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

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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).

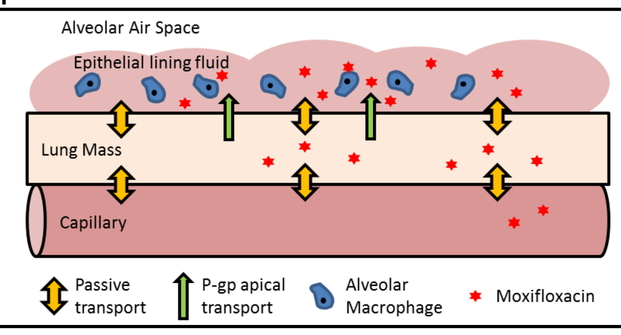

Figure 1| Representation of disposition of moxifloxacin (*) to the epithelial lining fluid from the lung capillary blood

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)[3].

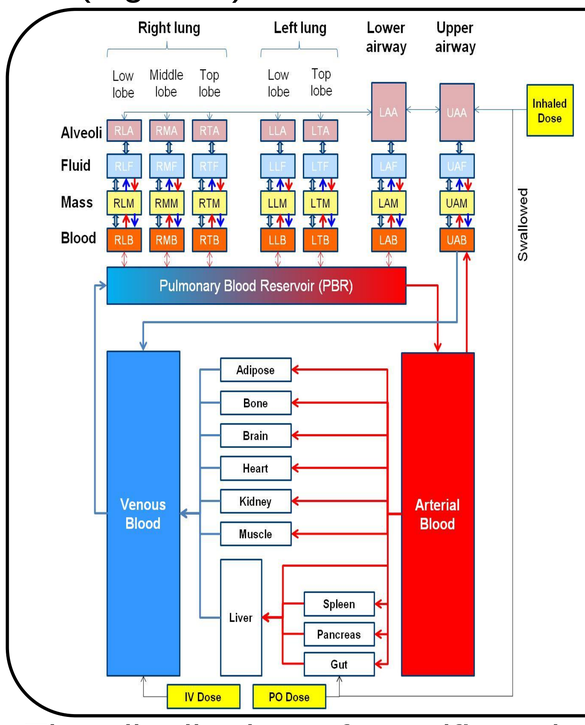

Figure 2| Full-PBPK model describing the distribution of moxifloxacin using a permeability-limited lung model.
The lung model consists of 7 segments:
1) right low lobe (rll),
2) right middle lobe (rml),
3) right top lobe (rtl),
4) left low lobe (lll),
5) left top lobe (ltl),
6) ower airway (la) and
7) upper airway (ua)[3].
Each segment is described by 4 compartments: alveoli air, fluid, mass and blood. The pulmonary blood reservoir distributes and receives blood to various lobe blood compartment as well as lower airway blood compartment. Upper airway is perfused by arterial blood.

- The distribution of moxifloxacin within the compartments of the lung PBPK model was predicted using *in vitro* permeability and P-gp kinetic data from Calu-3 cells[7]. The *in vitro* intrinsic clearance of moxifloxacin by P-gp (31.6 µL/min) was estimated using the Simcyp *in vitro* analysis (SIVA) toolkit (V1.0, Simcyp Ltd, Sheffield, UK) and was extrapolated to the *in vivo* situation accounting for differences in surface area.
- The concentrations predicted to occur in the ELF and lung tissue and the ratios of these concentrations to the plasma concentration were compared to reported values from human clinical studies[8-10].

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 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].

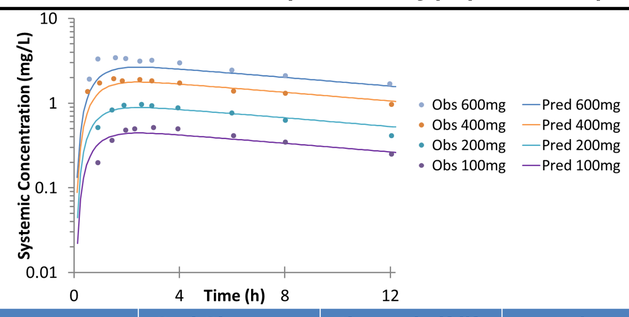

Figure 3| Mean plasma time concentration (10 trials of 7 Male healthy volunteers, 23-45 years) following a single dose of 100-600 mg moxifloxacin PO[11]

	Oral Clearance (L/h)	Plasma half-life (h)	Urinary Excretion (%)
Observed 400 mg PO[11]	14.9 ±1.18 (12.1-19.3)	13.1 ±1.06 (12.2-14.6)	20.1 ±1.20 (15.7-24.7)
Predicted 400 mg PO	16.1 ±3.0 (10.3-24.2)	12.3 ±3.2 (6.84-21.23)	18.3 ±4.2 (10.7-28.2)

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

- Following oral dosing with moxifloxacin (400 mg), lung tissue:plasma ratios of 1.7–4.4 and ELF:plasma ratios of 3.5–7.4 have been reported[8-10].
- Purely accounting for passive distribution processes in the lung led to a reasonable estimate for the lung tissue: plasma moxifloxacin concentration ratio (5.5) but under-predicted moxifloxacin concentration in ELF (ELF:plasma ratio 0.6) (Figure 4, Table 2).
- Using *in vitro* data to describe the effect of P-gp transport of moxifloxacin from lung tissue to ELF increased this ratio to 2.3-4.9, but this still underpredicted the observed concentration ratios. A sensitivity analysis was undertaken to examine the impact of increasing the P-gp apical efflux intrinsic clearance on the ELF:plasma ratio.
- Good predictions of the ELF:plasma ratio (4.0-9.1) were seen using a 2-fold higher P-gp intrinsic clearance.

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

	lung tissue:plasma ratio	ELF:plasma ratio
Observed 400 mg PO [8-10]	3.6-5.5	5.2-7.0
Predicted (Passive only)	5.5	0.6
Predicted (Passive + Active apical efflux)	4.9-5.5	2.3-4.9
Predicted (Passive + 2 fold higher Active apical efflux)	5.5	4.0-9.1

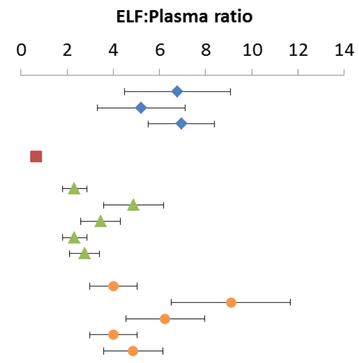

Figure 4| Observed ELF:plasma ratio (blue)[7-9], simulated assuming passive diffusion only (red), active apical efflux ELF:plasma ratios for rll, rml, rtl, lll and ltl, respectively (green), and two-fold higher active apical efflux ELF:plasma ratios for rll, rml, rtl, lll and ltl, respectively (orange).

Conclusions

- The model described the plasma pharmacokinetics of moxifloxacin well, however ELF:plasma ratios were underpredicted assuming only passive transport.
- Improved predictions of the ELF:plasma 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.*

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