

**Best Pharmaceuticals for Children Act (BPCA)
Renal Disease Working Group Conference Call and Webcast
July 7, 2011
2:00 p.m.–2:45 p.m. ET**

Participants

Jeffrey Blumer, M.D., Ph.D.
Laurie Conklin, M.D.
Abraham Karkowsky, M.D., Ph.D.
Frederick Kaskel, M.D., Ph.D.
Kelley Norris, Pharm.D., B.C.P.S.
Uptal Patel, M.D.
Ronald Portman, M.D.
Michael Reed, Pharm.D., F.C.C.P., F.C.P.
Douglas Silverstein, M.D.
Perdita Taylor-Zapata, M.D.
Phil Walson, M.D.
Thomas Wells, M.D., M.B.A.

Purpose

The purpose of the call was to brainstorm ideas about therapeutic needs in pediatric renal disease.

The BPCA Program

Dr. Taylor-Zapata reviewed the background of the BPCA legislation and the work being carried out in the BPCA program, which is a collaboration between the U.S. Food and Drug Administration (FDA) and the National Institutes of Health (NIH). The goal of the BPCA program is to improve the effectiveness and safety of medicines used in children. The *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD) is the lead agency responsible for funding studies that will address and subsequently close knowledge gaps for therapeutics used in children. As of June 2011, under the 2007 BPCA and 2003 Pediatric Research Equity Act, about 346 studies have been completed, leading to about 410 labeling changes. Dr. Taylor-Zapata noted that the FDA Web site at www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/ucm049867 is a good resource.

The NIH pediatric drug development program has two main components: (1) developing and establishing a prioritization process that will identify gaps in pediatric therapeutics, including drugs and biologics, that need further study; and (2) conducting clinical trials of primarily off-patent drugs that have been prioritized for further study. The activities within the 2007 BPCA for drug development and testing fall into three general categories:

- Identifying and prioritizing therapeutic needs

- Developing Written Requests and Proposed Pediatric Study Requests
- Conducting studies.

BPCA outreach efforts include key experts in the field of pediatric pharmacology, mass outreach to major pediatric organizations, therapeutic area working groups, and annual meetings to present working groups' recommendations and develop a priority list of needs in pediatric therapeutics. The BPCA program has continued to improve the prioritization process by making it more objective, increasing global outreach with a broader range of stakeholders and earlier expert input, and including outside evaluators.

Each year, the NICHD identifies three new areas for focus for that calendar year. Therapeutic area working groups are pulled together to discuss the therapeutic needs in that area of pediatric medicine. The NIH asks for recommendations of drugs (drug classes), biologics, and/or other areas of research that affect therapeutics that need further study in pediatrics.

For 2011, the therapeutic areas are pulmonary, hematology, and renal. Working groups for these three areas have been formed. The renal group can expect to meet via teleconference about three times prior to the 2011 annual BPCA prioritization meeting, which will be held in December this year. Minutes of meetings will be posted on the BPCA Web site and distributed to working group members. The working groups' recommendations will be presented at the annual meeting and could lead to future studies, workshops, and publications. Working groups will be invited to participate in the annual meeting.

The BPCA mandate is to identify needs in pediatric therapeutics. The NICHD is fully aware that other institutes have led research efforts and funded studies in each of the therapeutic areas. The NICHD is not trying to duplicate any other research efforts.

The NICHD became interested in the following needs in the renal disease therapeutic area due to recommendations from the 2010 BPCA outreach process:

- Effect of continuous renal replacement therapy (CRRT) on the pharmacokinetics of medication used in children with acute kidney injury (AKI), in particular life-saving medications
 - Developing models to predict blood levels of life-saving drugs used in children receiving CRRT (examples include antibiotics, medications for blood pressure support, and sedatives/analgesics)
 - Testing these models in critically ill children with AKI
- Efficacy and safety of erythropoiesis-stimulating agents (ESAs) in children with chronic kidney disease (CKD).

Open Forum

- Both of the areas identified would be excellent areas to start on. Little is known about how drugs are metabolized and cleared in CRRT. There are different methods for CRRT, and data have been difficult to get mainly because so few children receive CRRT. Probably only about 200–300 children receive CRRT per year. To obtain sufficient data, many centers

would need to buy in to the study. Drugs at the top of the list for study would include antibiotics, blood pressure support medications, analgesics, and chemotherapeutic agents for cancer. There are some data about antibiotics. Such research would be very worthwhile and clinically relevant, but to get adequate numbers for a study would take years.

- There are some data showing that ESAs do work and seem safer in children than adults. Cardiovascular disease is a concern, but it takes children a long time to develop cardiovascular disease. There is a need to study safety with these agents. Again, the number of patients is limited—about 2,000 children are receiving dialysis. There are about 10,000 children with CKD. Data from dialysis networks are readily available.
- In a current NIH trial in children with CKD with more than 600 enrollees, at the initial entry visit about 40 percent were anemic, despite the availability of ESAs and therapies. There is a treatment gap that should be closed. Anemia is associated with more frequent hospitalizations, infections, and cardiovascular risk, which is a long-term issue, particularly for adults, and has not been adequately studied in children. Anemia can affect neurocognitive development, which has not been studied in the nephrology cohort. Short-term and long-term growth is an issue, as is cardiac dysfunction with anemia in CKD. Quality of life is affected in children.
- The focus should be on more commonly used sedatives, analgesics, and blood pressure support drugs rather than antibiotics. There are data available about antibiotics, and it would be difficult to decide which ones to pick. Commonly used drugs used in CRRT should be easy to determine. Some data will be needed to help decide which drugs would be best to study. Clearance of drugs is different with the two different modalities of CRRT.
- A literature review about pediatric studies that was prepared for the Centers for Medicare & Medicaid Services (CMS) is available.
- A meeting, “Reducing the Impact of Chronic Kidney Disease: Opportunities for Randomized Clinical Trials,” will be held at the Natcher Conference Center July 19–20, with the goal of developing studies in CKD. Four areas targeted for trials to be developed include anemia, acidosis, hypertension and proteinuria, and calcium and phosphorus. Pediatric trials will be considered as well as adult trials. Dr. Kaskel will send information about the conference to Dr. Taylor-Zapata to send to group members.
- Early therapy for dyslipidemia in CKD may be worth looking at. Patients with CKD are at risk for dyslipidemia, and most patients with end-stage renal disease, especially those on hemodialysis, have lipid abnormalities. This would also need to be a long-term study. Statins are being used in the CKD population, but only about one-third of patients are being treated for dyslipidemia. Some patients’ dyslipidemias are not persistent, so there is a tendency to wait to see if the patient’s primary disease gets under control. However, treatment for dyslipidemia is low risk, and the medication can always be stopped.
- A major area of clinical research is bone disease. Osteodystrophy has been a big problem in children in the past. The evolution of treatments has involved calcium supplements, vitamin D, phosphate binders, and diet—which often fails. An article in the *Journal of the American Medical Association* summarizes new data from an adult study that found a marker for cardiovascular risk—fibroblast growth factor 23 (FGF-23), a phosphaturic hormone—is elevated in the blood of patients with CKD even before parathyroid hormone levels rise. Data in children also show that FGF-23 is elevated. FGF-23 has adverse cardiovascular effects.

- Some trials are under way related to short-term use of statins for the prevention of AKI. This could be an area where the pediatric community could lead the way. Adult studies are a bit confounded by the large proportion of people already taking a statin. There is good evidence to show that statins might be beneficial in AKI as preventive therapy. The treatment in younger ages would be short term.
- The working group should consider how any research would affect the label for therapeutics.

Dr. Taylor-Zapata said the wish list would be pulled together in the next week. During the next conference call, the group will discuss these areas in more detail.

Next Steps:

- Dr. Kaskel will send information about the July 19–20 NIH conference to Dr. Taylor-Zapata to send to working group members.
- Meeting minutes will be distributed to the working group.
- The next conference call will be scheduled in 4 to 6 weeks.