Asthma Exacerbations and Formoterol

To the Editor:

We read with interest the article by Dr. Mann and colleagues in a recent issue of CHEST (July 2003), outlining risk of serious asthma exacerbations in asthmatics treated with higher doses of formoterol. However, we do have several concerns. Although salmeterol and formoterol have been well established as effective treatments for asthma in combination with inhaled corticosteroids (ICS), this study (along with others) has questioned whether use of these medications alone or in higher doses may contribute to the development of serious asthma exacerbations. For example, the Serevent Multi-center Asthma Research Trial (SMART) was halted early due to increased exacerbations in asthma patients receiving salmeterol who were not concurrently treated with ICS. In SMART, only 47% of patients were treated with ICS.

The retrospective review by Dr. Mann and colleagues looked at three randomized placebo controlled trials with formoterol administered at 12 μg or 24 μg bid. The review concluded that patients receiving the higher dose of formoterol had a greater number of serious asthma exacerbations. The authors stated that since the data analysis was post hoc, the findings of their study do not merit statistical analysis to determine if this greater number of exacerbations was potentially significant, but then discussed, in detail, the implications of the higher exacerbation rate. The data from each of the three individual studies do not reach statistical significance when evaluated by a Fisher exact test. When the data provided from the three trials are pooled and evaluated by the χ² method, these changes do reach a level of statistical significance (p < 0.05). A potentially important confounding factor of the combined analysis may be the rate of exacerbations over the course of treatment, as these data combine two 12-week trials and one trial of a year in duration. A very important factor is that the numbers of patients within these three trials treated with ICS or other anti-inflammatory medications was unavailable for evaluation. As was noted in SMART, the use of concomitant ICS may be an important factor influencing exacerbations. We agree that post hoc analyses of existing data are important for hypothesis generation. We caution against the reliance on such data for other purposes, including drawing specific treatment-related conclusions.

The above results raise important questions about the proper use of inhaled long-acting β-agonists. Current National Asthma Education and Prevention Program guidelines recommend ICS in all asthematics with persistent disease. It is difficult to estimate the importance or validity of this slight increase in the rate of asthma exacerbations with higher doses of formoterol when we do not know the rates of concomitant anti-inflammatory medication usage in these patients. Information concerning markers of airway inflammation in these patients would also have been of interest.

Reliance on β-agonists alone may mask worsening underlying inflammation, and delay awareness of asthma progression, and an imminent exacerbation. Also, β₂-adrenergic receptor genotype may alter the response to β-agonists. It has been reported that asthmatic patients who are homozygous for arginine at the nineteenth locus of this receptor have a decrease in peak expiratory flow rate when treated with regularly scheduled albuterol inhalations four times daily, and that regular use of albuterol is also associated with an increase in asthma exacerbations in patients with this genotype. It has been postulated that the response to long-acting β-agonists could be affected by this