Best Pharmaceuticals for Children Act (BPCA)
Cough and Cold Therapeutic Working Group Conference Call
March 31, 2009
12:30 p.m.–1:40 p.m. ET

Participants

Danny Benjamin, M.D., Ph.D., M.P.H., Duke University Clinical Research Institute
Jeffrey Blumer, M.D., Ph.D., Case Western Reserve University, Rainbow Babies and Children's Hospital
Norma Gavin, Ph.D., RTI International
Thomas Green, M.D., Northwestern University
Alyson Karesh, M.D., Center for Drug Evaluation and Research (CDER), Food and Drug Administration (FDA)
Rae-Ellen Kavey, M.D., M.P.H., National Heart, Lung, and Blood Institute, NIH
Kenneth Kim, M.D., West Coast Clinical Trials, LLC
Jan Leahey, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development (NICHD), NIH
Lynne G. Maxwell, M.D., Children's Hospital of Philadelphia
Robert "Skip" Nelson, M.D., Ph.D., FDA
Laura Panko, M.D., University of Pittsburgh School of Medicine
Ian Paul, M.D., Pennsylvania State University College of Medicine
Rachael Carlisle Roehrig, Ph.D., Consumer Healthcare Products Association (CHPA)
Heinz Schneider, M.D., CHPA
David Siegel, M.D., NICHD, NIH
Brian Smith, M.D., M.H.S., Duke University Clinical Research Institute
Amy Taylor, M.D., M.H.S., CDER, FDA
Perdita Taylor-Zapata, M.D., NICHD, NIH
Ronald Turner, M.D., University of Virginia School of Medicine
John Van Den Anker, M.D., Ph.D., Children's National Medical Center
Teri Moser Woo, R.N., Ph.D., CPNP, University of Portland
Anne Zajicek, M.D., NICHD, NIH

Purpose

The purpose of the meeting was to:
- Review BPCA activities (history, accomplishments, studies, therapeutic areas)
- Identify current needs in research related to the use of cough and cold therapeutics in children.

Introduction

Dr. Taylor-Zapata welcomed the call participants and explained that this working group is one of a series of working groups convened this year to gather information on needs in pediatric therapeutics. She provided a PowerPoint presentation (which will be made available to the

group) with background information on BPCA legislation, NICHD's role in BPCA, and the process of prioritizing drugs for study. When BPCA was reauthorized in 2007, the focus shifted to identifying gaps in pediatric therapeutics, including indications as well as drugs. The BPCA Web site (http://bpca.nichd.nih.gov) is where the list of drugs selected as priorities to date can be found. A new priority list will be available within a few weeks; it will be published in the *Federal Register*.

Dr. Taylor-Zapata presented an overview of studies currently being done under BPCA and prioritized therapeutic areas. The goal for BPCA is to advance labeling and advance the science. NICHD is developing new partnerships and multidisciplinary teams to reach this goal. The prioritizing process involves gathering data from existing studies, literature reviews, and consultations with experts to identify knowledge gaps. The annual BPCA meeting will be held November 3–4, 2009, in the Bethesda, MD, area. At the meeting, an expert panel will decide what research to pursue. Prioritization stakeholders include NIH, NICHD, FDA, expert panels, and working groups.

The purpose of the conference call was to get information on needs related to the use of cold and cough medicines in children as a follow up to the 2008 FDA Advisory Meeting on the topic. A draft of the minutes will be sent to working group members for input, and then the revised minutes will be posted publicly on the BPCA Web site. Recommendations from the working groups will be presented at the annual meeting. Outcomes of this process can include studies, publications, conferences, and workshops.

Regarding cold and cough medicines, in March 2007, FDA received a citizens' petition that raised concerns about the safety and efficacy of cough and cold medicines in children younger than age 6. FDA issued a public health advisory in August 2007 (updated in January 2008) that recommended not using these kinds of medicines in children younger than age 2 due to safety concerns. In October 2008, FDA held a public hearing. Subsequently, FDA and NIH decided a smaller working group was needed to discuss the specific issues in more detail and what research is still needed for this therapeutic area.

Dr. Taylor-Zapata said that although there are strong opinions both ways on whether these drugs should be studied, the view from the FDA hearing was that if these drugs are going to be used, studies should be done because of the lack of clear safety and efficacy data, particularly in children ages 2–6 and 6–12. There has been a big gap in pharmacokinetic (PK) studies, but pharmaceutical companies are planning and conducting PK studies on certain drugs. The main issue is whether safety and efficacy studies should be done, and if so, what are the designs of these studies.

Discussion

Dr. Nelson said a draft revised monograph is now going through FDA internally. The monograph will likely answer some of the questions about the use of cough and cold medicines in children. He was not sure when it will be completed or whether it will be ready before the November

BPCA meeting. The issue is not so much whether studies need to be done, but how they need to be done. Revisiting questions that have been asked and answered should not be necessary.

Dr. Schneider explained that he is vice president of science and medical affairs of CHPA and part of the industry group that is committed to do studies. He agreed with Dr. Nelson that the timing is very important. PK studies in children ages 2–11 are under way on the following eight cough and cold medicine ingredients: dextromethorphan, guaifenesin, phenylephrine, pseudoephedrine, doxylamine, chlorpheniramine, brompheniramine, and diphenhydramine. There are already results for some of these drugs, and other PK study results will become available during 2009. Efficacy studies are in the planning phase for the same ingredients and are planned for the winter seasons 2009–10 and 2010–11. However, there are gaps regarding the methodology of these studies.

Dr. Benjamin asked about the status for children younger than 2 regarding what is in the pipeline for industry and what the NIH priorities are. Dr. Taylor-Zapata said her understanding was that, based on the public health recommendations, there are no recommendations for studies to be done in that age group, and her understanding of the NICHD's position is the same. NICHD has not entertained studies in children younger than 2 under BPCA at this time.

Dr. Schneider said in the task group he represents, the scope of the task group is the monograph ingredients, and the scope of the research does not include children younger than 2. Research in this age group can be considered in the future by individual companies, probably under new drug applications.

Dr. Nelson asked what the gaps were, assuming that industry is performing PK studies leading into efficacy and safety studies. There are eight ingredients on the table in the monograph. There may be other ingredients that have been left out that should be studied. Although the monograph is constrained by age group, that does not mean an ingredient in a younger age group cannot be studied.

Dr. Van Den Anker said that although it is easy to argue against studying children younger than 2, parents of children in the first year of life want something to prevent children from coughing all night—not only for the child's health but also to allow the parents to sleep. This is an opportunity to get some information on how to use and dose these younger children.

Dr. Paul described this as a stepwise situation due to safety concerns. Regarding the adverse events (AEs) profile, companies have found that most AEs occur in the first 2 years. Without good efficacy data for older age groups, it is hard to justify examining the younger age group. If some of these ingredients are shown to be effective in older children, that finding might warrant examination in younger children.

Dr. Nelson said the logical conclusion was that with these studies in older children being done, that gap potentially would not be filled until after the cold season 2010–11. Dr. Benjamin noted that getting the planning off the ground for children younger than 2 may take quite a bit longer than that because of how long it takes for data from studies to be analyzed and disseminated. As

Dr. Paul pointed out, much of the use of these drugs occurs in that age group, but that group is also where the safety problems are. These products are not likely to go away.

Dr. Taylor-Zapata said the American Academy of Pediatrics (AAP) has strong recommendations about not using these drugs in children younger than 2. Dr. Paul noted that AAP has a specific policy statement about only dextromethorphan. The testimony to FDA said AAP does not support the use of these medicines in children, especially those younger than 2. Dr. Nelson commented that if the AAP board approves the federal testimony, it is policy, even though it is not published through its review process. Saying there is no evidence of efficacy and that there are safety concerns does not mean there should not be a study.

Dr. Paul agreed and said that there might be a couple of compounds that will be shown to be effective for older children, and these compounds might be effective for younger children as well. It might be wise to do PK studies in children younger than 2, but not on all ingredients.

Dr. Schneider explained that one reason the industry task force excluded children younger than 2 was the biology and PK experience in older children. From a PK point of view, older children do behave like small adults, as opposed to the younger children. In the youngest age group, probably more must be done than standard PK followed by efficacy studies.

Dr. Benjamin commented about the lengthy timeline for moving from thinking that doing a study is a good idea to getting a study done. Doing PK on a couple of key products in children younger than 2 is something the group can consider as a gap that needs to be filled. People like Dr. Paul and others with expertise about products that might be suitable targets could provide guidance.

Dr. Taylor-Zapata summarized that the pharmaceutical industry is doing studies of eight ingredients and then will do efficacy studies in the next two winter seasons. But, as pointed out, there are huge gaps in the methodology of how to do the studies. She asked the group for comments about these gaps.

Dr. Paul said that assessing the efficacy of medicines in these children is difficult. Subjective or objective measurements are needed; both have some advantages and some limitations. For subjective measures, there is a lack of validated surveys or scoring systems for desired outcomes (symptoms). With objective measures, things like rhinorrhea are challenging to study. Cough can be monitored objectively, but there is some difficulty with the amount of time and resources to analyze the data. Also, there is lack of agreement on clinically significant endpoints and differences and what would qualify as clinically meaningful. All these issues are unresolved.

Dr. Schneider said there is a difference in what can be done in different age groups. Some things that can be done in older children (e.g., children ages 8–11) that will work well are close to what can be done with young adults, versus what can be done in children ages 4–6, for instance. Younger children seem to be the most challenging ones methodologically.

Dr. Nelson said he assumed that these issues would need to be resolved before industry gets into efficacy trials during the next two cold seasons and that endpoint issues would need to be

resolved before NIH would be involved. He asked whether the group saw a role for doing endpoint validation independent of the efficacy trial. Dr. Schneider replied that regarding methodology, any help, particularly regarding younger, preschool-age children, would be complementary and timely.

Dr. Paul cautioned that industry-defined clinically significant endpoints might be different than clinician- or academic-defined endpoints. What is statistically significant may not be clinically meaningful or subjectively apparent. Dr. Nelson said he was thinking more of the problems of taking some of the older measurements used in adults and using them in children. Dr. Paul noted that there are few validated measures in adults either. There are chronic cough questionnaires, but they do not apply to settings where the medicines are used.

Dr. Turner noted that FDA has reviewed and approved antihistamines in adults based on subjective symptom criteria (the Jackson criteria), which have been compared to Dr. Bruce Barrett's criteria at the University of Wisconsin in a publication. There is a long history of use.

Dr. Schneider noted that his industry group has been planning the studies in consultation with FDA. Nothing will be done in isolation by the companies. The studies will be very resource intensive and will rely on input from the other stakeholders.

Dr. Nelson suggested that, because the industry studies will start in children ages 8–12, there may be an opportunity to do some methodological work in the 2–7 age group, given that the endpoints are less secure. Dr. Schneider agreed. Dr. Nelson said that was one area this group could think about.

Regarding making changes to the monograph, Dr. Nelson said that changes go through the rule-making process, which is different from the usual drug approval process.

Dr. Taylor-Zapata summarized that there is a large gap for older children as well as for younger children. There are researchers interested in studies in children younger than 2, including PK studies and maybe efficacy studies if some additional information on objective and subjective measures and outcomes can be obtained.

Dr. Nelson asked whether anyone thought that there are ingredients other than those eight specified that should be studied. Just because industry selected those ingredients for study under the monograph does not mean those are the only ones that should be studied.

Dr. Schneider commented that industry picked these eight because they are the ones used in 95 percent of cough and cold products. The eight ingredients are used in four therapeutic categories:

- Expectorants (guaifenesin)
- Oral cough suppressants (dextromethorphan)
- Oral nasal decongestants (phenylephrine, pseudoephedrine)
- Antihistamines (doxylamine, chlorpheniramine, brompheniramine, diphenhydramine).

Although there are numerous other antihistamines, Dr. Schneider said he was not aware of evidence that additional antihistamines would be worth studying.

Dr. Paul commented about the need for studies on topical and intranasal medications for cough/cold, for which there are also very limited efficacy data.

Dr. Kim pointed out that a model exists in the literature in studies of antihistamines that were in the prescription marketplace first, such as Zyrtec, Allegra, and Claritin. Studies on these were done in the 4–11 age group and in people 12 and older. Symptom scores were collected. He suggested using those studies as models for looking at some efficacy parameters in future trials. There are also some efficacy parameters for ages 2–5 generated through perceptions of the primary caregiver.

Dr. Taylor-Zapata asked whether, for future safety studies, there is a need for a type of registry trial or surveillance program for these classes of drugs.

Dr. Schneider described an ongoing safety surveillance program funded by CHPA. The program focuses on passive surveillance and is coordinated by the Rocky Mountain Poison and Drug Center. An independent group of experts found that the vast majority of events can be attributed to unsupervised ingestion (which is also supported by data from the Centers for Disease Control and Prevention [CDC]) and medical errors. In the big picture, those cases that are potentially attributed to therapeutic doses are so rare that one could hardly capture them in prospective study—a huge study population would be needed to capture these events.

Dr. Nelson added that based on CDC methodology out of emergency departments, it is sometimes hard to know the specific product that may have been involved in an event. There are many questions worth answering. He agreed that a prospective trial might not be best for answering these questions because of the numbers and because fewer events might occur if people know you are watching.

Dr. Taylor-Zapata said that industry has done educational programs and FDA has done the public health advisories. She asked whether any educational programs are being sponsored or planned for providers as well as the public.

Dr. Schneider said CHPA is working with CDC, FDA, poison centers, and industry experts to identify gaps in education. There is FDA educational material. There is a CHPA national campaign on television. But CHPA feels those efforts can be enhanced. The work from root-cause analysis can help fill in what is missing in these education efforts. Any good thinking or help is welcome. Cooperation with CDC has just started. Wrong assumptions are common, and a realistic understanding of what is happening in homes is needed.

Regarding the next steps for this group, Dr. Taylor-Zapata said that BPCA staff will go through the group's discussion. Then, the plan was to have a second, follow-up call to get more specific about what to do next. The second call will be scheduled in May or June. Findings from these

working groups will be presented to the BPCA annual scientific panel to discuss what BPCA can and should do in this area.

Dr. Benjamin asked about the structure of BPCA trials going forward. Dr. Taylor-Zapata said the structure will change somewhat because of the broadening of the legislation. More information will be available later this year.

Dr. Benjamin asked Dr. Paul what products out of the eight under study might go to children younger than 2 first. Dr. Paul said he would pick the one that would work: pseudoephedrine. The best adult data are for that drug compared with the other compounds. Dextromethorphan is effective as a cough suppressant with a large enough dose, but then children get high from the drug. For most medicines, there are no data. For example, there are no adult or pediatric published data on guaifenesin. Phenylephrine is very questionable, which is why it was not around so much until pseudoephedrine began to be sold behind the counter. There are some adult data on antihistamines, so they might be a second choice for children after pseudoephedrine. Dr. Paul noted that there are safety issues for giving a drug that is also a sedative in young children who might be having respiratory difficulty.

Dr. Turner commented that in adults, the effect size for the first generation antihistamines for rhinorrhea is in the 30 percent range. The effect size for pseudoephedrine for nasal obstruction is usually in about the 20 percent range.

Next Steps

- Circle will prepare and distribute a draft of the meeting minutes.
- The working group members will review and comment on the draft minutes.
- The next conference call will be in May.
- Circle Solutions will poll the working group members to determine the best date for the conference call.

Addendum: Comments from Dr. Paul and from Wayne R. Snodgrass, M.D., Ph.D.

Dr. Paul:

- There are differing dextromethorphan products based on their anion, and these need separate study especially for PK, but also for efficacy.

Dr. Snodgrass:

- Lack of knowledge of the primary biochemical mediators of symptoms and signs of coryza may limit the potential drugs/drug categories to be considered for study. For example, zifirlukast (Accolade) has been shown in adults to have efficacy for common cold symptoms/signs (if I recall correctly, the effect size was approximately in the 30 percent range). Thus, leukotrienes may be mediators of some symptoms/signs.

- Limiting study drugs to only monograph drugs may limit the development of effective drug therapies. Other rational mechanism-based drugs might be hypothesized and considered for

study, e.g., leukotriene receptor blockers, or type-1 antihistamines (fexofenadine; loratadine) that do not cross the blood-brain barrier to the same extent as some of the older monograph antihistamines, or ICAM-1 (intracellular adhesion molecule-1) blocker drugs to block adhesion of virus(es) prior to cell entry, etc.

- In the eight monograph drugs that are being considered, which antihistamine (are there any animal data? —if not, such studies could be done) has the lowest steady-state ratio of cerebrospinal fluid (CSF) to plasma levels, so as to minimize brain accumulation and thus potential sedation? [Note: adult human CSF to plasma ratio of diphenhydramine is 6 to 1; thus, there is 6 times greater CSF level compared to plasma level.] [Note: late gestation rat fetus brain and early postnatal rat pup brain has 5 times greater concentration of active type-1 histamine receptors per cubic centimeter of brain tissue compared to adult rat brain; thus, older type-1 antihistamines with high brain levels are perhaps more likely to produce sedation in infants and young children.] [Note: Merle Paul, Ph.D., at FDA research facility in Arkansas has data showing adverse cognitive effects (impaired learning and memory) in young rhesus monkeys of various ages given typical over-the-counter dose of diphenhydramine.]

- If pseudoephedrine is to be studied, careful attention to adverse systemic cardiovascular effects should be considered, even with short-term use, e.g., elevated blood pressure, decreased vascular compliance following therapy, the extent of plasma catecholamine changes and their persistence, secondary renal responses (e.g., altered renin secretion), etc.

- Should not more consideration be given to further study of (patentable) viscous sugar solutions, e.g., honey (data of Ian Paul, M.D.) or similar products, that may decrease irritant-type firing of nerve receptors in the hypopharynx and thus decrease the degree of cough in patients with coryza?

- Which groups of genes are activated with infection due to viruses (e.g., the most common rhinoviruses) that cause the common cold? Gene-array studies? Would such data potentially identify new targets for drug therapy?