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

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Background

Tuberculosis (TB) remains a major global health problem. According to World Health Organisation (WHO) report, an estimated 9.6 million people developed TB and 1.3 million died from the disease in 2012 [1] Current therapies for pulmonary TB use combinations of orally dosed drugs that need to reach adequate concentrations in the lungs of infected individuals to achieve therapeutic benefit. The ability to predict lung concentration of anti-TB drugs primarily from in vitro experiments would be of great benefit in screening new drug candidates and designing appropriate dosing regimens for novel TB drugs.

Objectives

The aim of this study was to develop a physiologically-based pharmacokinetic (PBPK) model to predict the concentration of different anti-TB drugs in the human lung.

Methods

Simulations were conducted in the Simcyp simulator V14 R1 (Simcyp LTD, Sheffield, UK). The structure of the lung model is shown in Figure 1.

Model assumptions

Each compartment is homogeneous, with constant physiological and pharmacological parameters.

No fluid or mucus moves from the lobes to the airways.

Each compartment is homogeneous, with constant physiological and pharmacological characteristics.

Drugs passively diffuse (Clum) between compartments within a segment and active uptake (CUW and efflux transporters (CUT) at the basal (mass-blood) and apical (fluid-mass) membranes of the tissue mass compartments are considered.

Metabolism (CET) can occur in tissue mass compartments.

Immediate equilibrium, defined by the air:fluid partition coefficient (Kf).

Results

The simulated and observed ELF:plasma ratio (Figure 2) for rifampicin, pyrazinamide, isoniazid and ethambutol. The simulated ELF:plasma ratio in virtual subjects differs with respect to the observed values. The average simulated ELF:plasma ratio was 1.2 +/-1.9 in fast acetyators and 3.2 +/- 8.1 in slow acetylators.

Conclusions

Some utility in predicting the lung pharmacokinetics of anti-TB drugs and testing of the model with a wider range of compounds is underway.

For some compounds assuming purely passive diffusion between the plasma and ELF results in underprediction of the lung mass concentration. The clearance of the efflux transporter was set at 0 (black line), 0.06 (red), 0.6 (green), 6 (purple) and 60 L/h (light blue).

REFERENCES


Figure 1. Structure of the multiple-compartment permeability-limited lung model embedded in Simcyp full-PBPK model which consists of 12 perfusion-limited tissue compartments, in addition to the lungs. The lung is approximated by 7 segments, namely, upper (UA) and lower (LA) anterior, left front lower lobe (LFL), right front lower lobe (RFL), left back lower lobe (LBL), right back lower lobe (RBL), and lower right [LR] segments. The model contains 4 compartments representing pulmonary capillary blood, pulmonary tissue mass, fluid and air. In particular, an equilibrium is assumed between the fluid and the air, and between the air and interstitial fluid contained in the tissue compartments. The double arrows represent bi-directional passive permeability between adjacent compartments within the same segment. The single arrows represent the active transport across the basal and apical membranes of pulmonary tissue. Metabolic elimination exists in the mass compartments.

Figure 2 Observed (blue diamonds) and predicted (red squares) ELF:plasma ratios for rifampicin, ethambutol, isoniazid, and pyrazinamide. The simulated values are presented as mean value with the range simulated in the virtual population. For rifampicin and pyrazinamide the concentrations in the right lower lobe of the lung are shown. For ethambutol the concentration in the right lower lobe of the lung are shown. The three red squares from left to right represent the concentration in the whole population in and in slow acetyators respectively. The biological value of the observed clinical values is denoted by a symbol and where it is available the SD has also been shown as a block line (error bar). For some studies only the range of observed values was available and these have been shown on the graph by a dark blue line with no symbol.

Figure 3 Observed (blue diamonds) and predicted (red squares) ELF:plasma ratios for rifampicin, ethambutol, isoniazid, and pyrazinamide. The simulated values are presented as mean value with the range simulated in the virtual population. The average simulated ELF:plasma ratio was 1.2 +/-1.9 in fast acetyators and 3.2 +/- 8.1 in slow acetylators.

Figure 4 Effect of adding the action of an efflux transporter between the lung mass and epithelial lining fluid on (A) systemic plasma concentration; (B) lung epithelial lining fluid concentration and (C) the lung tissue mass concentration. The clearance of the efflux transporter was set at 0 (black line), 0.06 (red), 0.6 (green), 6 (purple) and 60 L/h (light blue).

Table 1 Compound specific information used to develop PBPK models for isoniazid, ethambutol and pyrazinamide.