Pediatric Drug Trials, Lessons Learned

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Challenges in Pediatric Trials

- Relative rarity of specific diseases
  - disease heterogeneity
  - incompletely defined natural history
- Lack of research infrastructure
- Ethical issues in pediatric research
  - Children cannot give consent
  - Benefits must outweigh risk
- Difficulty in identifying valid clinical endpoints
- Large amount of clinical practice variation
Pediatric Cardiovascular Drug Studies

- Hypertension
- Congestive heart failure
- Antiarrhythmic agents
- Antithrombotic agents
Lesson 1: PK/PD studies are important precursors to efficacy studies

- Developmental changes in children
- Absorption, distribution, binding, clearance of drugs are age-dependent
- Pitfalls when using extrapolated dosing
Lesson 1: PK/PD studies are important precursors to efficacy studies

- Use preliminary PK/PD studies to guide dose selection
- Sub-therapeutic dosing will lead to an efficacy study with no effect
- Over-dosing may lead to an increase in adverse events
- PK/PD information to see a positive slope in a dose response curves (hypertension)
  - Closely spaced dosages will may yield overlapping exposures among dose groups
  - If overlap is substantial, the dose response could appear flat and fail to demonstrate a dose response relationship (amlodipine, fosinopril, irbesartan)
Lesson 2: Appropriate formulations are important for drug delivery

- Liquid formulations allow for more precise dosing per kg
- Crushed tablets suspended in aqueous medium are bitter
- Ideal oral drug for children should be effective, well tolerated, have good stability, and have good palatability with acceptable taste, after-taste and smell
- Stability and bioequivalence testing of liquid formulations require additional time and expense
Lesson 2: Appropriate formulations are important for drug delivery

- Many failed antihypertensive studies (amlodipine, fosinopril, irbesartan) did not develop a liquid formulation with resulted in imprecise dosing throughout the trials.
- PICOLLO study (clopidogrel)
  - Extemporaneous solution
  - Very bitter and stability of only several days
- Carvedilol
  - Combination liquid and pill
Lesson 3: Obtain clinical equipoise

- The ethics of clinical research require equipoise
  - state of uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial
- Equipoise required for colleagues, referring physicians and parents as well
- Parents often have therapeutic bias
  - Will hesitate to enroll their children in RCT with placebo arm when they are aware that the active agent is readily available for adults or off-label.
Lesson 3: Obtain clinical equipoise—example

- Conflicting data reported from trials of ACE inhibitors for MR in both adults and children
- Pediatric Heart Network/NHLBI ACE Inhibition in Mitral Regurgitation Study
  - Enalapril vs. placebo in children after AVSD repair with at least moderate MR and LV dilation
  - Of 139 subjects with at least mild to moderate MR on a screening echo, 47 were already on ACEi
Lesson 4: It’s all in the primary endpoint!

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Surrogate Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACEi, ARB, β-blockers</td>
<td>Hypertension</td>
<td>BP lowering effect (DBP vs. SBP)</td>
</tr>
<tr>
<td>Statins</td>
<td>Hyperlipidemia</td>
<td>LDL lowering effect</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>Atherosclerosis in children with lupus</td>
<td>Carotid IMT</td>
</tr>
<tr>
<td>Enalapril</td>
<td>Infant Single Ventricle</td>
<td>Growth</td>
</tr>
<tr>
<td></td>
<td>Mitral regurgitation post AVSD repair</td>
<td>LV end-diastolic dimension Z-score</td>
</tr>
<tr>
<td>Sildenafil</td>
<td>Pulmonary hypertension</td>
<td>Exercise tolerance</td>
</tr>
<tr>
<td>Ataluren</td>
<td>Duchenne’s muscular dystrophy</td>
<td>6 min walk test</td>
</tr>
</tbody>
</table>

- Knowledge of the natural history with regard to surrogate endpoint and its relationship to the clinically meaningful endpoint is vital.
- Ability to accurately obtain the test.
Lesson 4: It’s all in the primary endpoint!

<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Composite Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Milrinone</td>
<td>Post-op congenital HD</td>
<td>Death, or low cardiac output syndrome requiring additional or new pharmacologic or mechanical support</td>
</tr>
<tr>
<td>Carvedilol</td>
<td>Heart failure</td>
<td>Worsened, unchanged, or improved. Worsened defined as death, hospitalization requiring IV meds, treatment failure, worse HF class or global assessment score</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Post-op systemic to pulmonary artery shunt</td>
<td>Death, shunt thrombosis, or intervention &lt;120 days for a condition of a thrombotic nature</td>
</tr>
<tr>
<td>Alglucosidase alfa</td>
<td>Pompe disease</td>
<td>Death or need for invasive ventilation at 18 months of age</td>
</tr>
</tbody>
</table>

- Mostly a combination of a hard endpoint and soft components
  - Addresses broader aspects of a multi-faceted disease
  - Soft endpoints are subject to ascertainment ambiguity and clinical practice variation between centers