

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.
- PICOLO 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!

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

- 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!

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

- **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**