Best Pharmaceuticals for Children Act (BPCA)
Cough and Cold Therapeutic Working Group Conference Call
May 18, 2009
11:00 a.m.–11:45 a.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
Bernard Brownstein, M.D., Premier Research Group
Thomas Green, M.D., Northwestern University
Kenneth Kim, M.D., West Coast Clinical Trials, LLC
Lynne G. Maxwell, M.D., Children's Hospital of Philadelphia
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)
William Rodriguez, M.D., Ph.D., Office of Pediatric Therapeutics, FDA
Heinz Schneider, M.D., CHPA
David Siegel, M.D., NICHD, NIH
Wayne Snodgrass, M.D., Ph.D., University of Texas Medical Branch
Amy Taylor, M.D., M.H.S., Center for Drug Evaluation and Research, FDA
Perdita Taylor-Zapata, M.D., NICHD, NIH
Ronald Turner, M.D., University of Virginia School of Medicine
Teri Moser Woo, R.N., Ph.D., CPNP, University of Portland

Purpose

The purpose of the meeting was to:
- Briefly review the BPCA program
- Discuss issues, comments, and recommendations from the first conference call in March
- Determine next steps.

Introduction

The Cough and Cold Therapeutic Working Group was formed under the auspices of BPCA, which is part of the reauthorized Food and Drug Administration Amendments Act of 2007. The NICHD Obstetric and Pediatric Pharmacology Branch oversees the BPCA program. The program's mandate is to determine the needs in pediatric therapeutics. The program's ultimate goal is to advance the science and labeling for drugs used to treat children and adolescents. Cough and cold therapeutics was assigned as a priority area after the FDA advisory meeting in fall 2008. The purpose of the working group is to identify gaps in knowledge and needs in research in pediatric cough and cold therapeutics.

Dr. Taylor-Zapata briefly reviewed the goals of the BPCA program, the program's prioritization structure, the prioritization stakeholders, the process of the annual BPCA scientific prioritization meeting, and some currently prioritized therapeutic areas. For the annual meeting in November, the Cough and Cold Therapeutic Working Group will develop and prioritize the top four areas of research needs in cough and cold therapeutics under BPCA. The working group's recommendations will be presented and discussed at the meeting.

Follow-up from March Conference Call

Dr. Taylor-Zapata listed the issues, comments, and recommendations as follows:

- Pharmacokinetic (PK) studies on eight cough and cold ingredients are being conducted by CHPA companies: dextromethorphan, guaifenesin, phenylephrine, pseudoephedrine, doxylamine, chlorpheniramine, brompheniramine, and diphenhydramine.
- There are methodological challenges for efficacy studies.
  - With regard to subjective measures, there is a lack of validated surveys or scoring systems for desired outcomes in adults or children.
  - Objective measures (cough, rhinorrhea) are challenging and difficult to study because they are difficult to quantify and qualify.
  - Clinically meaningful endpoints have not yet been determined or agreed upon.
    - Recommendations for endpoint validation independent of efficacy trials include the Jackson criteria used in adults and symptoms scores used in studies of antihistamines in children (e.g., Allegra, Zyrtec, and Claritin).
  - The targeted age range for additional research could be 2–7 years of age because industry studies are in children ≥8 years of age.
- There are concerns about studying younger children (<2 years old). The working group recommended gathering good efficacy data on older children before considering studies (primarily PK) of younger children due to the high number of adverse events in younger children.
- The working group recommended the study of topical and intranasal medications in children for coughs and colds.
- Some products (e.g., dextromethorphan) are different based on their structure and may be good candidates for PK and efficacy studies.
- There is a need for more knowledge of primary biochemical mediators of symptoms. Animal studies of drugs that do not cross the blood–brain barrier should be considered.
- New targets for drug therapy should be considered (e.g., studies of viscous sugar solutions).
- Ongoing passive safety surveillance by CHPA companies should be considered. Other types of follow-up studies should be identified. Prospective trials for safety are probably not feasible due to the large number of subjects required.
- The BPCA program could enhance educational materials regarding pediatric use of cough and cold medicines.
- The BPCA program could develop surveys for realistic assessment of in-home use of pediatric cough and cold medicines.

Discussion

Dr. Schneider commented that current PK studies are conducted in children ≥2 years old. He noted that the first wave of BPCA efficacy studies will focus on children 6–11 years old.

Dr. Benjamin said PK studies in younger children should start as soon as the PK studies in older children are completed. There are scientific, operational, and public health reasons for doing so. From an operational standpoint, it may be 5–6 years before results from efficacy trials in older children are published. PK studies must be conducted first, industry and FDA must agree on the type of efficacy trial (e.g., in a phase 2 setting), and funding must be arranged. In the meantime, children <2 years old will be receiving cough and cold medicines anyway (regardless of recommendations from any professional organization), and PK studies will be essential to determine appropriate dosing before efficacy study results are available. Dr. Benjamin noted that the BPCA study mechanism works better with smaller numbers of subjects across fewer study sites with PK-type objectives rather than with larger studies with efficacy-type objectives. He concluded that PK studies in children <2 years old fill a scientific need and fit the BPCA mechanism well.

Dr. Rodriguez inquired about other justifications for conducting these studies in this age group. Dr. Benjamin said an ethical response could be derived from the results of a survey on the use of cough and cold medicines in children <2 years old. If the survey reveals a high incidence of product use, it is ethically imperative to ensure that the children are not receiving toxic doses. Young children in the PK studies might benefit from the therapeutic effects of the cough and cold medicines because of their purported efficacy. There are public health, potential benefit, and ethical rationales for conducting PK studies in young children.

Dr. Paul noted that the results of an NPR/Kaiser Family Foundation/Harvard School of Public Health survey on the use of over-the-counter cough and cold medicines in children were released in December 2007 (http://www.kff.org/kaiserpolls/upload/7726.pdf). Dr. Benjamin proposed a second survey, the results of which would be released just before funding is requested. A comparison of results from the two surveys might show the impact of professional organizations' recommendations and pronouncements subsequent to release of the first survey results.

Dr. Paul said it may be appropriate to conduct PK studies of some cough and cold ingredients, but pharmacogenetic differences may be problematic. For example, some children (about 10% of the general population) are slow metabolizers of dextromethorphan. It will not be known before a PK study which children are rapid metabolizers and which children are slow metabolizers. Dr. Benjamin said the products could be ranked on the need for PK studies.

Dr. Snodgrass said older monographed drugs should be studied in younger children only if they have first been shown to be efficacious in older children. Animal studies could address important questions about additional mediators of the signs and symptoms of the common cold. Identifying mediators could help develop therapeutic targets of new agents that might not produce side effects.

Dr. Schneider asked whether research and development of new chemical entities is within the scope of the BPCA program. Dr. Taylor-Zapata clarified that this type of research is not within the scope of NIH's part of the BPCA program but is within the general scope of the overall BPCA program. Dr. Rodriguez explained that the Written Request process now allows the use of other comparators. Drugs currently under development could be compared with older monographed drugs as well as standards of care. Dr. Snodgrass said it is important to be flexible and open to those agents that might have some reasonable efficacy.

Dr. Brownstein noted that because there is no consensus on how to measure efficacy of cough and cold medicines in younger children, it will be challenging to conduct any type of efficacy trial in this age group. Dr. Benjamin agreed and said this is one reason the BPCA program should not conduct efficacy studies. Validation of endpoints is another area in which the BPCA should not become involved. Dr. Brownstein said several endpoints have been studied (e.g., nasal flow rates, computerized cough counts, and intranasal cross-sectional area), but no consensus has been reached on which endpoints are acceptable as efficacy surrogates. Tests of efficacy could be added to PK studies.

Dr. Turner said that although there are methods to measure efficacy of cough and cold medicines in adults, the efficacy of these medicines in adults has not be adequately demonstrated. Therefore, the likelihood of demonstrating efficacy in pediatric PK studies would probably be low. The BPCA program should be careful of efficacy studies in children—where the methods are less certain—for drugs that have not shown efficacy in adults (e.g., dextromethorphan). As an example, Dr. Schneider explained that the efficacy of Tamiflu has not been clearly demonstrated and there have been many challenges to Tamiflu efficacy studies.

Dr. Snodgrass asked whether there is an approach to identifying which objective endpoint or endpoints should be studied. Dr. Schneider said videotaping and cough recording have been studied in adults. A subjective scoring system has been developed for nasal symptoms. These approaches could be applied to validate endpoints in children.

Next Steps

- Circle will prepare and distribute a draft of the meeting minutes.
- Working group members will review and comment on the draft minutes.
- The NICHD and Circle Solutions will coordinate the following:
  - Working group members will individually rank order the priority areas of research needs and share them with other group members.
  - The working group will review the individual priority lists and identify and prioritize the top four areas for consideration under BPCA.
- The working group will send its recommended priority areas to Dr. Taylor-Zapata by July 1.
- The final recommendations will be submitted for discussion at the annual BPCA scientific prioritization meeting, November 3 and 4, 2009.