Best Pharmaceuticals for Children Act (BPCA)
Pulmonary Therapeutic Area Working Group Conference Call and Webcast
November 18, 2011
1:00 p.m.–2:00 p.m. ET

Participants

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John Alexander, M.D., M.P.H.
Louis Chicoine, M.D.
Jonathan Davis, M.D.
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Thomas Green, M.D.
Nadia Hejazi, M.D.
Abraham Karkowsky, M.D., Ph.D.
Frederick Kaskel, M.D., Ph.D.
Greg Kearns, Pharm.D., Ph.D.
Matthew M. Laughon, M.D., M.P.H.
Christopher J. Newth, M.D.
Heber C. Nielsen, M.D.
Hanna Phan, Pharm.D., B.C.P.S.
Michael Reed, Pharm.D., F.C.C.P., F.C.P.
George Z. Retsch-Bogart, M.D.
Perdita Taylor-Zapata, M.D.
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Purpose

The purpose of this conference call and webcast was to discuss the working group's recommendations.

Discussion

Dr. Taylor-Zapata thanked the participants for preparing the recommendation documents, which were distributed via e-mail. Dr. Nielsen will combine the recommendations into a summary document, which he will present at the December BPCA Annual Meeting. Dr. Taylor-Zapata and Brandy Weathersby of Circle Solutions, Inc., will use the combined document to create a score sheet that the group members will use to prioritize the recommendations.

Pulmonary Arterial Hypertension (PAH)

Sildenafil. Dr. Laughon explained that the most common pulmonary morbidity associated with premature birth is bronchopulmonary dysplasia (BPD). Up to 40 percent of premature infants with BPD who develop PAH die, usually due to cardiorespiratory failure and right heart failure.

Sildenafil is a potent inhibitor of type 5 phosphodiesterase and metabolizes cyclic guanosine monophosphate. It produces pulmonary vasodilation and is labeled for adults with PAH. The drug is extensively metabolized by CYP450 3A4 (80 percent) and 2C9 (20 percent), and the primary metabolite has activity toward producing pulmonary vasodilation. Data show that off-label sildenafil use in neonates has dramatically increased between 2001 and 2009. Dr. Laughon described how sildenafil meets all of the five challenges that the BPCA is charged with meeting.

Dr. Laughon was asked about the approved intravenous (IV) solution. He answered the IV sildenafil solution could be given orally, but there are no oral products.

Dr. Abman agreed that sildenafil is important and explained that it is overused inappropriately. A problem with designing an efficacy study is that the infants are not phenotyped well enough. Echocardiogram is not reliable for defining PAH or assessing its severity. With earlier use of sildenafil, retinopathy may be a problem. Learning about pharmacokinetics (PK) and pharmacodynamics (PD) and finding a more uniform way of administering the drug would be advances, but many studies need to be done.

Dr. Alexander said that while the inaccuracies of echocardiograms have been discussed for many years, many cardiologists do not agree. By the time children need sildenafil, the vascular injury is extensive, and the efficacy of long-term therapy is uncertain. He asked whether the group could be focusing on agents to prevent the development of PAH in BPD.

Dr. Nielsen suggested that participants e-mail questions to Dr. Laughon.

Asthma

Inhaled Corticosteroids. Dr. Green proposed studying the use of corticosteroids in children younger than age 5. Inhaled corticosteroids have been proven safe and effective in treating asthma and reactive airway disease in adults and children older than age 5. These agents are used for reactive airway disease in children younger than 5, and there are questions about whether they are efficacious, absorbed, and safe. Potential complications may be related to systemic absorption and effect on growth. Inhaled corticosteroids are commonly administered by nebulizers and metered-dose inhalers with a spacer.

A combination of PK and efficacy studies, along with toxicity studies, is recommended. Studies can include a large patient population to compare metered-dose inhalers with nebulizers, document systemic absorption, and follow growth velocity. Efficacy, in terms of reduction in exacerbations and asthma-free days, could be examined in the same or similar studies.

Beta Agonists. Dr. Newth explained that very few IV beta agonists are available for children in the intensive care unit (ICU). Of the selective beta agonists, only terbutaline is available in an IV formulation. It is not approved for treating asthma in children, and there are few data on its use. PK/PD and toxicity studies in an ICU setting would be useful. The formulation has a large volume, which creates problems in dosing children. A tool for assessing the severity of asthma in children and response to therapy is needed.

Omalizumab. Dr. Green said that omalizumab has been used to inhibit immunoglobulin E (IgE) binding to its receptor and mast cells and is efficacious in reducing the number of exacerbations and severity of illness in older children and adults with IgE-related allergic asthma. There is a significant population of children younger than age 5 for whom allergies are the precipitating cause of asthma. Preliminary data suggest that desensitization with this agent might decrease the continued development of allergies in children.

Controlled clinical trials, supported by immunologic and physiologic studies, are recommended. Long-term follow-up could determine the incidence of persistent asthma. The clinical tools necessary to support such a study are present and reasonable.

Dr. Nielsen asked whether one or more asthma assessment tools need to be developed. Dr. Green said reasonable measures are available for outpatient studies. Dr. Newth added that an asthma-assessment tool for the ICU is needed and would involve sophisticated monitoring devices.

Dr. Alexander added that a high-efficiency aerosol device is needed.

Cystic Fibrosis (CF)

Beta-Lactams. Dr. Phan said that she attended a recent North American Cystic Fibrosis conference, and beta-lactams were a popular topic. PK, safety, and efficacy data are lacking in pediatric CF patients. Beta-lactams are being used without appropriate data. A study comparing extended and continuous infusion with multidrug-resistant pathogens is needed.

Dr. Nielsen asked whether the beta-lactams could be prioritized. It may be easier to design a study of one antibiotic, and a single nationally recommended antibiotic could be useful. Dr. Phan said that ticarcillin/clavulanate is one of the more common first-line beta-lactams. A study of this drug could be translated to piperacillin/tazobactam. Meropenem should be reserved as much as possible. She will modify the recommendation and send it to Dr. Nielsen.

Colistin. Dr. Phan said that IV colistin is used with nebulizers, but there is not a formula for nebulization. Safety, efficacy, and PK are uncertain, especially in younger patients. The rise of multidrug-resistant pathogens has forced the use of IV or nebulized colistin at dosing suggested for adults. Using both IV and nebulized forms for resistant pathogens has been discussed.

Dr. Nielsen noted that, as with asthma, appropriate aerosolization is an issue. Dr. Phan said that if the reconstituted powder used for nebulization sits for more than 1 hour, the concentration of colistin increases. A safer solution is needed.

Ibuprofen. Dr. Reed said that, for decades, investigators have been searching for the perfect anti-inflammatory agent to prevent or diminish the rate of decline of pulmonary function. He was involved in early studies of ibuprofen in CF. Ibuprofen is a nonspecific cyclooxygenase inhibitor and is primarily labeled for use to treat pain and fever. IV formulations are labeled for use for pain and fever and for patent ductus arteriosus closure in neonates.

Data show that in CF, high-dose, long-term therapy will improve lung function or minimize decline. Only 4–10 percent of the CF population are using ibuprofen due to concerns about abdominal discomfort and gastrointestinal (GI) bleeding or perforation. The Cystic Fibrosis Foundation registry has long-term data on a large number of patients that suggest that ibuprofen is safe. GI bleed and perforation are extremely rare; abdominal discomfort is more common. These side effects can be managed by more vigilant monitoring or concurrent medications.

Ibuprofen is not labeled for use in CF, and doses used for CF are much higher than normal. Studies would address safety and the need for less intensive therapeutic monitoring.

Dr. Nielsen asked whether aerosol delivery would prevent side effects. Dr. Reed said that there would be GI effects with any type of administration. However, if the drug were delivered by aerosol, the dose might be low enough to ameliorate GI effects.

Proton Pump Inhibitors (PPIs). Dr. Kearns said that PPIs are widely used in pediatrics. In children with CF, PPIs have off-label uses, such as adjuvant therapy with enzyme replacement drugs. The current labeling is extensive. There are few adverse affects, but there are recent data on severe hypomagnesaemia associated with prolonged PPI use, which is a consideration in children with CF. The predominant formulations are oral solids, but data are also available on extemporaneous oral formulations. Because PPI biotransformation is largely associated with CYP3A4 and CYP2C19, numerous drug-drug interactions are possible. Many interactions are well characterized and do not occur in drugs commonly used in children with CF.

PK data in adults have established an association between systemic exposure and effect. The dose/exposure/response correlation can be assumed to be the same in children with CF, but no studies have verified this. The studies can be done with new knowledge of how to study PPIs. Hundreds of patients would not be needed because there is a rich database. PPIs are candidates for a bridging study.

Dr. Nielsen asked about the mention of area under curve (AUC) in the recommendation document. Dr. Kearns said that in adults, the plasma concentration AUC needed to alter intragastric pH and maintain that alteration is known. In pediatrics, adult PK/PD data could be extrapolated, and target plasma concentration AUC could be used as a surrogate endpoint for effect unless there are disease-specific alterations in the biotransformation of these drugs. Earlier studies indicate that the only alteration is with profound changes in body composition. A study would need to pay attention to 2C19 polymorphism, which is related to exposure variability.

Itraconazole and Voriconazole. Dr. Retch-Bogart said that these antifungal agents are very similar, but there are differences in metabolism, warnings, and side effects. Antifungal therapy is used in patients with CF to minimize corticosteroid therapy in patients with allergic bronchopulmonary aspergillosis and increasingly to treat fungal pathogens in lower airways. There is not much experience in long-term use of these agents in people with CF.

The absorption of itraconazole is affected by the gastric environment. The majority of patients with CF who have pancreatic insufficiency may have problems with predictable absorption. Limited PK and absorption information is available in the CF population. Voriconazole has more reliable absorption but carries worries about potential drug-drug interactions, hepatic toxicity, and other emerging problems with longer term use. Courses of treatment tend to be used long-term in CF patients without clear justification. Information about toxicity and side effects with long-term use is needed. For both agents, important issues include absorption, PK in the CF population, and the effect of PPIs on the gastric environment. Reliable dosing and serum concentrations could be linked to studies of efficacy.

There are no ongoing trials for voriconazole; clinical trials in other countries have looked at itraconazole in the CF population.

Pathophysiology and Biomarkers

Dr. Chicoine explained that in the neonatal population there is no reliable measure of the degree of PAH, evolution of the disease, and response to treatment. Echocardiogram is not a reliable tool, and biomarkers are important. More work has been done on biomarkers in adults than in neonates. Biomarkers for neonates should be minimally invasive and age appropriate, reflect disease progression and response to treatment, and be reproducible. Biomarkers for specific disease pathways would enhance the study of PAH.

Plasma-based biomarkers include N-terminal pro-brain natriuretic peptide, growth differentiation factor 15, interleukin 6, creatinine, and red blood cell distribution. Genetic-based biomarkers include known genes associated with PAH, known genes in the pathways of pulmonary vascular diseases, genes associated with a predisposition to severe BPD and associated PAH, and single-nucleotide polymorphisms. In the future, a combination of clinical, plasma, genetic, and hemodynamic biomarkers may be used to predict long-term survival and determine treatment. A registry and tissue bank are needed for the neonatal and pediatric populations.

Dr. Nielsen suggested that Dr. Chicoine organize a conference call for members of the working group. He will send Dr. Chicoine a summary of a recent National Institutes of Health (NIH) conference on PAH in children.

Dr. Nielsen said that the working group would receive a form for prioritizing recommendations. The goal is not to eliminate any recommendations but to help with short- and long-term priorities. Some information from the individual reports will be lost as the recommendations are summarized. Working group members should vote on priorities by December 1. Members can send any additional information to Dr. Nielsen.

Action Items:

- Participants will e-mail questions about sildenafil to Dr. Laughon.
- Dr. Phan will modify the beta-lactams document and send it to Dr. Nielsen.
- Dr. Nielsen will send Dr. Chicoine a summary of an NIH conference on PAH in children.
- Working group members should vote on priorities by December 1.