

Wrap Up: Day 1

Session 1: Chronic hypertension

- Most drug development for treatment of hypertension are conducted in adults first
 - FDA can require pediatric development under certain circumstances
 - Cannot use retroactively for drugs already approved
 - FDA can incentivize studies
- 61 drugs approved in adults; on 16 drugs approved in children
 - ACEI; ARB; only 1 CCB and 1 beta blocker!
 - 9/16 approved 6 years of age and older
 - 3/16 approved < 6 years of age: enalapril (1 month of age), candesartan and valsartan (1 year of age)
 - 4/16 “approved”; have dosing information for children : hydralazine; chlorothiazide and hydrochlorothiazide; minoxidil approved 1979

Session 1: Chronic hypertension

- Current state of antihypertension development
- New dosage forms—FDA can require studies under PREA
- Here is the opportunity: when and how do we collect information to fill gaps in approvals (e.g., < 6 years of age)
 - What studies are needed?
 - What studies are feasible?
- How can pediatric extrapolation be used?
- What off-label use can be leveraged?
- What study designs can be considered?

Similarities and Differences between adult and pediatric chronic hypertension



- Similar pathophysiology
- Similar biology
- Target organ damage is the same
 - Physiology is similar; alterations in pulse wave velocity; CV disease; kidney disease; retinopathy; stroke and dementia
- Measurement is the same
- BP norms are different: static vs. age/percentile-based thresholds
- Comorbidities less common in children more common in adults
- Etiologies are different: primary hypertension more common > 6 years of age; less common < 6 years of age
- Treatment paradigms different
 - adults generally use common dose and escalation; emphasis on combination therapy
 - Pediatric: lack of data on combination therapy
- Fewer patients
- HTN trials have relied on validated surrogate (BP): SBP in adult trials but DPB in some pediatric trials

Similarities and Differences between adult and pediatric chronic hypertension



- Endpoint measurement in clinical trials
 - SBP reduction compared to placebo based on office BP or use of ABPM
 - Achievement of target BP (responder analysis)
- Efficacy seen in all classes studied
- Anti-hypertensives lower BP in all age groups
 - RAAS blockers may have greater response given greater incidence of secondary HTN
- Older HTN drugs lack good dosing information

Off-label Prescribing Practices and Medication Errors



- Off label prescribing common for pediatric HTN
- Outpatient HTN medication usage study: 70% were off-label
- Neonatal hypertension: 100% off label
- Clearly are gaps between needs and guidelines and FDA labeling
- Liquid preparations
 - Issues with palatability (taste, smell, volume)
 - Issues with shelf life; administration
 - Osmolarity issues with small infants
- Newer dosage forms
 - Minitabs/pellets: no taste, no refrigeration
 - Neonates can take minitab down to 2mm minitab
- Appropriate dosage forms are not always available
- When appropriate formulation not available
 - Crush/mix: appropriate food to mix with
 - Compounding pharmacies not always available
 - Access issues
- Compounding errors can occur always occur when there is a need to manipulate the product

Age-appropriate Pediatric Formulations

- Needs: Can a child take it and Will a child take it?
 - Flexible and accurate dose methods of administration
 - Stability
 - Safety of excipients both based on type and amount
 - Acceptability
 - Palatability (taste, texture, smell)
 - Swallowability (size, shape, texture)
 - Administration
- Challenges
 - Low volume products
 - Requires manufacturing equipment and validation
 - Supply chain
 - In-process controls and equipment checks for accurate dosing capabilities; content uniformity

Panel 1

- What are the most significant unmet needs in the pharmacological management of hypertension in pediatric patients?
 - Approved treatments for patients < 6 years of age
 - More treatment options for older age children and adolescents with primary hypertension and metabolic syndrome
 - New agents and fixed dose-combinations for HTN and treatments for uncontrolled hypertension
 - Agents with longer acting medications and drugs that do not have drug interactions
 - Dosage forms that are suitable for all age groups particularly in neonates
 - Surrogate marker endpoints (comparative efficacy)
 - Excipients that are safe especially in neonates
 - Assessment of safety of excipients

Panel 1



- What are differences between pediatric-onset and adult-onset hypertension?
 - Differences between etiologies between < 6 year-olds and > 6 year-olds so RAAS blockade seen to be useful but treatment of HTN could include both HTN regardless of etiology
 - Response to treatment will depend on etiology
 - Is there an expectation that anti-hypertensive drugs would not work
 - Measurement issues exist but can be addressed
 - Diastolic BP elevations higher in CKD and secondary HTN
 - Systolic BP elevations higher in primary hypertension
 - Endpoint in adult trials are different than endpoints in pediatric trial
 - Differences in PD response between pediatric and adult hypertension
- Would any of these differences preclude inclusion of these patients in a pediatric HTN trial?
 - No

Panel 1

- Is the pharmacologic response to antihypertensive drug classes broadly expected to be similar across adult and pediatric patients?
 - Expected response should be similar between adults and adolescents
 - Neonates: are they different?
- Are there differences in drug responses within the pediatric age spectrum and what biological/developmental factors are most likely to drive those differences?
 - RAAS is more involved in secondary hypertension, particularly CKD
 - Safety/Toxicities should also be considered
- Would any of these differences preclude inclusion of these patients in a pediatric HTN trial?
 - No

Dose Response and Exposure Response Relationships for ARBs and Safety



- Candesartan
 - Exposure response and dose-response relationships between older and younger patients are similar
- Valsartan
 - Slightly lower response but there is overlap between older and younger children is similar
- Supports the acceptability of extrapolation of efficacy from older pediatric patients to younger patients for ARBs
 - Must consider similarity of disease
 - Must consider safety
- Safety Considerations
 - Different classes of drugs carry different potential risks
 - Age dependent risks based on maturation and development of glomerular and tubular function
 - Underlying disease and comorbidities affect risk

Panel 2

- Lessons learned and recommendations
 - Use weight-based dosing
 - Similarities in endpoint measurement in pediatric studies, particularly in younger population
 - Consider pooling of placebo patients across studies
 - Acceptability of placebo arm in trials
 - Reluctance of families to enroll in studies if safety is not clear
 - Optimizing communication and involving patients in trial design
 - Long-term extension
 - How long is long enough? 4-month study for durability of lowering of BP effect
 - Consider burden to family
 - Based on safety questions that need to be answered; e.g. longer-term for growth/development; cardiac sequelae

Modelling and Simulation and Dose Prediction



- Dose selection is challenging particularly for patients < 6 years of age
 - Iterative process based on accumulating data in adults and then children
 - Develop PBPK and/or popPK model
 - Collect pediatric data and then optimize model for younger pediatric patients
- Developmental changes that affect dosing
 - Metabolizing enzymes CYP system; UGT
 - Renal function; hepatic transporters; renal transporters
 - Modelling of mAbs also have special considerations
- Blood sampling scheme should take into account the acceptable limits

Innovative Trial Designs and Leveraging Existing Data



- Newer designs available
 - Use of novel controls: external control; hybrid; synthetic control
 - Adaptive design
 - Bayesian design
 - Master protocols: basket; umbrella
 - Patient/Family Unit centered study design considerations: incorporate patient and family choice in study designs early

Panel 3

- What are the gaps in knowledge for HTN for the following classes in patients 1-6 years of age
 - ARB/ACEi: Confidence in ARBs < 6 years of age for exposure response; gap for all the other drug classes
 - Similarity in CKD and non-CKD in exposure response
 - No comparative effectiveness studies in children
 - Safety findings including neurocognitive effects and long-term safety and efficacy
 - Combination therapies vs. maximizing single agents
 - Dosing changes as child grows; would PK data help to understand this observation
- BUT, the trials conducted to date demonstrate that the drugs that work in adults also work in controlled pediatric clinical trials
- What studies can be designed to address these gaps in knowledge
 - PK studies in children 1-6 for dosing (can be in children already being treated—prevalent population)
 - Include patients down to 6 years of age in all new anti-HTN drugs
 - Use sources such as PedsNet to collect safety data
 - External control arm could be used
 - What data are needed to evaluate certain specific risks? Clinical trial data would certainly help; communication with families can also help but also to study what matters to families—cognition, absenteeism, appetite
 - Needs to be feasible and generalizable
- What about neonates?

- What other infrastructure must be in place to collect this information to make these studies more feasible?
 - Decentralized trials
 - Involve families in trial design
 - Minimize discomfort
 - Communication with patients from clinicians (nephrology community)

Day 2: Uncontrolled Hypertension

- Drugs are now being developed for uncontrolled hypertension in adults
- FDA has the opportunity to require studies in children based on adult drug development under PREA under certain circumstances
- Is there an unmet need in children?
- If so, what population of children can be defined?
- What types of study designs can be considered?

Uncontrolled and Resistant Hypertension



- Adult
 - Uncontrolled hypertension is clearly a risk factor for stroke, MI, Cardiorenal metabolic syndrome
- Uncontrolled hypertension: BP is greater than goal
- Resistant hypertension: maximally treated with at least 3 drugs, including a diuretic, continued BP greater than goal or BP controlled with 4 or more antihypertensive medications
- Categories of uncontrolled hypertension severity similar to hypertension criteria
- Pediatrics
 - No definitions for uncontrolled or resistant hypertension
- Pathophysiology: multifactorial
 - Socioeconomic factors cannot be ignored
 - Adult: arterial stiffness; ET-1 elevation (e.g., obesity, sleep apnea)
 - Pediatrics: secondary hypertension: RAAS activations (aldosterone excess, RAAS resistance, primary hyperaldosteronism)
- An opportunity to better define uncontrolled hypertension in pediatrics

Treatment of uncontrolled hypertension in adults and pediatrics



- Additional considerations:
- Again, socioeconomic factors
- Nonadherence including the need to take multiple pills
- Comorbid conditions and drug interactions
- Medications available
 - Direct Renin Inhibitors: Aliskirin—(approved for hypertension) not approved in children
 - Aldosterone synthase inhibitors: Lorundrostat; Baxdrostat; not approved for children
 - Endothelin receptor antagonists: ambrisentan; macitentan; not approved for hypertension but approved for PAH; aprocitentan approved for uncontrolled hypertension
 - Angiotensinogen synthesis inhibitor: (small interfering RNA) not approved yet in any population
 - Potential treatments: SGLT2, GLP-1
- Role of combination products: combination products at lower maximum doses can achieve better effect

Panel 3

- Based on the adult programs is there a pediatric population that could benefit from drugs being developed?
 - Could define the population and use as add on therapy; those who need an additional agent
 - Strict definition of treatment resistant may not be absolutely necessary; the basic principle is similar between adults and pediatric patients; that they are not optimally controlled despite therapy
 - Etiology of the hypertension in this situation may not matter but not confident yet
 - Population would include pediatric patients 1-17 years of age
- Study design considerations
 - May not need RCTs for PK/PD and safety—confidence that the approved in adults provide confidence that the drug will likely work in pediatric patients in patients 6-17
 - Could potentially do a similar trial in 1-6 years of age but would be important to carefully evaluate the potential safety particularly in patients < 2 years
 - Need for long-term safety information particularly for agents with a novel mechanism of action. How long?
 - Do we need controlled safety?

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Thank You