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 creatinine clearance (GFR) and GFR was estimated from reported creatinine clearance for all subjects. The specific PStc was fitted to match the AUC and Vss across all subjects.

Results

As the raw Cp-time profile after IV administration of capreomycin was not available, the calibrated PBPK model was used to simulate the systemic disposition of capreomycin. The calibrated PBPK model was used to simulate the systemic disposition of capreomycin (Figure 3).

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