International study on fragile newborns challenges current practices

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One of the largest clinical trials done in infants with congenital (present at birth) heart diseases, published in the *New England Journal of Medicine*, shows that the increasingly common practice of using the drug clopidogrel (Plavix) to reduce shunt-related blood flow issues is not effective in the dose studied.

"Once again, pediatric-specific research shows that newborns and infants are not little adults," said David Wessel, MD, Chief Medical Officer, Children's National Medical Center, and lead author on the international study published in the June 20, 2013 issue of the *New England Journal of Medicine*. "The take away message for pediatric cardiac care providers is to reconsider use of Plavix in certain cases. In pediatric medicine, the assumption is that smaller doses of a drug that works in adults will work in infants, but our study shows that this is not true for these young patients. For the parents of these fragile newborns, it is important to understand that research informs best practices, and they need to be informed advocates for their children."

The objective of this international trial, which included more than 900 patients seen across 134 centers in 33 countries, was to evaluate the efficacy of Plavix® compared with placebo for the reduction of all-cause mortality and shunt-related morbidity in neonates and infants with cyanotic congenital heart disease palliated with systemic-to-pulmonary artery shunts. Many forms of congenital heart disease can be repaired in early infancy, and pulmonary blood flow with shunts is an important consideration during initial treatment that may include reconstructive

heart surgery for defects in heart ventricles.

As the authors note, effective prevention for thrombosis (blood clots) in neonates and infants with these heart conditions had not been previously tested, although aspirin treatment was associated with significantly lower risk of mortality and shunt thrombosis in a separate registry developed before this trial. Preventive treatment in adult patients who develop clots in coronary arteries often combines aspirin and Plavix®. As happens with many drugs approved for use in adults, Plavix® use is spreading into pediatric practice without sound evidence, according to study authors. In fact, they continue, use of this drug has increased 15-fold from 2001 to 2009 in children's hospitals in the U.S.

This study showed no benefit from adding Plavix to current treatment, which often includes aspirin. As noted in the study, the use of Plavix® to address thrombosis in newborns and infants being palliated with systemic-to-pulmonary artery shunts does not reduce all-cause mortality or shunt-related morbidity.

Further analysis (not part of the original trial design) supports the notion that aspirin alone may be effective at reducing the risk of clot formation in these infants. The study authors point out that the trial suggests that switching from aspirin alone to Plavix alone at the dose studied is not a good idea.

"This is a good illustration of the successful collaboration between industry and academia to conduct clinical research in children under the written request process of FDA's Best Pharmaceuticals for Children Act (BPCA), noted Edward Connor, MD, MBE, Director of Innovation Development at Children's National and internationally recognized expert on drug development. "Studies of drugs in children are essential to inform child health care providers regarding safety and efficacy in this population. The need for data in newborns is especially important,

given known developmental differences in this population compared to adults."

With the enactment of the Pediatric Provisions of the Food and Drug Administration Safety and Innovation Act (FDASIA) in 2012, BPCA and the Pediatric Research Equity Act have become permanent, providing both requirements and incentives for the conduct of clinical trials in children. FDASIA recognizes the value of conducting studies in the neonates and enables FDA to add personnel with expertise in newborns. Incentives to manufacturers include patent extensions if a trial is properly designed, executed, and approved by the FDA.

Worldwide, heart defects are the most common congenital birth defect; tens of thousands of children are born with heart defects each year, and many of these defects can be treated with medications or with procedures, including reconstructive surgery or interventional catheterization.

The Clopidogrel to Lower Arterial Thrombotic Risk in Neonates and Infants Trial (CLARINET) was a double-blinded, randomized, placebo-controlled, parallel group, event driven trial. The study was sponsored by a collaboration between Sanofi-Aventis and Bristol-Myers Squibb.

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