Extrapolation of lung pharmacokinetics of antitubercular drugs from preclinical species to humans using PBPK modeling

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1. Introduction

Drugs against pulmonary tuberculosis (TB) need to be transported from the blood to the lung of TB patients and in particular to the pulmonary lesions and the caseum regions that have been formed therein to reach their intended target, the mycobacteria. Hence, the drug distribution to the sites of mycobacterial infection within the lungs of TB patients and animals is obstructed, resulting in compromised TB treatment [1]. Our aim is to build Physiologically Based Pharmacokinetic (PBPK) models to extrapolate lung pharmacokinetics to humans, utilizing literature microdissection homogenate data in various sites of the lung that are available in the literature. More specifically the final output of the model is the free drug concentration in each lung compartment while in the experimental data only the total concentration in homogenates is available.

Our aim is to build PBPK models to extrapolate lung pharmacokinetics across species, utilizing literature microdissection homogenate data in various sites of the lung that are available in the literature.

2. Methods: Extrapolation of lung PK to humans

Datasets for the plasma and lung PK of the standard antituberculosis drugs rifampicin, pyrazinamide, isoniazid and moxifloxacin are available in literature for various species, including mice, rabbits and humans [2-6]. Initially, empirical models were used for the plasma PK of each species and drug in Monolix. For each drug, the central-plasma compartment was connected to a multicompartment permeability-limited lung PBPK model consisting of the vascular, extra-cellular and intra-cellular compartment of the healthy lung as well as the cellular lesion and caseum of the infected tissue. The model is described by a set of differential equations while an appropriate physiological parametrization was utilized could be scaled across species. For all drugs, the vascular and extracellular compartments were assumed in instantaneous equilibrium, except for the low lipophilic drug isoniazid and moxifloxacin which is a p-glycoprotein substrate. Furthermore, rifampicin and moxifloxacin, which both have a strong basic pKa>7, were assumed to bind mainly to the acidic phospholipids within the intracellular space of lung-tissue. Key distribution parameters, regarding both healthy/uninvolved lung and infected tissue, were estimated utilizing the respective preclinical in vivo lung PK profiles. These parameters involved affinity constants obtained through fraction unbound (e.g., affinity constant for lung acidic phospholipids in case of moderate-to-strong bases), lung permeability values regarding healthy/uninvolved tissue, as well as rates and ratios of distribution concerning the infected lung tissue. In vitro values, such as pH values of cellular lesions, intracellular to extracellular ratios for macrophages, and human surrogate fraction unbound values in caseum were also utilized. Finally, the lung PK profiles were extrapolated to humans by keeping the values of these distribution parameters constant across species and altering appropriately the physiology of each species.

Table 1. Basic drug-related parameters for the antituberculosis drugs and for each species

	Isoniazid	Pyrazinamide	Rifampicin	Moxifloxacin
Molecular Weight (g/mol)	137.14	123.11	822.9	437.9
pKa	3.27 (base)	3.53 (base)	pKa_1=1.7 (acid) pKa_2=7.9 (base)	pKa_1=6.25 (acid) pKa_2=9.29 (base)
Blood to plasma ratio	0.84 (Mice) 0.89 (Humans)	0.79 (Mice) 1.12 (Humans)	0.58 (Mice) 0.66 (Rabbits) 0.59 (Humans)	0.89 (Rabbits) 1.05 (Humans)
Unbound Fraction in plasma	0.396 (Mice) 0.516 (Humans)	0.591 (Mice) 0.719 (Humans)	0.029 (Mice) 0.0605 (Rabbits) 0.078 (Humans)	0.70 (Rabbits) 0.72 (Humans)

3. Methods: Structure of PBPK model

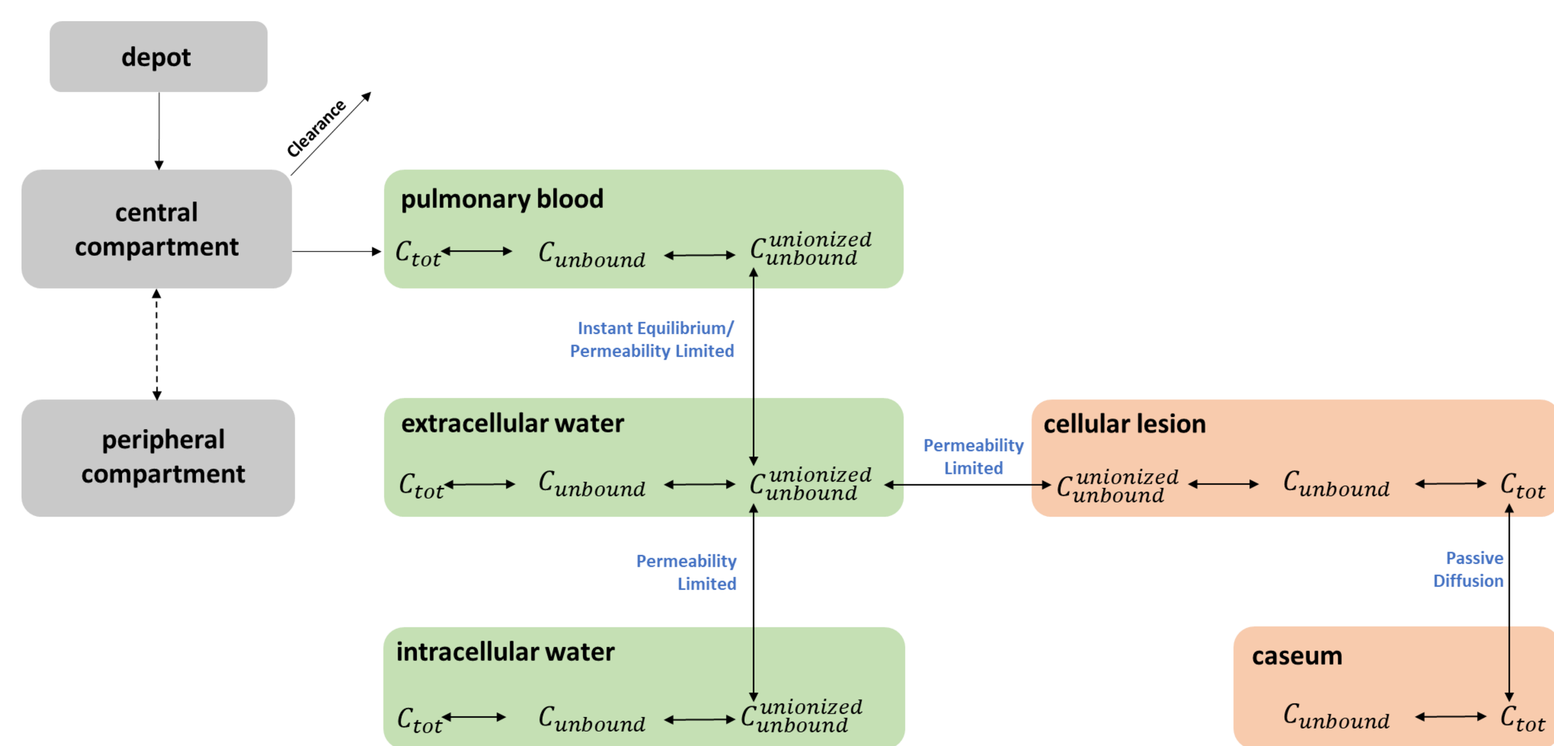

Figure 1. General Structure of the PBPK model

Differential Equations used in our model:

Extracellular Water

$$\left(V_{EW}+\frac{V_{VS}}{K_{EW:B}}\right)*\left(\frac{1}{fu_{EW}}\right)*\frac{dCu_{EW}}{dt}=Q_{lung}*C_{blood}-\left(Q_{lung}\right)*\left(\frac{1}{fu_{EW}}\right)*\frac{Cu_{EW}}{K_{EW:B}}+$$
$$+Perm*\mathrm{SA}_{\mathrm{ExtraCellular-IntraCellular}}*\left(\frac{Cu_{IW}}{a}-\frac{Cu_{EW}}{W}\right)$$

Intracellular Compartment:

$$\left(V_{Lung}*f_{IW}\right)*\left(\frac{1}{fu_{IW}}\right)*\frac{dCu_{IW}}{dt}=Perm*\mathrm{SA}_{\mathrm{ExtraCellular-IntraCellular}}*\left(\frac{Cu_{EW}}{W}-\frac{Cu_{IW}}{a}\right)$$

Cellular lesion:

$$\frac{dC_{Lesion}}{dt}=\mathrm{rate}_{Lesion}*\left(\frac{Cu_{EW}}{W}-fni_{Lesion}*fu_{Lesion}*C_{Lesion}\right)$$

Caseum:

$$\frac{dC_{Caseum}}{dt}=\mathrm{rate}_{Caseum}*\left(PC_{Caseum-Lesion}*C_{Lesion}-C_{Caseum}\right)$$

4. Results

In rabbits, the optimized unbound fractions in intracellular water of rifampicin, and moxifloxacin were 0.015 and 0.056 respectively, while the optimized unbound fractions in extracellular water of pyrazinamide and isoniazid in mice were 0.25 and 0.17 respectively. Additionally, in humans all mean predicted/extrapolated daily AUC and Cmax values of various TB-infected lung regions were within 2-fold of the observed ones. Contrary to the common belief, that plasma free drug concentration is a good surrogate for tissue unbound concentration, differences for some drugs were found in our analysis. These differences concern drugs with significantly different ionization between EW and cellular lesion compartments as well as limited exposure to the hard-to-reach caseum.

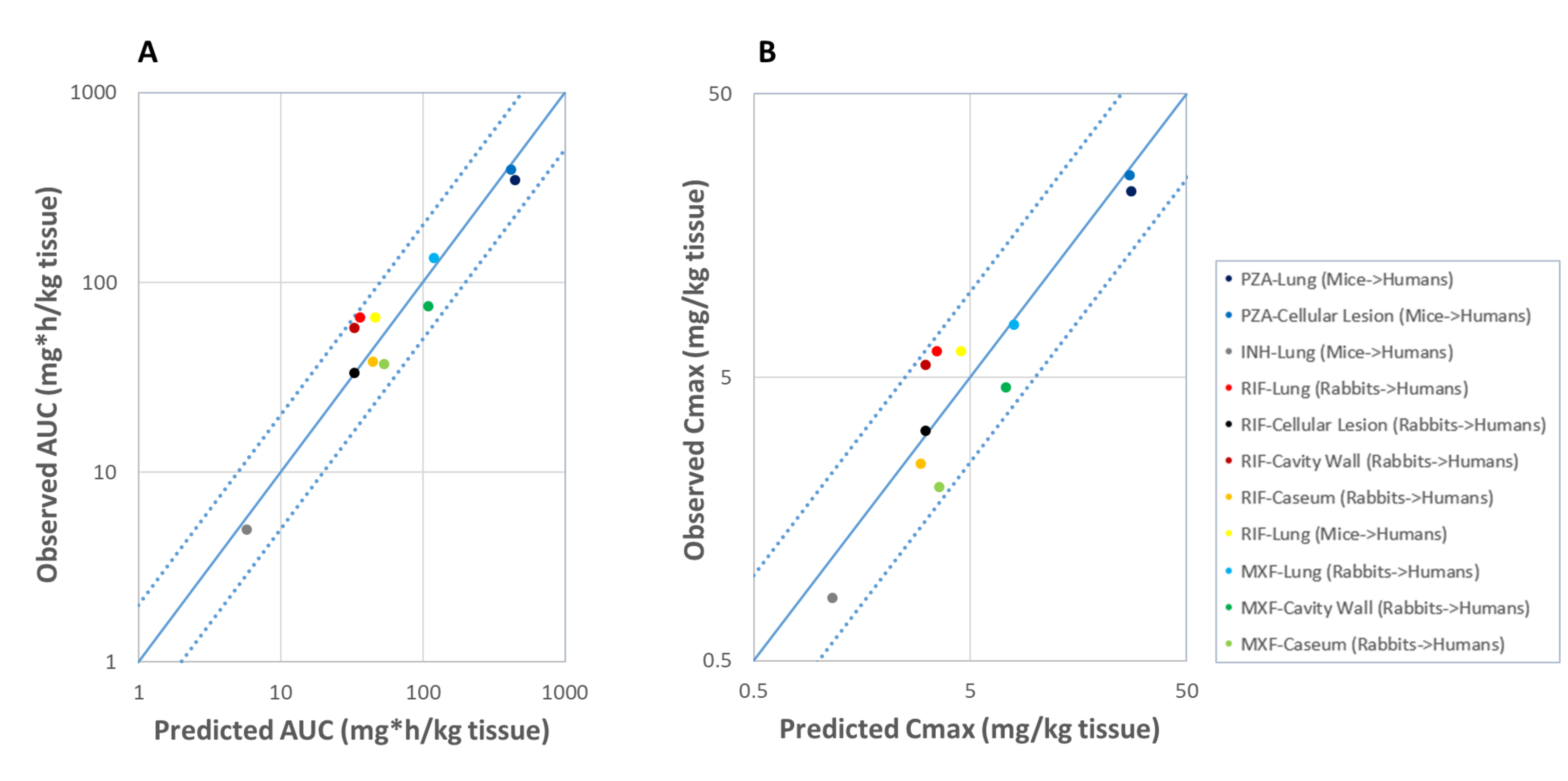

Figure 2. Mean observed versus extrapolated/ predicted daily AUCs (A) and Cmax (B) after a single-dose administration of Isoniazid (INH), Pyrazinamide (PZA), Rifampicin (RIF) and Moxifloxacin (MXF).

5. Conclusions

Middle-out, multicompartment, permeability-limited lung PBPK models were developed to extrapolate healthy/uninvolved lung as well as lesion (including cellular lesion and caseum) PK from small preclinical species to humans, for several anti-TB drugs. This PBPK approach presented could be used to extrapolate lung and lesion PK of new anti-TB drugs from preclinical species to humans.

The details this work can be found in the new publication [7]

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