Liver Disease Research in Children

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Shire;
Objectives

• Challenges facing Pediatric Hepatology
• Pediatric specific developmental factors that influence clinical trial design
• Pediatric specific physiologic factors that influence clinical trial design
• Examine common pitfalls that investigators experience when failing to design their trial for children
• Review ethical challenges in pediatric liver research
Why do Research in Children?

• Disease processes in children are different than in adults, and some do not occur in adults (e.g., biliary atresia)
• Physiological make-up and their pharmacodynamic responses to drugs vary with age (and differ from adults)
• Therapies used for adults, such as tablets, are not well tolerated particularly in younger children because they are difficult to administer or unpalatable or incorrect doses
• Clinical trials need to focus on medications relevant to children’s clinical needs where there is limited evidence of efficacy
Burden of Pediatric Liver Disease (USA)

• Neonatal Cholestatic Diseases: 1 in 2,500 live births
  ➢ including Biliary Atresia: 1 in 8,000 to 18,000 live births
  ➢ Cystic Fibrosis Liver Disease: 10% of 1 in 2,000
  ➢ Alpha-1 antitrypsin Deficiency: 20% of 1 in 3,000

• Hepatitis C viral infection: 1 in 200 to 500 children

• Non-alcoholic fatty liver disease: 10-20% of children

• Autoimmune Liver Disease: Rising incidence
Challenges in Pediatric Hepatology

• However - No approved therapy for NASH/ NAFLD, pediatric cholestasis, and most genetic/metabolic diseases

• Most recent DAA therapies for HCV in adults yet to tested and approved in children

• Children are a small market compared to adults, challenges in conducting clinical trials, safety and endpoints, age differences, small population for many rare diseases - barriers

• Children do not vote, and therefore do not have political capital

• As pediatricians, we must be the voice for children
Pediatric Hepatology Practice

- Cholestatic liver diseases
- Chronic viral hepatitis
- NAFLD
- Cirrhosis and portal hypertension
- Acute liver failure, DILI, ICU patients
- Autoimmune liver diseases
- Hepatoblastoma
- Intestinal Failure Associated Liver Disease
- Liver transplantation
- Metabolic and Genetic Diseases
Pediatric Hepatology Practice

- Cholestatic liver diseases
- Chronic viral hepatitis
- NAFLD
- Cirrhosis and portal hypertension
- Acute liver failure, DILI, ICU patients
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- Hepatoblastoma
- Intestinal Failure Associated Liver Disease
- Liver transplantation
- Metabolic and Genetic Diseases
Mountain of Genes

Use of Cholestasis Gene Panels (68 genes)
Find New Therapies For Childhood Liver Diseases

- Sustainable Infrastructure
- Knowledgeable Workforce
- Cooperative Networks for Rare Diseases
- Efficient Regulatory Processes
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Example: **Childhood Liver Disease Research Network (ChiLDReN)**

- 17th year – funded by National Institutes of Health
- 15 study centers in North America - collaboration
- Studies 9 rare childhood liver diseases (cholestatic)
  - have enrolled 1800 patients with biliary atresia, 400 with alpha-1 antitrypsin deficiency liver disease, 350 with Alagille syndrome, 300 with PFIC, etc.
- Longitudinal cohorts; data, specimens, DNA; define natural history; pathogenesis and outcomes; biomarkers and endpoints; conduct clinical trials
ChiLDReN Diseases Studied

1. Biliary atresia
2. Idiopathic neonatal hepatitis
3. Alpha-one antitrypsin deficiency
4. Alagille syndrome
5. Progressive familial intrahepatic cholestasis (PFIC) and BRIC types 1, 2, 3, 4, 5, 6 and non-typeable
6. Bile acid synthesis defects
7. Mitochondrial hepatopathies – respiratory chain and fatty acid oxidation defects
8. Cystic fibrosis liver disease
9. Primary sclerosing cholangitis
Specific Challenges for Pediatric Clinical Studies and Trials
1. Selecting the Right Population

All pediatric subpopulations are not equal

• Example: “Newborn population” may have variable PK parameters and outcome measures because of differences in
  ➢ Post-conceptional age
  ➢ Gestational age
  ➢ Postnatal age
  ➢ Asphyxia at birth, PDA, prenatal drug exposure

• Example: 10-14 year old female population – pubertal status, menarche, etc.
2. Selecting the Right Drug Formulation

- **Age Appropriate Formulation** – may not be able to use adult formulation.
- **Form**: Solid, liquid, chewable, dissolvable, sprinkles, rectal, parenteral, intraocular, intranasal
- **Palatability**: consider taste, color, texture, temperature. Country-specific flavors may be different based on taste preferences.
- If using Adult Dosage Form – solid oral tablet –
  - Need to verify placebo swallow in study enrollment
  - You may bias enrollment because you will not have younger children (<4-6 yr)
  - Cannot titrate the dose so you may exceed the adult dose
  - May not be sustainable for a child
2. Selecting the Right Drug Formulation

- Options for changing the dosage form
  - Tablets dissolved with water or crushed in pudding – will be tolerated will be based on age – thus there may be changes in PK that may be due to formulation effect and not age effect – cannot separate these two

- Extemporaneously compounded drug at each site: cannot depend on same concentration of drug and you may be delivering higher or lower dose

- Example: Empty contents of capsule into cup and add formula or apple juice – pH vs. food could interfere with intestinal transport (unanticipated)
3. Sample Collection and Analysis

- **Allowable blood volume** for PK studies may limit what can be done:
  - IRBs have restrictions and studies may exceed these
  - Max of: 3% blood volume within 2-4 wk. period of time (including clinical draws)
  - Max of: 1% blood volume at single draw (including clinical draws)

- May need to develop micro-assays so that less blood is needed

- Draw fewer levels and vary them from child to child

- Finger Stick cannot be the solution - 20 sticks per child not tolerable

- Sampling scheme: differences with age in gastric HCl production
4. Physiological Differences in Children

• **PK profile** – less stomach acid early life - less drug decay in stomach acid, more drug available for absorption

• **Gastric emptying** slower in infants, reduced intestinal motility, altered splanchnic blood flow - delayed gastric emptying and delayed absorption

• Developmental differences in expression of **BSEP** in infants, so less bile salts secreted into intestine and lipophilic drugs will be absorbed less well

• **Skin absorption**: epidermal and stratum corneum thickness changes in first months of life, and water content of skin, and surface area to volume ratio.

• **Rectal delivery**: more frequent stooling and will not allow for absorption in infants – lower concentrations

• **Muscle** - higher capillary density in infants - better IM absorption
4. Physiological Differences in Children

- **Body composition**: higher body water content in infants and young children – for hydrophilic drugs there is larger VD and lower concentrations

- **Renal elimination**: GFR and tubular function are developmentally regulated.

- **P450 expression**: Different ages for P450s to be expressed in the liver.

- **Analysis**: If only have enough blood to analyze it once, if above or below limits of quantification, you will have missing data. Thus, need a pilot to determine dilution factors needed for analysis.

- **Protein Bound Drugs**: albumin is lower in children and thus less bound drug and child can clear the drug more rapidly (more free drug)

- **Impact of feeding**: formula vs. breast fed may have differences in absorption – look at subpopulations and design the study accordingly – measure sooner or later samples
5. Study Design

- **Inappropriate volumes** – take with 200 ml of water and maintain heavy oral fluid intake may exceed fluid volume appropriate for children
- **Impractical**: 24 hour urine collection days 1-8: hard to do in a non-potty trained or even potty trained child
- **Visit Numbers**: Study requires multiple visits: Implications for school attendance, sports, parents working hours
- **Restrictive**: chocolate, soda and caffeine when sometimes unnecessary
- **IV Drug**: Must use 2 IVs and not draw back through line that drug given
- **Nonsensical protocol** - adjusted from adult consent form
- **Coercion**: Many consent form issues about coercion
Ethical Issues

Risk vs. Benefit

• **Risks**: physical, psychological, or social, and may be immediate or delayed

• **Minimal risk** is defined as the probability of harm or discomfort not greater than that ordinarily encountered in daily life or during routine tests

• **Benefit**: defined as progress in treatment, diagnosis or prevention for the child or the group of children affected

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Sammons, Starkey. PAEDIATRICS AND CHILD HEALTH 2011; 22:2
Allowable Risk-Benefit – EU Guidance

• **Minimal risk** with benefit for the individual or the group

• **Minor increase over minimal risk** with benefit to individual or group, and with the benefit to risk balance being at least as favorable as alternative approaches

• **Greater than minor increase over minimal risk** with benefit for the individual that is especially favorable in relation to available alternative approaches for the individual’s condition
Risk and Research in Children

• In the United States, studies can be approved that do not offer a prospect of direct benefit to healthy children when they pose either only minimal risk or minor increase over minimal risk.

• The EU guidance states that research on healthy children should not be performed. Exceptions to this include palatability testing of medications and vaccine trials (prevention).
Informed Consent

• Voluntary agreement, to participate in research based on adequate knowledge and understanding of relevant information.

• Families and children need to be viewed as partners in research.

• As the child (minor) is unable to provide legally binding consent, and his/her assent does not have sufficient authority to authorize research, the parent(s)/legal representative is required to provide consent on the behalf of the child or participation.

• The parent(s)/legal representative is required to provide consent on the behalf of the child for participation.
Assent

• Ethical and legal obligation, to obtain a child’s permission for their participation in research
• Assent is a child’s (7 yr and older) affirmative agreement to participate in research
• Mere failure to object should not, absent affirmative agreement, be construed as assent
• Assent should depend on other factors than age, such as intelligence, developmental stage, diagnosis and life experience
Coercion

• It is important that consent is given free from coercion

• Payment in research around the world is common but controversial

• Payment can enable participation in research without disadvantage and boost recruitment, but it must not lead participants to ignore or significantly undervalue risk.

• This can have an added complexity when the inducement is offered to the parent and not the child taking the risk.
Coercion

• It has been found that when inducements have been offered, this can influence parental reasons for consent, with a positive correlation between the importance of free medication as a reason for consent and lower income families.

• The EU Paediatric Regulation states that there must be no financial inducement to enroll a child in a trial, with exception of compensation for time and expenses.

PAEDIATRICS AND CHILD HEALTH 2011: 22:2
Take Home Points

• Children are not little adults and may have PK, drug formulation, physiological and other differences that need to be addressed in pediatric clinical trials

• Risk vs. Benefit needs to be assessed carefully and depends on country-specific guidelines

• Without involvement of families and children as partners, important research for childhood liver diseases cannot be performed - partnership
Thank you