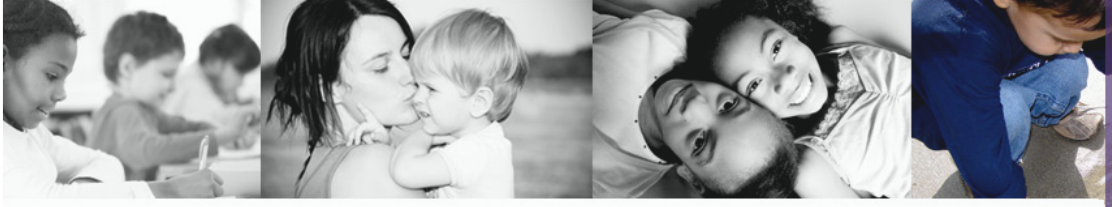
PTN POST
FALL 2013 • ISSUE 7
Leading the Way



The PTN Breaks Ground on Several New Studies

Over the past year, the Pediatric Trials Network has been given the green light to begin a number of studies designed to improve medical treatments for infants, children, and adolescents. In this issue of *The PTN Post*, we provide a bird's-eye view of new research projects in the pipeline. As always, please visit our website (**www.pediatrictrials.org**) to get the latest news about PTN studies.

A Message from the Lead Principal Investigator

Danny Benjamin, MD, PhD, MPH

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

We are pleased to showcase a number of studies that have gotten underway in 2013, thanks to the ongoing support of the National Institute of Child Health and Human Development (NICHD). The PTN comprises a truly unique collaboration between academic medicine and government, one that is bearing fruit in the form of labeling changes and scientific publications that will improve pediatric health care.

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 Effect of Obesity on the Pharmacokinetics of Pantoprazole in Children and Adolescents

The World Health Organization has called childhood obesity "one of the most serious public health challenges of the 21st century." The alarming childhood obesity epidemic brings with it increasing need for pediatricians to treat obesity-related diseases (e.g., type II diabetes mellitus, hypertension, hyperlipidemia, gastroesophageal reflux disease [GERD]) that traditionally have not had origins in childhood or adolescence. Given that obese participants are often excluded from clinical trials during the drug development process, little to no information exists regarding the impact of obesity on drug disposition and action or the appropriate dosing of drugs in obese pediatric patients.

Obese children are more frequently diagnosed with GERD than children of normal weight. Proton pump inhibitors, such as pantoprazole, have become key components in the pharmacologic management of GERD in pediatrics. In this multi-center, open-label, single-dose study of pantoprazole, the PTN will examine the pharmacokinetics of the drug in obese children who require treatment with an acid-modifying agent. The data collected in this study will be compared to existing pharmacokinetic data in non-obese subjects.

The study population will comprise obese male and female children and adolescents, ranging in age from 6–17 years (inclusive) with the diagnosis of GERD. Approximately 40 participants will be enrolled at up to 3 sites.

Antibiotic Safety in Infants with Complicated Intra-abdominal Infections (SCAMP)

Complicated intra-abdominal infections are common and often fatal in premature infants. These infections often occur as a result of necrotizing enterocolitis (NEC), the pathogenesis of which involves intestinal mucosal injury, usually associated with intestinal ischemia and bacterial overgrowth. NEC has a high overall mortality (15%) and, in extremely-low-birth-weight infants (≤1000 grams), mortality for surgical NEC is nearly 50%. Survivors often suffer from complications, including stricture formation, and life-long morbidities such as short bowel syndrome. Infants who have had NEC are also at increased risk of poor neurodevelopmental outcomes.

Recommended antibiotics for complicated intra-abdominal infections in infants include combinations of ampicillin, piperacillin-tazobactam, meropenem, metronidazole, clindamycin, or gentamicin. In spite of their frequent use, however, the safety and efficacy of these antibiotics in infants with complicated intra-abdominal infections have not been established.

The PTN is seeking to fill this information gap with SCAMP, a randomized, multicenter, open-label **s**afety study of **c**lindamycin, **a**mpicillin, **m**etronidazole, and **p**iperacillin-tazobactam in infants with complicated intra-abdominal infections. The primary objective of this study is to determine the safety of these drug regimens in this specialized context; secondary objectives include determining the drugs' effectiveness, their pharmacokinetics in this unique population, biomarker association with disease severity and antibiotic exposure, and diversity or shift of intestinal microbiota. Approximately 350 infants will be enrolled at approximately 50 sites. Total length of study participation is 100 days, including 10 days of treatment and up to 90 days of follow-up assessments.

Extremely-low-birth-weight Infants Exposed to Furosemide or Bumetanide in the Neonatal Intensive Care Unit

The most common serious disease associated with premature birth is bronchopulmonary dysplasia (BPD). More than 60,000 infants are born ≤29 weeks gestational age each year in the United States, and nearly 40% of those develop BPD.

Premature infants with BPD are challenging to treat and frequently suffer from multiple morbidities such as pulmonary hypertension, prolonged hospitalization, and life-long neurodevelopmental problems. Because the consequences of BPD can be catastrophic, neonatologists frequently use diuretics such as furosemide and bumetanide to reduce pulmonary edema, improve pulmonary mechanics, minimize exposure to mechanical ventilation, and, ultimately, to prevent BPD.

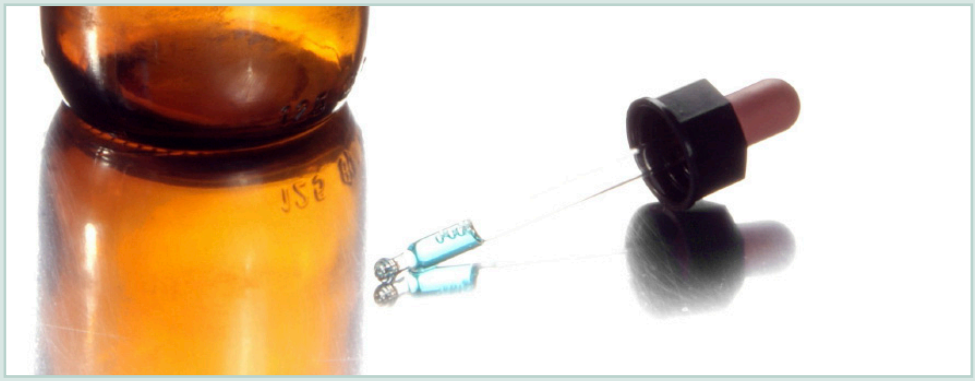
The understanding of the safety profile of furosemide and bumetanide in premature infants, however, is limited. This is due, in part, to concerns about exposing premature infants to the risks of prospective drug studies. Fortunately, retrospective observational studies carry no risk for participants.

We will conduct an observational, retrospective study using medical records from approximately 700 extremely-low-birth-weight infants admitted to neonatal intensive care units. The data analyzed will provide valuable safety information for the use of these drugs in premature infants and will facilitate the design of future clinical trials.

Pharmacokinetics of Multiple-dose Methadone in Children

Critically ill children routinely receive opioids for analgesia and sedation with the goals of reducing pain and stress, facilitating ventilation, and avoiding secondary complications. Continuous infusions of opioids can induce tolerance, however, sometimes resulting in withdrawal symptoms if the drugs are discontinued abruptly. In fact, opioid withdrawal is a major problem in the pediatric intensive care unit, where it is estimated to occur in up to 57% of patients. Withdrawal symptoms are not only unpleasant but can be life-threatening and may prolong the need for hospitalization.

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. Methadone is an opiate commonly prescribed to hospitalized children, particularly in younger age groups. We know that methadone levels in the blood vary dramatically in adults, especially after oral administration. That is likely to be the case in children, but there are virtually no studies to guide dosing in children. The methadone product label currently states that safety and effectiveness in patients below the age of 18 years have not been established, and no dosing information is provided.



The primary objective of this prospective, multi-center, open-label, multiple-dose study is to determine the pharmacokinetics of enteral methadone in children treated for opiate withdrawal. The study population will include children aged >90 days to <18 years of age prescribed methadone per routine care. As many as 36 participants will be enrolled at up to 5 sites. 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). To find out more, 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.