**APPLICATION OF A MULTI-COMPARTMENT PERMEABILITY-LIMITED LUNG MODEL TO PREDICT LUNG CONCENTRATIONS OF MOXIFLOXACIN IN VIRTUAL HUMAN SUBJECTS**

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1 Tissue left Moxifloxacin Use Tuberculosis

**Introduction**

- Tuberculosis (TB) remains a major global health problem[1].
- Current therapies for pulmonary TB use combinations of orally dosed drugs to achieve adequate concentrations in the lungs of infected individuals to gain therapeutic benefit.
- Moxifloxacin, a fluoroquinolone antibiotic has been used in conjunction with standard therapy to treat pulmonary TB[2].
- A permeability-limited lung model was previously constructed and used to simulate lung concentrations for a range of therapeutic drugs assuming only passive movement of drugs within the lung compartments[3].
- Moxifloxacin is known to be transported by P-glycoprotein (P-gp), a transporter that is expressed in the lung[4].
- In this study, the effect of including P-gp transport on the lung disposition of moxifloxacin was assessed (Figure 1).

**Aims**

- Develop a full-PBPK model to describe the pharmacokinetics of the anti-TB drug moxifloxacin.
- Use a multiple-compartment permeability-limited lung model to predict distribution to the lungs after systemic administration.

**Methods**

- A full-PBPK model was constructed for moxifloxacin using the population-based Simcyp simulator (V14R1).
- Tissue-to-plasma partition coefficients were predicted using the methods described by Rodgers and co-workers[5]. Absorption was described using the Advanced distribution, absorption and metabolism (ADAM) model[6].
- The lung (airways and lobes) were represented by a total of 7 permeability limited compartments. Each of the compartments was divided into sub-compartments representing the pulmonary capillary blood, pulmonary tissue mass, epithelial lining fluid (ELF) and alveolar air (Figure 2)[5].

**Results**

- Model performance was verified by comparing predictions to the reported plasma time-concentrations of moxifloxacin at oral doses of 100-600 mg (Figure 3). The pharmacokinetics of moxifloxacin are linear over this dose range.
- The predicted clearance for a 400 mg oral dose was 16.1 (3.0) L/h (mean (SD)), plasma half-life 12.3 (3.2) h and urinary excretion 11-28% were within the range of reported values (12.1-19.3 L/h, 12.2-14.6 h, and 15.7-24.7%, respectively) (Table 1)[11].

**Conclusions**

- The model described the plasma pharmacokinetics of moxifloxacin well, however ELF-PLA ratios were underestimated assuming only passive transport.
- Improved predictions of the ELF:PLA ratio (4.0-9.1) were seen when active apical efflux was incorporated. A 2-fold higher P-gp intrinsic clearance was required suggesting further refinement of the in vitro-in vivo extrapolation procedure is needed.
- A possible reason for the discrepancy between the in vitro and in vivo situation include the difference in P-gp expression/activity in the in vitro system and in vivo.

**References**

3. Goyal and et al. (2015) CPT Accepted

**Figure 1** Representation of disposition of moxifloxacin (*) to the epithelial lining fluid from the lung capillary blood

**Figure 2** Full-PBPK model describing the distribution of moxifloxacin using a permeability-limited lung model. The lung model consists of 7 segments:
1. right low lobe (rlb),
2. right middle lobe (rml),
3. right top lobe (rtl),
4. left low lobe (llb),
5. left top lobe (ltl),
6. ower airway (la) and
7. upper airway (ua)[5].

Each segment is described by 4 compartments: alveoli air, fluid, mass and blood. The pulmonary blood reservoir distributes and receives blood to various blood compartment as well as lower airway blood compartment. Upper airway is perfused by arterial blood.

**Figure 3** Mean plasma time concentration (10 trials of 7 Male healthy volunteers, 23-45 years) following a single dose of 100-600 mg moxifloxacin PO[10]

**Table 1** Observed and predicted mean ±SD (range) pharmacokinetic parameters for 400 mg PO moxifloxacin in healthy volunteers.

**Table 2** Observed and predicted mean lung tissue:plasma and ELF:plasma ratios

**Figure 4** Observed ELF:plasma ratio (blue)[4], simulated assuming passive diffusion only (red), active apical efflux ELF:plasma ratios for rll, rml, ll, and III, respectively (green), and two-fold higher active apical ELF:plasma ratios for rll, rml, ll, and III, respectively (orange).