PEDIATRIC TRIALS NETWORK
Making drugs safer & more effective for use in the youngest patients

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PTN Post

A Message from the Lead Principal Investigator

Danny Benjamin, MD, PhD, MPH

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

During the first quarter of 2016, the network met a number of milestones: the unveiling of our refreshed website, the activation of two UK sites for POPS, a successful showing of PTN data at the 2016 Pediatric Academic Society (PAS) Meeting in Baltimore, and most importantly, based on PTN findings, the FDA approved the label change for lisinopril dosing in children after kidney transplant.

In this issue, learn more about the lisinopril label change, get an update on POPs, hear from Dr. Salerno about her piperacillin research, and follow the link to our newly refreshed website where you can stay up-to-date on all things PTN. While you're at it, like us on Facebook and send us a tweet.

Onward we go. Happy summer to all, and thanks so much for all that you do each and every day towards making drugs safer and more effective for use in the youngest patients.

Spotlight on POPs

POPs = Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care

PTN studies managed via the POPs paradigm seek to determine the appropriate dosing of understudied drugs in children by using samples collected as part of regular care (for example, blood draws). The data collected

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Our **updated website** features a refreshed look, streamlined navigation, and new content, video, and infographics.

Visitors can view the latest updates on the network's growing portfolio of studies and there are also publications and resources for healthcare professionals, parents, and families.

Check it out: pediatrictrials.org.

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

PTN Study Results in Label Change for Hypertension Drug

Redacted from *DCRI News*

A study conducted by the PTN has resulted in a labelling change for a widely used drug. The change could affect the hundreds of children who are prescribed lisinopril after kidney transplants each year.

Lisinopril is an angiotensin converting enzyme inhibitor that is commonly prescribed to treat high blood pressure or heart failure in adults. It is also given to children who have hypertension, including children who have undergone kidney transplants. As with many other drugs, however, there has been little research to suggest the optimal dose for pediatric transplant patients. The PTN was established to answer these types of questions about drugs given to children and adolescents.

"There is a great medical need but a small market for these types of studies," said Daniel Benjamin, Jr., MD, MPH, PhD, the PTN's principal investigator. "This is why the PTN was formed—to conduct the studies that no one else will."

A study led by DCRI researcher Howard Trachtman of New York University, MD, and other researchers for the PTN recently resulted in a decision by the U.S. Food and Drug Administration (FDA) to update the label for lisinopril. In addition to Trachtman, the study's authors included: Adam Frymoyer, MD, of Stanford University; Laurence Greenbaum, MD, PhD, of Emory University; Daniel Feig, MD, PhD, of the University of Alabama at Birmingham; Debbie Gipson, MD, of the University of Michigan; Bradley Warady, MD, of Children's Mercy Hospital of Kansas City; Jens Goebel, MD, of Cincinnati Children's Hospital; George Schartz, MD, of the University of Rochester; and Uptal Patel, MD, of Duke University.

The study was a multicenter, open-label pharmacokinetic (PK) study of daily oral lisinopril in 22 children, aged 7–17 years, with stable kidney function following transplant.

The researchers found that the pharmacokinetics of lisinopril in children who underwent kidney transplant were similar to hypertensive children who did not receive kidney transplants. Lisinopril was generally well tolerated by the patients and was accompanied by a lowering of blood pressure at approved pediatric doses in the study population.

The results of the study were published in the July 2015 issue of *Clinical Pharmacology & Therapeutics*.

Approximately 1200 children in the United States develop end-stage renal disease (ESRD) each year. Because kidney transplantation has become the primary method of treating ESRD for children, many of these patients will be prescribed lisinopril. As a result of the FDA's recent decision, Benjamin noted, doctors will now have a better understanding of the correct dose. "This has been a problem for over 60 years, and we're only now addressing it," he said. "With the PTN, we now a have a vehicle to make those changes."

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.

Spotlight on POPs (continued from page 1)

provides valuable PK and dosing information for drugs in different pediatric age groups and special pediatric populations (such as obese children).

Dr. Ram Yogev, POPs Investigator at Lurie Children's Hospital of Chicago, explains, "The current empirically-based dose selection for pediatric patients can be improved by applying evidence-based dosing strategies. POPs studies provide important information about how best to dose medications in children and adolescents, and support dosing strategies that provide the best chance for any given drug to demonstrate both efficacy and acceptable tolerability."

Since its inception, POPs has investigated 48 understudied drugs with 19 currently enrolling. POPs has a total of 31 active sites, and **in March, two UK sites joined the ranks**, Southampton General Hospital and Alder Hey Children's Hospital. As of June 1, POPs sites enrolled 1904 participants of the targeted 3000.

PTN / PAS Presentation Summary

USING POPULATION PK AND EHR TO ASSESS PIPERACILLIN SAFETY IN INFANTS

by Sara Salerno, MD

Piperacillin-tazobactam (Pip-Tazo), because of its broad spectrum coverage, is frequently used in infants to treat nosocomial infections, but there are limited safety data in this population. Using electronic health records (EHR) from national databases can help overcome the challenges of performing traditional clinical trials in infants. Although EHR data can be used to describe drug safety in infants, frequently there is no measure of drug exposure. The study team leveraged a previously published population PK model developed using PTN data to simulate piperacillin exposure in infants from the Pediatrix Clinical Data Warehouse, a large database of infants discharged from 333 NICUs. We then related exposure to the incidence of clinical and laboratory adverse events, and identified 747 infants who received piperacillin with a median (range) gestational and postnatal age of 29 weeks and 10 days, respectively. We observed that infants with higher exposure had an increased odds of developing seizures compared to infants with lower exposure, albeit the number of infants was small (n=10). Additional studies to further assess this relationship are warranted. Overall, Pip-Tazo had a favorable safety profile in infants and this study showed that combining PK modeling with EHR data, a novel method to evaluate drug safety in infants, is feasible.

PTN at the 2016 Pediatric Academic Society (PAS) Meeting in Baltimore, April 30–May 3

PAS / PTN PRESENTATIONS

- *Use of Pediatric and Adult Midazolam Population Pharmacokinetics to Assess IM Dosing and Early Drug Exposure for Status Epilepticus.*
  Presenter: E Capparelli with co-authors, K Chiswell, B Smith, D Siegel, S Weinstein, S Muchohi, M Reed, J Barrett, S de Wildt, E Jaqc-Aigrain, J Ma, T Glauser
- *Dosing of antimicrobials in the neonatal in the NICU: Does clinical practice reflect published recommendations?*
  Presenter: M England with co-authors RG Greenberg, RH Clark, M Laughon, M Cohen-Wolkowiez, DK Benjamin Jr, PB Smith
- *Using Population Pharmacokinetics and Electronic Health Records to Assess Piperacillin Safety in Infants.*
  Presenter: S Salerno with co-authors C Hornik, M Cohen-Wolkowiez, PB Smith, R Clark, D Gonzalez