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Leading the Way

A Message from the Lead Investigator

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Welcome to the second issue of The PTN Post, your bimonthly source for information about key issues in pediatrics and the work of the Pediatric Trials Network (PTN).

I am pleased to draw your attention to Congress's recent renewal of legislation that is crucial to the work that we do. **The Best Pharmaceuticals for Children Act (BPCA)** was first enacted in 2002 to establish a process for studying on- and off-patent drugs for use in pediatric populations and to improve pediatric drug development through collaboration in scientific investigation, clinical study design, weight of evidence, and ethical and labeling issues. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development leads BPCA efforts on behalf of the National Institutes of Health. Renewed in 2007 and again this year, this legislation helps to ensure that the PTN can continue its efforts to find the right drugs at the right doses for infants and children.

In this issue, we review the implications of serious infection in infants, as well as two PTN studies designed to ensure that doctors have optimal dosing information for drugs often used to treat such infections. We also take a look at dried blood spot sampling—an innovative trial technique that permits us to study the impact of drug therapies on infant bodies while posing only very minimal risk to these fragile trial participants.

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**).

Serious Infection in Preemies: Causes and Consequences

A newborn's immature immune system is not as capable as that of an adult or an older child in fighting off infection. Premature babies are at even greater risk of developing a serious disease from bacteria or viruses that might cause an illness which could be easily cured in an older child.

As a result, neonatal infections (i.e., those occurring within 28 days of birth) can have serious consequences if they aren't treated quickly or effectively. Because babies' organs are rapidly maturing, any interruption to this development can create complications, including neurological, cardiac, and respiratory problems. In severe cases, neonatal infections can even result in death.

Numerous viruses, fungi, parasites, or bacteria pose a threat to premature infants. Some of the most common neonatal infections include:

Meningitis—This inflammation of the membranes surrounding the brain and spinal cord is caused by viruses, fungi, and bacteria, including GBS and *E. coli* (see below). Newborns encounter these pathogens during birth or in their surroundings and are particularly vulnerable if they have weakened immune systems.

Sepsis—This serious infection involves the spread of germs throughout the body's blood and tissues. It can be caused by viruses, fungi, parasites, or bacteria.

Group B *Streptococcus* (GBS)—This common bacterium can cause a variety of infections, including pneumonia, meningitis, and sepsis. GBS is usually transmitted to babies from their mothers during birth.

***Escherichia coli* (*E. coli*)**—This bacterium can lead to urinary tract infections, sepsis, meningitis, and pneumonia. *E. coli* exists on the body, and babies can become infected during birth or through contact with caregivers in the hospital or home.

Candidiasis—This is an overgrowth of the common yeast *Candida*, which is found on everyone's body. In newborns, it usually manifests as diaper rash but can also develop as oral thrush in the mouth. Newborns with thrush often come into contact with the fungus during delivery or breastfeeding. In premature babies, *Candida* can invade the bloodstream and other internal organs.

Early diagnosis, treatment, and close monitoring are critical for helping babies overcome such infections. Because infection in young infants with very low birth weight (<1500 g) can result in devastating outcomes such as death and neurodevelopmental impairment, appropriate dosing recommendations for agents such as metronidazole (see below) are needed in this especially vulnerable population.

The PTN's First Study: Metronidazole for the Treatment of Infection in Infants

On November 1, 2011, the Pediatric Trials Network completed enrollment of its study of metronidazole, and the research team is now putting the finishing touches on the clinical study report for the Food and Drug Administration (FDA).

Metronidazole is an antimicrobial agent often administered to infants suffering from necrotizing enterocolitis (NEC). This disease, which causes the intestinal lining to die, occurs frequently in premature infants and can be fatal. Doctors have long prescribed metronidazole to infants suffering from NEC, even though there was no reliable information about correct dosage amounts for children. Metronidazole was not unique in this regard, as prescription medicines are rarely packaged with information about appropriate doses for pediatric patients.

The metronidazole study began enrolling patients in January 2011. Its purpose was to examine the pharmacokinetics and safety of the drug in young children, thereby determining an appropriate dosing regimen. This trial was the first to enroll

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The POPS Study: Studying Drugs Used in Children While Minimizing Risk

Only about 25% of approved drugs marketed in the United States have sufficient pediatric data to support product labeling by the FDA for dosing, safety, or efficacy in children. Similarly, in the European Union, only 33% of drugs are authorized for use in children by the European Medicines Agency. These knowledge gaps in pediatric drug dosing, safety, and efficacy place children at risk for adverse events and potential therapeutic failure.

Since 1997, legislative efforts in the United States have resulted in a substantial increase in pediatric drug research, generating more than 900 pediatric studies and resulting in labeling changes for pediatric use of more than 400 products. However, despite these achievements, substantial off-label use of drugs in children continues in the outpatient and hospital settings. In fact, approximately 25% of drugs prescribed in the emergency room and over 50% of drugs administered in the hospital are unapproved or used off-label in children.

Several limitations inherent to trials involving children prevent researchers from studying medications in this population. These include low rates of informed consent among caregivers; the limited blood volume available to conduct drug profiling studies; lack of pediatric clinical pharmacology expertise to design, conduct, and analyze data from clinical trials; difficulties associated with the rigid timing of biological sample collection in traditional drug trials; and a lack of robust infrastructure to support pediatric clinical trials.

The goal of the POPS (Pharmacokinetics of Understudied Drugs Administered to Children per Standard of Care) study is to characterize the pharmacokinetics of understudied drugs for which specific dosing recommendations and safety data are needed by overcoming several of these limitations using novel trial techniques. In the POPS study, understudied drugs are being administered to children by their treating physicians according to local standards of care. The only study procedure involves biological sample collection at the time of drug administration. Researchers are further limiting the impact of study participation on children by using advanced sampling techniques like dried blood spot sampling (see below), which yields useful information using very little blood. Approximately 500 children aged <21 years who are receiving the drugs of interest are being enrolled into this study.

By taking advantage of procedures done as part of routine medical care, the POPS study will provide better understanding of drug exposure in children while minimizing the risks of trial participation. The data collected will also provide valuable pharmacokinetic and dosing information for drugs in different pediatric age groups, as well as special pediatric populations (such as obese children). For more information about POPS, visit the clinicaltrials.gov website: **http://www.clinicaltrials.gov/ct2/show/NCT01431326?term=pops&rank=4**

Dried Blood Spot Sampling

Traditional blood sampling for pharmacokinetic studies involves collection of plasma or whole blood in a sample collection tube. When plasma is the desired end product, however, blood needs to be centrifuged to extract the plasma. As such, the blood volume needed per sample is usually double the amount of plasma needed for analysis, thereby increasing the amount of blood collected.

Over the past few years, a novel sample collection method using dried blood spots (DBS) has emerged and is increasingly being used by the pharmaceutical industry in drug development. This method involves collecting 15–30 microliters of whole blood on blotting paper. (To put this amount into perspective, 1 microliter equals 1/1000 [0.001] milliliter.) This sampling method offers many advantages, not the least of which is the low sample volume needed for analysis. Given that the average full-term infant has a total blood volume of only 16 tablespoons, DBS sampling provides an ethical and efficient means for conducting studies in these vulnerable patients.

The PTN's First Study *(from page 1)*

patients and complete its study under the PTN contract. Michael Cohen-Wolkowiez, MD, PhD, of the Duke Clinical Research Institute served as principal investigator.

Twenty-four preterm infants (<32 weeks gestation at birth) were enrolled at three study centers. Researchers divided the infants into two groups based on age: one group comprised infants younger than 14 days, and the other included infants aged 14–90 days. Both groups received equal doses of metronidazole adjusted by weight at different frequencies according to age over a period of several days. Researchers took blood samples from the infants during the trial to determine how the drug levels behaved within the infants' bodies.

The trial team intends to submit new dosing guidelines for metronidazole use in infants to the FDA, with the hope that the agency will subsequently update the drug's package insert.

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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