GOLDILOKs: Can Precision Therapeutics for Children Become a Reality

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Disclosures

- I have no relevant financial relationships with the manufacturers (Eli Lilly) of any commercial products (Strattera) and/or provider of commercial services discussed in this CME activity.
- The use of dextromethorphan as a phenotyping probe to estimate cytochrome P450 2D6 (CYP2D6) activity is not an approved use of the drug.
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  - CYP2D6 Genotyping: Andrea Gaedigk, PhD
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  - PK Simulations: Jenny Sager and Nina Isoherranen, PhD (U Wash)
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Challenges and Approaches to Precision Therapeutics in Children: Objectives

1. **Challenge:** Introduce ontogeny and genetic variation as two primary sources of inter-individual variability in drug disposition and response in children (warfarin as an illustrative example)

2. **Approach:** Describe the "GOLDILOKs" initiative, and its focus on the concept of "drug exposure" as the key to addressing variability in drug response

3. Present atomoxetine (Strattera®) for ADHD as a prototype project for implementing precision therapeutics in children

Ontogeny and Genetic Variation: Warfarin as a Case Study

In pediatric patients, age has more impact on dosing of vitamin K antagonists than VKORC1 or CYP2C9 genotypes

<table>
<thead>
<tr>
<th>FACTOR</th>
<th>Adult</th>
<th>N-G</th>
<th>Biss</th>
<th>Moreau</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKORC1</td>
<td>28.3%</td>
<td>2.8%</td>
<td>26.6%</td>
<td>18.2%</td>
</tr>
<tr>
<td>CYP2C9</td>
<td>11.8%</td>
<td>0.5%</td>
<td>12.8%</td>
<td>2.0%</td>
</tr>
<tr>
<td>CYP4F2</td>
<td>1.1%</td>
<td>-</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Age</td>
<td>15.0%</td>
<td>31.2%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Sex</td>
<td>1.2%</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Height</td>
<td>-</td>
<td>29.8%</td>
<td>48.1%</td>
<td>-</td>
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<td>Indication</td>
<td>-</td>
<td>3.2%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Target INR</td>
<td>-</td>
<td>-</td>
<td>4.4%</td>
<td>-</td>
</tr>
</tbody>
</table>

TOTAL Genetic 40.1% 3.3% 38.4% 20.2%
Sub-Group Analysis: Fontan Patients

- Fontan procedure: A palliative surgical procedure used when infants have a single effective ventricle, such as hypoplastic left heart syndrome.
- Lower target INR.
- Total genetic contribution ~63%; not influenced by “developmental” factor.

Sub-Group Analysis: Non-Fontan Patients

- Non-Fontan patients largely various thromboembolic disorders.
- Higher target INR.
- Total genetic contribution 5.3% (age) to 14.3% (weight).

Implication of the Warfarin Case Study for Precision Therapeutics in Children

1. We often include all children receiving the drug of interest in studies to ensure “adequate power.”
2. The Dose → Exposure → Response relationship may not be the same for different pediatric indications (e.g., post Fontan surgery vs thromboembolic conditions).
3. Inclusion of all patients receiving the medication of interest may obscure real associations.
4. Focus on “dose” and “response” (INR) ignores contribution of variability in exposure; “exposure” is more proximal to therapeutic response than “dose.”
GOLDILOKs Concept
Targeting the Drug Exposure→Response Relationship

Finding the Dose That is “Just Right” for Pediatric Patients

- Genomic- and Ontogeny-Linked Dose Individualization and Clinical Optimization for Kids
- “Not too big, not too small … the dose of medication that is ‘just right’ for your child”
- Takes into consideration those factors that make each child unique
  - Genome
  - Stage of development (ontogeny)
- “Response → Exposure → Dose” paradigm
- Focus on the individual’s drug target genotype, determine the right exposure for that genotype, and the dose required to achieve the target exposure

Concentration (Exposure)-Response Relationship (Basics)

Different drug concentrations (exposures) give rise to different responses
Genetic Variability in Drug Target Contributes to Variability in Response

The same drug concentration (exposure) results in different responses, depending on drug target genotype.

Dosing to a common "therapeutic range" results in different ranges of responses in patients with different drug target genotypes.

… But What If Recommended Dosing Guidelines Result in a 10-Fold Range of Exposures

Impossible to characterize the contribution of genetic variation in drug target to variability in response ... unless there is a means of controlling the exposure.
GOLDILOKs Prototype
Atomoxetine and Cytochrome P450 2D6 (CYP2D6) Pharmacogenetics

Proof-of-Principle Project
Atomoxetine and CYP2D6 Pharmacogenetics

- A selective norepinephrine reuptake inhibitor
- Commonly utilized as non-stimulant alternative to amphetamines or methylphenidate in pediatric attention-deficit/hyperactivity disorder (ADHD)
- Considered second line agent; third-line behind clonidine and guanfacine by some
- Preferred (locally) to stimulants; perception that it "doesn't work"

Atomoxetine Dosing Guidance
(Product Monograph)

5.12 Laboratory Tests
Routine laboratory tests are not required.

CYP2D6 interaction - Atomoxetine metabolism has been shown to be affected by the CYP2D6 genotype. Individuals with CYP2D6 activity (i.e., rapid, extensive, intermediate, and poor metabolizers) can have potentially higher AUC (area under the curve) and a 3-fold higher peak concentration to a given dose of STRATTERA compared with extensive metabolizers (EM). Approximately 7% of the white population are PMs, laboratory tests are needed to identify CYP2D6 PMs. For CYP2D6 PMs on atomoxetine, the maximum dose should be limited to 40 mg daily. The use of atomoxetine in CYP2D6 PMs as an initial therapy is not recommended.

5.14 Concomitant use of other CYP2D6 inhibitors or inhibitors known to be CYP2D6 PMs: Atomoxetine is primarily metabolized by the CYP2D6 pathway to 4-hydroxyatomoxetine. Dosage adjustment of STRATTERA may be necessary when concomitantly administered with potent CYP2D6 inhibitors (e.g., paroxetine, fluoxetine, and quinidine) or when administered to CYP2D6 PMs. (See Management of Atomoxetine (4.5) and Drug Interactions (7.3))
2.4 Dosing in Specific Populations:

This dosing strategy is not consistent with individualization ...

**GOLDILOKs: CYP2D6 Pharmacogenomics**

Translating Genotype to Phenotype

<table>
<thead>
<tr>
<th>Activity Score (AS)</th>
<th>Allele 1</th>
<th>Allele 2</th>
<th>Examples of Alleles</th>
<th>Phenotypes Assignment</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.5</td>
<td>Null</td>
<td>Reduced</td>
<td><em>5</em>/<em>5</em>, <em>5</em>/<em>4</em></td>
<td>PM</td>
</tr>
<tr>
<td>1</td>
<td>Null</td>
<td>Functional Reduced</td>
<td><em>4</em>/<em>4</em>, <em>4</em>/<em>3</em></td>
<td>EM</td>
</tr>
<tr>
<td>1.5</td>
<td>Reduced</td>
<td>Functional</td>
<td><em>4</em>/<em>2</em>, <em>2</em>/<em>2</em></td>
<td>EM</td>
</tr>
<tr>
<td>2</td>
<td>Functional</td>
<td>Functional</td>
<td><em>2</em>/<em>2</em>, <em>2</em>/<em>1</em></td>
<td>EM</td>
</tr>
<tr>
<td>&gt;3</td>
<td>Functional</td>
<td>Overactive (Functional AS)</td>
<td><em>2</em>/<em>2</em>, <em>2</em>/<em>1</em></td>
<td>EM</td>
</tr>
</tbody>
</table>

GOLDILOks: Ontogeny of CYP2D6 During Adolescence

- 3-year longitudinal study; age 7-15 years at start
- Phenotype assessment every 6 months
- Weight, height, BMI, Tanner stage and concurrent medications recorded at each visit
- 0.5 mg/kg dextromethorphan orally after overnight fast; dose subsequently reduced to 0.3 mg/kg
- Four hour urine collection

GOLDILOks: CYP2D6 Genotype-Phenotype Concordance

Oral presentation ISSX 2014; manuscript in preparation

Modest Effect of Age on CYP2D6 Activity

Manuscript in preparation
**CYP2D6 Genotype-Stratified Pharmacokinetic Study**

- Previous participants (n=23) of the longitudinal CYP2D6 phenotyping study during adolescence
- Primary diagnosis of ADHD
- Selected to participate based on CYP2D6 genotype
  - 2 (or more) functional alleles (n=8 “EM”)
  - 1 functional allele (n=8 “IM”)
  - 0 functional alleles (n=4 “PM”)
- Additional three subjects with Activity Scores of 0.5
- Plasma sampling at 0, 0.5, 1, 2, 4, 6, 8, 12, 16, 20, and 24 hr; additional samples at 48 and 72 hr for PMs
- Analysis for atomoxetine and metabolites in plasma and urine

Brown et al., Poster Presentation ASCPT 2015; manuscript in preparation

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**Effect of CYP2D6 Genotype on Atomoxetine Exposure (AUC) Following 0.5 mg/kg Dose**

- Mean AUC differs 14.2-fold between PM and EM2 groups
- 11.4-fold difference in PM and EM2 mean AUCs when corrected for dose
- 50-fold absolute range in AUC values
- 25.8-fold when corrected for dose

Brown et al., Clin Pharmacol Ther (in press)

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**Consequences of Observed Variability in Atomoxetine Dose-Exposure Relationship**

Brown et al., Clin Pharmacol Ther (in press)
Summary of ATX Data and Implications for Precision Therapeutics

- The range of systemic exposures within a population exceeds the cited 10-fold difference in means in the product monograph
- Current dosing guidelines are a compromise, and one consequence is inadequate exposure in some EM2s
- For PMs, additional biotransformation pathways must be considered: 2-methyl hydroxylation (CYP2B6) and non-CYP2D6-mediated 4-hydroxylation (CYP2E1; CYP2J2)
- For non-PMs, address factors regulating level of CYP2D6
  - Genetic: long range regulatory SNPs
  - Physiologic: retinoic acid (?)
  - Endogenous biomarkers

“The difficulty lies not so much in developing new ideas as in escaping from old ones” - John Maynard Keynes

- From a pediatric perspective, the current strategy is to find the dose that, on average, produces exposures similar to adults (and presumably the desired therapeutic response)
- Clinically, individual children are not small average adults
- Challenge is to find the dose that provides the right exposure for an individual child
- ... But what is the right exposure? For whom?
- Focus on variability in drug target: Stratify by drug target genotype and individualize dosing to achieve the same exposure to assess exposure-response relationship

Reframing the Question to Implement Precision Therapeutics

- Move beyond Dose→Exposure relationship to focus on Exposure→Response relationship
- Reframe challenge as an “aggregation of individuals” as opposed to a “population” approach
- Determine exposure required to increase probability of clinical response, given patient’s drug target genotype
- Use knowledge of ADME ontogeny and genetic variation to individualize dose to achieve the target exposure
- Develop bottom-up approaches to better inform the design of initial Dose→Exposure studies
Different Drug Exposures Required to Achieve Equivalent Drug Response

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Concept of “Aggregation of Individuals” and “Nearest Neighbor” to Inform Dosing

- Weight
- Age
- PM
- EM1
- EM2
- Size=AUC

- Variable differences in drug metabolism.
- Different drug exposures are needed to achieve equivalent clinical responses.
- Individualizing drug dosing based on patient-specific genetic and metabolic traits.

- Use of precision medicine principles to tailor drug dosing.
- Importance of understanding ADME (Absorption, Distribution, Metabolism, Excretion) in personalized therapy.
- Incorporating genetic variation and pharmacodynamic responses to optimize therapeutic outcomes.

- Visual representation of drug response variability across different patient subgroups.
- Identification of critical biomarkers for predicting drug response.
- Development of algorithms to predict and optimize individual drug dosing.
GOLDILOKs Concept Has Broad Application

- Several other CYP2D6 substrates used in pediatrics (risperidone, fluoxetine, clonidine, pimozide, flecainide, quetiapine …)
- Non-invasive phenotyping of the histaminergic component of asthma; Bridgette Jones, MD, MSCR
- Predicting response to methotrexate in JIA; Mara Becker, MD, MSE
- Effect of obesity on the CYP2C19 genotype-phenotype association for PPI metabolism and clearance, Tina Shakhnovich, MD
- Effect of SLCO1B1 genotype on the dose-exposure relationship for statins in dyslipidemic children; Jon Wagner, DO
- Biomarkers to predict hypersensitivity reactions to Bactrim; Jennifer Goldman, MD, MSCR
- Determinants of risk for neonatal abstinence syndrome, variability in response to NSAIDs in PDA; Tamorah Lewis, MD, PhD
- Busulfan decision-support tool for Bone Marrow Transplant team

Precision Therapeutics:
Individual Children Are Not Small Average Adults

- Ultimate, individualizing drug therapy must involve investigating variability in drug response at the target of drug action
- Individualizing “Dose” is the end result of a process that begins at the drug target, and progresses through consideration of the “right exposure”, given an individual’s drug target genotype, and then the “right dose” to achieve the desired exposure
- Also must consider additional factors that impact the Response-Exposure-Dose relationship, such as sex, stage of development, disease phenotype, diet, concurrent medications, etc

Complex Problems, Multidisciplinary Teams

Pharmacogenetics:
Andrea Gaedigk, PhD
Roger Gaedigk, PhD
In Vitro/Vivo Phenotyping:
Robin Pearson, PhD
Gene Regulation:
Carrie Vyhlidal, PhD
Analytical chemistry:
Leon van Haandel, PhD
Quantitative pharmacology:
Susan Abdel-Rahman, PharmD
Brett Malzuka, PhD

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