# Cardiac Safety Research Consortium: Pediatric Think-Tank

December 10th, 2010

White Oak Facility, FDA Headquarters

Silver Springs, MD

Dr. Dianne Murphy, Director

Office of Pediatric Therapeutics

Office of the Commissioner, FDA

# Drug Development Surveillance and Pediatric Cardiovascular Safety: Where Are We and Where Do We Need to Go?

# Overview

- Cardiovascular Products studied in Pediatrics under BPCA and PREA
- “Failures”
- Extrapolation
- Safety

# Pediatric Cardiac Trials: BPCA and PREA Trials Resulting in Labeling

- Hypertension: N= 12
- “In hospital” decrease of BP: N=1

- Heart Failure: N=1

- Lipid Lowering: N= 8

- Arrhythmia: N= 1

- Imaging: N=1

# High “Failure” Rate

- Hypertension: N=13
  approximately 50% failure
- Heart Failure: not successful N=1
- Arrhythmia: Not successful N=1
- Lipid Lowering: usually successful

# Pediatric Hypertension Failures

- **Pediatric Antihypertensive Trial Failures: Analysis of Endpoints and Dose Range**
  Daniel K. Benjamin, Jr., MD, PhD, MPH; P. Brian Smith, MD; Pravin Jadhav, PhD;Jogarao V. Gobburu, PhD; M. Dianne Murphy, MD; Victor Hasselblad, PhD; Carissa Baker-Smith, MD; Robert M. Califf, MD; and Jennifer S. Li, MD, MHS
- **Hypertension 2008;51;834-840, March 10, 2008**

# Hypertension: Pediatric Failed Trials

- Looked at 6 trials
- Successful: enalapril, lisinopril, losartan
- Unsuccessful: amlodipine, fosinopril, irbesartan
- Possible Explanations:
  - Dose Range too narrow and weight discrepancy in dose
  - Success on sitting Diastolic vs Systolic EP

# Heart Failure: Possible Reasons for "failure"

The study did not detect a treatment effect of the drug on the primary composite end point

- Children and adolescents with CHF do not receive benefit from this drug due to differences in the etiologies of heart failure in children and adolescents: dilated cardiomyopathy and congenital heart disease compared with adult ischemic heart disease.
- Several factors in the study design and enrolled population could also have influenced the final result.

  -There was no attempt to establish the appropriate age-related dose prior to the study. The higher dose was chosen on the basis of a linear, weight-based, extrapolation from adult doses. The lower dose was arbitrarily chosen to be half the higher dose.

  -Trough drug plasma levels measured during the study were lower in children and adolescents than in adults given a similar dosage per unit weight.

  -Subsequent work suggests that the ontogeny of this drug's pharmacokinetics depends on age as well as weight and the doses used in this study may have been too low.

# Heart Failure (cont'd)

- The composite end point used in the study was not validated for heart failure studies in children and adolescents, and may be inappropriate for developing children.
- The power calculation was based on adult data and greatly underestimated the 19% improvement in the placebo group during the 8 months of the study.
- In addition, there was no provision to examine a possible dose response effect; the prespecified primary analysis compared the combined study product group (low and high dose) with placebo.
- Also, the results suggested that there may be a differential effect of this therapy in children and adolescents depending on the underlying pathophysiology. Further work would be needed to prove this.

- Although the study is uninterpretable, these findings will inform future trials in children and adolescents with CHF.

# Extrapolation of Efficacy

- To “extrapolate” efficacy from adults or an older pediatric population one needs to determine:
  - The disease AND
  - The response to therapy

    ARE SUFFICIENTLY SIMILAR
- If they are, then efficacy studies are not needed but other studies to determine dose and safety are needed

# Extrapolation (cont'd)

- If one canNOT extrapolate then 2 adequate and well controlled trials are required.
- One may not be completely certain and wish to have other efficacy data:

  - 1 adequate and well controlled trial

  - Various "Exposure/Response" trials

# Extrapolation: Hypertension

- Fenoldopam:  for  induced hypotension during surgery
- Tanner Stage: 1-2 to 12 years
- MC, PK/PD trial:  R, initial  DB,PC, dose-ranging study then open label dose-titration of IV infusion.
- Short term (around 2 hours)
- Extrapolated efficacy from adults, supported by data from dose response study.
- Labeled.

# Extrapolation: Exposure/Response

- lisinopril, fosinopril,benazepril,ramipril,enalapril,
- eplenerone,losartan,valsartan,irbesartan,
- bisoprolol,metoprolol,felodipine,amlodipine)

- Extrapolation based on continuity between adults and children.

- 6-16 years;  PK and safety data in all age groups

- single, DB, R, PC, PG, DR, efficacy and safety study 2 week study period (choice of designs suggested)

# Extrapolation: Exposure/Response

- Most dose response studies conducted in ages 6-16 years.
- If effective, the drug is indicated in the age group in which the pediatric clinical trial was conducted.
- While PK data may be available for younger age groups (not studied in the clinical trial), these data are not included in the label since the drug's effectiveness is unknown in the younger age group.
- Sponsors are warned that if a placebo arm is not included in the DR trial then the trial may be uninterpretable if there is no significant difference between the doses tested.

- Ramipril, eplenerone, fosinopril, bisoprolol, metoprolol, felodipine, amlodipine,irbesartan not labeled.
- Enalapril labeled for 1month -16 years.
- Lisinopril, benazepril, losartan, valsartan labeled for 6 years+.

# Extrapolation: Exposure/Response

- Peri-operative hypertension (coarctation of the aorta)
- Esmolol:  0-6 years, 2-7 years
- Single R, DB, 3 dose level, DB study. PEPs measured at 5 minutes. Follow up 24-48 hours. SD, uncontrolled PK study
- Study uninterpretable because flat dose response and no placebo arm. Would have extrapolated from coarctation to other surgical situations.
- Uncontrolled study in patients with SVT undergoing catheterization. Efficacy
- data collected but uninterpretable as no placebo arm.
- Not labeled.

# Extrapolation: Exposure/Response

- Congestive heart failure (CHF)
- Carvedilol:  2 months-17 years
- Single PC safety and efficacy study plus pK and safety data. (Study failed)
- Pediatric CHF more likely due to congenital HD (IHD for adults).
- FDA discussed requiring same level of evidence as adults as disease process not the same. (ie 2 trials at $p<0.05$ or one trial at $p<0.00125$). Finally requested single trial at $p<0.0535$
- Not labeled.

# Safety of Products Studied in Pediatrics

- Most studies stated there were no differences in reported AE's for pediatrics
- For the "sartans", warnings against using in patients with decreased glomerular filtration and potential effects on developing kidney.
- Benazepril: there were comments on the higher clearance

# Safety from Pediatric Trials

- The largest set of studies for an individual product was over 400 pediatric patients.
- Most studies for hypertension involved less than 300 pediatric patients
- The study for CHF involved over 300 pediatric patients

# Post Marketing Safety: 1 year after labeling from Pediatric Trials

- Mandated 1 year Post marketing Pediatric Safety Review
- Beginning in 2002 with BPCA and enhanced to include PREA in 2007
- Must be public discussion= goes before the Pediatric Advisory Committee for review and recommendations.
- Focus is on pediatric population

# Pediatric PM Safety Reviews

- Hypertension Products: N= 9

  7 return to routine monitoring

  1: (Benazepril) requested additional f/U-then routine

  1: (Valsartan) requested additional information re potential for development of pulmonary hypoplasia

- Lipid Lowering Products: N=7

  2 requested additional monitoring

  and for Lipitor requested additional labeling concerning increase in hallucinations and agitated behavior in the pediatric population

# Pediatric PM Safety Reviews

- Carvedilol: requested label change to add same information re hypoglycemia that is in the propanolol label

- Cardiolite: routine monitoring

# Summary

- We need better pediatric endpoints
- We are learning from even the “failed” pediatric studies
- Pediatric safety signals will have to occur at about or higher than 1% frequency if we are going to identify them in the studies.
- Cardiovascular studies tend to be some of the larger drug pediatric studies.
- Post marketing Pediatric focused reviews have not revealed any serious, new pediatric signals for the cardiovascular products.
- Overall, this process has identified new, or more severe AE’s in the pediatric population in 10- 20% of products.