PTN POST
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Leading the Way

Sickle Cell Anemia in Kids: Hope on the Horizon

Sickle cell disease is an inherited disorder that results in sickle-shaped red blood cells (RBCs). RBCs contain hemoglobin, an iron-rich protein that carries oxygen from the lungs to the rest of the body. Normally, RBCs are disc-shaped and glide easily through blood vessels. Sickle cells, in contrast, contain abnormal hemoglobin called sickle hemoglobin (or hemoglobin S), which causes the cells to develop a sickle (or crescent) shape and makes them stiff and sticky. As a result, they can block blood flow in the vessels of the limbs and organs, causing pain, infection, and organ damage. Sickle cells also have a shorter-than-normal life span, which can lead to anemia.

In the United States, approximately 1000 babies are born with sickle cell disease each year. An estimated 100,000 Americans live with sickle cell, and millions more are affected around the world.

Sickle cell disease is usually diagnosed at birth as a part of routine newborn screening. Because children with sickle cell are at greater risk for infection and other complications, early diagnosis and treatment are critical. Currently, more than 40 states require newborn screening for the disease.

Symptoms of sickle cell disease range from mild to severe. Most kids with sickle cell are anemic to some degree and may develop one or more of the following conditions:

- **Acute chest syndrome:** fever, respiratory distress, infiltrate on chest x-ray, chest pain
- **Aplastic crisis:** slowed production of RBCs, resulting in severe anemia
- **Hand-foot syndrome:** painful swelling of the hands and feet
- **Infection:** increased risk for certain bacterial infections
- **Painful crises:** pain occurring in any part of the body, often lasting for days
- **Splenic sequestration crises:** enlargement of the spleen, trapping abnormal RBCs and leading to severe anemia
- **Stroke:** impaired blood flow to the brain due to blockage by sickle-shaped RBCs

Other possible complications include leg ulcers, gallstones, delayed growth, and damage to the bones, joints, kidneys, and/or eyes.

Bone marrow transplant is the only known cure for sickle cell disease. Transplants are complex and risky, however, and currently only a small subset of patients with severe complications is eligible.

Promisingly, in 1998, the U.S. Food and Drug Administration approved the drug hydroxyurea for use in adults with sickle cell disease. Although it has not yet been approved for use in children, the drug is commonly used by pediatric hematologists for children and young adults with sickle cell disease.

Hydroxyurea is the only available drug that can modify the disease course for sickle cell disease. It has been shown to decrease pain and other complications in both children and adults. The Pediatric Trials Network (PTN) is currently conducting a study to better understand how this drug works in children (see below). To learn more about sickle cell disease and the potential benefits of hydroxyurea, check out this video from the National Heart, Lung, and Blood Institute: http://youtu.be/iKQmQHh4E2w.

The PTN Hydroxyurea Trial

The only major medical breakthrough in sickle cell disease in the past 20 years, hydroxyurea is also the only drug approved by the FDA for use in adults with sickle cell. In spite of the fact that it is not labeled for use in children, the drug is often prescribed to children who exhibit signs of severe sickle cell disease. Recent data suggest that hydroxyurea therapy in infants with sickle cell is feasible, well-tolerated, and efficacious; however, only limited pharmacokinetic and pharmacodynamic studies of hydroxyurea use in children exist. The PTN is seeking to fill this knowledge gap.

We are currently enrolling approximately 40 children with sickle cell disease into a trial in which they will be given a liquid formulation of hydroxyurea. Sixteen participants aged 2 to ≤5 years will be included in a pharmacokinetic study, and up to 24 participants aged >5 to 17 years will participate in a relative bioavailability study (in which the liquid formulation will be compared with the pill form [Droxia®]). Blood samples are obtained after hydroxyurea administration to determine study drug concentrations in the body and its elimination. The study period lasts a minimum of 30 days from the first dose of the drug.

Results from the PTN hydroxyurea study are expected by the end of 2013, and the study team hopes to submit dosing guidelines for hydroxyurea use in children to the FDA soon thereafter.

A Message from the Lead Investigator

Danny Benjamin, MD, PhD, MHS, Lead Principal Investigator

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

In this issue, we explore the devastating consequences of sickle cell disease in children, as well as the potential for its safe and efficacious treatment with hydroxyurea. As with many drug therapies, hydroxyurea has been shown to be effective in adults, but data are lacking to inform its use in children. The PTN's mission is to fill these critical knowledge gaps, making medicine as kid-friendly as possible.

We also provide updates on other PTN trials, such as the Mercy Method™ tape study of a novel weight estimation device and a study of the pharmacokinetics of antistaphylococcal antibiotics in infants.

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 PTN Examines Pharmacokinetics of Anti-staphylococcal Antibiotics in Infants

Sepsis is an illness in which the body has a severe response to bacteria or other germs. Neonatal sepsis may be categorized as early-onset (within the first 72 hours of life) or late-onset (within 4–90 days of life). The majority of late-onset bacterial sepsis episodes in the neonatal intensive care unit (NICU) can be attributed to coagulase-negative *Staphylococcus*, and *Staphylococcus aureus* is the second most commonly isolated pathogen. *Staphylococcus aureus* is associated with overwhelming septic shock, severe necrotizing pneumonia, and high risk of mortality (up to 40%). The majority (95%) of coagulase-negative *Staphylococcus* isolates and 40% of *Staphylococcus aureus* isolates are methicillin-resistant (MRSA). Infants with these infections have prolonged hospitalizations and an increased risk of neurodevelopmental impairment.

Rifampin, clindamycin, and ticarcillin-clavulanate all have activity against *Staphylococcus* species. Rifampin is often added to facilitate bacterial eradication in infants with persistent staphylococcal (including MRSA) bacteremia. Clindamycin has activity against staphylococcal species including MRSA. Ticarcillin (often used in combination with clavulanic acid, a beta-lactamase inhibitor) is a semisynthetic penicillin with activity against a wide range of gram-negative and gram-positive organisms including methicillin-sensitive *Staphylococcus aureus* (MSSA). The correct dosing and safety of these three antibiotics have not yet been established in all infant populations.

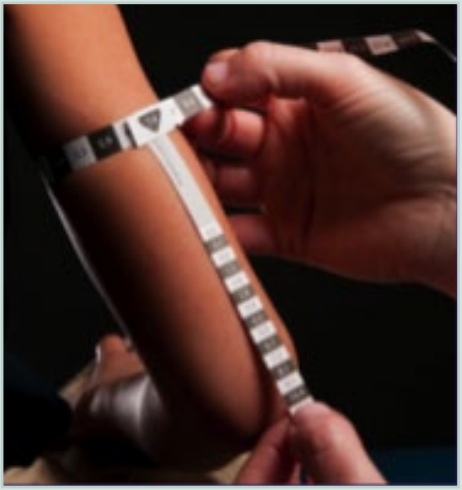
Dosing for these hepatically cleared therapeutics in preterm and term infants is likely to vary greatly from older children and adults due to immaturity of metabolic and renal pathways. The objective of this PTN study is to determine the pharmacokinetics of rifampin, ticarcillin-clavulanate, and clindamycin in infants. We will enroll up to 32 infants for each drug. The drugs will be given over 2–4 days, and the infants will be monitored for another 7 days for any drug side effects. Enrollment is slated to begin in December of this year.

Database Locks in the Mercy Method™ Tape Study

In September 2012, the PTN's Mercy Method™ tape study locked its database containing information from 625 patients. The trial concluded enrollment in April of this year.

The Mercy Method™—developed at Children's Mercy Hospital in Kansas City—estimates weight based on measurements of arm length and upper arm circumference using a novel measuring device designed for simple fabrication and use. The goal of the device is to guide delivery of age-appropriate, weight-based interventions, which remain the most accurate approach to delivering care in children. This study is the first device trial undertaken by the Pediatric Trials Network.

Database lock means that all clinical trial data have been reviewed, queries have been resolved and issues addressed, and the database cannot be altered in any way. Study results are forthcoming.



The Mercy TAPE in action

A Note to Sites

If you are interested in participating in PTN studies, please complete the general survey located at **https://duke.qualtrics.com/SE/?SID=SV_71CKi1cRf6jfPJr**. Your general survey will be kept on file indefinitely and reviewed as new trials surface. If an NICHD trial is awarded that matches your therapeutic area, you will receive a study-specific feasibility survey. A team of physicians and operational staff reviews the feasibility surveys and assesses sites for study-specific requirements. You will receive a letter indicating whether your site is under further consideration as a clinical site for a particular project.

Please be advised that your participation in the study will be confirmed upon notification following the on-site or phone study qualification visit. In preparation for the qualification visit/phone call, we ask that you supply a few regulatory documents (CV, Human Subjects Protection). Please note that the EMMES Corporation, our operational partner, will collect additional essential regulatory documents upon official site selection. Whenever possible, we will share with EMMES documents that you provide to us to prevent duplication of your effort.

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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