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Pediatric Cardiovascular Drug Trials, Lessons Learned

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Abstract

Few drugs have been labeled for pediatric cardiovascular indications and many children with cardiac disease are prescribed drugs off-label. Recent initiatives have narrowed this gap and as a result there are an increasing number of cardiology trials in the pediatric population. Many studies, however, have either failed to show a dose response in children or have not shown efficacy in children when they have established efficacy in adults. Clinical trials are challenging in children; many factors such as lack of development of a liquid formulation, failure to fully incorporate pharmacokinetic information into trial design, poor dose selection, the lack of clinical equipoise, and the use of difficult surrogate and composite primary endpoints have led to the difficulties and failures observed in several pediatric cardiovascular trials. These lessons learned may help to inform future pediatric clinical trial development.

Randomized clinical trials have resulted in remarkable advances in cardiovascular care. During the 1990s, results from more cardiovascular clinical trials were published than in the previous three decades combined, ushering in the current era of evidence-based cardiovascular medicine. (1) Cardiovascular trials have established novel treatments resulting in major improvements in patient outcomes and have also enhanced our understanding of heart disease and the impact of risk factors and adverse events. Certain populations, however, have been underrepresented in cardiovascular clinical trials, including women, the elderly, minority populations, and children (1-3).

Many barriers impede the design and conduct of randomized clinical trials in children, including the relative rarity of specific diseases, disease heterogeneity, incompletely defined natural history, lack of research infrastructure, ethical issues in pediatric research, and difficulty in identifying valid clinical endpoints. Systematic controlled studies of medications in children with congenital heart disease have thus been limited and most medications are not labeled for pediatric use. Therefore, treatment decisions in this population are often based on clinical experience, small observational studies, and extrapolation from adult data, rather than clinical trial evidence. Fewer than 25% of approved drugs marketed in the USA have sufficient pediatric data to support approval for labeling for dosing, safety, and efficacy in children. Inadequate dosing and safety information places children at risk for adverse events and denies them potential therapeutic benefits. Pediatricians must therefore prescribe drugs to children for whom the dose, efficacy, and safety have not been studied. This practice known as “off label use” may result in benefit, no effect, or harm. This lack of information has had a negative impact on pediatric therapeutics, including reliance on anecdotal practice patterns, adaptation of data from adult trials that may not be applicable to children, and the use of extemporaneous formulations that may be inconsistently bioavailable. A recent study by Pasquali et al

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showed that in over 30,000 children hospitalized with cardiovascular disease, 78% received more than one cardiovascular medication off-label, and 31% received more than three cardiovascular medications off-label (4).

In order to narrow this knowledge gap, there have been significant advances over the past several years including legislative initiatives and National Institutes of Health (NIH) cooperative networks for children. The Food and Drug (FDA) Modernization Act in 1997 and the Best Pharmaceuticals for Children Act in 2002, authorized an incentive program known as Pediatric Exclusivity in the form of 6 additional months of marketing exclusivity for manufacturers who conducted pediatric clinical trials in response to a FDA written request. The Pediatric Research Equity Act in 2003 codified the authority of the FDA to require pediatric studies of certain drugs and biological agents. These key programs were reauthorized in the Food and Drug Administration Amendments Act of 2007. The European Medicines Agency has recently started to require drug studies in children and has begun to receive pediatric investigation plans for new molecular entities. In an attempt to narrow the scientific gap in the pediatric cardiovascular population, the National Heart, Lung, and Blood Institute established the Pediatric Heart Network (PHN) in 2001(5). The PHN is a cooperative network of eight clinical centers and one data coordinating center. The mission of the PHN is to achieve public health advances through the conduct and dissemination of collaborative research leading to evidence-based treatment options for and improved outcomes of pediatric patients with congenital and acquired heart disease. The network approach is an effective, flexible way to study adequate numbers of patients with uncommon diseases, such as congenital cardiovascular malformations. Efficiencies are achieved through a common infrastructure with standardized methods for recruiting, monitoring, and following subjects.

These initiatives have lead to many clinical trials of cardiovascular medications in children. Of note, however, many of these studies performed to date have failed to show a dose response or have demonstrated lack of efficacy in children when they are effective in adults. As this pattern emerged, several key lessons in planning and executing pediatric cardiovascular drug trials became apparent. These factors are discussed below.

1. Development and Use of a Liquid Formulation

Several of the trials of orally administered agents (particularly antihypertensive agents used in the trials that failed to show a dose response) did not develop a pediatric (e.g. liquid) formulation and, thus, exhibited a wide range in exposure within each weight stratum. Other clinical trials used either an extemporaneous formulation (clopidogrel study) or a combination of a liquid formulation and a pill (carvedilol study). Precise dosing is not feasible using a limited number of tablets; liquid formulations allow for more precise dosing per kilogram of body weight. An ideal oral drug for children should be effective, well tolerated, have good stability, and have good palatability with acceptable taste, after-taste and smell. Modern medications are complex mixtures containing many other components besides the active ingredient. These are called 'inert ingredients', or excipients, and consist of bulk materials, flavorings, sweeteners and coloring agents. These excipients increase the bulk, add desirable color, mask the unpleasant taste and smell, and facilitate a uniform mixture of the active ingredient in the final marketed preparation. Unlike the active ingredients, excipients are not well regulated in most countries. Although mostly well tolerated, some adverse events and idiosyncratic reactions are well known for a variety of excipients. These components play a critical role, especially in liquid and chewable preparations that are mostly consumed by infants and children (6) Development of a liquid formulation is often challenging because bioavailability can be unreliable, and dissolving the agent in liquid can require high concentrations of alcohol. In addition, stability and

bioequivalence testing of liquid formulations also require additional time and expense. Moreover, it is important that the liquid formulation be palatable and often crushed tablets suspended in an aqueous medium are bitter which ultimately will affect drug compliance. Despite these issues, pediatric formulations should be requested in the Pediatric Drug Development Programs whenever possible. Development of these formulations is now more economically feasible because of benefits provided to companies for successfully completing trials requested by FDA as part of this program.

2. Pharmacokinetic evaluation

Infants and children are far different from adults in terms of drug absorption, distribution, metabolism, and elimination. In addition, there are differences in the ability to deliver therapy in children compared with adults (e.g. vascular access and formulation) and there are dietary differences between children and adults which can effect drugs which have interactions with food (e.g. warfarin). Therefore, formal pharmacokinetic evaluation is needed in order to properly select the dosages of drug used in an efficacy trial particularly since smaller children may have different dosing needs than larger children. For example, a pharmacokinetic study of sotalol showed that its clearance is linearly correlated with body surface area and creatinine clearance with smaller children displaying greater drug exposure than the larger children (7).

Many studies to date, however, have used extrapolation from adult studies when selecting the dose. Extrapolating from adult studies can lead to either underestimation or overestimation of the target dose. For example, the standard adult dose of clopidogrel is 75 mg po q day (i.e. roughly 1 mg/kg/day) which provides 30-50% inhibition of 5 μ mol/L ADP induced platelet aggregation; this dose has been shown to treat and prevent major cardiovascular events in adult trials. However, in infants and children ages 0-24 months, a dose of 0.2 mg/kg/day achieves a mean 30-50% inhibition of 5 μ mol/L of ADP-induced platelet aggregation, a significantly lower dose (8). On the other hand, the American College of Chest Physician Guidelines recommend 0.75 mg/kg bid of Lovenox for neonates and 0.50 mg/kg bid for children > 2 mos in order to achieve anti-activated factor X (Xa) levels of 0.5-1 and 0.1-0.3 U/ml respectively (9). However, a recent study in 299 children, 59% with deep venous thrombosis showed that those <1 year of age required ~1.5 mg/kg with frequent dose changes to achieve target therapeutic range, a considerably higher dose than that obtained from extrapolating from adult data (10).

Thus, precise pharmacokinetic and pharmacodynamic dosing data are important in children and this information should be available prior to executing an efficacy study. Sub-therapeutic dosing may lead to an efficacy study with no effect while over dosing may lead to a larger number of adverse events in the efficacy study.

3. Dose Response

For anti-hypertensive agents, the FDA has requested dose response information with regard to blood pressure lowering effect (Table 1). The results of many, but not all, of the clinical trials of anti-hypertensive agents in children have resulted in publications in scientific journals (11-23). Review of the various anti-hypertensive trials performed to date reveals that the dose-range received by children randomly assigned to low- and high-dosage groups is extremely variable between trials. For example, in the amlodipine trial which did not show a dose response, there was only a 2-fold difference between the high-dosage and low-dosage groups (11). Children in the high dosage group received 5 mg and children in the low dosage group received 2.5 mg. In the fosinopril, valsartan and irbesartan trials, a similar pattern of lack of dose response was also seen with small dosing ranges at 6-, 8- and 9-fold, respectively (17,18,23). The enalapril, lisinopril, and losartan trials (which were successful

in demonstrating a dose response) had considerably higher dosing ranges, at 32-fold, 32-fold, and 20-fold, respectively (14,19,20). The successful trials thus incorporated a wide range of doses. The lowest clinical trial dose should be lower than the lowest approved dose in adults, and the highest clinical trial dose should at least be 2-fold higher than the highest approved dose in adults, unless contraindicated for safety concerns.

Successful trials therefore provided large differences across low-, medium-, and high-dosage strata. Successful trials used dosages much lower (nearly placebo) than the dosages approved in adults. For example, the recommended initial lisinopril dose in adults is 10 mg, and the usual dose range is 20 to 40 mg. The lowest dosage used in the pediatric clinical trial was 0.625 mg, thus providing a wider range for exploring dose response. The selection of wide dosage ranges has important pharmacokinetic/ pharmacodynamic implications because closely spaced dosages will likely yield overlapping exposures among dose groups. If overlap is substantial, the dose response could appear flat and, thus, fail to demonstrate a significant dose response relationship.

4. Clinical equipoise

The ethics of clinical research require equipoise--a state of uncertainty on the part of the clinical investigator regarding the comparative therapeutic merits of each arm in a trial (24). A recent failure of the Pediatric Heart Network's Angiotensin Converting Enzyme (ACE) Inhibition in Mitral Regurgitation Study highlights the importance of clinical equipoise in pediatric trials (25). The study investigators sought to evaluate the efficacy of the drug enalapril versus placebo in reducing left ventricular volume overload in children with at least moderate mitral valve regurgitation following surgical repair of atrioventricular septal defect. The investigators had clinical equipoise with each arm in the drug trial based on conflicting data reported from trials of ACE inhibitor therapy for the treatment of mitral regurgitation in both the adult and pediatric populations. Equipoise, however, could not be uniformly established among their colleagues at the participating centers. A total of 47 patients screened for the trial with at least mild to moderate mitral regurgitation noted in the chart were already on ACE inhibitors or had ACE inhibitor use planned by their primary cardiologists. These physicians may have felt compelled to use medical therapy because they believed that such therapy might delay the need for repeat mitral valve surgery despite the lack of evidence showing benefit of ACE inhibitors in this setting. Others may have used ACE inhibitors because they were not fully informed of the study and used the medicine routinely in their patients after atrioventricular septal defect surgery. The lack of clinical equipoise was a significant factor leading to under accrual of subjects into the studies, which ultimately lead to its subsequent failure.

In addition to the importance of clinical equipoise, there is the concern about therapeutic bias on the part of parents. Many parents will hesitate to enroll their children in studies involving drugs which involve a placebo arm when they are aware that these agents are readily available for adults. In addition, parents may have other concerns regarding conflict of interest in research between their physicians and pharmaceutical sponsors.

5. Primary Endpoint

It is often impractical to conduct a pediatric clinical trial to gather a statistically significant number of hard clinical endpoints. Thus, many pediatric trials use either surrogate or composite endpoints. The use of such endpoints while beneficial for sample size may cause concerns with meaningful clinical validity and substantial correlation to a desired outcome that cannot be effectively measured (morbidity or mortality).

Surrogate endpoints

A surrogate endpoint of a clinical trial is a laboratory measurement or a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient functions or survives. Changes induced by a therapy on a surrogate endpoint (e.g. blood pressure lowering effects, exercise capacity) are expected to reflect changes in a clinically meaningful endpoint.

Many successful pediatric hypertension trials used change in diastolic blood pressure (DBP) as the primary endpoint. Several unsuccessful studies (e.g. trials of amlodipine, irbesartan, and fosinopril) used change in sitting systolic blood pressure (SBP) as the primary outcome. A study evaluated the reduction in SBP and DBP related to several agents and found that a reduction in DBP was more closely related to the dosage of agent administered (26). For example, in the enalapril trial where DBP elevation was the entry criteria, the dosage was more closely related to a reduction in DBP than SBP (coefficient 0.19 [P=0.001] versus coefficient 0.12; P=0.08). We also observed a closer relationship between DBP reduction and dosage in the lisinopril trial (coefficient 0.12 [P=0.001] versus coefficient 0.08; P=0.09). The reason for this closer relationship between DBP reduction and dosage may be related to the fact that there is less variability associated with measurement of DBP compared to SBP. Perhaps more likely is the fact that inclusion of DBP as a primary entry criteria tends to select children with secondary forms of hypertension. These patients are more likely to respond to drugs affecting the renin-angiotensin-aldosterone system, as seen with the lisinopril, enalapril, and losartan studies.

In pediatric heart failure and pulmonary hypertension clinical trials, surrogate endpoints have been difficult to utilize with success. For example, sildenafil trials in pediatric pulmonary hypertension have attempted to use exercise capacity as the primary outcome but found that it could not be reliably measured in children less than 7 years of age who are often developmentally unable to perform the test. This difficulty was compounded in children with Down syndrome who are predisposed to the development of pulmonary hypertension (27).

In the Pediatric Heart Network, a trial was launched to evaluate the effects of enalapril on mitral regurgitation in children after atrioventricular septal defect repair (25). The surrogate endpoint was the change in left ventricular end diastolic dimension body surface area-adjusted (LVEDD BSA-adjusted) Z score. For eligibility, the subjects were required to have the presence of at least moderate mitral regurgitation with either a proximal regurgitant jet area $\geq 6 \text{ mm}^2/\text{m}^2$ or a regurgitant fraction $\geq 30\%$ with evidence of left ventricular dilation demonstrated by a LVEDD BSA-adjusted Z-score ≥ 2 . This definition was adapted from published guidelines in adults. The selection of these criteria combined a quantitative measure of the severity of mitral regurgitation with evidence of left ventricular enlargement. However, after screening 349 patients, only 9 patients were eligible; 34 patients met the criterion of regurgitant jet area but surprisingly did not have left ventricular dilation. In retrospect, problems arose due to reliance on methodology developed in adult populations with different disease mechanisms and the absence of adequate data to define the natural history of the disease process under study. In this study, it was presumed that left ventricular dilation would be a mechanistic consequence of significant mitral regurgitation, but in fact there was failure to detect ventricular dilation in a significant number of subjects who met adult quantitative criteria for at least moderate mitral regurgitation. Prior to initiating this trial, there was insufficient natural history data to define the frequency and timing of onset of ventricular dilation as a consequence of mitral regurgitation after atrioventricular septal defect repair.

Another example of the use of a surrogate endpoint was the use of growth in the Pediatric Heart Network Infant Single Ventricle Trial to evaluate the use of enalapril for heart failure (28). The study randomized 230 infants to enalapril or placebo with the primary endpoint of weight for age Z-score at 14 months. Weight-for-age z score was not different between the enalapril and placebo groups and there were no significant group differences in height-for-age z score, Ross heart failure class, brain natriuretic peptide concentration, Bayley scores of infant development, or ventricular ejection fraction. The incidence of death or transplantation was 13% and did not differ between groups. Thus administration of enalapril to infants with single-ventricle physiology in the first year of life did not improve somatic growth, ventricular function, or heart failure severity.

Composite endpoints

A composite endpoint in a randomized controlled trial consists of multiple single endpoints that are combined. Each single endpoint should have clinical significance and interpretability in its own right. The composite endpoint then becomes a measure of effect from a combined set of different variables. The motivation to use a composite endpoint in a clinical trial is driven by the fact that a composite endpoint can reduce the size of the trial if the components of the composite increase the number of events. In addition, a composite endpoint can address broader aspects of a multifaceted disease and can combine “soft” components (e.g. re-hospitalization) that have more frequent events with “hard” components (e.g. mortality) that occur infrequently. In general, components should add to the total treatment effects in the same direction and be easily ascertainable with regards to occurrence.

Examples of composite endpoints used in randomized pediatric cardiovascular trials are shown in Table 2. Of note, these studies used a combination of hard components which are clinically convincing with unambiguous ascertainment (e.g. death) as well as soft components which may be considered less clinically convincing and subject to difficulties with ascertainment (e.g. clinical worsening) and to differences in clinical practice (e.g. re-intervention) among centers. This level variability in the trial can make the relationship between the composite and components weaker than desired and may have contributed to some of the negative trial results from some of these clinical trials.

Conclusion

Pediatric drug trials are often conducted after a product has been developed for adults, and information developed from previous adult trials is often used to design pediatric trials. Yet, because of the small number of pediatric patients with a given disease and the ethical mandate that children should not be exposed to additional risks without potential benefit, pediatric studies tend to be smaller in size. Pediatric drug trials are thus technically challenging; they are a substantial investment and children cannot give consent and the ethical bar is higher. However, well-powered safety and efficacy trials for therapeutics are a critical component of pediatric health. Given evidence indicating different toxicities and benefit for drugs in children compared with adults (32), pediatric clinical trials are necessary to appropriately assess therapeutic agents.

.As a result of important initiatives, much has been learned about the treatment of cardiovascular disease in children and adolescents in the last decade. This expansion of our knowledge base allows for improved understanding of efficacy and safety of these agents. Understanding clinical trial design in pediatric studies is paramount: lack of liquid formulation development, failure to fully incorporate pharmacokinetic information into trial design, poor dose selection, the lack of clinical equipoise, and the use of difficult surrogate

and composite primary endpoints have led to the difficulties and failures observed in several pediatric cardiovascular trials.

Many issues regarding pediatric study design need further evaluation. In the future the development of exposure-response models using adult and pediatric data and the use of these models to perform clinical trial simulations of pediatric studies and to explore trial designs and analysis options would be of potential benefit. In addition, pediatric registries and studies which better define the natural history of pediatric cardiovascular conditions will facilitate the conduct of randomized clinical trials involving these conditions (27-29). Progress in the treatment of children with cardiovascular disease will depend on the future of these multi-center collaborative clinical trials. Hopefully, the issues discussed and the lessons learned from these past studies will facilitate improved research for children.

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Table 1**Pediatric Antihypertensive Drug Clinical Trials**

Drug [ref]	Sample size	Dose response	Label change
Amlodipine [11]	268	No	Yes
Benazepril	107	No	Yes
Bisoprolol [12]	94	Yes	No
Candesartan [13]	240	No	Pending
Enalapril [14]	110	Yes	Yes
Eplerenone	304	No	Yes (negative)
Felodipine [16]	133	No	No
Fosinopril [17]	253	No	Yes
Irbesartan [18]	318	No	Yes (negative)
Lisinopril [19]	115	Yes	Yes
Losartan [20]	175	Yes	Yes
Metoprolol [21]	140	No	Yes
Quinapril [22]	112	No	No
Ramipril	219	No	No
Valsartan [23]	351	No age 1-5/Yes age 6-16	Yes

Table 2

Pediatric Cardiovascular Trials with Composite Endpoints

Drug [ref]	Indication	Composite Endpoint
Milrinone [30]	Post-operative congenital heart disease	Death, or low cardiac output syndrome requiring either additional or new pharmacologic or mechanical support
Carvedilol [29]	Heart failure	Worsened, unchanged, or improved. Worsened defined as death, hospitalization requiring IV medications, treatment failure, worse HF class or global assessment score
Clopidogrel [31]	Post-operative shunt	Death, shunt thrombosis, or intervention <120 days for condition of a thrombotic nature