Physiologically based pharmacokinetic (PBPK) model to describe absorption and disposition of inhaled capreomycin

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Introduction

The current work describes the simulation of capreomycin pharmacokinetics (PK) after IV and pulmonary administration. Capreomycin is an antibiotic used to treat tuberculosis. It is eliminated mainly by renal secretion and is poorly absorbed from the gastrointestinal tract. It is administered by intravenous (IV) or intramuscular (IM) injection. Preclinical studies showed poor distribution of capreomycin into lung from the systemic circulation [1]. Effective treatment of tuberculosis requires adequate exposure in lung and systemic circulation (for extrapulmonary sites of infections) [2]. Inhaled administration offers the potential to achieve sufficient drug exposure in both lung and systemic circulation and PBPK modeling can help in the development of such formulations.

Methods

Capreomycin pulmonary absorption and pharmacokinetics were simulated using GastroPlus™ 9.0 (Simulations Plus, Inc., Lancaster, CA). Capreomycin distribution pharmacokinetics was simulated using the PBPKPlus™ module in GastroPlus:

- A PBPK model with all permeability-limited tissues was used
- Human organ weights, volumes, and blood perfusion rates were generated by the program's internal Population Estimates for Age-Related (PEAR™) Physiology™.
- Tissue/plasma partition coefficients (Kp's) were calculated using Poulin's equation for drug partitioning into extracellular space (Poulin 2002) from *in vitro* and *in silico* physicochemical properties (ADMET Predictor™ 7.2, Simulations Plus, Lancaster, CA).
- The specific permeability-surface area product (PStc per mL tissue) was fit against reported PK parameters (CL, Vss, AUC) after IV administration of capreomycin in subjects with normal and mild/moderate renal impairment. PStcs for individual tissues were calculated as a product of the specific PStc and the total cell volume of each tissue.
- Renal clearance was calculated as the product of fraction unbound in plasma (fup) and glomerular filtration rate (GFR).

The Pulmonary Compartmental and Absorption and Transit (PCAT™) model within the GastroPlus Additional Dosage Routes Module™ was used to model pulmonary deposition, absorption, and transit.

- Total lung deposition was set to 55% based on *in vitro* data [3], while distribution of drug in different lung regions was estimated from particle size distribution using the built-in ICRP66 [4] deposition model.
- Permeability in different lung regions was estimated using the built-in model.
- The systemic absorption rate coefficient (the diffusion rate between lung tissue and systemic circulation) was fit against the plasma concentration-time (Cp-time) profile for a 25-mg inhaled dose.
- The model was used without further changes to predict Cp-time profiles after inhalation of 75, 150, and 300 mg of capreomycin.

Results

As the raw Cp-time profile after IV administration of capreomycin was not available, the PBPK model was calibrated using the PK endpoints (Figure 1) reported for healthy subjects and patients with mild and moderate renal impairment [5].
Renal clearance was calculated as fup*GFR and GFR was estimated from reported creatinine clearance for all subjects. The specific PStc = $7x10^{-6}$ mL/s/mL tissue cell volume was fitted to match the AUC and Vss across all subjects.

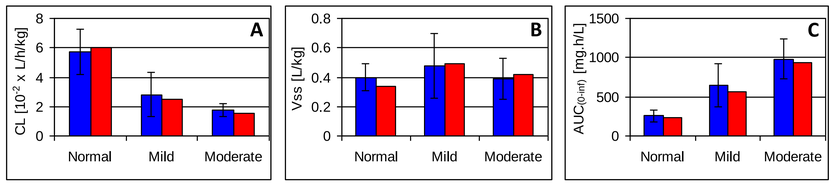

Figure 1: Observed (blue) and simulated (red) clearance (A), volume of distribution (B), and AUC (C) in groups of healthy subjects with normal renal function and patients with mild and moderate renal impairment used to calibrate the capreomycin PBPK model. Observed data was obtained from literature [5].

The calibrated PBPK model was used to simulate the systemic disposition of capreomycin. Based on the reported mass median aerodynamic diameter (MMAD) = 4.74 µm and *in vitro* total lung deposition of ~50% [3], the ICRP66 model predicted a large portion of the dose delivered to the lung to be deposited in the alveolar-interstitial region, with smaller fractions deposited in extrathoracic, thoracic, and bronchiolar regions (Figure 2).

Pulmonary absorption (fitted systemic absorption rate coefficient) was calibrated using the data for a 25-mg inhaled dose. The complete model without modification then provided excellent prediction of the Cp-time profile for three higher inhaled doses of capreomycin (Figure 3).

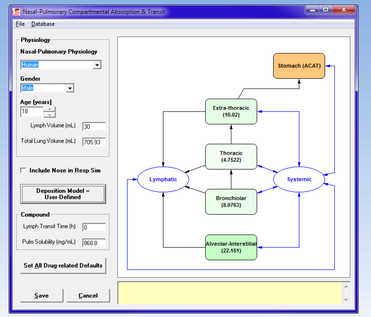

Figure 2: Schematic layout of the compartments in the PCAT model. The numbers in parentheses show estimated percents of the capreomycin dose deposited in different lung regions. The total lung deposition was set to 55%.

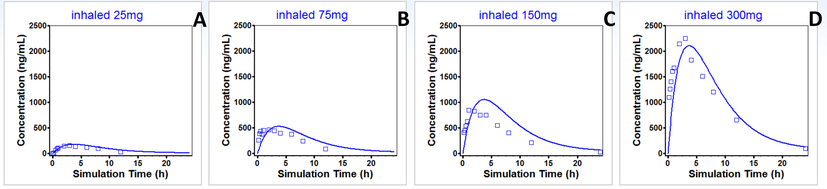

Figure 3: Observed (points) and simulated (lines) Cp-time profiles after 25 mg (A), 75 mg (B) , 150 mg (C), and 300 mg (D) inhaled administration of capreomycin. The observed Cp-time profile after a 25 mg dose was used to fit the systemic absorption rate coefficient, and the remaining doses were well-predicted using the same model parameters. Observed data was obtained from literature [2].

Conclusions

PBPK modeling is routinely utilized in the drug development process, mainly for IV and oral administration routes. It, however, also has great potential to help with the development of formulations for other administration routes, and the current work shows an example of a predictive PBPK model for inhaled administration.

References

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