PTN POST SPRING 2014 • ISSUE 9

Leading the Way

PTN Lisinopril Study Reaches Key Milestone

The PTN study of the **Safety and Pharmacokinetics of Lisinopril in Pediatric Kidney Transplant Recipients** has reached its enrollment goal. This prospective, open-label, pharmacokinetics **study** included kidney transplant recipients, 2–17 years of age, who had stable allograft function and needed medication to control hypertension. Lisinopril is approved by the FDA for the treatment of hypertension in adults and children aged 6+ years. Children and adolescents who have received a kidney transplant are at particularly high risk of hypertension; however, the appropriate dose for use in this group is not known. The goal of this study, therefore, was to measure lisinopril concentrations following once-daily dosing in this vulnerable population. With this information, safe and effective dosing can be determined for better treatment of hypertension and higher long-term graft survival.

"We experienced some challenges with enrollment," notes Uptal Patel, principal investigator. "When you're working with a fragile population like children and adolescents who are transplant recipients, many factors can impede study participation, not the least of which is parental hesitation to involve their children, who are otherwise doing well, in clinical research. We truly have our remarkable site personnel to thank for carefully explaining the study—its protocol and impact—to parents and potential participants and helping us to make it to this critical goal." Patients were enrolled at 8 sites: University of Alabama–Birmingham, Arkansas Children's Hospital in Little Rock, University of Michigan at Ann Arbor, New York University Langone Medical Center, Albert Einstein University Hospital in New York, Cincinnati Children's Hospital, Children's Mercy Hospital in Kansas City, and Emory University & Children's Healthcare of Atlanta.

Participants were stratified by lisinopril dose group: low dose = 0.1 mg/kg; middle dose = 0.2 mg/kg; and high dose = 0.4 mg/kg. The levels of drug in each person were measured, thus providing data that will help determine the best dose of lisinopril to reduce high blood pressure among these unique patients.

The study team recently locked the database, and analyses of the data should be completed in summer 2014. Data will be submitted to the FDA and a manuscript written by late 2014.

A Message from the Lead Principal Investigator

Danny Benjamin, MD, PhD, MPH

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

A lot is happening in the PTN right now, as is evidenced by the articles in this newsletter. Studies are starting up, closing out, and delivering results. Of note, a trial involving many PTN investigators that examined the effect of fluconazole prophylaxis on candidiasis and mortality in premature infants was recently published in **JAMA**. The culmination of years of research and multi-institutional collaboration, this work embodies the primary goal of the PTN—to improve care for children through innovative study design and streamlined implementation.

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**).

The Sildenafil Study Expands

The **Pharmacokinetics of Sildenafil in Premature Infants** study recently met an enrollment milestone and made some changes to the protocol to increase the sample size and maximize the safety of the study.

Sildenafil is approved by the FDA for the treatment of pulmonary arterial hypertension in adults. The drug is increasingly being used off-label by neonatologists to manage pulmonary arterial hypertension associated with lung disease due to premature birth, even though the effectiveness of sildenafil in pediatric patients has not been established. This study will determine pharmacokinetics of sildenafil in premature infants to determine the optimal dose for the next phase of drug development. The overall goal of the sildenafil drug development program is to determine if sildenafil is beneficial to prevent or treat lung disease in premature infants.

Enrollment is planned in two cohorts: Cohort 1 originally was to include 12–16 infants receiving standard-of-care sildenafil. After enrolling the first 12 participants, the interim PK results from these patients suggested wide variability in the PK and the need for a larger sample size. Accordingly, the maximum enrollment was increased to 25. The cohort currently includes 16 participants. Cohort 2 will receive a single dose of sildenafil based on safety data collected from Cohort 1. The FDA recommended a lower dose than the 0.5 mg/kg stated originally in the protocol. Dosing for the first 8 infants in Cohort 2, therefore, will commence at a lower dose (0.25 mg/kg), with continuous safety monitoring and specific halting and stopping rules in place. Once safety has been established at that dose, the second 8 infants will receive the originally planned 0.5 mg/kg dose. Cohort 2 will begin enrollment in May 2014.

Sites currently participating in the sildenafil study include: Duke University, Indiana University, Medical University of South Carolina, University of Alabama at Birmingham, University of Louisville, and the University of North Carolina at Chapel Hill. To learn more about this study, visit **clinicaltrials.gov**.

POPS Adds More Drugs to Study

In the last issue of the *PTN Post*, we focused on the **Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care (POPS)** study and its expansion to international sites. This time, we're turning the spotlight on the recent expansion of its drugs-of-interest (DOI) list.

As the goal of POPS is to characterize the pharmacokinetics of understudied drugs for which specific dosing recommendations and safety data are lacking, it can be a challenge to decide on what drugs to include given the overwhelming dearth of such information. As a result, the POPS study team, in close collaboration with PTN partners at the National Institute of Child Health and Human Development, has expanded the DOI list (see sidebar).

The majority of these drugs are 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 DOI list with the purpose of gathering preliminary pharmacokinetic data and examining feasibility for future study in clinical practice. A few others were selected due to their inclusion in the **Strategic National Stockpile** (SNS).

"POPS has proven to be an extremely successful study for collecting information about drugs used every day in children," observes Chiara Melloni, principal investigator. "Because we're not subjecting anyone to treatment they would not otherwise receive as standard of care, we're able to study more drugs in more patients and in less time than traditional randomized trials."

Interim pharmacokinetics data are currently being analyzed and the results published for the following drugs: clindamycin, ampicillin, methadone, and trimethoprim-sulfamethoxazole. Visit **clinical trials.gov** to learn more about this study.

MEDICINES ADDED TO THE DOI LIST INCLUDE:

- Midazolam
- Aripiprazole
- Olanzapine
- Quetiapine
- Risperidone
- Ticarcillin-clavulanate
- Oseltamivir
- Vasopressin
- Norepinephrine
- Milrinone
- Nicardipine
- Rifampin
- Dopamine
- Amphotericin B deoxycholate
- Levofloxacin
- Ceftazidime
- Polyethylene glycol (PEG) 3350

PTN Methadone Study Kicks into High Gear

The **Pharmacokinetics of Multiple-dose Methadone in Children** study is off and running. On January 10, 2014, the site team at the Medical University of South Carolina enrolled the first participant and has enrolled 5 more participants to date. The University of Michigan recently enrolled its first patient, and 3 more sites will be enrolling patients soon: Duke University Medical Center, All Children's Hospital in St. Petersburg, Florida, and Children's Mercy Hospital in Kansas City.

This multicenter study will determine the pharmacokinetics of enteral methadone in children treated for opiate withdrawal. Critically ill children routinely receive opioids for analgesia and sedation to reduce pain and stress, facilitate ventilation, and avoid secondary complications. Continuous infusions of opioids can result in tolerance, however, frequently leading to withdrawal symptoms if the drugs are discontinued abruptly. Fortunately, gradual opioid tapering is possible with drugs such as methadone, which can be substituted for narcotic infusions during the weaning process to prevent withdrawal symptoms. Although methadone is commonly prescribed to hospitalized children, particularly in younger age groups, there are virtually no studies to guide dosing in this population.

The PTN methadone study in enrolling children aged >90 days to <18 years of age prescribed methadone per routine care. As many as 36 participants will be enrolled. Participation in the study will last up to 10 days (up to 5-day treatment period, up to 5-day observation period after study drug administration to monitor for adverse events and collect elimination samples).

For more information about this study, please visit **clinicaltrials.gov**.

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**.

The Pediatric Trials Network is supported by The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, and U.S. Department of Health and Human Services.