

Breath of Fresh Air

Volume 10, No. 1 *Information, news and advice for improving asthma well-being*

Spring 2006

A “Black Box” for Asthma Treatment

“**B**lack box warnings” are the strongest warning about possible harmful side effects that the Food and Drug Administration (FDA) can require a pharmaceutical manufacturer to add to its drug information (“package insert”). It calls attention to a significant risk for serious and potentially life-endangering side effects. The name derives from the way the warning is presented: text printed within a square or rectangular black box.

Beginning in March, 2006, the FDA has required a new black box warning for all packages of Advair. Advair is the most widely prescribed asthma controller medication in the United States. It contains two controller medications mixed together: Advair is the combination of the long-acting bronchodilator, salmeterol, and the anti-inflammatory steroid, fluticasone. Both salmeterol and fluticasone are also sold separately, as Serevent and Flovent, respectively.



Concerns regarding the safety of salmeterol

The concern regarding potential harmful effects of Advair relates to the salmeterol component of this combination medication. Salmeterol is a long-acting bronchodilator, specifically a long-acting inhaled beta-agonist bronchodilator. Formoterol (Foradil) is another long-acting inhaled beta-agonist bronchodilator. The manufacturers of both salmeterol (Serevent) and formoterol (Foradil) have also been required to include a black box warning with their drug information.

The Advair black box warning looks like this:

Long-acting beta₂-adrenergic agonists, such as salmeterol, one of the active ingredients in ADVAIR DISKUS, may increase the risk of asthma-related death. Therefore, when treating patients with asthma, physicians should only prescribe ADVAIR DISKUS for patients not adequately controlled on other asthma-controller medications (e.g., low- to medium-dose inhaled corticosteroids) or whose disease severity clearly warrants initiation of treatment with 2 maintenance therapies. Data from a large placebo-controlled US study that compared the safety of salmeterol (Serevent[®] Inhalation Aerosol) or placebo added to usual asthma therapy showed an increase in asthma-related deaths in patient receiving salmeterol (13 deaths out of 13,176 patients treated for 28 weeks on salmeterol versus 3 deaths out of 13,179 patients on placebo) (see WARNINGS).

Here, then, is the dilemma. One of the most effective and popular treatments for asthma (and chronic obstructive pulmonary diseases, such as emphysema), both in the United States and internationally, contains as one of its two ingredients a medication that has been associated with an increased risk of fatal or near-fatal attacks of asthma. What can we make of this paradox?

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Before continuing discussion of this topic, the staff of *Breath of Fresh Air* needs to note that this newsletter receives an educational grant in support of its publication and distribution from GlaxoSmithKline, the makers of Advair.

Seeking explanations for these findings

The short answer to this puzzle is that we don't know why in the large study of salmeterol (more than 26,000 persons with asthma participated), more persons who were assigned to receive salmeterol died compared to those assigned to receive a placebo. Was it because patients used the medication in the wrong way, as if it were a rescue bronchodilator to be taken for quick relief during an asthmatic attack? Was it because many of the participants in the study were not taking an inhaled steroid? They used a powerful bronchodilator without an anti-inflammatory medication to reduce the swelling and mucus production in the bronchial tubes. Without an inhaled steroid, they allowed their asthmatic inflammation to worsen to the point of no return – swollen, plugged bronchial tubes too narrow to sustain effective breathing.

Or is it because some patients respond to the long-acting beta-agonist bronchodilators differently than most? Evidence indicates that we are born with genetic differences in the receptor molecule (the beta receptor) to which salmeterol binds in the airway wall. Some of us may have a beta receptor which, when stimulated with salmeterol, causes worsened lung function rather than bronchodilation. Still other possibilities exist: might in some patients the long-acting beta-agonist bronchodilators prevent the quick-acting bronchodilators, like albuterol, from working? Or are there effects of the long-acting beta-agonists – unique to some people -- that we simply have not yet identified?

We do know the following. For most people, Advair improves lung function, prevents asthmatic attacks, and improves their quality of life. We know that deaths from asthma are very rare, and they have not risen significantly since

Advair came onto the market in 2001. The large study described above tested the safety of salmeterol added to “usual asthma therapy”; it did not directly assess the safety of Advair.

We agree with the recommendations of the FDA. Advair is not recommended for mild asthma. Mild asthma can be treated with a steroid inhaler alone or with a leukotriene blocker such as montelukast (Singulair) or zafirlukast (Accolate). The combination of an inhaled steroid and a long-acting inhaled beta-agonist bronchodilator (such as the combination in Advair) is still the recommended treatment for moderate and severe asthma. It is recommended for those who do not achieve adequate asthma control with an inhaled steroid alone.

Points to remember

Here are our “take home” points:

- Do not use your long-acting beta-agonist inhaler as a rescue medication for quick relief of symptoms.
- In most instances, long-acting beta agonists should only be used in conjunction with an inhaled steroid.
- If your asthma seems to worsen after starting a long-acting beta-agonist bronchodilator, notify your asthma care provider.
- If you are taking a long-acting beta agonist and suffer an asthmatic exacerbation that does not respond normally to quick-relief treatments, seek medical care promptly and notify your asthma care provider.

Breath of Fresh Air

Editor-in-chief

Christopher H. Fanta, M. D.

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Telephone: (617) 732-4353 Fax: (617) 732-7421

Internet: <http://www.asthma.partners.org>

E-mail: asthma@partners.org

News About Asthma

New medications

Mometasone (Asmanex) is a new inhaled steroid available to treat asthma. It is the same steroid molecule that has been available as a nasal spray to treat allergic rhinitis (Nasonex). Mometasone is delivered via a dry-powder inhaler, called a Twisthaler. It is approved for use once-daily in mild and moderate asthma. The Twisthaler has a counter device that indicates the number of doses remaining in the container. The Asmanex Twisthaler is sold with inhalers containing 30, 60, or 120 doses; each inhalation delivers 220 micrograms of medication. It is approved for use in children age 12 and older.



Levalbuterol (Xopenex HFA) is now available as a metered-dose inhaler. You may be familiar with this medication in its liquid form delivered via nebulizer. Like albuterol (Proventil and Ventolin), it is a quick-acting (“rescue”) bronchodilator, with an effect that lasts approximately 4 hours. It may have less stimulatory side effects than albuterol. Each puff of medication delivered from the inhaler contains 45 micrograms of levalbuterol; there are 200 doses in each new canister. It is approved for use in children age 4 and older.



Albuterol HFA, the same medicine as contained in Proventil HFA and Ventolin HFA metered-dose inhalers, is being marketed by IVAX laboratories. Albuterol is the most widely used quick-relief bronchodilator in the United States. Most albuterol inhalers use chlorofluorocarbons (CFCs) as propellants to release medication from the pressurized canisters. Alternative, environmentally safe propellants, called hydrofluorocarbons (HFAs), are now available for use in asthma medications given by metered-dose inhaler. With the impending ban on all manufacture and commercial use of CFCs, more and more HFA-driven medications



are being released. Like Proventil HFA and Ventolin HFA, albuterol HFA contains 200 doses per canister, releases 90 micrograms of medicine with each puff, and is approved by the FDA for use in children 12 years and older.

New Understanding about Asthma

In a recent report picked up by the news media, researchers at Children’s Hospital in Boston described their discovery of “natural killer T cells” in the bronchial tubes of persons with asthma. Their discovery is indeed important, although it has nothing to do with “natural killers.”

Lymphocytes are cells in our bodies that play an important role in our immune system. They regulate our immune defenses, detect and destroy cancerous cells, and help distinguish what is “us” and what is foreign to our bodies. They also actively participate in inflammatory reactions, including the allergic-type inflammation that takes place in the bronchial tubes of persons with asthma.

Lymphocytes come in many different subtypes. Sometimes they can be recognized by differences in their appearance under the microscope; most often they are identified by the molecules that are detected on their surface and the specific chemicals that they release when stimulated. Using very sophisticated immunologic techniques, researchers found that the lymphocytes in the airways of a small group of patients with moderate or severe asthma were of a type not previously suspected. They are stimulated by specific types of allergens, have unique molecules on their surfaces, release characteristic inflammatory chemicals, and interact with other lymphocytes in specific ways.

That they have been called “natural killer T cells” is not of importance, even to Hollywood! What does matter is that their discovery opens up new understanding about the mechanisms of inflammation and “twitchy airways” in asthma and new targets for future development of asthma therapies.

Happenings at Partners Asthma Center

Dinner-Dance and Silent Auction

It was a wonderful bash! The first-ever Partners Asthma Center Dinner-Dance and Silent Auction was held at the Boston Marriott Hotel in Newton on September 22, 2005. Physicians, patients with asthma, and representatives from the pharmaceutical industry gathered to share our common interest in asthma, to raise money for Partners Asthma Center projects, and ... to have a good time together.

At the event we honored two women who have had a major impact on asthma care in Boston. Our first Asthma Awardees were Jean Zotter, Esq., founder and director of the Boston Urban Asthma Coalition, and Ne-Aldra Osgood, member of the Boston Urban Asthma Coalition and project director of its Strengthening Voices Project, a community outreach and education program.



From left to right: Ne-Aldra Osgood, Dr. Christopher Fanta, Dr. Albert Sheffer, and Jean Zotter, Esq.

We also celebrated the accomplishments of three of our Asthma Center patients. The 2005 Partners Asthma Center honorees were Alex and Abby Leonardi, outstanding students and competitive skiers; Kathryn Kalan, who climbed Mt. Kilimanjaro; and Richard Wilson, who raced his trimaran solo across the Atlantic Ocean and created the experiential on-line learning programs at www.site-salve.com.

Many people contributed to the success of the

evening. Special appreciation goes to members of the Dinner-Dance planning committee: Mark Anderson, Judi Botting, Elaine Carter, Rachael Charles, Maria Fusco, Kay Coady, Jose Portuondo, and Jacqueline Rodriguez-Louis.

Our pharmaceutical sponsors were:

Gold sponsor – Genentech/Novartis;
Bronze sponsors – Dey Pharmaceuticals and Neighborhood Health Plan.

Individual contributions were made by:

Frank Aliquo, Rita Bastianelli, Jeffrey and Erica Drazen, Giusto Gulla, Fay Mittleman, Wendy Nye, Sheila Palandjian, Vincent Ragosta, Benjamin Rubin, Mr. and Mrs. John Russo, Ronald Skates, and Carol and George Tenney. We also received donations from the New England Chapter of the Asthma and Allergy Foundation of America, Casa d'Italia, Pat's Place at Brigham and Women's Hospital, and in honor of Roberta Eldridge and Teresa Salerno.

We received generous donations to the Silent Auction from the following:

- Hampshire House (Boston)
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- Salem Food Store (Waltham)
- Silver Lake Liquor Store (Newton)
- Josiah Spaulding
- Watertown Savings Bank

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White Swan Bed and Breakfast (Plymouth)

Wish Restaurant (Cambridge)



Albert L. Sheffer Professorship at Harvard Medical School

In recognition of a remarkable career in allergy and asthma that has spanned more than four decades and touched untold numbers of lives through his medical care, Dr. Albert Sheffer—Partners Asthma Center member and “founding father”—was honored with establishment of a named Professorship in Medicine (Allergy) at Harvard Medical School this fall. We, his colleagues at Partners Asthma Center join you, his friends and patients, in celebrating this singular achievement. This named professorship will forever give recognition to his lasting contributions to the medical care of asthma and other allergic diseases.



New Members of Partners Asthma Center

Partners Asthma Center welcomes to its ranks *Drs. Mariana Castells* and *Anne Fuhlbrigge*.

Dr. Castells is an allergist practicing at the Allergy Center at 850 Boylston Street in Chestnut Hill. Her special interest is medication allergies, including aspirin-sensitivity in patients with asthma.

Dr. Fuhlbrigge is a pulmonary physician at Brigham and Women’s Hospital. Her research interest is evaluation of health outcomes in asthma.



Mariana Castells, M.D.



Anne Fuhlbrigge, M.D., M.S.



Patient Educational
Spring Asthma Symposium

Tuesday, May 2, 2006
(World Asthma Day)

“Preventive Maintenance: Being Prepared to Deal with Asthmatic Attacks”

6:00 – 8:00 p.m.
Huvos Auditorium
Faulkner Hospital
1153 Centre Street, Jamaica Plain

Come join us for presentations by Partners Asthma Center staff and informal discussion with questions and answers. All are invited; there is no fee. For more information, call Elaine at 617-732-7419.



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Brigham and Women's Hospital
Massachusetts General Hospital
Faulkner Hospital
Newton-Wellesley Hospital
North Shore Medical Center
75 Francis Street
Boston, MA 02115
1-800-9PARTNERS

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