Using In Silico Methods For Predicting Drug Pharmacokinetics In Children

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INTRODUCTION

- The prediction of pharmacokinetic (PK) differences in children compared to adults is important for dosage adjustment, therapeutic response analysis and risk assessment
- Physiology-based pharmacokinetic (PBPK) modeling is a tool for simulation of concentration-time profiles based on physiology (body and organ weights, blood flows, partition coefficients, etc)
- **Objective:** Evaluate the accuracy of the PBPK modeling software, PK-Sim®, to predict paediatric pharmacokinetic profiles

METHODS

Physiological Scaling

- PK-Sim® includes the age-dependent scaling of body & organ weights, organ composition and blood flows. The age-dependence of physiological parameters were summed and compared with literature values for:
  - Blood Volume
  - Cardiac Output
  - Total Body Water
  - Extracellular Water
  - Body Fat

Pediatric Simulations

- Pediatric simulations, for **5 compounds** with widely varying physico-chemistry, followed a specific work-flow **(Figure 1)** and were based on accurate simulation models in adults. Pediatric clearance scaling was done using a physiology-based method (see adjacent poster).

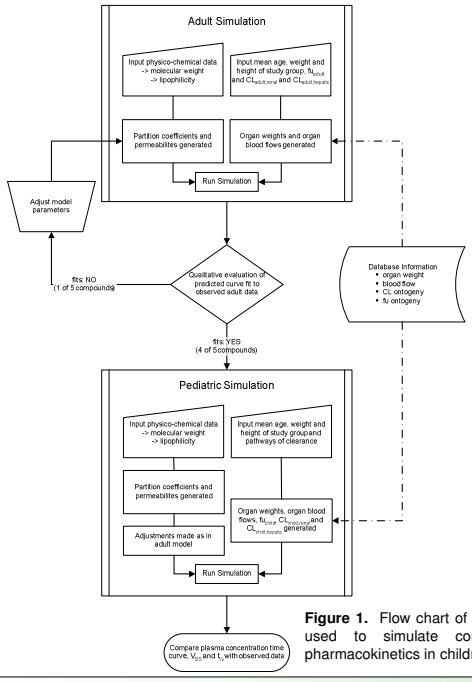

Figure 1. Flow chart of process used to simulate compound pharmacokinetics in children.

RESULTS

Physiological Scaling

- All anatomical (body weight, height, organ weights) and physiological (blood flows, cardiac output, total body water, lipid and protein) parameters were age-dependent.
- Body water & lipid changes due to the age-dependence of interstitial space in adipose & muscle tissue (**Figure 2 & 3**).

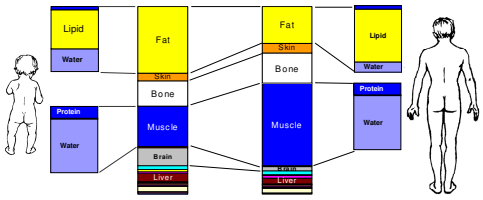

Figure 2. Body composition differences between a child of one year and an adult.

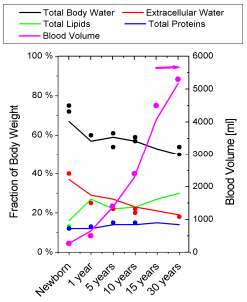

Figure 3. Observed (•) and calculated (-) composition by age.

Paediatric Simulations

- Both simulated and experimental data suggested that distribution was more rapid in premature & term neonates compared to older children and adults.
- Trends associated with age groups were well-represented by simulations (e.g. **Figure 4**):
  - premature & term neonates had higher plasma concentrations compared to adults
  - children over 6 months had lower plasma concentrations compared to adults
- Distribution volumes corresponded to observed values, and half-lives were slightly over predicted (**Figure 5**). There was no age bias, except in premature neonates.

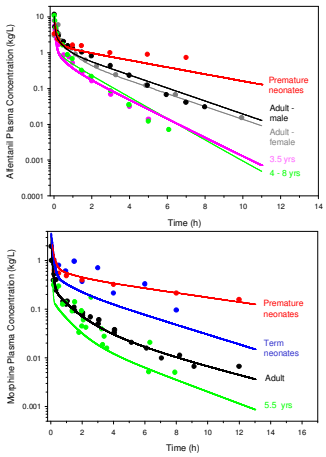

Figure 4. Observed (•) and predicted (-) plasma concentration vs. time curve following intravenous administration of alfentanil (top) and morphine (bottom) to adults (black/gray) and children of various age.

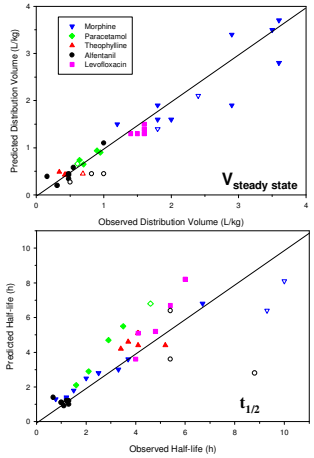

Figure 5. Observed vs. predicted volume of distribution at steady state and half-life for five compounds. Open symbols indicate values for premature neonates.

CONCLUSIONS

- **Paediatric concentration time curves were well predicted using our work-flow.**
- **The prediction of partition coefficients in children led to accurate Vss and $t_{1/2}$ predictions, a scaling procedure that can only be performed through physiology-based modeling.**
- **Paediatric clinical trial development could benefit from the use of this PBPK model. Uses include the guidance of dosing regimens and sampling times.**

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