Predicting Pharmacokinetics in Children using PK-Sim®

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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: determine the appropriateness of the PBPK software, PK-Sim®, to predict plasma concentration-time curves in children.

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

Clearance Scaling
- Clearance was predicted using a ‘Combined Physiology-based and Enzyme Ontogeny Approach’ (see other poster) as described in Edginton et al. (2005). The age-dependence of unbound fraction was predicted using the method of McNamara and Alcorn (2002).

Simulations
- Box 1 describes the PK-Sim® inputs required to simulate plasma concentration-time curves in children.
- Adult simulations were compared to literature values. Adjustments in partition coefficients were made if necessary. The altered model was used for simulations with children. Mean age & weight of studied group was used as input.
- Observed children values superimposed over simulated curve.

Box 1: PK-Sim® Input Information
- Physiochemical Data of Compound
- [L-hippribility, Molecular Weight]
- Plasma Protein Binding
  - [Age-dependence predicted - McNamara & Alcorn (2002)]
  - [Age & Weight of Simulated Individual(s)]
  - Administration Regime
  - Renal and Hepatic Clearance Value
    - [Age-dependence predicted - Edginton et al. (2005)]

RESULTS

Table 1. Observed (Obs) cardiac output, blood volume, total body water [% of body weight (BW)], total extracellular water (% BW) and total body lipid (% BW) and the corresponding values as predicted in PK-Sim (Pred). Values are for males aged birth to adult. References available on the reverse side of the handout. NA = not available.

<table>
<thead>
<tr>
<th></th>
<th>Newborn</th>
<th>1 yr</th>
<th>5 yrs</th>
<th>10 yrs</th>
<th>15 yrs</th>
<th>30 yrs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Output</td>
<td>Pred</td>
<td>Obs</td>
<td>Pred</td>
<td>Obs</td>
<td>Pred</td>
<td>Obs</td>
</tr>
<tr>
<td></td>
<td>0.59</td>
<td>0.50</td>
<td>1.5</td>
<td>3.2</td>
<td>4.4</td>
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<tr>
<td>Blood Volume</td>
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<td>0.27</td>
<td>0.63</td>
<td>0.50</td>
<td>1.3</td>
<td>2.2</td>
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<tr>
<td>Total Body Water</td>
<td>66</td>
<td>60</td>
<td>56</td>
<td>59</td>
<td>56</td>
<td>57</td>
</tr>
<tr>
<td>Extracellular Water</td>
<td>36</td>
<td>34</td>
<td>28</td>
<td>25</td>
<td>22</td>
<td>20</td>
</tr>
<tr>
<td>Total Lipid</td>
<td>17</td>
<td>NA</td>
<td>29</td>
<td>25</td>
<td>NA</td>
<td>23</td>
</tr>
</tbody>
</table>

Physiological Scaling
- All anatomical and physiological parameters were age-dependent and well-represented by PK-Sim (See Table 1 for an example).
- Differences in body water & lipid primarily due to the age-dependence of interstitial space in adipose and muscle tissue (Baker, 1969; Boulton et al., 1978; Dickerson & Widdowson, 1960).

Simulations in Children
- The distribution phase was well-predicted. Both simulated and experimental data suggested that distribution was more rapid in premature & term neonates compared to older children and adults.
- Trends associated with differing age groups were well-represented by PK-Sim (Figure 1) where, premature & term neonates had higher plasma concentrations compared to adults
- children over 6 months had lower plasma concentrations compared to adults.

CONCLUSIONS
- The PBPK modeling tool, PK-Sim®, accurately predicted plasma concentration time curves for all ages, based on physio-chemical & physiological principles.
- In conjunction with appropriate clearance prediction, pediatric clinical trial development could highly benefit from the use of PK-Sim®. Possible uses of this technology inlude the guidance of dosing regimes and sampling time, and ultimately reduce the number of subjects required.