Developing a mechanistic physiologically based lung model and its application in modelling rifampicin pharmacokinetics in the lung

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Background

Being able to predict the lung concentration of anti-TB drugs, and how these concentrations change in different stages of TB infection and resultant inflammation, would be of great benefit in designing appropriate dosing regimes for novel TB drugs.

As a first step in this process the aim of this study was to develop a physiologically-based pharmacokinetic (PBPK) model to predict the distribution of drugs in different regions of the lung.

Method

Model structure

A multiple-compartment permeability-limited lung model was developed and linked to a 12 tissue perfusion-limited compartmental whole-body PBPK model.

The lung model includes 7 segments for airway and lobes, with each of the segments containing 4 compartments representing pulmonary capillary blood, pulmonary tissue mass, epithelial lining fluid (ELF) and alveolar air (Figure 1).

The model accounts for pulmonary enzyme metabolism within the tissue compartments and incorporates transporter functionality at the basal and apical membranes of the alveoli-blood barrier (ABB).

The model allows drug administration via PO, IV or inhalation with part of the inhaled drug being swallowed and available for absorption via the gut.

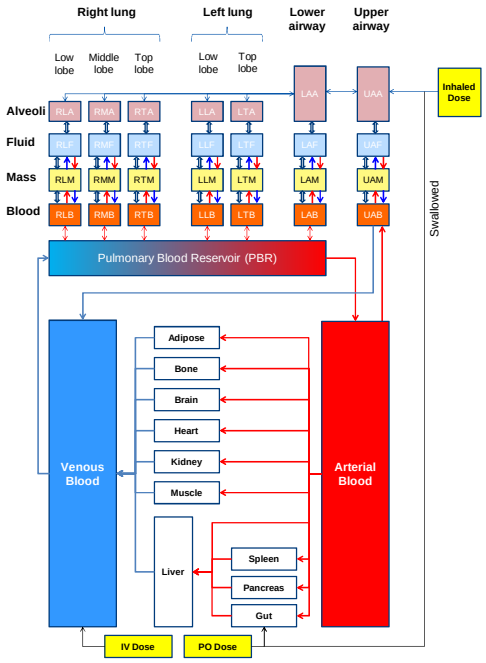

Figure 1. Schematic description of the multiple compartment lung model and its embedding in a whole-body PBPK model.

Model parameterization

The system-related parameters for the whole-body PBPK model were based on Simcyp PopRep – a representative subject of Simcyp Virtual Population (Simcyp Limited, Sheffield, UK). Lung physiological and anatomical attributes and data on transporter abundance in the ABB have been collated from the published literature (Table 1).

The majority of the drug-related parameters for rifampicin were based on the Simcyp compound library file. The passive permeability coefficient of rifampicin via ABB was obtained by scaling *in vitro* permeability data measured in Calu-3 monolayers (Tewes et al., 2008).

Table I – System-related data for lung model

	Blood	Mass	Fluid	Alveoli
Volume	✓	✓	✓	✓
Surface area	✓	✓	✓	✓
Flow rate	✓	✓	✓	✓
pH	✓	✓	✓	NA
Enzyme	✓	✓	✓	NA
Transporters	NA	✓	NA	NA

NA – Not Applicable.

Model verification

Rifampicin was used as a model compound. Simulation results were compared to clinical observations on the concentrations of rifampicin in plasma, ELF and alveolar cells in healthy subjects after a single standard oral dose (600mg). Note the clinical data was not used to refine the model.

Simulation results

Preliminary simulation results are comparable to clinical observations, indicating the model is able to describe rifampicin PK in healthy volunteers (Figure 2) and in TB patients (Figure 3).

Rifampicin PK in healthy volunteers

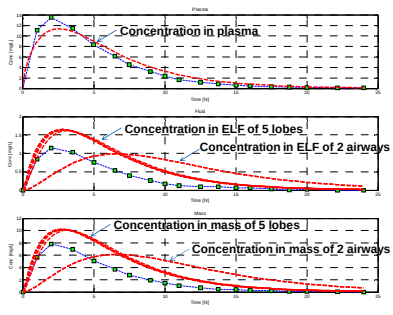

Figure 2. Predicted concentrations (dashed line) vs. observed concentrations (squares, Goutelle et al., 2009) in plasma, ELF and mass in healthy volunteers .

Rifampicin PK in TB patients

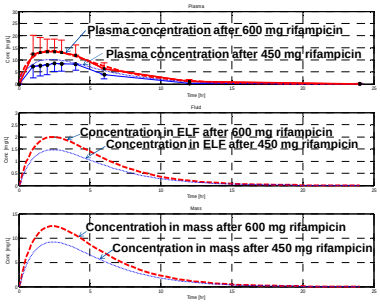

Figure 3. Predicted concentrations in plasma, ELF and mass of right lower lobe in a virtual patient. The clinical plasma data are from Ruslami et al., 2007.

Table II – Simulated PK in TB patients

Parameters	Location	600 mg Simulated	600 mg Observed (n=23)	450 mg Simulated	450 mg Observed (n=24)
AUC_{0-24} (mg*h/L)	RLF	13.1	-	9.9	-
	RLM	81.7	-	61.3	-
	Plasma	90.3	79.7 (38.7-138.1)	67.7	48.5 (26.7-72.8)
Cmax (mg/L)	RLF	2.0	-	1.5	-
	RLM	12.4	-	9.2	-
	Plasma	13.7	15.6 (5.1-26.6)	10.2	10.5 (6.2-16.6)
T_{max} (h)	RLF	2.5	-	2.2	-
	RLM	2.5	-	2.2	-
	Plasma	2.2	1 (1-6)	2.2	1.9 (1.5-5.2)

Discussion

The predicted concentrations of plasma, pulmonary tissue mass and epithelial lining fluid after an oral dose of rifampicin were comparable to those observed in clinical healthy subjects.

Using *in vitro* permeability data for rifampicin in the calu-3 cell line it was possible to extrapolate to a value of *in vivo* permeability that reasonably accurately predicted the observed clinical data. It will be important in future studies to test how well this approach works for other drugs.

The structure of the PBPK lung model is amenable to study the effect of TB-induced changes in physiological parameters (eg AAG and albumin levels, haematocrit, lung pH etc) on concentration-time profiles in different parts of the lungs.

Conclusion

This *in-silico* PBPK lung model provides a tool to help better understand the drug concentrations within the human pulmonary system.

References

Goutelle S, et al., (2009) Antimicrob Agents Chemother 53: 2974-81.

Ruslami R, et al., (2007) Antimicrob Agents Chemother 51: 2546-51.

Tewes F, et al., (2008) J Con Rel 129: 93-9.