Physiologically Based Pharmacokinetic (PBPK) Modelling in Vulnerable Populations

PBPK in young children: the importance of ontogeny

March 14th, 2019
Jean Dinh PharmD, PhD
Disclosures

- Consultant for ReveraGen BioPharma
Highlights

• **Target population**: children

• **Specific population issues prime for PBPK as a tool**: ontogeny

• **Why PBPK may out-perform other pharmacometric tools**:  
  • Minimize ethical and technical concerns with conducting intense pharmacokinetic studies in children, particularly young children.  
  • Incorporation of ontogeny functions.  
  • Can adjust physiological parameters to model specific pediatric population of interest.
Precision Medicine

Precision Diagnosis
- Understanding mechanism of pathophysiology
- Determine the biological processes that are dysregulated
- Biomarkers of disease progression

Precision Therapeutics
- Determine the “right” medication
- Determine the “right” dose
- Anticipate efficacy and possible adverse events
**Precision Therapeutics: Making better decisions for the child, based on the child’s data**

<table>
<thead>
<tr>
<th></th>
<th>Response</th>
<th>Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td>yes</td>
<td>25%</td>
<td>25%</td>
</tr>
<tr>
<td>yes</td>
<td>25%</td>
<td>25%</td>
</tr>
<tr>
<td>no</td>
<td>25%</td>
<td>25%</td>
</tr>
<tr>
<td>no</td>
<td>50%</td>
<td>13%</td>
</tr>
</tbody>
</table>

Covariates that affect PK, PD, response

Population Informed Dosing

Individual Informed Dosing
Precision Therapeutics Strategy: Stratification with Biomarkers

**Demographic Information**
- Age (Ontogeny!)
- Weight
- Gender
- Ethnicity

**High-Throughput Information**
- Genomics
- Transcriptomics
- Proteomics
- Metabolomics
Ontogeny Definition

Ontogeny

The development, or course of development, of an individual organism

The development of individual to maturity: the development of an individual from a fertilized ovum to maturity

- Age in the case is a (crude) biomarker of complex biological processes.
  - Biomarker that correlates with activity/function of biological process that is critical to drug PBPK.
Considerations when studying/modelling a pediatric population

Clinical studies to characterize PK

- Ethics (particularly young children)
- Highly heterogenous, increased noise (age range represents large change in physiological process of interest)
  - NICHD age group recommendation: term neonatal (Birth – 27 days); infancy (28 days – 12 months); toddler (13 months – 2 years); early childhood (2-5 years); middle childhood (6-11 years); early adolescence (12-18 years); late adolescence (19-21 years)

Modeling to anticipate PK

- Typically scaled down from adult
- Assumption:
  - Disease presentation, clinical targets, drug pharmacokinetics and pharmacodynamics are similar between adults and children.
The Role of Ontogeny →
Metabolism, Clearance, and PBPK

- Functional drug biotransformation capacity is acquired in gene-specific patterns ("developmental trajectories")
  - Group 1: Primarily fetal expression (CYP3A7; SULT1E1)
  - Group 2: SULT1A1, CYP2C19, CYP3A5, GSTA1
  - Group 3: CYP1A2, CYP2C9, CYP2D6, CYP3A4, UGTs
- Observed variability greatest in first 3 months of life

De Wildt et. al, (2014)
Variability in Group 3 Trajectories
Caveats when Scaling Adult Models for Children

- Same pathways of clearance between adults and children (DMEs, transporters, etc.)
- Comprehensive data available for children about physiological, biochemical, and physiochemical processes (or good estimates).
- Drug does not impact trajectory of gene expression and/or protein content.
Valganciclovir: PopPK + PBPK

- Valganciclovir (VGCV) is an oral prodrug of ganciclovir (GCV) → prevention and treatment of cytomegalovirus (CMV) infection.
- Goal: approval of dosing algorithm of children < 4 months old.
- Method: PopPK ("Top-Down") + PBPK ("Bottom-Up") = "Middle-out"
  - GCV PopPK → Covariates of importance to clearance were CrCl and ht (assoc with Vd).
  - PBPK adult VGCV model → esterase activity (conversion of VGCV → GCV); renal excretion of GCV; active transport processes (MRP4, OAT1, OCT1, MATE1, MATE2-K, PepT1)
VGCV–Dosing Algorithm Development

Jorga et al, (2016)
Atomoxetine Exposure Prediction

- Pediatric liver samples (n=78) genotyped for CYP2D6
- 0.5 mg/kg dose simulated
- *In vivo* within-genotype variability confirmed *in vitro*
- Activities of metabolic pathway determined by formation of 4OH-ATX, NDM and 2-OH pathways
- Inter-individual variability in competing pathways become important sources of variability in dose-exposure relationship for PMs and IMs
Scale contribution of enzymes by abundance (CYP Protein content) and genotype.

\[ Cl_{\text{int},uij} = 'Global' \times Cl_{\text{int},u} \times f_{mi,j} \]

\[ 'Global' \times Cl_{\text{int},u\text{,genotype}} = \sum_{i=1}^{n} \left( \sum_{j=1}^{n} Cl_{\text{int},u} \right) \]

Whole organ \( Cl_{\text{int,genotype}} \)

Scale by liver weight and Microsomal Protein Per Gram Liver (MPPGL)

Factor in liver blood flow and hematocrit

\[ Cl_{H\text{,genotype}} = \frac{Q_H \times f_{UB} \times Cl_{\text{int,genotype}}}{Q_H + f_{UB} \times Cl_{\text{int,genotype}}} \]

Determine oral clearance

\[ Cl_{po\text{,genotype}} = \frac{Cl_{H\text{,genotype}} + Cl_r}{f_{a} \times F_G \times F_H} \]
CYP2D6 Protein Content

CYP2D6 content stratified by CYP2D6 activity score

- AS=0
- AS=0.5
- AS=1
- AS=1.5
- AS=2
- AS=3

CYP2D6 content (pmol/mg)

CYP2D6 Activity Score
MPPGL Ontogeny

MPPGL (mg/g) vs. Age

- Median Age: 11.00 years, MPPGL: 24.05 mg/g
- Mean Age: 15.93 years, MPPGL: 26.56 mg/g
- Minimum Age: 0.00 years, MPPGL: 7.93 mg/g
- Maximum Age: 79.00 years, MPPGL: 69.77 mg/g

n = 153
MPPGL (0 – 25 yo)

MPPGLvAge_0-25yo

n = 128

MPPGL (mg/g)

Age (years)
Conclusions

- PBPK can be useful tools to extrapolate PK parameters for special populations, particularly in young children.
- A “middle-out” PBPK methodology is a useful approach for anticipating drug pharmacokinetics in younger population.
- Pediatric-derived bottom-up PBPK models may be utilized to develop pediatric specific PBPK models.