PTN POST
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Leading the Way

Timolol for Infantile Hemangiomas under Review

Since first reported in 2008 that propranolol, a beta blocker, was effective in the treatment of Infantile Hemangiomas (IH)—a birthmark that most commonly appears as a bright red nodule of extra blood vessels in the skin, commonly called a "strawberry"—this class of drug has been used as the first line of therapy for infants with IH. Timolol, also a beta blocker, is available in topical formulation, and increasingly used off-label for small, non-complicated IH. The popularity of timolol is likely due to its perceived safety as a topical drug. However, data on timolol efficacy, safety and pharmacokinetics are limited.

PTN's timolol study will enroll 100 infants between the ages of 32–49 weeks postmenstrual age. The infants will be treated with timolol for 28 days then randomized into 2 groups. One group will continue timolol treatment while the other will be withdrawn from treatment. Both groups will remain on the study in their respective groups for up to 120 days. The study will begin to enroll in the first quarter of 2016 at approximately 10 US sites, and will end in the fall of 2017. The data received from the study will be presented to the FDA to support the use of timolol for the treatment of IH.

Beth Drolet, MD, protocol chair for the timolol study, noted that this investigation comes as a result of the 2014 Best Pharmaceuticals for Children Act stakeholders' meeting, and springboards off pilot data from another PTN study (POPS). She concluded, "we will examine a drug that is being administered not only for a new indication, but in a unique way—skin application vs. the FDA-approved method of intraocular inoculation—in a vulnerable population for a common and benign condition. For this reason alone, it is of utmost importance to evaluate its safety and efficacy."

Distinct Anti-epileptic Drug Dosing for Obese Children Needed

Childhood obesity has increased over the last decade. Due to altered pharmacokinetics (PK) associated with obesity, dosing for anti-epileptics in obese children may vary from that in non-obese children. Inappropriate dosing may increase the risk for drug toxicity or therapeutic failure. PK studies are urgently needed to determine appropriate dosing strategies for anti-epileptics in obese children.

The Pharmacokinetics of Anti-epileptic Drugs in Obese Children (AED) study will enroll approximately 100 children, 2–17 years of age, with a body mass index ≥95th percentile, who are receiving levetiracetum, valproic acid, topiramate, or oxcarbazepine, per standard of care. Enrollment will begin in the first quarter of 2016 at 10 US sites. Results from the study are expected by early 2017—soon thereafter, the study team hopes to submit dosing guidelines to the FDA.

A Message from the Lead Principal Investigator

Danny Benjamin, MD, PhD, MPH

In our final month of 2015, we welcome you to the *fifteenth* issue of the *PTN Post*, your quarterly source for information about the work of the Pediatric Trials Network (PTN).

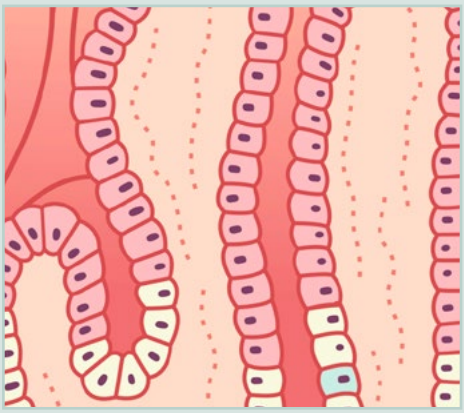
In the summer issue, we reflected on the many achievements of the network, and today we offer our most recent highlights: A new study, an offspring of PTN POPS, investigates timolol in infants with hemangiomas; two studies investigate dosing requirements for obese children, anti-epileptics and pantoprazole for gastroesophageal reflux disease (GERD); and a new trial begins enrollment for infants taking furosemide for bronchopulmonary dysplasia (BPD). Read all about it.

As we near the end of a productive year, I, on behalf of the PTN Team, thank you for your continued encouragement and support, and wish you a wonderful holiday season. We look forward to continuing the good work in 2016.

We welcome your input about topics of interest for future issues. Please contact us with your suggestions via the PTN website.

Pantoprazole Trialists Consider Public Health Impact

As of September 1, a study investigating pantoprazole in obese children completed enrollment with 41 patients who were diagnosed with GERD (6–17 years of age) across 4 activated sites: Children's Mercy Hospital in Kansas City, Arkansas Children's Hospital Research Institute, East Carolina University, and University of Utah Hospitals and Clinics.



In a recent interview with Valentina Shakhnovich, MD (PI) and Jaylene Weigel (Coordinator), they proudly reported that they enrolled 21 patients into the study at the Children's Mercy Hospital. Dr. Shakhnovich emphasized the importance of this trial, and others like it that are specifically designed to evaluate dosing guidelines for obese children. Despite that obese children are a growing patient population, they have traditionally been excluded from clinical trials, as most studies are designed to assess drug disposition and response in the average healthy child; thus, obese children, by definition, are excluded. However, acid-suppressing drugs, like pantoprazole, are some of the most frequently prescribed drugs for overweight and obese children, who are six times more likely to have acid-related diseases and complications.

Thus, this study is very timely and will address a significant knowledge gap, faced by prescribers who take care of these children.

Dr. Shakhnovich is grateful that organizations like PTN have taken the lead in exploring dosing guidelines for overweight and obese children. She stated, "These kids have been under-represented in studies for a very long time, and deserve to be included to make sure that we are prescribing medications thoughtfully and accurately—we need to do better by these children, and that means conducting more investigations like this one."

The study team expects to send dosing guidelines to the FDA by March 31, 2016.

Furosemide Trial Now Enrolling

Premature infants with BPD often die and survivors have life-long morbidities. BPD is the most common morbidity of prematurity, and affects ~17,000 infants per year in the US. Because consequences of BPD are catastrophic, neonatologists frequently use drugs, including diuretics, in an attempt to prevent BPD. Furosemide is a loop diuretic approved by the US Food and Drug Administration (FDA) for treatment of pulmonary edema in adults. In small trials in premature infants, furosemide improved short-term lung compliance reducing the need for exogenous oxygen and increased ventilator support, both implicated in the development of BPD. These findings suggest that furosemide may be an effective therapy to prevent BPD.

Matt Laughon, MD, protocol chair for the furosemide study, and the PTN research team are performing a randomized, controlled, masked, tiered, safety, phase II trial for 4 weeks. Furosemide will be administered in up to 120 premature infants who are at high risk for BPD, randomized (3:1) to receive 1 mg/kg furosemide every 24 hours intravenously vs. placebo. The dosage will be increased after a safety review is completed for of each group of 40 participants.

As of this writing, three clinical sites have been activated: Wesley Medical Center in Wichita, KS (3 patients enrolled); Wolfson Children's Hospital in Jacksonville, FL; and University of Florida Jacksonville Shands Medical Center in Jacksonville, FL. Dr. Laughon anticipates activating all sites, up to 25, by March 2016. He states, "At the conclusion of the study, we will submit these data to the FDA, and provide critical safety, preliminary effectiveness, and PK data for the pivotal phase III efficacy trial which, if successful, will provide evidence for the only therapeutic conducted under federal regulatory oversight to prevent BPD in premature infants."

The Pediatric Trials Network (PTN) is made possible by the Best Pharmaceuticals for Children Act (BPCA). The BPCA, first enacted in 2002, provides mechanisms for studying on- and off-patent drugs in children. Visit us on the web at www.pediatrictrials.org.

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