

The “black box” warning and allergy drugs

Donald W. Aaronson, MD, JD, MPH *North Chicago, Ill*

In the past years, several drugs commonly used by allergy specialists have received a “black box” warning added to their package insert at the direction of the Food and Drug Administration (FDA). A “black box” warning is the highest level of 5 possible warning categories found in the package insert. The FDA has never articulated the basis for “black box” warnings. They generally appear to be based on clinical data, but occasionally can be based on serious animal toxicity. In the last several years, several drugs commonly used by allergists have received recommendations for “black box” warnings. Long-acting β -agonists (salmeterol and formoterol) received “black box” warnings because of reports of the occurrences of severe asthma exacerbations in some patients with asthma, with some associated death. Topical calcineurin inhibitors (tacrolimus and pimecrolimus) received a recommendation for application of a “black box” warnings because of a possible increase of cancer developing in patients taking these drugs. Although the addition of a “black box” warning was recommended by the FDA Pediatric Advisory Committee for these 2 topical agents, the FDA has not yet implemented this warning. Informed consent principles require that a patient be adequately informed of the risks (among other components) of any recommended treatment. The risks, as described, of the long-acting β -agonists and topical immunosuppressants should be presented to the patients to aid them in deciding whether they are willing to take these drugs when recommended by their physician. (*J Allergy Clin Immunol* 2006;117:40-4.)

Key words: “Black box” warning, long-acting β -agonists, topical immunosuppressive agents, informed consent, Food and Drug Administration

All drugs have side effects. Adverse reactions to drugs are a leading cause of death.¹ Drugs are on the market and are prescribed for patients because, after study, it is concluded that their benefits outweigh their risks, both in the mind of the prescribing physician and in the mind of the regulators—in this case, the US Food and Drug Administration (FDA). The public, physicians, other health care providers and ordinary citizens are aware of the benefits (indications) and the risks (side-effects) from the drug label or the package insert. Before their release, drugs are studied to establish safety and effectiveness.

Abbreviations used

FDA: US Food and Drug Administration
SMART: Salmeterol Multi-Center Asthma Research Trial

These studies are performed in limited numbers of patients and for limited periods. Once released for use by the general public, there is an exponential increase in the numbers of doses administered. The FDA requires postmarketing studies because they recognize this increased use frequency results in the identification of additional adverse effects, some of them severe, which were not identified in the limited use clinical studies leading up to their release.²

Almost 20 million patients took at least 1 of 5 drugs removed from the market between September 1997 and September 1998.³ Three of the drugs that were removed from the market were new, having been on the market less than 2 years. In select instances, the FDA may require special labeling, especially if they determine that there is an increased risk of death or serious injury but decide to leave the product on the market for the present. These select instances occur when the FDA determines that the increased risk of death or dying is not sufficient to make them withdraw the drug from the market but does call for a special warning. In this situation, the FDA may require that the increased health risks be identified by placing the warning in a prominently displayed box or “black box.”⁴ Where the warnings are placed in the package insert depends on the relative severity of the risk of the drug to the patient. The most severe warning is the “black box,” followed in descending order of importance by “contra indications,” “warnings,” “precautions,” and “adverse reactions.”

This article looks at “black box” warnings as they apply to drugs commonly used by allergists and concentrates specifically on the recent hearings that examined safety warnings on long-acting β -agonist drugs and also on earlier hearings that resulted in a recommendation for a “black box” warning on topical calcineurin inhibitors.

LEGAL BACKGROUND

Among the requirements for drug labeling under the statute⁵ are rules for drugs with potentially very serious adverse effects. Specifically, the Food and Drug Act requires drugs with special problems, particularly those

From the Finch University School of Health Sciences, Chicago Medical School.

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Reprint requests: Donald W. Aaronson, MD, JD, MPH, 3500 N Lake Shore Dr, #9C, Chicago, IL 60657. E-mail: doclaw@post.harvard.edu.

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that may lead to death or serious injury, display a warning in a prominently displayed “black box.” The boxed warning ordinarily is based on clinical data, but serious animal toxicity may also be the basis of a boxed warning in the absence of clinical data.⁶ This is the extent of the statutory regulation of “black box” warning. The FDA has not stated the scope of studies it relies on to determine the need for a “black box” warning; thus, it is difficult to determine in advance what will form the basis for the FDA to require a “black box” warning.

LONG-ACTING β -AGONISTS

At a meeting held on July 13, 2005, the Pulmonary-Allergy Drugs Advisory Committee of the FDA considered “black box” labels for long-acting β -agonist drugs. The committee recognized that products containing salmeterol and formoterol are effective bronchodilators used for the treatment of patients with asthma and chronic obstructive pulmonary disease. The committee also was informed about adverse events associated with these drugs.⁷ While noting that the drugs had adverse effects, events typical of β -adrenergic agonists, the committee focused its attention on the occurrence of severe asthma exacerbations reported only in a few asthma patients. These were reported in a large postmarketing study by the manufacturer of salmeterol and phase III clinical studies by the manufacturer of formoterol.

Salmeterol findings

Currently, there are 2 salmeterol containing products available for sale in the United States: Serevent Diskus (Salmeterol Xinafoate Inhalation Powder; GlaxoSmith-Kline, Research Triangle Park, NC) and Advair Diskus (fluticasone and salmeterol in combination; GlaxoSmith-Kline). The clinical development program for salmeterol (including studies of all dosage forms) was performed in 11 placebo-controlled studies. These studies supported the efficacy and safety of salmeterols as both a single ingredient or as a combination product with fluticasone. The studies did not identify a problem of severe asthma exacerbations.

The first salmeterol product was approved for sale in the United States in 1994. Although the studies performed to support approval of salmeterol for sale in the United States failed to show a problem of acute asthma exacerbation associated with salmeterol, isolated reports of this began to appear in the literature.⁸ A study reported in the *British Medical Journal* in 1993 involving 25,000 patients (16,787 on salmeterol and 8393 on albuterol) demonstrated that chronic use of salmeterol (16 weeks) was associated with a small percentage of asthma-related deaths. Because of increasing numbers of these types of reports, the manufacturer undertook a large controlled prospective study to address the issue: the Salmeterol Multi-Center Asthma Research Trial (SMART) began in 1996. This study was a randomized, double-blind study that enrolled patients with bronchial asthma not currently using long-

acting β -agonist agents. The study was eventually scheduled to enroll 60,000 patients, but was halted prematurely in 2003 after a total of about 30,000 patients had been enrolled. The reason for the early termination was that an interim analysis of the data suggested that salmeterol might be associated with an increased risk of severe asthma exacerbations, including death.

The manufacturer reported this information to the FDA. Subsequent discussions between the FDA and the manufacturer resulted in a decision by the manufacturer to incorporate the results of the study into the product label (package insert) and to add a “black box” warning about the use of salmeterol in patients with asthma. It should be noted that the labeling changes were voluntarily made by the manufacturer expeditiously, before a full agency review of the SMART data, because of the seriousness and importance of the findings. There was no formal assessment of the effect on concomitant use of inhaled corticosteroids, and the SMART study was not designed with this goal in mind.

The data were analyzed to determine whether there was any suggestion of a protective effect coming from the inhaled corticosteroids. Although the numbers studied were too small to form the basis for any firm conclusion, there was no apparent evidence of a protective effect from inhaled corticosteroids. The boxed warning was applied to all salmeterol-containing products, including Advair.

Formoterol

Only 1 formoterol product is currently available for sale in the United States. Three placebo-controlled randomized clinical trials that evaluated multiple doses of formoterol were reported to the FDA.⁹ Two 12-week, double-blind placebo-controlled studies were evaluated, which included 541 and 554 adult and adolescent (older than 12 years) patients with mild to moderate asthma (FEV₁ ranging from 40% to 80% and at least 15% reversibility), respectively. Each study had 4 arms comparing inhaled placebo albuterol, 180 μ g, 4 times a day; formoterol, 12 μ g, twice daily; and formoterol, 24 μ g, twice daily, respectively. There was 1 placebo-controlled pediatric study of 518 patients, age 5 to 12, that compared placebo, formoterol 12 μ g, and formoterol 24 μ g. For entry, these patients have an FEV₁ between 50% and 85% and at least 15% reversibility. At entry, all patients used daily doses of short-acting β -agonists for symptom control. Patients in the adolescent and adult study were allowed to maintain stable regimens of inhaled or intranasal corticosteroids, oral theophylline, and short-acting antihistamines or allergen immunotherapy.

Pediatric patients were treated with daily inhaled corticosteroids or cromolyn and were permitted to continue stable regimens of nasal corticosteroids, theophylline, and allergen immunotherapy. Albuterol as needed was permitted as a rescue in all 3 studies. All 3 studies demonstrated the efficacy of both doses of formoterol, but because there was no remarkable increased benefit from the 24- μ g dose compared with the 12- μ g dose, only the 12- μ g dose was approved for sale in the United States.

In addition, the safety assessment noted that formoterol 24 µg every 12 hours was associated with more episodes of severe asthma exacerbations than the other 3 study arms. In the 2 adolescent/adult studies, a total of 9 patients treated with 24 µg formoterol had serious asthma exacerbations. All 9 required hospitalization; 1 died of a cardiorespiratory arrest, and 2 required intubations with mechanical ventilation. All events occurred between 10 days and 2.5 months after the start of treatment.

Because of the safety concerns raised, the FDA asked the manufacturer to conduct a phase IV postmarketing clinical study to investigate further the relative safety of the 2 different doses of formoterol. This phase IV study was a randomized, blind, placebo-controlled study with a duration of 16 weeks. A total of 2307 patients 12 years or older with mild to moderate persistent asthma were enrolled. The participants were allowed to use liberal amounts of anti-inflammatory medication. There were 3 Foradil (Novartis Pharmaceuticals Corp, East Hanover, NJ) arms and 1 placebo arm of study. There were no deaths in this study. Although the number of severe asthma exacerbations was too small to draw any firm conclusions, the trend was to corroborate the previous phase III studies. The final recommendation of the long-acting β-agonist hearing was continued marketing of both products, but addition of a “black box” warning to formoterol.

TOPICAL IMMUNOSUPPRESSIVES

In February 2005, the Pediatric Advisory Committee met to “consider approaches to communicating about and minimizing the possible risk of cancer from the use of topical immuno-suppressants (calcineurin inhibitors).”¹⁰

There are 2 commercial topical calcineurin inhibitors¹⁰: tacrolimus (Protopic; Fujisawa Healthcare Inc, Deerfield, Ill) and pimecrolimus (Elidel, Novartis Pharmaceuticals Corp). I consider these agents together in this discussion, because the findings are quite similar. Both drugs are approved for short-term and intermittent long-term therapy in the treatment of certain forms of atopic dermatitis. Tacrolimus was released in December 2000 for treatment “of patients with moderate to severe atopic dermatitis (AD) in whom the use of alternative conventional therapies is deemed inadvisable because of potential risks or in the treatment of patients who are not adequately responsive to or are intolerant of alternative, conventional therapies.”¹⁰

Both the 0.03% and the 0.1% strength were approved for adults, but only the 0.03% strength was approved for use in children older than 2 years. In December 2001, pimecrolimus 1% cream was approved for “short-term and intermittent long-term therapy in the treatment of mild to moderate AD in non-immuno-compromised patients two years of age and older, in whom the use of alternative conventional therapies is deemed inadvisable because of potential risks or in the treatment of patients who are not adequately responsive to or intolerant of alternative

conventional therapies.”¹⁰ Neither product is approved for use in children younger than 2 years.

When these products were approved for long-term safety, the profile for each drug was not known, although “both products had pre-clinical animal carcinogenicity studies that demonstrated evidence of immune-suppression mediated carcinogenicity.” This finding raised FDA concerns about whether these products could lead to increased incidents of Hodgkin and non-Hodgkin lymphoma and melanoma or nonmelanoma skin cancers.

Since approval of the 2 agents, there have been several malignancy adverse events reported that are considered related to the use of one of the products. Ten malignancy adverse events related to the use of pimecrolimus and 19 related topical tacrolimus had been reported.¹¹ Seven of the cases were reported in children (pimecrolimus, 7; tacrolimus, 0). The most serious outcomes reported were death (tacrolimus, 2; pimecrolimus, 0) and hospitalization (tacrolimus, 8; pimecrolimus, 1). The malignancies reported included EBV associated with malignancy (1), carcinoma (8), Kaposi sarcoma (1), and lymphoma not otherwise specified (1). The median onset of malignancy symptoms was 150 days for tacrolimus and 90 days for pimecrolimus.

As a result of the hearing in February 2005, it was decided by the Pediatric Advisory Committee to recommend the addition of a “black box” warning to both products for malignancy. As of August 2005, that recommendation has not been implemented by the FDA, and neither product contains a “black box” warning at this time.

INFORMED CONSENT

The basic principle underlying the doctrine of informed consent is that in the absence of an emergency, a patient has a right to make decisions concerning their body. This right was articulated almost 100 years ago by Justice Cardozo in what is probably the best known case involving informed consent.¹² In that case, Justice Cardozo stated that “every human being of adult years and sound mind has a right to determine what shall be done with his own body....” The general rule is that this right extends also to minors, but except in certain circumstances not germane to this discussion, it requires that a parent or legal guardian exercise the right on behalf of the minor.¹³

There are 2 standards that govern the scope of the information that must be provided to the patient or their parent or legal guardian. The states are fairly evenly divided over which standard applies; therefore, one must consult a local attorney to determine the local rule. Under the professional disclosure standard, a reasonable medical practitioner must disclose that amount of information customarily provided by similarly trained physicians in the same or similar environment.¹⁴ The other standard requires physicians to provide that amount of information that a reasonable patient would want to know under the

same or similar circumstances.¹⁵ The right of a patient to receive informed consent is also articulated in the American Medical Association Principles of Medical Ethics,¹⁶ which call for informing and educating the patient of their condition and recommend that the patient should understand and approve their treatment.¹⁷

The elements of informed consent require that a physician must explain to the patient the nature of the disease and its treatment. The physician must not only provide information about the recommended treatment but also inform the patient about reasonable alternative treatments and probable outcomes if no treatment at all is provided. Finally, the physician must inform the patient of any risks that would be material to deciding whether to accept or reject medical recommendations.¹⁸ As far as the scope of informed consent, the recommendation of this author is that, regardless of the standard in your state, you should follow the reasonable patient standard. The law seems to be moving in this direction, and the added burden of providing the amount of information a reasonable patient would want does not appear to be an excessive burden, especially when it covers drugs that have “black box” warnings.

The requirement to provide information not only on the recommended treatment but also on alternative treatments is especially important in the case of drugs with “black box” warnings. It is particularly important to ensure that patients are aware of alternative therapies and the possibility of no treatment at all. Each of these scenarios requires the physician to inform the patients of “all material risks of treatment that are not remote or merely theoretical....”¹⁹ This requires that patients be specifically informed that the drug in question has a “black box” warning and given the reason for the “black box” warning. Specifics of warnings recommended for topical calcineurin inhibitors were discussed in a recent publication.²⁰ This becomes particularly important to ensure the patient understands the existence of feasible alternative therapies to drugs with “black box” warnings and the potential side-effects of each alternative therapy as well as of no therapy at all.⁴ Although the recommendations of the calcineurin task force are helpful, they do not cover all aspects of required informed consent. It would be useful to the specialty if the professional societies were to develop a complete informed consent guideline for each of the product groups covered in the discussion in this article.²⁰

Documentation requirements for informed consent are subject to debate. Although oral consents are acceptable, in the case of drugs with “black box” warnings, it would not be prudent to rely on oral consents, which might not be subject to sufficient proof to satisfy the court. Rather, it is strongly recommended to have written documentation of the consent discussion. In the case of drugs with “black box” warnings, I would suggest obtaining the signature of the patient confirming the informed consent

discussion. It is not clear whether there should be a listing of all of the risks explained to the patient or merely documentation of the disclosure of appropriate risks during the discussion. In general, the most prudent approach would be to record the fact of the informed consent discussion and list several of the most serious and most common risks specifically associated with the drug. Legal sources should be consulted for further discussion on the scope of the documentation necessary.

You should document the fact of the existence of “black box” warnings and the information provided relative to the reason for the requirement of a “black box.” Although the Pediatric Advisory Committee, which reviewed the calcineurin inhibitors, recommended a “black box” warning for both products, the FDA has not implemented that recommendation as of August 2005. We believe, however, that because the information on the development of malignancies in association with the use of these products was sufficient for the Committee to recommend a “black box” warning, patients should receive “black box”-type warnings from their physician when these products are prescribed.

CONCLUSION

There is substantial controversy over recent revelations about potentially serious adverse events caused by drugs commonly used by the allergy community to treat common allergic conditions, bronchial asthma, and atopic dermatitis. Advances in pharmacologic research have given us new products that offer our patients the promise of substantially greater relief than that afforded by older therapeutic agents. However, this relief comes with a price: a possible increase in the frequency of serious drug-related adverse events, including death.

The FDA seems to have taken a middle-of-the-road approach in not giving us clear guidelines governing the use of these drugs. Do we give our patients with asthma long-acting β -agonists products when we know there is an increased risk of a severe asthma exacerbation and possibly death, while the frequency of this and the absolute proof of cause and effect await further study? Do we give our patients with atopic dermatitis, topical calcineurin inhibitors which may cause, but have not been proven to cause, an increased frequency of malignancy with the potential for death? In both of these instances, the FDA has chosen to leave these products on the market and leave the decision on using them to the patient in consultation with the individual physician. Was the FDA shirking its role and not giving us clear rules? I think the answer is that they are doing as good a job as they can. There is no clear answer as to the safe use of these drugs. The FDA has taken us where the pharmaceutical firms would not. They have given us as much information as they could, then left the decision up to us.

We physicians know our individual patients better than anyone else, so we know what to recommend to our patients. Our patients trust us to do what is right, and we

⁴Traditional texts should be consulted for a full discussion of all components of informed consent, which is beyond the scope of this article.

do that by weighing whether the use of these drugs with “black box” warnings is reasonable. We do this by reviewing alternative therapies, with their risks and benefits. Finally, we do this by recognizing that the ultimate decision about what will be done to the patient’s body belongs solely to the patient. We complete our obligation by making sure the patient knows the risks and benefits of treatment with the drug that has a “black box” warning. We fulfill our obligation by making certain our patients know the risks and benefits of feasible alternative therapies or of no therapy at all. And finally, we realize our obligation by supporting our patients in whatever decision they make. We monitor them closely to try and identify when the risk of the adverse event that generated the “black box” drug use has become greater than the potential benefit. At that time, we try to guide our patients to reconsider the decision. There is no correct answer to the management of drugs with “black box” warnings. There is only the responsibility to our patients, which we accepted when we became physicians.

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