

**Best Pharmaceuticals for Children Act (BPCA)
Hematology Working Group Conference Call and Webcast
November 7, 2011
11:00 a.m.–12:00 p.m. ET**

Participants

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Introduction

Dr. Taylor-Zapata said the purpose of the call was to review the submissions from the working group's subgroups, which are based on the discussions conducted over the past few months regarding gap areas. Dr. Thornburg has been working hard to pull together all the information. The working group's recommendations will be presented during the BPCA annual meeting, to be held December 8 and 9. The meeting will cover the entire BPCA picture. Three working group presentations will occur on the afternoon of the first day. Dr. Taylor-Zapata asked that anyone who has not received registration materials let her know; she hopes everyone will register and attend the meeting. She thanked working group members for their hard work on the templates and the recommendations.

Review of Subgroup Submissions and Recommendations

- **Epidemiology/Prevalence (Thrombosis):** Dr. Thornburg reviewed this submission, which she prepared. Venous thromboembolism (VTE) is rare in children but the incidence is increasing. Although there is some epidemiologic information, it would be useful to have data on the prevalence and characteristics of VTE in high-risk groups, for example, children in the pediatric intensive care unit setting. It is important to understand the risk factors, including underlying diseases, as these can affect the pharmacokinetic/pharmacodynamic (PK/PD) response to anticoagulants and safety/efficacy. Additional data are needed to better define which children are at highest risk for VTE and to inform risk-stratified treatment and prevention strategies.

There is a need for prospective research or public health surveillance to identify and characterize pediatric patients (especially inpatients) with VTE. Several networks are available for collaborative research, and there are several ongoing clinical trials. The subgroup's recommendation is to identify funding resources to support prospective research or surveillance to define the current epidemiology of pediatric VTE with a specific goal of using the information to inform therapeutic studies of anticoagulants in children.

- **Thrombosis and Pharmacodynamic Outcome Measurements:** Dr. Thornburg said that Dr. Nita Seibel worked with Dr. Luchtman-Jones on this gap area. Dr. Seibel focused mainly on PD outcomes. The only studies done in children report the doses required in children to reach therapeutic ranges determined for a specific indication in adults, and it is unlikely that these ranges are optimal for the management of children. Little is known about what therapeutic targets should be and how they correlate with clinical outcomes. There is a need to develop new assays, age-appropriate reference ranges, and clinical algorithms appropriate for infants and children. Dr. Seibel included information about the use of unfractionated heparin, low-molecular-weight heparin, warfarin, tissue plasminogen activator (tPA), and aspirin. The laboratory targets that give the best outcomes for safety and efficacy are not known. There is a need for larger studies looking at several characteristics.
- **Outcomes (Thrombosis):** Dr. Luchtman-Jones noted that there are currently no U.S. Food and Drug Administration (FDA)-approved indications for anticoagulant, antiplatelet, or antifibrinolytic medications in pediatric patients. Recommendations for anticoagulation, antiplatelet treatment, and fibrinolysis are based on data in adults. Most publications in pediatric patients are uncontrolled studies, case reports, and underpowered clinical trials. There are some recent studies in infants and children that have looked at efficacy and safety of anticoagulation and antiplatelet therapy, as well as case series of the use of some additional anticoagulants. Clearly there is much more to do, and better agents are needed. Some agents may have different, more attractive mechanisms and may work better.

Based on her review of the literature, Dr. Luchtman-Jones listed the diseases studied, cross-checked against the CHEST guidelines from 2008, and prepared a table. One issue is that many clot-forming disorders are covered by other specialties. She noted that the strategy for treating clots is different in neonatology and hematology, and some of the diseases are different. She presented the table of clinical challenges, divided into age groups, with some outcome measures. Some major categories of the table include central line-related thrombi, cerebral sinovenous thrombosis, pulmonary embolism, arterial clots, antiphospholipid antibody syndrome, cardiac surgery, stroke, and transient ischemic attack.

- **Treatment Alternatives/Novel Agents (Anticoagulation):** Dr. Thornburg commented that Dr. Allan Doctor had covered this discussion point; he could not participate in the call, so that information will be covered at a later time.
- **Parenteral Iron in Total Parenteral Nutrition (TPN):** Dr. Klein said that after reviewing the literature and discussing this issue with Dr. David Driscoll of the Deaconess Hospital in

Boston and Harvard Medical School, he decided to withdraw this proposal from consideration by the working group. He recommended omitting the topic from the agenda because any iron compound currently on the market will cause emboli, including pulmonary emboli. Much more developmental work on iron will have to be done before it can be considered in a complete TPN solution.

- **Long-Term Use of Sodium Heparin:** Dr. Klein said that this issue is important and can easily be studied as part of prospective studies being done. Many of the components of TPN solutions are variably loaded with aluminum. The components are either naturally contaminated and not purified properly or contaminated during the manufacturing process. There have been reports in the past of heparin-associated osteoporosis in adults, but bone density evaluation in those days was not so good. Now bone density studies can be done on neonates, and aluminum in urine can be measured. These measurements can provide good clues as to whether there is loss of bone density and whether it is associated with aluminum loading. This issue will need to be revisited with the FDA because of its rule regarding oral solutions that contain aluminum meant for use in TPN. The rule does not apply to heparin or biologicals.
- **Drug Dosing Studies:** Drs. Buck and Leeder worked on this template. Dr. Buck said that drug dosing studies are probably the last studies to be done after determining efficacy and PD. Pediatric anticoagulant dosing recommendations have been largely based on clinical experience and several small-scale clinical studies. The limited numbers of infants and children who require therapy and the lack of consensus on treatment strategies have made larger trials methodologically difficult and cost prohibitive. New strategies are needed to determine optimal dosing recommendations, which will likely require innovative study design, use of simulation and modeling techniques to allow minimal sampling, and the use of existing or development of new collaborative research networks.

The subgroup looked at off-patent drugs used in pediatric populations, such as aspirin, clopidogrel, heparin, and warfarin. The only drug with a pediatric indication is heparin, but heparin is not approved for neonates because of alcohol in the preservative. The warfarin label includes pediatric information but is not approved for pediatric use. The template lists the studies the subgroup thought would have the biggest impact. Studies are needed for just about every drug. Dr. Buck briefly reviewed a number of ongoing studies, which include a new study about genotyping in children who received warfarin.

The subgroup's recommendations are to work with existing collaboratives, such as the Pediatric Oncology Group, PALISI, and the Pediatric Trials Network, to develop a series of clinical trials to address pediatric anticoagulant dosing. Initial trials should focus on (1) establishing appropriate laboratory values to measure dose response for each agent, (2) performing PK and dose-ranging studies in the largest patient populations, and (3) PK/PD studies in unique populations known to be at risk for undertreatment (neonates, obese children). Adequately powered sample size is an issue. In the future, simulation/modeling may produce better information with smaller sample size.

Dr. Leeder commented that Dr. Neville could talk about the warfarin studies because she is leading an FDA-sponsored study in collaboration with Dr. Ron Hines and Dr. Joan Gill; Dr. Hines has an R01 to study pharmacogenomics in children. There is also a larger international initiative that involves some people from Sweden; it may be operating through the Pharmacogenomics Research Network.

Dr. Neville said that everyone has had trouble accruing patients for these studies. The purpose of her study was to be a quick pilot to look at the effect of pharmacogenomics on dosing; the study is purely observational.

Dr. Leeder said with regard to the effect of age on clearance, PK modeling might help to uncover some of the genetic risk factors that are obscured by the age dependency of the data. The drug target side is another issue. Dr. Neville agreed and said accrual is a general problem regardless of the drug studied. Age related modeling might help solve this problem. Considering the problems with accrual, it will be necessary to be very intentional when designing PK studies.

- **Pathophysiology Including Biomarkers (Pediatric Stroke):** Dr. Thornburg said Dr. Surendra Varma prepared this discussion point. The incidence of stroke in children is low, but this is an area needing study. There is not much information available for the use of thrombolytic agents in children with stroke. Concerns include safety, in terms of bleeding, but there is not much evidence that there is much difference in risk or rate of bleeding in children compared with adults.
- **Drug Dosing (Stroke and Thrombosis):** Dr. Thornburg said this template was prepared by Dr. Athena Zuppa; the template focuses on tPA. Dosing recommendations for tPA vary widely. A research question is whether this drug should be used in children in the critical hours after stroke as well as in children with congenital heart defects with a veno-occlusive thrombus. PK studies are limited, and it would not be ethical to include healthy children in studies. Dr. Zuppa included a comprehensive section on FDA approved indications and contraindications. The blueprint section includes three steps. Step 1 would be to perform adult PK studies to determine the target therapeutic concentration achieved with current dosing. This can be done in patients who are receiving the drug as standard of care for treatment of stroke. Step 2 would be pediatric PK and safety studies using dose escalation. Step 3 would be a randomized controlled trial of optimal dose versus placebo to determine safety and efficacy.

Next Steps

Dr. Thornburg said that she will go through the list of studies that can be done based on the gap area templates and discussion points provided by the subgroups. The next step will be to send working group members a scoring card to prioritize the list of recommended studies to be done.

Dr. Taylor-Zapata said she will send out the scoring card by e-mail in the next couple of days. She thanked the subgroup leaders who prepared the materials and urged all working group members to provide their input by completing a scoring card. The cards should be filled out and

returned to her and Brandy Weathersby, Circle Solutions. A summary of the results will be sent to Dr. Thornburg, who will ultimately pull together the results to present at the annual meeting.

Drs. Neville and Durmowicz agreed to work together to compare the working group's recommendations with the similar issues discussed at the November 2 FDA anticoagulation subcommittee meeting and will provide their comments using the scoring card.

Action Items:

- Dr. Taylor-Zapata will e-mail working group members a scoring card to be used to priority rank recommendations for studies.
- Working group members are asked to complete the scoring card and return it to Dr. Taylor-Zapata and Ms. Weathersby.