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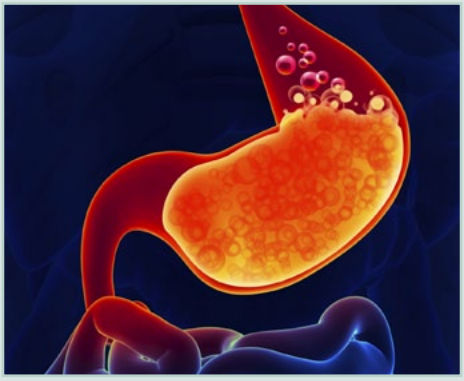
Leading the Way

The Pantoprazole Study Takes Off

The PTN study of the effect of obesity on the pharmacokinetics of pantoprazole in children and adolescents is well underway. After enrollment of its first patient in July, the trial has accrued an additional 10 patients in just under a month. Brian Smith of Duke University credits this rapid enrollment to the hard work of the sites. "We have committed staff at each of our 3 study locations," he says, "who are doing a stellar job of identifying and getting patients into this important study."

The pantoprazole trial will fill a critical gap in pediatric knowledge. Obese children are more frequently diagnosed with gastroesophageal reflux disease (GERD) than children of normal weight. Proton pump inhibitors, such as pantoprazole, have become key components in the pharmacological management of GERD in pediatrics. Unfortunately, obese participants are often excluded from clinical trials during the drug development process, so little to no information exists regarding the impact of obesity on drug disposition and action or the appropriate dosing of drugs like pantoprazole in obese kids. In this multicenter, open-label, single-dose study, the PTN is examining the pharmacokinetics of this drug in obese pediatric patients who require treatment with an acid-modifying agent. The data collected will be compared to existing pharmacokinetic data in non-obese subjects.

The study population includes obese male and female children and adolescents, ranging in age from 6–17 years with the diagnosis of GERD. Approximately 40 participants will be enrolled at the 3 sites. To learn more about this study, visit **clinicaltrials.gov**.



A Message from the Lead Principal Investigator

Danny Benjamin, MD, PhD, MPH

Welcome to the tenth issue of the *PTN Post*, your quarterly source for information about the work of the Pediatric Trials Network (PTN).

It has been a busy summer for the PTN. As detailed in these pages, our studies are enrolling patients, meeting milestones, and expanding their reach to include new drugs for which pediatric dosing information is desperately needed. Notably, the results of several studies are being disseminated in the scientific literature, which is a major step towards making real change happen in clinical practice. We thank our many investigators and their site staff for the hard work that has made this possible.

As always, we welcome your input about topics of interest for future issues. Please contact us with your suggestions via the PTN website (**https://pediatrictrials.org/contact-info**).

PTN Investigators Publish Fluconazole Findings in JAMA

Major findings from investigators of the Pediatric Trials Network were recently published in the **Journal of the American Medical Association**. The research team, led by PTN lead principal investigator Danny Benjamin Jr. of Duke University, found that extremely premature babies generally should not routinely be given fluconazole to prevent *Candida* infections. This research provides guidance for neonatologists, who often must decide whether to dose low-birth-weight babies with prophylactic anti-fungal medicine or wait until an infection has been diagnosed.

"There has been some controversy about whether to use fluconazole as a routine preventive for candidiasis," observes Dr. Benjamin. "Previous studies found a benefit, but they looked at reducing infections at centers with high rates of disease. Most neonatal intensive care units in the United States and Europe have low rates of disease, so questions have remained about whether the risks of using the drug among these babies are justified."

The JAMA article reports that fluconazole did not significantly reduce the combined risk of death or invasive candidiasis. This finding stemmed from a randomized, prospective study involving 32 U.S. neonatal intensive care units. PTN investigators enrolled 361 extremely premature infants, randomizing approximately half to receive fluconazole twice weekly for 42 days and the other half to get placebo.

While fewer infants who received fluconazole developed candidiasis, the death rate was the same (14%) for the 2 groups, leading researchers to conclude that the drug did not provide a statistically significant benefit for infants treated at centers with low incidence of infection. Study co-author Brian Smith notes, however, that "it's important to stress that using the drug in units with moderate-to-high rates of disease is likely beneficial."

The PTN is currently working on a study to evaluate the safety of fluconazole prophylaxis by analyzing safety data from 3 completed randomized trials, including the JAMA study. To learn more about this effort, visit the **PTN website**.

The Anti-Staph Trio Trial Completes Enrollment in the Clindamycin Cohort

PTN investigators involved in the Anti-Staph Trio study have completed enrollment into the cohort of babies receiving clindamycin, 1 of 3 anti-staphylococcal antibiotics being evaluated in this study.

Seventy percent of late-onset infections in the neonatal intensive care unit are due to staphylococcal species, many of which are methicillin-resistant. Infants with these infections experience long hospitalizations and have an increased risk of septic shock, severe necrotizing pneumonia, and neurodevelopmental impairment, as well as a high risk of death. Clindamycin, rifampin, and ticarcillin-clavulanate are used to fight staphylococcal species, but the correct dosing and safety of these antibiotics has not been established for all infant populations.

The PTN is measuring the levels of clindamycin, rifampin, or ticarcillin-clavulanate in enrolled babies, thereby gauging how the infant body absorbs and distributes the drugs. By understanding these pharmacokinetic properties, we can determine the best doses for treating staphylococcal infections in these vulnerable patients.

The trial is enrolling up to 32 infants for each drug. The drugs are given over 2–4 days, and the infants are monitored for another 7 days for any drug side effects. To find out more about this study, visit clinicaltrials.gov.

POPS to Include Timolol on Drug-of-Interest List

The Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care (POPS) study will once again expand its drugs-of-interest (DOI) list to include timolol, a beta-andrenergic receptor blocking agent indicated for the treatment of hypertension and glaucoma. Timolol is frequently prescribed for infantile hemangioma to reduce the size and extension of the hemangioma; however, it is not indicated for this use. The POPS study will gather pharmacokinetic data on the use of timolol in children with this condition.

The majority of drugs included on the POPS DOI list are also on the Best Pharmaceuticals for Children Act priority list, meaning that they have been identified as drugs used commonly in children that require study for safe and effective use. Others were added to the list with the purpose of gathering preliminary pharmacokinetic data and examining feasibility for future study in clinical practice.

POPS is characterizing the pharmacokinetics of understudied drugs for which specific dosing recommendations and safety data are lacking by taking advantage of procedures done as part of routine medical care (for example, blood draws). The goal is to provide better understanding of drug exposure in children.

Visit clinicaltrials.gov to learn more about this study.

Stay Tuned: Results Forthcoming from the Lisinopril and Hydroxyurea Trials

Two PTN studies have recently locked their databases and analyzed their data, with the goal of publishing their results in the scientific literature by the end of the year.

The Safety and Pharmacokinetics of Lisinopril in Pediatric Kidney Transplant Recipients and the Hydroxyurea in Pediatric Patients with Sickle Cell Anemia studies are in the final stages of manuscript preparation. Stay tuned for information about their findings in the future issues of the *PTN Post*.

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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