The In Silico Child: PK/PD Modeling in Pediatric Drug Development

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Model-Based Drug Development

A multi-disciplinary approach that integrates the relationships between diseases, drug characteristics, and individual variability

- A framework for synthesizing information and extrapolating beyond what is traditionally studied in RCTs
- A tool for rationale, critical decision making
- From drug discovery to post-marketing
- A mathematical explanation of the relationships needed to explain clinical outcomes over a timeframe of interest at its core
- Away from study centric approach: seamless data mining and knowledge management strategy that quantitatively integrates data across studies and development phases
**Challenges in Pediatric Pharmacotherapy**

- Molecular & physiologic processes determining PK & PD undergo developmental changes based on a child’s maturational progress.
- Different patients follow different developmental trajectories so that usual predictors such as PNA, PMA, or GA do not fully capture the variability in PK and PD related to developmental changes.
- Clinical studies in pediatric patients are challenging and limited due to ethical and logistic constraints.
- Off-label use more the rule rather than the exception.
- Development of dosing recommendations:
  - Scaling from adult information
  - Preclinical information
  - Empirical: Anecdotal evidence/personal experience
Central Paradigm of Clinical Pharmacology

Dose → Concentration → Efficacy, Toxicity

Pharmacokinetics: Concentration → AUC
Pharmacodynamics: Effect (%)

Determinants of Drug Response in Children

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Low sensitivity</th>
<th>Medium sensitivity</th>
<th>High sensitivity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low exposure</td>
<td>No efficacy</td>
<td>No toxicity</td>
<td>Therapeutic efficacy</td>
</tr>
<tr>
<td>Medium exposure</td>
<td>No efficacy</td>
<td>Therapeutic efficacy</td>
<td>No toxicity</td>
</tr>
<tr>
<td>High exposure</td>
<td>Therapeutic efficacy</td>
<td>Therapeutic efficacy</td>
<td>No toxicity</td>
</tr>
</tbody>
</table>

Läer, Barrett, Meibohm, J Clin Pharmacol 2009, 49, 889-904
Pediatric Study Decision Tree (FDA)

Reasonable to assume (pediatrics vs adults)
- Similar disease progression?
- Similar response to intervention?

NO → YES TO BOTH
- Conduct PK studies
- Conduct safety/efficacy trials

Reasonable to assume similar concentration-response (C-R) in pediatrics and adults?

NO → NO
- Is there a PD measurement that can be used to predict efficacy?

YES
- Conduct PK/PD studies to get C-R for PD measurement
- Conduct PK studies to achieve target concentrations based on C-R
- Conduct safety trials

Meibohm et al., AAPS J 2005, 7, 475-87

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The Three Pillars of Science

Therapeutic problem

Hypothesis

Optimal drug response

Modelling & simulation

Clinical experiment

Läer, Barrett, Meibohm, J Clin Pharmacol 2009, 49, 889-904

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Modeling & Simulation

Modeling

- Models are simplified descriptions of certain aspects of reality by mathematical means, thereby allowing to concentrate on the factors believed to be important
- Summarizing measured data by integrating different measures and prior knowledge about biological processes
- Identify the best model that sufficiently describes the data (Rule of Parsimony: simplest model)
- Purpose-driven: Level of model complexity defined by its intended use

Simulation

- Modeling is a prerequisite for simulations: Application of the developed model
- Predictions beyond the measured data: inter- or extrapolations
- Validity of simulations depends on model (and the purpose is was developed for)
- Prediction error and uncertainty

Simulation Approaches

Deterministic vs. Stochastic

Deterministic

- "Best guess" parameter point estimates used for simulation
- One discrete outcome of simulation
  - E.g. a discrete drug concentration vs. time profile
- Parameters may be dependent on covariates
- Pro: Simplicity; ease of understanding
- Con: No uncertainty in parameter estimates considered

Stochastic (Monte-Carlo Simulations)

- Distributions for each specific parameter that capture the degree of uncertainty
  - Repeated random sampling of parameters from these distributions to simulate the outcome based on the underlying structural model.
- Distribution of outcomes with central tendency and spread
- Pro: provides inherently a measure of credibility and likelihood for simulation outcomes
- Con: increased complexity and thus difficult understanding and acceptance
**Simulation Approaches**

**Deterministic vs. Stochastic**

- **Discrete Concentration-Time Profile**
- **Probability Distribution of Concentration-Time Profiles**

**Top Down Approaches**

**Deductive or Analytic Approaches**

- Based on generalized concepts in medical sciences
  - Verification-driven data mining process
  - Allows expression of preconceived facts or theories in model terms
  - Testing their validity within the context of the model system and the available data
  - Identify reasons for the validation or invalidation
  - Constant rebuilding and refinement of the model given the results of the continuous hypothesis testing
  - Only limited assumptions necessary

- Data-driven process, in which the model is iteratively refined to optimally describe observed data
Top Down Approaches

Deductive Reasoning

Dataset

Theory

Hypothesis testing

Model refinement

Confirmation

Vancomycin

Clinical Issues in Pediatrics

- **Current dosing guidelines**
  - Different dosing regimens are proposed for vancomycin in pediatrics over last several years
    - One standard dose for all neonates (DR1)
    - PMA based dosing (DR2)
    - PMA and PNA based dosing (DR3)
    - Serum creatinine based dosing (DR4)
  - No consensus among clinicians on the use of any standard vancomycin dosing regimen in term and preterm neonates
    - Comparative evaluation in clinical trial hampered by logistic and ethical constraints
  - Initial dosing frequently followed by *a posteriori* individualization based on Sawchuk-Zaske method or Bayesian forecasting
  - Comparative clinical study nearly impossible due to logistic and ethical constraints of studies in neonates

- **Objectives**
  - To evaluate the four standard dosing regimens in silico for their ability to achieve target vancomycin concentrations
Step 1: PopPK Analysis

Establish pharmacostatistic vancomycin disposition model based on local population

- Retrospective, non-interventional clinical study
  - LeBonheur Children's Medical Center, Memphis, TN
- Inclusion criteria:
  - Full term and premature neonates with PMA ≤ 44 wks
  - At least one vanc serum concentration level
  - Documented vanc dose, dosing schedule, and time of blood draw
- Exclusion criteria:
  - Concurrent nephrotoxic drugs (i.e., amphotericin B, cisplatin)
  - Extracorporeal membrane oxygenation or hemodialysis
- Covariates tested:
  - Gestational age (GA), postnatal age (PNA), postmentrual age (PMA), weight, serum creatinine, blood urea nitrogen, and urine output.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Model</th>
<th>Estimate (%RSE)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CL (L/hr)</td>
<td>θ₁(WT/2.5)^0.75*(SCR/0.42)⁰.⁶³*(PMA/37)⁰.⁶³</td>
<td>0.18 (3.5)</td>
</tr>
<tr>
<td></td>
<td>θ₂</td>
<td>0.7 (9.0)</td>
</tr>
<tr>
<td></td>
<td>θ₃</td>
<td>1.41 (15.4)</td>
</tr>
<tr>
<td>V (L)</td>
<td>θ₁(WT/2.5)</td>
<td>1.7 (7.3)</td>
</tr>
</tbody>
</table>

BSV CL: Between subject variability in Clearance

BSV V: Between subject variability in Volume

Residual error:

- Proportional: 16.4% (36.7%)
- Additive: 1.5 µg/ml (37.5%)

- Parameters allometrically scaled for weight using exponent of ⅔ for CL and 1 for Vd
- SCR and PMA explained 53% of the BSV in CL
Step 2: Simulations of DRs

- Monte-Carlo simulations based on PopPK model
  - Each dosing regimen was treated as a different scenario having
    - 200 replicates per scenarios
    - 100 subjects per replicate
  - Multivariate age-weight distributions
    - Term Neonates: CDC growth charts
    - Preterm neonates: intra-uterine and postnatal growth charts
  - Covariance between PNA and SCR based on original dataset

- Outcome metrics
  - Trough concentrations 0.5 hr prior to next dose
  - Percentage of subjects having trough concentration between 5-15 µg/ml

Multivariate Covariate Distribution

Physiologically reasonable covariate vectors

- Premature: GA 20-34 wks
  - PNA<7d
  - 10th percentile of IUG as mean
  - Intrauterine growth charts

- Transitional: GA 35-38 wks
  - PNA<7d
  - 10th percentile of IUG as mean
  - Intrauterine growth charts

- Term: GA 39-42 wks
  - PNA<7d
  - CDC growth charts 2000

Alexander et al., 'A United States reference for fetal growth', Obstetrics & Gynecology 1996, 87, 163-8
Virtual Patient Population

In silico Comparison of DRs

Box plot for dosing regimens (DR-1 to DR-4) stratified based on gestational age
Bottom Up Approaches

Inductive or Synthetic Approaches

- Synthesize individual pieces of information to form broader generalizations and theories
  - Observations
  - Data
  - Patterns

- Individual elements are linked together to form larger subsystems based on **Systems Biology**
  - Subsystems are linked via many levels to form a complete top-level model
  - Assumption-rich approach
  - Hypotheses are driven by observed patterns and interdependencies
  - Predictions possible without experimental (clinical) data

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**Bottom Up Approaches**

**Inductive Reasoning**

- Data - Observations - Patterns
- Subsystems
- Hypothesis testing
- Theory
- Confirmation

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Bottom Up Approaches

Example: Physiologic PK Modeling

Integration of information from multiple sources

- Types of data:
  - Anatomical & Physiological
  - Pathophysiological
  - Drug-specific
  - Molecular
- Relevant organ & tissue function individually considered
- Based on 'typical' parameters for specific subpopulation
- Uncertainty may be implemented

Kuepfer, Mol Syst Biol 2010, 6, 409
Rowland et al., Annu Rev Pharmacol Toxicol 2011, 51, 45-73

Developmental Changes in Physiologic Factors Affecting Drug Disposition

Ontogeny of Hepatic DME (I)

**CYP2C**

Koukouritaki et al., J Pharmacol Exp Ther 2004, 308:965-74

Ontogeny of Hepatic DME (II)

**Hepatic Phase I & Phase II Enzymes**


Strassburg et al., Gut 2002, 50, 259-62
Ontogeny of Hepatic DME (III)

Modeling of Developmental Trajectories


Example: CYP2E1 & Toluene Clearance

CYP2E1 content vs. age

Toluene intrinsic clearance vs. age

Toluene hepatic clearance vs. CYP2E1

Nong et al., Toxicol Appl Pharmacol 2006, 214, 78-87
**The In Silico Child**

**Dual Direction Up & Down Approach**

- **Top Down Approaches**
- **Bottom Up Approaches**

**Dosing Recommendations & Dosage Individualization**

- Usually not sufficient data available to describe full bottom up model system
  - Dependence on assumptions with associated uncertainty
- Incorporation of bottom up subsystem components in top down methodology to explain residual variability
  - Multi-scale models based on systems biology
- Combination of both methodologies is the most promising approach to give birth to the *In Silico Child*
Example #1

Inhalational Anthrax in Children

Levofloxacin therapy

- Rare bacterial infection with *B. anthracis*
  - Inhaled spores germinate in lower respiratory tract, leading to toxin-mediated necrotizing pneumonia with respiratory failure and death
  - Bioterrorism threat
  - Efficacy studies not feasible

- Fluoroquinolones as empirical therapy
  - Despite usually limited use in children due to lesions in the cartilage of juvenile animals
  - Potentially life-saving treatment outweighs risks

- Development of an optimized pediatric dosing regimen for children from 6 months to 17 years
  - Based on exposure in animal experiments that prevents progression of pulmonary anthrax after inhalation exposure
  - Extrapolating adult data to children
    - No difference in C-R relationship
    - Beneficial and adverse drug effects similar between children and adults
    - Only adjustment for PK differences

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Inhalational Anthrax in Children

Levofoxacin Population Pharmacokinetics

- PK characteristics
  - Linear PK
  - 99% oral bioavailability
  - Renal excretion as major elimination pathway (fe = .87)

- Development pharmacology
  - Disposition as function of body size
  - Maturation of renal function within first 2-3 yrs

- Available PK data
  - 90 pediatric patients (7 mg/kg) and 47 healthy adults (500 or 750 mg)

  $CL \sim BW^{0.43} \times \left(\frac{\text{Age}}{[\text{Age}+A_50]}\right); \quad A_50=0.34 \text{ yr}$
  - Allometrically weight-adjusted clearance with maturation function for renal elimination
  - Renal function maturation: 60% for 6-month old; 75% for 1-yr old
  - Strictly limited to lower age range of 6 months

  $V \sim BW$

33 Li et al., Antimicrob Agents Chemother 2010, 54, 375-9 © Bernd Meibohm, PhD, FCP, University of Tennessee

Inhalational Anthrax in Children

Maturation of Renal Excretion Function

Creatinine Clearance vs. Postnatal Age

Estimated based on Levofoxacin PopPK Analysis

Holliday et al., Pediatric Nephrology, Williams & Wilkins 1994

Li et al., Antimicrob Agents Chemother 2010, 54, 375-9 © Bernd Meibohm, PhD, FCP, University of Tennessee
Inhalational Anthrax in Children

Pediatric Dosing Recommendations

- **Simulation of exposures**
  - To match adult exposures for 500 mg QD with $AUC_{24}$, $C_{\text{ss,max}}$, $C_{\text{ss,min}}$
  - 15 mg/kg QD in children matches adult 500 mg QD
  - $C_{\text{max,ss}}$ exceeds adult values: 7.5 mg/kg BID dosing
  - For children >50 kg: 500 mg QD (adult dose)

<table>
<thead>
<tr>
<th>Age</th>
<th>PK parameter</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$AUC_{24}$ (mg.h/ml)</td>
<td>$C_{\text{max,ss}}$ (µg/ml)</td>
</tr>
<tr>
<td>6 mo to &lt; 2 yr</td>
<td>51.7 (26.8–75)</td>
<td>5.6 (3.2–7.3)</td>
</tr>
<tr>
<td>2 to &lt;5 yr</td>
<td>50.4 (41.7–65.2)</td>
<td>5.4 (4.2–6.6)</td>
</tr>
<tr>
<td>5 to &lt;10 yr</td>
<td>55.6 (46.9–83.3)</td>
<td>5.4 (3.7–7.1)</td>
</tr>
<tr>
<td>10 to 18 yr</td>
<td>55.7 (42.0–83.5)</td>
<td>6.3 (4.6–8.1)</td>
</tr>
<tr>
<td>Adult</td>
<td>47.7 (41.8–55.1)</td>
<td>5.5 (5.0–6.8)</td>
</tr>
</tbody>
</table>

* Data are presented as the median (10th percentile to 90th percentile). The dosage regimen was 7.5 mg/kg b.i.d (not exceeding 250 mg/dose), 500 mg q.d. for children more than 50 kg

- **Final recommendation**
  - 8 mg/kg BID (500 mg QD for children >50 kg)

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Example #2

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Sotalol in Pediatric Supraventricular Tachycardia

Sotalol Plasma Concentrations in a 5 month-old (5.5 mg/kg; open circles; 7.8 mg/kg; closed circles) and a 26 yr-old Patient (2 mg/kg)

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Sotalol in Pediatric Patients

Pharmacokinetic Properties

- BCS class 1 (hydrophilic; secondary amine)
- Oral bioavailability 90-100%
- Linear PK
- No plasma protein binding
- Elimination
  - Terminal half-life: ~12 hr (adults)
  - 80-90% renal excretion in unchanged form
  - Essentially no metabolism
  - Renal CL > GFR (~1.5 x) and reduced by cimetidine coadministration

Study Population

<table>
<thead>
<tr>
<th></th>
<th>N (%)</th>
<th>Mean (SD)</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [yrs]</td>
<td>82</td>
<td>3.0 (4.2)</td>
<td>0.03 - 13.7</td>
</tr>
<tr>
<td>Newborns</td>
<td>14 (17)</td>
<td>0.050 (0.015)</td>
<td>0.03 - 0.07</td>
</tr>
<tr>
<td>Infants</td>
<td>38 (46)</td>
<td>0.53 (0.43)</td>
<td>0.09 - 1.7</td>
</tr>
<tr>
<td>Children</td>
<td>30 (37)</td>
<td>7.6 (3.7)</td>
<td>2.1 - 13.7</td>
</tr>
<tr>
<td>Sex (male)</td>
<td>51 (62)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>14.3 (15.8)</td>
<td></td>
<td>2.2 - 84.3</td>
</tr>
<tr>
<td>Height [cm]</td>
<td>84 (36)</td>
<td></td>
<td>35 - 178</td>
</tr>
<tr>
<td>BSA [m²]</td>
<td>0.55 (0.41)</td>
<td></td>
<td>0.17 - 2.04</td>
</tr>
<tr>
<td>SCr [mg/dL]</td>
<td>0.44 (0.15)</td>
<td></td>
<td>0.2 - 1.0</td>
</tr>
<tr>
<td>GFR [mL/min]</td>
<td>42.8 (45.6)</td>
<td></td>
<td>3.1 - 232</td>
</tr>
<tr>
<td>NGFR [mL/min/1.73m²]</td>
<td>103 (45.5)</td>
<td></td>
<td>31.5 - 217</td>
</tr>
</tbody>
</table>

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**Sotalol in Pediatric Patients**

- **Age-Specific Pharmacokinetics**
  - \( CL \sim BW^{0.75} \times (1+S \times Age^{0.142}) \); \( S=1 \) for Age <1 yr; else \( S=0 \)
    Allometrically weight-adjusted oral clearance is reduced within the first months of life, probably due to maturation of renal elimination processes, including glomerular filtration and transporter-mediated active tubular secretion.
  - \( V \sim BW \times (1+S \times Age^{-0.101}) \); \( S=1 \) for Age <1 yr; else \( S=0 \)
    Weight-adjusted volume of distribution is increased for the first months of life, probably due to higher percentage of total and extracellular body water at early age.

- **Age-Specific Pharmacodynamics**
  - \( \Delta QTc \sim 1+S \times Age^{-0.296} \); \( S=1 \) for Age <1 yr; else \( S=0 \)
    Increase in QTc per unit drug concentration is higher in young compared to older pediatric patients.

Laer et al., *J Am Coll Cardiol* 2005, 46, 1322-30

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**Sotalol - Pharmacodynamics**

*Age-dependent \( \Delta QTc \)*

- Independent of methodology for heart rate correction of QT interval

Laer et al., *J Am Coll Cardiol* 2005, 46, 1322-30

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**Sotalol – Pediatric C/R**

EC$_{50}$: ~0.45 µg/mL  
EC$_{95}$: ~1.00 µg/mL  
Filled circles = neonates

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**Age-Specific Pediatric Dosage Recommendations**

Based on Exposure-Response Relationship

<table>
<thead>
<tr>
<th>Group</th>
<th>(Start/Target) (mg/kg/day)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonates</td>
<td>2/4</td>
</tr>
<tr>
<td>Infants &lt;6 months</td>
<td>3/5</td>
</tr>
<tr>
<td>Infants &lt;2 yrs</td>
<td>3/6</td>
</tr>
<tr>
<td>Children &lt;6 yrs</td>
<td>3/5</td>
</tr>
<tr>
<td>Children &gt;6 yrs</td>
<td>2/3</td>
</tr>
</tbody>
</table>

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Läer et al., J Am Coll Cardiol 2005, 46, 1322-30

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Läer et al., J Am Coll Cardiol 2005, 46, 1322-30
The Future

The In Silico Child in Drug Development & Clinical Practice

- Integrated M&S using all available sources of information
  - Molecular & Mechanistic Information
  - Anatomy, Physiology and Pathophysiology
  - Ontogeny
  - Clinical observations and their between-subject variability
  - Historic data
  - Comparator compounds
  - Class effects
  - Species & subpopulations

Methodologies
- Bottom up & Top Down
- Bayesian priors
- Individual vs. population
- Monte Carlo simulations as core
- Easy user interface for widespread acceptance
- Education, education, education...

The In Silico Child: Using Simulation to Guide Pediatric Drug Development and Manage Pediatric Pharmacotherapy

Stephanie Lier, MD, PhD, Jeffrey S. Barrett, PhD, FCP, and Bernd Meibohm, PhD, FCP