Overview of Key Issues in Cardiac Safety and Drug Development in Pediatrics

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Pediatric Cardiovascular Disease Conditions

- Congenital heart defects
- Congestive heart failure
- Arrhythmias
- Acquired heart disease
- Hypertension
- Pulmonary hypertension
Drugs that Affect the Heart

- Infectious Disease Agents
- Oncological Drugs
- Psychiatric Drugs
- Neurological Drugs
- Asthma Drugs
- Anti-inflammatory Drugs
- Cardiovascular Drugs
Major Cardiac Toxicities of Drugs in Children

- Developmental abnormalities
  - Structure and Function
- Decreased Cardiac Function-postnatal
- Arrhythmias
  - Proarrhythmia
  - Conduction changes
  - Repolarization effects
- Long-term Cardiovascular Health
  - Increase coronary artery disease risks
  - Impair normal cardiac development
Cardiac Safety in Pediatrics

- **Acute Safety**
  - Torsades de Pointes

- **Short-term Safety**
  - QTc prolongation

- **Long-term Safety**
  - Doxorubicin/anthracyclines

*Lipschultz S*
*Semin Oncol 33:S8–S14; 2006*
Life-threatening Potential of Drugs that Affect the Heart

- Unmasking of underlying cardiac conditions
- Triggering of cardiac events in presence of cardiac disease (diagnosed or unknown)
- Long-term effects of long standing small increases in heart rate and blood pressure or other late effects
Why Does Cardiac Drug Safety Need Special Attention in Children?
Children Are Not Small Adults
What Makes Safety in Children Different from Adults?

- **Exposure**
  - Indirect → *maternal drugs*
    - Fetal
    - Breast feeding

- **Dosing Variations**
  - Pharmacodynamic and Pharmacokinetic Differences
  - Absence of dosing studies and “approved” labeling

- **Developmental Vulnerability and Variability**
  - Fetus
  - Neonate
  - Growing child
  - Puberty
What Makes Drugs Work Differently in Children?

<table>
<thead>
<tr>
<th>Pharmacology</th>
<th>Developmental</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Formulation</td>
<td>• Absorption</td>
</tr>
<tr>
<td>– Solubility, stability</td>
<td>• Distribution</td>
</tr>
<tr>
<td>• Dosing by wt or BSA</td>
<td>• Metabolism</td>
</tr>
<tr>
<td>Pharmacodynamics</td>
<td>• Elimination</td>
</tr>
<tr>
<td>• Pharmacokinetics</td>
<td></td>
</tr>
<tr>
<td>• Pharmacogenomics</td>
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</tbody>
</table>
Developmental Differences
Metabolism and Excretion

Hepatic Function
- Immaturity of enzymes

Renal Function
- ↓ Cr clearance in young

Clin Pharmacokinet 1999
Size and PK Differences between Children and Adults

- Doubling of body size by six months
- Triple body size by one year
- BSA doubles in first year
- PK differences
- Different presentation of diseases
Extrapolation of Adult Drug Information

• In children, drugs approved for adult use may be
  – Ineffective
  – Incorrectly administered
  – Toxic
• Extrapolation of adult data only appropriate if
  – Disease progression is similar in adults & children
  – Response to intervention is similar
  – Reasonable to assume similar concentration-response
    • Safety trials have been conducted
    • Similar levels to adults will be achieved
The Role of Children in the History of Drug Control

- Jim, a former milk wagon horse, was used to produce antitoxin for diphtheria
- 13 children died in 1901
- Jim had developed tetanus
- Led to 1902 Biologic Control Act, set stage for creation of FDA
Pure Food, Drugs and Cosmetic Act of 1938

- Mrs. Winslow’s Soothing Syrup for colicky and fussy babies contained morphine led to many infant deaths

- Elixir of Sulfanilamide was compounded with an untested solvent, *diethylene glycol*
  - Caused deaths in many children from renal failure

- Led to passage of Pure Food and Drugs Act 1938- prohibited interstate commerce in adulterated or misbranded drugs
Thalidomide

1961: FDA prevented approval, but several American children were born with the typical limb defects after exposure during “investigational” trials.

1962: Led to Amendments in the Food and Drug Act (Kefauver-Harris Amendment)
   - Manufacturers had to prove efficacy and safety.
Milestones in Drug Safety

• 1997: Congress passes FDAMA/Exclusivity Provision (voluntary)

• 1998: FDA publishes “Pediatric Rule” (mandatory)
  – Studies required if drug likely to be used in substantial number of pediatric patients
More Pediatric Based Milestones in Drug Safety

- 2002: Congress passed Best Pharmaceuticals in Children Act (BPCA)
  - Reauthorized exclusivity incentives
    - 6 months of patent extension
  - Required 1 year post exclusivity reporting of all AE's
  - Required all drug summaries be posted regardless of action
More Pediatric Based Milestones in Drug Safety

• 2003: Pediatric Research Equity Act (PREA) passed by Congress
  – Required study of drugs/biologics for pediatrics (for new ingredient, indication dosage form, regimen, or route)
  – Exceptions/waivers allowed if not applicable to peds
  – Allowed extrapolation of effectiveness from adult trials or from one pediatric group to another if PK-PD information known
  – Created Pediatric Advisory Committee of FDA
How Can Cardiac Drug Safety in Children Be Improved?

• Regulation and Surveillance
• Medication Error Prevention
• Research
  – Understanding of safety risks
  – Development of safer, more effective drugs
Monitoring for Cardiac Safety

- Effects on heart rate
- Effects on blood pressure
- Effects on ECG
  - PR interval
  - QRS duration
  - QT/QTc intervals, QT dispersion, JT/JTc interval
  - ST-T wave changes
- Heart rate variability
- Development of arrhythmias
- Worsening of underlying arrhythmia
- Biomarkers, e.g. troponin, BNP, others
- Acute, short, mid and long-term effects
- Post marketing changes in above along with AERs
Over 78% of drugs used in pediatrics don’t have labeling for use in pediatrics and/or for the indication for which they are used.
Prospective study of pediatric cardiology ward
- 76% of patients received off label drugs
- 39% of off label drugs were cardiovascular

Table 4 The ten most frequently prescribed off label drugs and unlicensed drugs

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Number (%) of prescriptions (n=961)</th>
<th>Reason(s) for unlicensed/off label status [17]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furosemide</td>
<td>143 (14)</td>
<td>Off label: dose</td>
</tr>
<tr>
<td>Lincomycin i.v.</td>
<td>89 (9)</td>
<td>Off label: dose</td>
</tr>
<tr>
<td>Digoxin</td>
<td>81 (8)</td>
<td>Off label: dose/age</td>
</tr>
<tr>
<td>Amoxicillin</td>
<td>64 (6)</td>
<td>Off label: dose/age</td>
</tr>
<tr>
<td>Propranolol</td>
<td>61 (6)</td>
<td>Off label: dose</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>43 (6) 14</td>
<td>Off label: dose unlicensed: modified licensed product</td>
</tr>
<tr>
<td>Acetylsalicylic acid</td>
<td>56 (5)</td>
<td>Unlicensed: under 12 years</td>
</tr>
<tr>
<td>Captopril</td>
<td>50 (5)</td>
<td>Off label: dose</td>
</tr>
<tr>
<td>Amikacin</td>
<td>32 (3)</td>
<td>Off label: dose</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>32 (3)</td>
<td>Unlicensed</td>
</tr>
</tbody>
</table>
Medical Errors in Drug Use in Pediatrics

- 31% error rate in pediatrics compared to 13% for adults (Crowley, Curr Ther Res 2001)

- 2.5% of medical errors in pediatrics result in harm (Kaushal JAMA 2001)

- 11 adverse drug events/100 pediatric admissions (Takata, Peds, 2008)
Common Sources of Medical Errors

- Calculation errors/Incorrect dose ordered
  - 70% of dosing errors
- Transcription errors/abbreviations
- Lack of standard dosing for off-label use of drugs
- Lack of pediatric dosing formulations
- Incorrect dose administered by caregiver
Therapeutic Categories Causing Cardiac Related ADRs

- Antimicrob
- Psych
- Respiratory
- Neuro
Adverse drug reactions in childhood: a review of prospective studies and safety alerts

A Clavenna, M Bonati

- 10.9% ADR in hospitalized children
- 29% of warnings with possible cardiac effects

**Table 3**  Warnings issued by the drug regulatory agencies in 2001–2007

<table>
<thead>
<tr>
<th>Drug</th>
<th>ADR</th>
<th>Countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHD drug products</td>
<td>Cardiovascular adverse events, neuropsychiatric symptoms</td>
<td>USA, Ca</td>
</tr>
<tr>
<td>Amisulpride</td>
<td>Potentially fatal and developmental side effects in neonates and infants</td>
<td>USA</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Increased risk of suicidal ideation</td>
<td>Ca, F, G, I, UK, USA</td>
</tr>
<tr>
<td>Aspirin</td>
<td>Reye’s syndrome</td>
<td>I, UK</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Increased risk of suicidal thinking in children and adolescents</td>
<td>Ca, G, B, UK, USA</td>
</tr>
<tr>
<td>Cefaclor</td>
<td>Severe allergic reactions</td>
<td>I</td>
</tr>
<tr>
<td>Ceftriaxone</td>
<td>Cases of fatal reactions with calcium-ceftriaxone precipitates in the lungs and kidneys in both term and premature neonates</td>
<td>USA, UK, F, G, I</td>
</tr>
<tr>
<td>Cedeine (nursing mothers)</td>
<td>Risk of severe ADRs in infants with ultra-rapid metaboliser nursing mothers</td>
<td>I, UK, USA</td>
</tr>
<tr>
<td>Cough and cold medicines</td>
<td>Serious adverse events (death)</td>
<td>I, USA</td>
</tr>
<tr>
<td>Desmopressin (intranasal)</td>
<td>Severe hyponatraemia and seizures</td>
<td>F, I, G, I, UK, USA</td>
</tr>
<tr>
<td>Dextromethorphan</td>
<td>Sudden death in patients with cardiovascular diseases</td>
<td>Ca, USA</td>
</tr>
<tr>
<td>Delantren</td>
<td>ECG abnormalities (QTc prolongation)</td>
<td>USA, I</td>
</tr>
<tr>
<td>Dopexamine</td>
<td>Risk of extrapyramidal symptoms</td>
<td>I</td>
</tr>
<tr>
<td>Halothane</td>
<td>Increased risk of cardiac arrhythmias</td>
<td>USA, UK</td>
</tr>
<tr>
<td>Immunostimulants</td>
<td>Benefit/risk profile unfavourable</td>
<td>F</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>Increased risk of potentially fatal rash in children</td>
<td>F, USA</td>
</tr>
<tr>
<td>Lopinavir/ritonavir</td>
<td>Accidental overdose</td>
<td>F, I, Ca</td>
</tr>
<tr>
<td>Metoclopramide</td>
<td>Risk of extrapyramidal symptoms</td>
<td>F, I</td>
</tr>
<tr>
<td>NSADS</td>
<td>Septic shock in infants with chickenpox</td>
<td>F</td>
</tr>
<tr>
<td>Omeprazole</td>
<td>Pneumothorax (close limiting side effect)</td>
<td>USA</td>
</tr>
<tr>
<td>Oseltamivir</td>
<td>Neuropsychiatric adverse events: suicidal ideation; delirium and abnormal behaviour leading to injury</td>
<td>Ca, F, I, USA</td>
</tr>
<tr>
<td>Palivizumab</td>
<td>Anaphylaxis</td>
<td>USA</td>
</tr>
<tr>
<td>Pemoline</td>
<td>Cardiovascular adverse events</td>
<td>USA</td>
</tr>
<tr>
<td>Promethazine</td>
<td>Respiratory depression, causing death in some children &lt;2 years old</td>
<td>USA</td>
</tr>
<tr>
<td>Propofol</td>
<td>Increased number of deaths</td>
<td>Ca, USA</td>
</tr>
<tr>
<td>Somatropin</td>
<td>Fatalities reported in paediatric patients with Prader-Willi syndrome with severe obesity/history of respiratory impairment or sleep apnoea/unidentified respiratory infection</td>
<td>USA</td>
</tr>
<tr>
<td>Topiramate</td>
<td>Oligohydramnios, hyperthermia</td>
<td>Ca, USA</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>Increased risk of oligohydrosis and hyperthermia in children</td>
<td>USA</td>
</tr>
</tbody>
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ARTICLE
Safety Monitoring of Drugs Receiving Pediatric Marketing Exclusivity

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Food and Drug Administration, Rockville, Maryland; Departments of Pediatrics and Medicine and Duke Clinical Research Institute, Duke University, Durham, North Carolina.

What’s Known on This Subject
Children represent a small percentage of the population receiving drugs for which AEs are reported to the FDA, so it is difficult to identify pediatric-specific problems because they are “submerged” among the numerous reports submitted for adults.

What This Study Adds
We describe the PAc recommendations concerning research ethics and pediatric drug labeling made in response to FDA safety reports.

ABSTRACT
OBJECTIVE: The Food and Drug Administration Modernization Act provided for an additional 6-month period of marketing exclusivity to companies that perform pediatric drug trials in response to a Food and Drug Administration–issued written request. Because many safety concerns cannot be detected until after the introduction of a product to a larger and more diverse market, the Best Pharmaceuticals for Children Act required the Food and Drug Administration to report to the Pediatric Advisory Committee on adverse events occurring during the 3-year period after granting pediatric exclusivity. We sought to describe the Pediatric Advisory Committee’s recommendations made in response to safety reviews informed by data from the Food and Drug Administration Adverse Event Reporting System in 67 drugs granted exclusivity.

METHODS: Pediatric Advisory Committee meetings and data presented by the Food and Drug Administration for all drugs were reviewed from June 2003 through April 2007. We divided the drugs into 2 groups: those that were returned to routine adverse event monitoring and those that had specific Pediatric Advisory Committee recommendations.

RESULTS: Forty-four (65.7%) drugs were returned to routine monitoring for adverse events. The Pediatric Advisory Committee, sometimes working with other advisory committees, recommended label changes for 12 (17.9%) drugs, continuing monitoring for 10 (14.9%), production of MedGuides for 9 (13.4%), and an update on label changes resulting from discussions with the sponsor for 1 (1.5%) drug. Some drugs had >1 action. Several of the adverse events revealed during this process were rare and life-threatening.

CONCLUSIONS: Safety monitoring during the early postmarketing period is crucial to detect rare, serious, or pediatric-specific adverse events. Fortunately, the majority of drugs given exclusivity had no adverse events of a frequency or severity that prevented a return to routine adverse event monitoring. Pediatrics 2008;122:e625–e633

Pediatric Advisory Committee Actions 2003-2007

- 65.7% returned to routine monitoring
- 17.9% recommended labeling changes
- 14.9% continued monitoring
- 13.4% MedGuides
- 1.5% update to label changes
Labeling Changes

- >250 pediatric labeling changes
- Cardiac drugs: antihypertensives, lipid lowering agents, carvedilol, sotolol, milrinone
- Publicly available summaries
  - [http://www.fda.gov/oc/opt/default.htm](http://www.fda.gov/oc/opt/default.htm)
Medication Guides

What is the most important information I should know about ADDERALL XR®?

ADDERALL XR® is a stimulant medicine. The following have been reported with use of stimulant medicines.

1. **Heart-related problems:**
   - sudden death in patients who have heart problems or heart defects
   - stroke and heart attack in adults
   - increased blood pressure and heart rate

Tell your doctor if you or your child have any heart problems, heart defects, high blood pressure, or a family history of these problems.

Your doctor should check you or your child carefully for heart problems before starting ADDERALL XR®.

Your doctor should check you or your child’s blood pressure and heart rate regularly during treatment with ADDERALL XR®.

Call your doctor right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting while taking ADDERALL XR®.

What is the most important information I should know about CONCERTA®?

The following have been reported with use of methylphenidate HCl and other stimulant medicines:

1. **Heart-related problems:**
   - sudden death in patients who have heart problems or heart defects
   - stroke and heart attack in adults
   - increased blood pressure and heart rate

Tell your doctor if you or your child have any heart problems, heart defects, high blood pressure, or a family history of these problems.

Your doctor should check you or your child carefully for heart problems before starting CONCERTA®.

Your doctor should check you or your child’s blood pressure and heart rate regularly during treatment with CONCERTA®.

Call your doctor right away if you or your child has any signs of heart problems such as chest pain, shortness of breath, or fainting while taking CONCERTA®.

It is not known if ZYPREXA is safe and works in children under 18 years of age.

It is not known if ZYPREXA taken with fluoxetine (Prozac) is safe and works in children under 18 years of age.
Challenges to Drug Safety in Children

• To develop better understanding of developmental variations
• Identify developmental windows of vulnerability
• Identify pharmacogenomic and other differences that increase or mitigate toxicities
• Identify and understand molecular and cellular mechanisms of drug toxicities
• Collect information on overall adverse events and severe adverse events such as death, either sudden or overall
  – Would a Sudden Cardiac Death Registry that provided drug history and other information help to identify signals from specific drugs?
• Determine most effective monitoring methods for short and long-term drug effects
Limitations of Pre-marketing Trials in Pediatrics

- Size, duration, study population, age group
- Limited number of pediatric trials
- Few children are enrolled with minimal data obtained
- Limited prior knowledge of pediatric efficacy, effectiveness and safety
Benefits of Post-marketing Studies in Children

- Pediatric information can be consolidated
- Effectiveness of the drug for the original indication in children
- Other beneficial effects of the drug
- Information on adverse effects in patients different from study subjects (different ages)
- Information on rare adverse effects not previously seen in adults
- Information on long-term safety
Why Is Pediatric Drug Research Not More Common?

- Smaller market for pharmaceuticals
- Harder to enroll children in trials
- Ethical issues of consent /assent

Problems

- Children are denied useful drugs
- Children are exposed to non-useful or toxic drugs
- Accurate dosing and efficacy not known
What Factors Impede or Enhance Effective And Safe Drug Development in Children?
Barriers to Drug Development in Pediatrics

- Dependence on Pharmaceutical Industry
  - Driven by market factors and prior drug development
- Fewer studies in children
- Incomplete understanding of disease processes and drug effects, both short and long-term
- Fewer individuals with pediatric expertise in pharmacoepidemiology, pharmacovigilence, pharmacogenetics, clinical toxicology, etc.
To Enhance Pediatric Drug Development

- Increase support of basic and clinical research of therapeutic agents for children including more pediatric trials
- Involve Pediatric Heart Network/NHLBI or other pediatric networks
- Increase pediatric comparative effectiveness studies of currently used drugs
- Support educational efforts in the field of pediatric therapeutics
- Support registries to collect information on severe adverse events such as sudden cardiac death and identify signals from drugs
- Develop and apply informatics infrastructure to pilot test regulatory requirements, e.g. hospitals/physicians to report all adverse drug events or medication errors in children
Thank You