Pediatric Drug Development
Current Challenges

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Disclosures

- I consult to Shire Genetics, Johnson & Johnson, Gilead, and ICON, but none of their products will be discussed in this presentation.

- I am not discussing treatment per se, but any drugs discussed that are used to treat newborns WILL be off-label, which is the essence of the challenge.
Good Morning! Welcome from Utah

Delicate Arch at Arches NP
Challenges in Pediatric Drug Development

The Child is Not Just a Small Adult
The Newborn is Not Just a Small Child

What does that really mean for drug development?

Cliché vs Truism vs Essence of the Challenge
Challenges in Pediatric Drug Development

- Few Pediatric Study Sites
- Adult Protocols Don’t Fit
- Endpoints Lack Validation
- Limited Academic Credit
- Few Pediatric Pharmacometricians
- Development: Renal Function
- Pain, Distress: Non-Verbal Patients
- Newborns Left Out
- Developmental Drug Metabolism
- Non-pediatric Regulators
Clinical outcome assessments (COAs) measure a patient’s symptoms, overall mental state, or the effects of a disease or condition on how the patient functions.

Pediatric patients present unique and sizable challenges to determine COAs.

Four types of COAs:

1. Patient-reported outcome (PRO) measures
2. Clinician-reported outcome (ClinRO) measures
3. Observer-reported outcome (ObsRO) measures
4. Performance outcome (PerfO) measures
BIOMARKERS

**Definition:** A defined characteristic that is measured as an indicator of normal biological processes, pathogenic processes, or responses to an exposure or intervention, including therapeutic interventions

*Updated definition from the BEST glossary*

A biomarker is not an assessment of how an individual feels, functions, or survives

**Types:** Molecular, histologic, radiographic, or physiologic characteristics

**Examples:** Serum creatinine, C-reactive protein, HIV viral load, *BRCA1* mutations, blood pressure, tumor volume by imaging

FEW BIOMARKERS ARE VALIDATED FOR PEDIATRIC PATIENTS (bp)
Sites for Pediatric Study: A Challenge

- Limited sites with trained coordinators, investigators causes slow enrollment and higher costs
  - Pediatric studies take roughly twice as long to enroll as adult studies
  - Increasing emphasis on long term (1-5 years) follow-up
- Limited academic recognition of importance of sponsored trials of new medication.
  - Most complex and sick pediatric patients receive care at academic institutions where promotion and tenure may not acknowledge sponsored, clinical studies
Challenges in Pediatric Drug Development
Vulnerable Populations

- Office of Healthcare Research Protections
  - Special protections for Children in Subpart D, §401-409
  - Special protections as a vulnerable population
  - Can not consent for participation in clinical trials
  - Parents must give permission for their child’s participation
  - Minimal risk without prospect of direct benefit
  - More than minimal risk if the information benefits a large population or if there is a prospect for direct benefit
Increasing Survival of Prematures 1981-2000
University of Utah Tertiary NICU

Weeks Gestation at Birth

%
Challenge for the Future:
470 gm, 22 5/7 wk EGA twin A
Pharmacokinetic Study Challenges

- Development, development, development
  - Nonlinear changes in drug metabolism & renal excretion
  - Differences in rates of change in drug metabolism among different enzymes.
  - Rapid changes in clearance
  - Blood volume of 90 ml/kg can be 45 ml (500 gm)
    - IRB limits research to 3-4 ml/kg
    - Safety laboratory studies (LFT, renal function, hematology) 1.5-1.8 ml, leaves 1-3 pk samples (population pK is essential)

- Pharmacometrician must understand pediatric physiology
  - Serum creatinine reflects maternal Cr for several days after birth
Procedural Pain: Frequency in Newborns

**Porter & Anand, 1998**
- 144 neonates: 7,672 procedures
- 53 procedures / patient, 87% heelsticks
- 3% procedures preceded by analgesia

**Simons, Tibboel, et al., 2003**
- N = 151 neonates over 14 days
- Total 19,674 procedures, 31% repeats
- 196 / patient, 63% suctioning
- VAS scores for moderate / severe pain
- <35% procedures preceded by analgesia

**Barker & Rutter, 1995**

The graph shows number of invasive procedures vs gestational age.
Relative Contribution to Drug Metabolism

Phase I Enzymes

- CYP3A4/5/7
- CYP2C19
- CYP2C9
- CYP2D6
- CYP2E1
- esterases
- ADH
- ALDH
- CYP2B6
- CYP2C8

Phase II Enzymes

- UGTs
- NAT1
- NAT2
- GST-M
- GST-T
- GST-P
- GST-A
- TPMT
- HMT
- COMV
- ST

Adapted from Evans & Relling, Science 1999
Cytochrome P450 3A7 (Fetal Form) To CYP 3A4 (Adult Form)

Redrawn from LaCroix et al: Eur J Biochem 1997;147:625
Maturational Patterns of CYP’s During Childhood

Developmental Change in Glomerular Filtration Rate (GFR)

Redrawn from: Engle WD, Arant BS, Jr: Kidney Int 1983;24:360
GFR in Infants

Guignard, J Pediatr 1975;87:268
Renal Tubular Transport
Beta 2 Microglobulin Excretion

- Beta 2 microglobulin – MW 11,800
- Filtered and reabsorbed in proximal tubules by endocytosis
- Transported to lysosomes and degraded
- Intact protein is not recycled
- Closely resembles gentamicin tubular processing
Maturation of Tubular Protein Transport In 32-34 Wk and 39-41 Wk Newborns

Conjugating enzymes vary dramatically in developmental maturation

Uridine Di-P glucuronosyltransferases (UGT’s) (n=>15)
- UGT 1A1 conjugates bilirubin; usually absent in fetus (unless induced by exposure to opioids or barbiturates) & then increases after birth,
- UGT 2B7 conjugates morphine; increases after birth

Sulfation, more mature at birth, may compensate for reduced glucuronidation, such as acetaminophen
Age-Related Acetaminophen Conjugation Glucuronidation vs Sulfatation

Morphine Metabolism to Activate & Inhibit

- Morphine undergoes extensive hepatic glucuronidation on 3, 6-OH sites
  - Morphine 6-glucuronide twice as potent an analgesic as morphine
  - Morphine 3-glucuronide is excitatory and may inhibit antagonize M6G analgesia
- Elimination is primarily by glomerular filtration of the glucuronides
- Reduced renal function prolongs its half-life with accumulation of M6G
Morphine Kinetics by PC Age (wk)
UGT Conjugation, Renal Excretion

J Pediatr 1999;135:423
Increasing Morphine Glucuronidation Can Become a Problem

Little opioid Activity

Anti-analgesia, dysphoria 10-fold more than M6G

Twice as potent As Morphine
Protein Binding & Interpretation of Total Drug Concentrations in Newborns

- Cord blood plasma binding of theophylline in full term newborns was compared to adults at a total plasma [theophylline] = 17 µg/ml

<table>
<thead>
<tr>
<th>Protein Binding</th>
<th>Free [Theo] (µg/ml)</th>
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<tbody>
<tr>
<td>Adult:</td>
<td>56.4±3.8%</td>
</tr>
<tr>
<td>Term NB:</td>
<td>36.4±3.8%</td>
</tr>
</tbody>
</table>

- A total [theo] of 17 µg/ml in term newborns produces a free [theo] of 10.9 µg/ml, equivalent to a total plasma theophylline of 25 µg/ml in adults.
  
  Aranda: NEJM 1976;295:413
Solvents and Excipients in Drug Formulations May be Toxic in Newborns

- **Benzyl alcohol** in saline flush accumulated to lethal levels causing the Gasping Syndrome with acidosis & cardiovascular collapse (Lancet 1982;I:1250. NEJM 1982;307:1384-1388)

- **Propylene glycol** (solvent and emulsifier in creams/silver sulfadiazine, i.v. phenobarbital) can cause hyperviscosity, seizures, apnea (Pediatrics. 1983;72:353. JAMA 1985;253:1606)

- **Polysorbate 80**, a solvent, was the likely cause of deaths from E-Pherol treatment to reduce ROP (Pediatrics 1986;77:593. ibid 1986;78:503. ibid 1989;83:244).

- Toxicity is often due to immaturity of organs of clearance causing low clearance

- New drugs should be checked for their solvents with the package insert
Many Challenges in Pediatric Drug Development

- Dosing to accommodate developmental changes in drug metabolism and elimination
- Endpoints in immature, often nonverbal patients
- Unique metabolism
- Limited blood volume and access complicate pharmacokinetic measurements
- Vulnerable populations require careful study designs that differ from those in adults
- Limited study sites and costly studies
- THESE CHALLENGES CAN BE OVERCOME!