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Leading the Way

Label Change Marks Major PTN Milestone

A precursor to the Pediatric Trials Network (PTN), the Multiple Dose Pharmacokinetic Study of Meropenem in Young Infants (<91 days) with Suspected or Complicated Intra-abdominal Infections has made its mark on pediatric medicine. Based on study findings, which were published in the Pediatric Infectious Disease Journal, the. U.S. Food and Drug Administration (FDA) recently changed the drug label to optimize the dosing regimen for meropenem in infants younger than 90 days old. The updated label is now available online.

Intra-abdominal infections are common in premature infants younger than 3 months of age and are often fatal. Meropenem, which effectively treats many types of bacterial infections, was originally approved for use in adults and older children and had long been prescribed for infants younger than 3 months despite a lack of data about the effects of the drug on these patients. Although the PTN was established, in part, to promote and support the studies needed to fill such gaps in the scientific literature, the meropenem study began prior to the PTN contract, with patient enrollment commencing in summer 2008. "Meropenem really served as a platform for us to prove we could do these much-needed studies safely and effectively," observed Danny Benjamin, MD, PhD, principal investigator for both the meropenem study and the PTN.

The trial included 200 infants at 24 neonatal intensive care units across the United States. Each patient was given a dose of meropenem based on his or her gestational age at the time of birth and postnatal age at the time of the study. Researchers acquired blood samples from each infant when blood was being sampled as part of the children's regular care.

The study team's findings suggested that meropenem as dosed in the trial is a safe alternative for young infants with intra-abdominal infections. With this information in hand, researchers approached the FDA to suggest the labeling modifications that have since been approved.

Beyond the obvious reward of improving drug therapy for a vulnerable population, the meropenem study provided a useful precedent for future PTN studies. As co-investigator Brian Smith of Duke University noted, "It was a model for the PTN trials as we move forward."

Data-sharing to Improve Child Health

To help expand the knowledge base for pediatric medicine, the PTN is pleased to share data from its completed and published studies with interested investigators. The first study to be made available is that of meropenem, which evaluated the safety, tolerability, and pharmacokinetics/ pharmacodynamics of meropenem in infants <91 days of age with suspected and complicated intra-abdominal infections (see article above).

"The PTN was created by the Eunice Kennedy Shriver National Institute of Child Health and Human Development with a mission to design and conduct pediatric clinical trials to improve health care for the youngest patients," said Danny Benjamin, MD, PhD, PTN principal investigator. "Being as transparent as possible with our data and other trial documents is a critical step in expanding the existing body of knowledge to achieve that goal."

Study documents relating to the meropenem trial are currently posted on the PTN website. To submit a request for data, please complete the "Data Sharing Request" form and email it to katherine.berezny@duke.edu.

A Message from the Lead Principal Investigator

Danny Benjamin, MD, PhD, MPH

Several years ago, the FDA, under the provisions of the Best Pharmaceuticals for Children Act, issued a formal written request for much-needed PK and safety/tolerability studies of meropenem in neonates and young infants. Meropenem possesses one of the broadest spectra of antimicrobial activity available, including most of the bacterial pathogens responsible for producing serious, life-threatening infections occurring in young infants, but product labeling only included recommendations for children ≥3 months of age.

In the study detailed herein, we filled that information gap, generating the PK and safety information needed to update drug labeling for use in very young infants. The expectations in the original written request were revised according to input from investigators from the NICHD-sponsored Pediatric Pharmacology Research Units and the Neonatal Research Network (NRN). Key epidemiologic data from the Pediatrix Medical Group and the NRN, clinical pharmacology data from Children's National Medical Center (van den Anker et al.) and UCSD (Bradley et al.), in addition to modeling and simulation led by UCSD (Capparelli et al.), were crucial to the success of the trial.

In the process of completing the meropenem study, we laid the groundwork for the Pediatric Trials Network, and it was through the PTN that we were able to complete the work and achieve the labeling change. It is on the foundation of the meropenem trial that the network has been steadily advancing our understanding of how to optimize use of drugs and devices in children. This issue of the *PTN Post* celebrates these accomplishments and looks ahead to what's next—from data-sharing and site successes to the dissemination of study results at meetings and in the literature.

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

Site Spotlight: Oregon Health and Science University

The second highest enrolling site in the POPS study, Doernbecher Children's Hospital at Oregon Health and Science University (OHSU) has recruited over 136 participants since joining the study in April 2013. The site attributes its success to its dedicated pediatric specialists, researchers, and hospital staff.

From left to right: Jeannie Glaspy, Amit Mehta, Amira Al-Uzri, Nancy Gadd, and Kira Clark.

Dr. Amira Al-Uzri, the site PI, is a professor of pediatrics with a specialty in pediatric nephrology and the medical director for the Pediatric Kidney Transplant Program at OHSU. Her team credits her enthusiasm for clinical research and for improving the lives of children as the driver behind its strong recruitment effort. Dr. Al-Uzri is joined by Dr. Amit Mehta (sub-investigator and PICU physician), Kira Clark (research coordinator), Nancy Gadd (pediatric pharmacist), and Jeannie Glaspy (research lab assistant).

"We owe our success as a site primarily to the wonderful patients and families that visit our hospital and outpatient clinics," notes Dr. Al-Uzri. "The most rewarding part of participating on the POPS study is when we are reminded that our patients join the study simply for the good of helping other children." Research coordinator Kira Clark adds, "Many times, we hear from the littlest kids to adolescents that they join 'to help other kids like me' or 'because if people didn't do these studies before me, I wouldn't be able to get better.'"

To learn more about the POPS study, visit clinicaltrials.gov.

News Bites

- The manuscript deriving from the Safety and Pharmacokinetics of Lisinopril in Pediatric Kidney Transplant Recipients study has been accepted for publication in *Clinical Pharmacology and Therapeutics*.

- Several researchers will present results from PTN studies at the annual meeting of the Pediatric Academic Societies in late April, including:
  - Jeremiah Momper of UC–San Diego, "Population Pharmacokinetics of Fluconazole in Extremely Low Birth Weight Infants"
  - Michael Smith of the University of Louisville, "Pharmacokinetics of Multiple-Dose Intravenous Clindamycin in Obese Children"
  - Jessica Ericson of Duke University, "Effectiveness of G-CSF in Hospitalized Infants with Neutropenia" and "Safety of Acyclovir in Infants with HSV in the Era of High-dose Therapy"
  - Lawrence Ku of Duke University, "Safety of Enalapril in Young Infants"

  The presentations will be posted on the PTN website in May.

- Enrollment in the Safety Study of Clindamycin, Ampicillin, Metronidazole, and Piperacillin-tazobactam in Infants with Complicated Intra-abdominal Infections (SCAMP) has been brisk, with 64 patients enrolled as of April 20.

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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