CHD related Pulmonary Arterial Hypertension in Children

▲Hong Gu, from Beijing Anzhen Hospital, Capital Medical University

Long term surgical outcome for children with congenital heart disease (CHD) have improved dramatically in the past few decades due to the improvements in pre-operative and post-operative managements, cardiopulmonary bypass and intra-operative techniques. However, pulmonary arterial hypertension (PAH) still is one of the most common causes of morbidity and mortality in children with congenital heart defects. Estimated prevalence of CHD related PAH remains 30% in unrepaired patients and 15% in repaired patients worldwide. In China, we have more children with PAH due to the huge CHD population,misconception of CHD-PAH, and late diagnosis and treatment.

Classification of pediatric PH has generally followed the WHO classification, but recognition of the importance of fetal origins of PH and developmental abnormalities have led to the formation of a new pediatric-specific classification. CHD-PAH occurs in several easily differentiated scenarios: (1) "dynamic" which is related to shunt flow and responds to control of the shunt (often termed "preoperative PAH"), (2) late, post-operative PAH, (3) shunt reversal or "Eisenmenger's pgysiolosy", (4) immediate post-operative or "reactive" PAH (in patients who may or may not have had PAH pre-operatively), and 5) defects requiring maintenance of lower possible PVR (Patients with single ventricle after repair).

The evaluation of patients with CHD and the evidence of PAH require full investi-gations, including chest x-ray, Electro-cardiogram, Echocardiogram, Blood work, pulmonary function test, Ventilation/perfusion scan, CT or MRI and sometimes right –heart catheterization with vasodilator testing.

Pulmonary vascular resistance (PVR) is a critical and essential parameter during the assessment and selection of modality of treatment in patients with CHD accompanied by PAH. Previous study showed higher mortality rate in patients with a PVRI 7U/M2.

The predictors of mortality for PH have focused mainly on patients with IPAH before but these are likely useful in patients with CHD-PAH as well. Poor NYHA function status (class III or IV), low 6-minute walk distances, elevated right atrial pressure, higher PA pressure, depressed cardiac output and an absence of response to vasodilator testing were found to be predictive of outcome.

Although the treatment with new selective pulmonary vaso-dilators (including endothelin receptor antagonists, prostacyclin analogs, and phosphodiesterase type 5 inhibitors) offers hemo-dynamic and functional im-provement in pediatric popu-lations, the treatments in children largely depend on results from evidence-based adult studies and experience of clinicians treating children. Further studies with different type vasodilators for children with CHD-PAH are needed.

PH in Children: a Global Problem

Ian Adatia had given a talk about Clinical trials in children and neonates—Report of PH-ARC pediatric advisory committee.

Children are an exceptional population with special ethical and clinical concerns. It is said that about 9.2 million children die annually from diseases, and the most likely reason is lack of pediatric formulations for common drugs. The world health organization (WHO) estimates that more than 50% of medicines are prescribed for children, including many of those on the model list of essential medicines for children, do not actually exist in dosage forms appropriate for children used against infectious disease. Clinical research is of paramount importance in developing safe medications, pediatric formulations, clinical interventions and best practice guideline.

He made detailed interpretation of the involved ethical consi-deration, safety issues such as long term pharmacovigilance and intrinsic pediatric specific issues in the conduction of clinical trials as well as the diagnostic, categories and phenotype.

Also he showed the issues that need to consider are the clinical trial within small sample sizes and Pharmacokinetics, compounding and dosing of tar-geted medications.

He stated that the dosage forms should be accurate, safe, effective and acceptable, and the administration of a medication should be appropriate for children of various ages. Children vary in size and dose ranges are broader. The regular administration of medicine to an unwilling infant or child is a huge source of parental stress. The availability of stable liquid formulation should follow certain principle, avoid toxins, avoid high sugar content and unpalatable or bitter lasting compounds. Take into consider interaction of medicines with common drinks and foods of childhood and feeding formulas of babies. A detailed concept paper on the formulations of choice for the pediatric population has been adopted by the European medicines agency.

He declared that specific therapeutic needs of children ought to drive investigation of efficacy safety ideally. Pedia-tricians explore if drugs on the market can be used in children. There are some deficiencies, for instance, lack of consensus among pediatricians, drugs regulatory agencies and pharmaceutical companies. Requirements for the validation of clinical endpoints for the assessment of efficacy and safety and standards for long-term safety monitoring and pharmacovigilance. Drugs have potential to affect children differently from adults. Neonatal and childhood pulmonary hypertensive vascular disease share similarities with adults type disease. But there are some Differences in term of epi-demiology, impact of disease and treatment on developing child and lung and associated developmental abnormalities. PHVD is unique to children, and classical sample size calculations often lead to unrealistic expec-tation of the number of children who can be recruited.

In conclusion, drug trials in neonates and children with pul-monary hypertensive vascular disease pose unique but not in-surmountable challenges. Panama classification of PHVD in child-hood facilitates a more precise definition of disease phenotype. Panama classification of functional class provides a robust, age-related means of assessing functional status from age 0-18 years. Vali-dated repeated parent/child ad-ministered questionnaires with specific evaluation of reported abnormalities. PVRI linked to meaningful measures that show symptomatic benefit to the child, but EMA and FDA is skeptical about PVRI.

(By Meihua GUO)