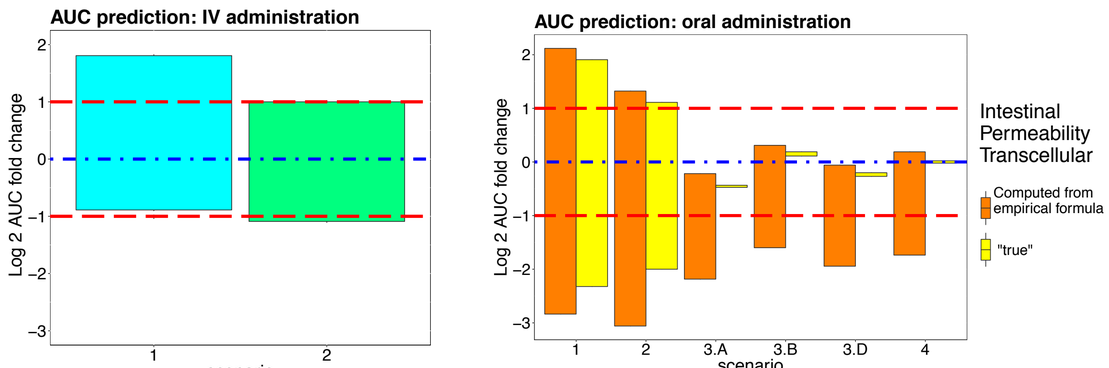
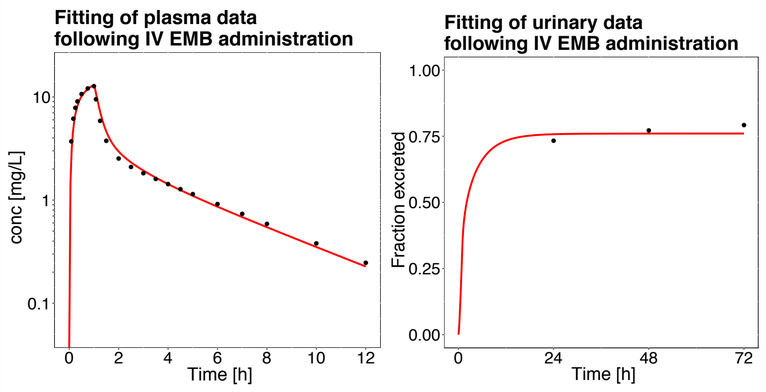
RESULTS:

FIRST IN HUMAN AND POOR DATA SCENARIOS



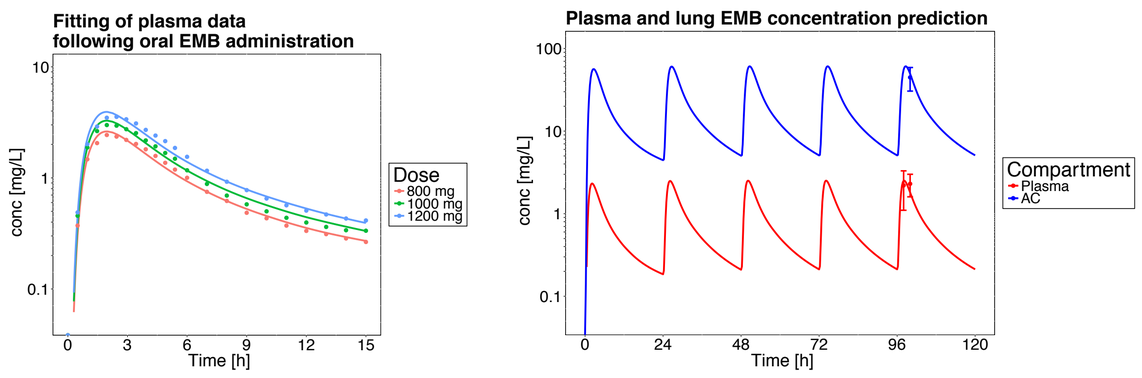
- the more the data available for model building are, the more precise the exposure predictions are;
- for drugs mainly excreted *via* the kidneys, such as EMB, information on the renal elimination is needed to make reasonably accurate predictions. Thus, both animal and human urinary data should be collected;
- intestinal permeability was found to be the crucial parameter to predict EMB exposure level in plasma following oral drug administration.

RICH DATA SCENARIOS

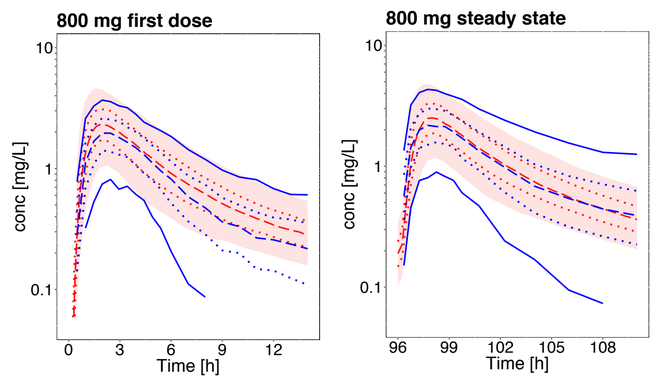


IV infusion data were used to estimate EMB distribution and elimination. Oral administration data were used to estimate EMB absorption.

<u>Scenario 5</u>. A PBPK model with hepatic clearance and both passive and active renal elimination was built. The PBPK model successfully described experimental data and predicted steady state EMB levels in plasma and lung at steady state



<u>Scenario 6</u>. Despite the use of mean parameter values during model building, the variability of the biometrics included in the PK-Sim internal database captures the observed interindividual variability in plasma concentration profiles.



CONCLUSIONS.

- Currently, emphasis is given to the mechanistic nature of WB-PBPK models, but challenges still exist for the prospective use of the approach with novel molecules, i.e., when full details of drug disposition properties are unknown or differ between species.
- Our case study illustrates the bias in WB-PBPK model predictions when supporting data on drug disposition are not available. This is often the case during lead optimisation and candidate selection.
- Critical parameters and data to obtain accurate predictions were identified, including permeability and metabolic route.
- When the PBPK framework is used retrospectively, adequate descriptions of drug disposition and distribution in tissues were obtained, confirming the importance of the model building phase.