THE CHALLENGES OF NEONATAL PRODUCT DEVELOPMENT: AN NIH PERSPECTIVE

FDA PEDIATRIC ADVISORY COMMITTEE
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General Challenges

1. Design of neonatal studies to establish dosing, safety and efficacy across all developmental areas
2. Conduct of neonatal studies
Best Pharmaceuticals for Children Act (BPCA)

• Purpose: improve pediatric labeling

• NIH Role
  • Prioritize drugs/therapeutic areas
  • Sponsor clinical trials
  • Submit data to FDA for labeling changes

• 2012 Legislative Addition: focus on “Neonates”
BPCA Prioritization Criteria

2002:
- Availability of safety/efficacy data
- Are additional data needed?
- Will new studies produce health benefits (severity/frequency)?
- Reformulation needed?

2007/2012:
- Therapeutic gaps
- Potential health benefits of research
- Adequacy of necessary infrastructure
Neonates

• Initial prioritized drugs in 2003: for neonatal hypotension (pressors) and BPD (diuretics)
• Therapeutic area: neonatology
• BPCA-sponsored activities
  • Prioritization process (76 FR 18228-18229)
  • CTSA co-fund for outcome measures
  • Neonatal Research Network study of hypotension
# Table 9. Neonatal Research Priorities

<table>
<thead>
<tr>
<th>Current or Proposed Listed Therapeutic Area</th>
<th>Current or Proposed Listed Drug</th>
<th>Gaps in Knowledge/Labeling</th>
<th>Type of BPCA Study and/or Scientific Needs</th>
<th>Plans and Progress</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonatal bronchopulmonary dysplasia (BPD)/lung development</td>
<td>Betamethasone</td>
<td>Dosing, efficacy</td>
<td>Determination of dosing and effectiveness</td>
<td>Reviewing existing data, current NICHD grant funding</td>
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<tr>
<td></td>
<td>Azithromycin (IV)</td>
<td>Dosing, efficacy</td>
<td>PK, efficacy in treating ureaplasma infections to prevent BPD</td>
<td>WR received from FL, current NICHD grant funding</td>
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<tr>
<td></td>
<td>Hydrochlorothiazide</td>
<td>Dosing, safety, and efficacy</td>
<td>Determination of dosing and effectiveness</td>
<td>Collaborations with the National Heart, Lung, and Blood Institute network data collection</td>
</tr>
<tr>
<td>Neonatal pain</td>
<td>Morphine</td>
<td>Pain</td>
<td>Optimization of dosing and biomarkers of pain in neonates</td>
<td>Current NICHD grant funding</td>
</tr>
<tr>
<td>Neonatal abstinence syndrome (NAS)</td>
<td>Methadone</td>
<td>PK, safety</td>
<td>Treatment strategies of NAS in opioid-exposed neonates</td>
<td>CTSA administrative supplement</td>
</tr>
<tr>
<td>Infections in neonates</td>
<td>Metronidazole</td>
<td>PK and efficacy in neonates with abdominal infections</td>
<td>PK study</td>
<td>Pediatric study under consideration by the PTN</td>
</tr>
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</table>
Clinical Trials (Legacy) Enrolling Neonates

- Azithromycin (neonates only)
- Morphine (neonates only)
- Lorazepam for Sedation
- Lorazepam for Status Epilepticus
- Nitroprusside
- Meropenem for severe intra-abdominal infections (neonates only)
Pediatric Trials Network Trials Enrolling Neonates

• Ampicillin
• Acyclovir
• Fluconazole
• Metronidazole
• Sildenafil (opportunistic)
• Pediatrix Database: NICU use, adverse events with proton pump inhibitors, octreotide
• Opportunistic data collections/scavenged samples
Outcome Measures: Partnership with NCRR/CTSA's

• Purpose: research on outcome measures in the areas of
  • Neonatology
  • Cardiovascular medicine
  • Neurology
Topic Areas: 8-neonatology, 5-neurology, 4-hypertension/hypotension, 3-“other”; >1 topic area possible

1 Duke  Development of a PK algorithm to improve neonatal outcomes
2 UTHSC  Advanced MRI to assess neonatal care and outcome
3 Columbia  Targets and Barriers for Hydroxyurea use in Sickle Hemoglobinopathies
4 Utah  Improving Management of the Neonatal Abstinence Syndrome
5 U Pitt  Cardiac Outcome Measures for Pediatric Muscular Dystrophy
6 UNC  Outcome Measures for chronic lung disease of prematurity
7 U-CO  Small volume fentanyl PK/PD & PG in neonates
8 UC-Davis  Outcome Measures for Trials in Children with Autism
9 Vanderbilt  Wireless Home-Based Tools for studying sleep in Autism
10 U-MI  Pediatric Cardiac Intensive Care Data Standards Repository
11 Stanford  Methadone vs. Morphine PD/PD in infants after cardiac surgery
12 Indiana  Predictors of Vincristine-induced peripheral neuropathy
13 UAB  Nasal Potential Difference Studies Utilizing CFTR Modulators
14 CWRU  Efficacy Outcomes Measures in Antihypertensive Trials in Children
15 CWRU  Effect of BMI on Exposure-Response Relationships to Lisinopril in Children
16 U-Wash  Advancing Patient Reported Outcomes (PROs) in children with Cystic Fibrosis
17 AECOM  Pediatric hypertension outcome measures
18 Tufts  Improving BPD predictors and outcomes for clinical trials
Medication Use and Outcomes Data Collections Co-Funding

- NHLBI: Pediatric Respiratory Outcomes Program (PROP)
- NINDS: Maternal Outcomes and Neurodevelopmental Effects of Antiepileptic Drugs (MONEAD) Trial
Topics

1. Design
   - Phenotyping
   - Outcome measures
   - Study designs
   - Developmental changes in PK/PD
   - Biomarkers/surrogate markers
   - Extrapolation

2. Conduct
   - Infrastructure: networks
   - Ethics and consent
   - Logistics-blood sampling
   - Dosage forms
   - Investigator training

- Design: factorial (hydrocortisone/dopamine)
- Results: 366 infants screened, 10 enrolled
- Issues:
  - eligibility (indomethacin contra-indicated with HC)
  - consent
Validating Endpoints for Neonates with "Hypotension"

• How is BP measured in the NICU?
• Have these methods been standardized or validated in this population?
• What is a normal neonatal BP at a given gestational or postnatal age?
• What is the definition of hypotension?
  • Value – systolic/diastolic/mean BP
  • “Perfusion”
  • Shock
  • Oliguria or anuria
• What is the clinical endpoint in the treatment of hypotension? How is this endpoint measured?
• Use of pilot feasibility study is valuable way of assessing feasibility

• Alternatives to pre-randomization informed consent, otherwise “we will continue using unproven and potentially dangerous therapies simply on the basis that we have always used them.”
Extrapolation

• Use of extrapolation/assumptions for efficacy
  • Spitting up = GER; GER responds to thickened feeds in infants

• Use of extrapolation/assumptions for safety
  • Generally Recognized as Safe (GRAS) for who?
Late Onset Necrotizing Enterocolitis in Infants following Use of Gum-Containing Thickening Agent

Jennifer Beal, MPH\textsuperscript{1}, Benson Silverman, MD\textsuperscript{1}, Jodeanne Bellant, MD\textsuperscript{2}, Thomas E. Young, MD\textsuperscript{3}, and K...

Adverse event reports submitted to the US Food and Drug Administration suggested a possible association between necrotizing enterocolitis and ingestion of a commercial feed thickener by premature infants. Review of 22 cases with exposure revealed a distinct illness pattern. \textit{(J Pediatr 2012;161:354-6)}

Necrotizing enterocolitis (NEC) is a leading cause of morbidity and mortality in neonates.\textsuperscript{1-3} Development of this multifactorial disease is hypothesized to begin with insults such as intestinal ischemia, infection, enteral feeding commencement, and/or translocation of enteric bacteria in a pre-mature immuno-compromised neonate. Intestinal radiographs, with surgical and/or autopsy results, show necrotic bowel. We excluded infants with a diagnosis of NEC prior to ingestion of SimplyThick. We evaluated 84 case reports, including 33 medical records of infants meeting our case definition and are included...
as congenital heart disease, almost all cases of NEC develop in the hospital, whereas 50% of the cases in our series developed NEC at home. Finally, whereas NEC frequently develops shortly after initiation of enteral feeding, the infants described here had fed enterally for a median of 43 days prior to NEC onset.

One potential mechanism by which SimplyThick might predispose to mucosal injury and NEC is through accumulation of short-chain fatty acids (SCFAs) produced by bacterial metabolism of its xanthan gum component. The intra-luminal administration of SCFAs in newborn rats induces intestinal mucosal injury with pathologic changes similar to those seen in NEC. Moreover, fecal bacteria from healthy adults who consumed 15 grams of xanthan gum for 10 days demonstrated an increased ability to ferment xanthan gum in vitro; the production of SCFAs was also significantly greater following the xanthan gum ingestion period. In our series, a median of 13 days transpired from the initiation of feeding with SimplyThick to onset of NEC, sufficient time, theoretically, for intestinal
Study Designs Incorporating Developmental Changes
Meropenem

- Purpose: evaluate safety and dosing of meropenem in 200 pre-term neonates with severe intra-abdominal infections
  - Age cohorts:
    - Group 1: Gestational age at birth < 32 weeks and post-natal age younger than 8 days;
    - Group 2: Gestational age at birth < 32 weeks and post-natal age of 8 - 90 days;
    - Group 3: Gestational age at birth ≥ 32 weeks and post-natal age younger than 8 days; and
    - Group 4: Gestational age at birth ≥ 32 weeks and post-natal age of 8 - 90 days
  - Background rates of safety events from Pediatrix
Conduct of Neonatal Studies

- Infrastructure
  - Network: investigators and patients, protocol development, statistics, pharmacy, drug assays, data analyses
  - Data Coordinating Center: Regulatory, data monitoring functions
Logistics

• Dosage Forms: neonatal dosage forms, dilutions of products designed for adults
• Blood sampling: scavenged sampling
Meropenem Vial
Investigator Training

• lack of training of academic investigators in regulatory science (i.e., how to train PIs to develop auditable data)
Study Design Concept

- COG model: Enrollment in NICU studies as the default
  - Evidence-based, protocolized approach to using old, unlabeled drugs
  - All [de-identified] data collected on all patients
  - Validated outcome measures
  - Standardized data collections: terms and fields, for short- and long-term follow-up
Study Design Concept

• Regulatory-research-academic collaborations
• Use of all currently available data, including the literature, to inform clinical trial designs, labeling
• Observational studies, practical clinical trials of drugs, devices
“…alternatives to traditional pre-randomization informed consent should be more widely used, otherwise we will continue using unproven and potentially dangerous therapies simply on the basis that we have always used them.”