Physiologically-based pharmacokinetic (PBPK) model for prediction of tobramycin pulmonary absorption and pharmacokinetics in children

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Purpose: To fit an absorption-pharmacokinetic model for simulation of tobramycin in adult and pediatric populations

Methods: Tobramycin pulmonary absorption and pharmacokinetics were simulated using GastroPlus™ 7.0 (Simulations Plus, Inc., Lancaster, CA). Tobramycin pharmacokinetics was simulated with a physiologically-based pharmacokinetic (PBPK) model with all permeability-limited tissues. 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 [1] from *in vitro* and *in silico* physicochemical properties (ADMET Predictor™ 5.0, Simulations Plus, Lancaster, CA). Single specific permeability-surface area product (PStc per mL tissue) was fitted against *in vivo* plasma concentration-time (Cp-time) data after *i.v* administration of tobramycin in adults with impaired renal function. The total PStcs for individual tissues were calculated as a product of the specific PStc and the total cell volume of each tissue. Renal clearance was fitted against Cp-time profile after *i.v.* administration of tobramycin in adults with normal renal function. The pulmonary component of the GastroPlus Additional Dosage Routes Module™ was used to model the pulmonary absorption. The deposition fractions for two formulations were used as reported in literature [2]. Pulmonary permeability was fitted against Cp-time profiles after pulmonary administration of a PulmoSphere (solid particulate) formulation of tobramycin in adults and validated by using the model to predict the Cp-time profile in adults after pulmonary administration of a TOBI (nebulizer) formulation. The same model (fitted against adult *in vivo* data) was then used to predict tobramycin pharmacokinetics after *i.v.* and pulmonary administration in children.

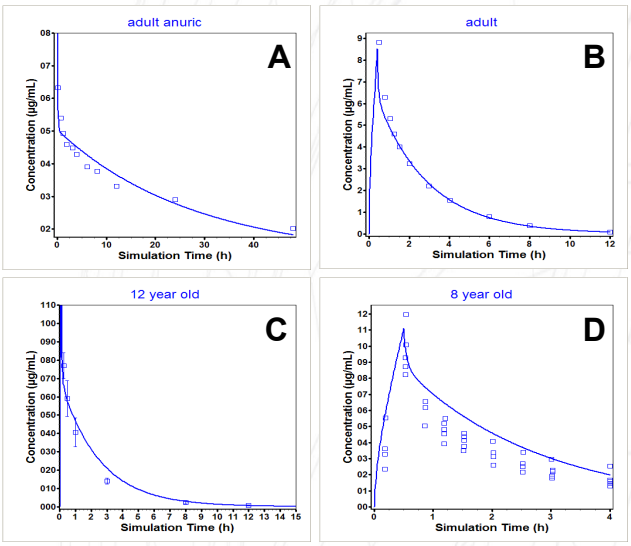

Figure 1. *Simulated (line) and experimental (points) Cp-time profiles of tobramycin after i.v. administration in adults and children: A – bolus dose of 1mg/kg [3] in adult patients not producing urine (used to optimize single specific PStc: 2E-6 mL/s/mL of cell volume); B – infusion dose of 1.5 mg/kg [4] in adults with normal renal function (used to optimize renal clearance: 10% of kidney blood flow); C – prediction of bolus dose of 15 mg/kg in 12 year old patients with cystic fibrosis [5]; D – prediction of infusion dose of 2 mg/kg in 8 year old patients [6]*

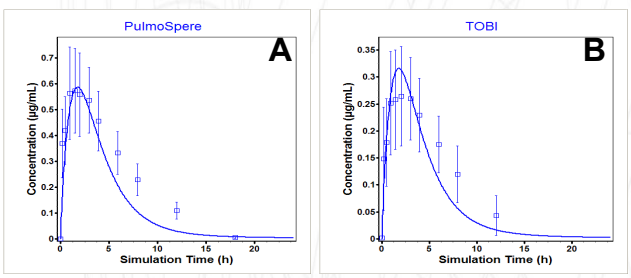

Figure 2. *Simulated (line) and experimental (points) Cp-time profiles of tobramycin after inhaled administration in healthy adults [2]: A – 80 mg dose of pulmosphere formulation (used to optimize pulmonary permeability); B – prediction of 300 mg dose of TOBI formulation. Simulations for both formulations are using experimental deposition fractions.*

Conclusions:

Ethical considerations prevent extensive clinical trials in pediatric populations. However, with the use of PBPK modeling, the *in vivo* data from adults may be used to explore the mechanisms of drug disposition and to predict pharmacokinetics in children after a variety of administration routes. Simulation tools also allow exploring the sensitivity of the exposure to individual processes involved in drug absorption, distribution and elimination and may help in design of clinical trials to maximize their efficiency.

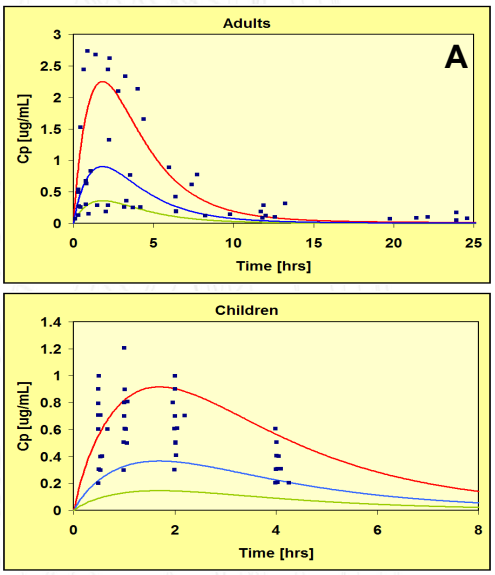

Figure 3. *Simulated (lines) and experimental (points) Cp-time profiles of tobramycin after inhaled (nebulizer) administration in adults and children (average age about 4 years): A – 600 mg dose in adults [7], blue - prediction assuming the same deposition fractions as reported for TOBI nebulizer, green and red – prediction assuming 2.5-times lower and higher, respectively, deposition efficiency than reported for TOBI nebulizer; B – prediction for 300 mg dose in children [8] after scaling the respective deposition efficiencies from adults, blue – scaled adult deposition reported for TOBI nebulizer, green and red – scaled the low and high adult deposition efficiency, respectively.*

Results:

- After accounting for differences in physiology and pulmonary deposition efficiency between children and adults (based on literature, the deposition is ~4 times lower in children [8]), the model produced excellent predictions of Cp-time profiles after *i.v.* and pulmonary administration of tobramycin in children.
- Simulations showed that a significant portion of inter-individual variability can be attributed to differences in deposition efficiency. It is expected that other factors (distribution, clearance) will also have an effect; however they were not investigated in this study.
- The model also gave a good estimate of tobramycin concentration in the epithelial lining fluid in the lower respiratory tract of children:
  - The simulated concentrations in bronchiolar and alveolar regions, respectively, 45 minutes after administration were:
    - 39 and 215 ug/mL for high deposition efficiency
    - 16 and 86 ug/mL for the medium deposition efficiency
    - 6 and 34 ug/mL for the low deposition efficiency
  - The mean reported [8] concentration from bronchoalveolar lavage was 90 ug/mL with concentration ranging from 16 to 204 ug/mL across all subjects.

References:

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