Long-term Inhaled Bronchodilator Therapy in Cystic Fibrosis

Inhaled beta-agonist bronchodilators are frequently prescribed for patients with cystic fibrosis despite the absence of studies on their long-term efficacy or toxicity, and despite conflicting results from studies on the immediate responses to single doses.

There are several reasons to anticipate that inhaled bronchodilators might be beneficial for patients with cystic fibrosis: 1) Bronchodilatation. There is wide variability among reports of the incidence of positive response to single inhalations of beta-agonist bronchodilators in patients with CF. One study indicates that close to one third of all CF patients will have such a beneficial response at some point, although few patients consistently have the same responses on repeated testing.\(^1\) Another (smaller) study found that 95 percent of CF patients had a positive response to bronchodilators on at least one of four tests in a one-year period.\(^2\) Few patients in any study have shown negative responses. 2) Increased mucociliary transport rates. In vitro studies indicate that beta agonists increase ciliary beat frequency.\(^3\) In vivo studies have had varying results. The only in vivo study performed in CF patients demonstrated an increase in mucociliary transport rate after terbutaline inhalation.\(^4\) 3) Less inflammatory damage of airways. These agents may modulate the airway inflammation that is so harmful to CF airways: in guinea-pig trachea, terbutaline decreased the inflammatory leaking of plasma into airway lumen.\(^5\) Other responses that have been demonstrated in noncystic fibrosis populations, such as increased exercise tolerance, decreased dyspnea, and slower decline in pulmonary function, might also apply in cystic fibrosis.

There are very few reasons to think that the long-term use of these agents might be harmful. These include the fact that roughly 10 percent of patients with CF will have a decrease in flow rates after inhaling these agents.\(^6\) However, very few patients with repeated testing have negative responses on all their tests. Two animal studies have suggested that beta agonists may induce mucous gland hypertrophy,\(^7,8\) but these results have not been demonstrated in humans.

In this issue of Chest (see page 1068), Eggleston and colleagues present a small but well designed and very clearly reported study of the effects of four weeks of bronchodilator inhalations compared with four weeks of placebo in patients with cystic fibrosis that begins to illuminate the effects of such treatment in cystic fibrosis. Despite the weaknesses of relatively small numbers of subjects, quite short duration for a study entitled "... long-term bronchodilator therapy ...," lack of information about possible seasonal influences, and lack of demonstrable changes in standard laboratory pulmonary function tests, the study is strong enough to make the authors' conclusions compelling: it appears that the subset of CF patients who have a clear bronchospastic response to methacholine challenge derive some benefit (seen mostly in improved daily peak flows) from albuterol inhalations over a period of one month, while they do not derive such a benefit from placebo inhalations, and their peers who clearly lack the methacholine response do not derive the same benefits from the bronchodilator.

There are further interesting conclusions, including that response to a month of four-times-a-day albuterol cannot be predicted by the response to a single inhalation of isoproterenol, and that symptoms are not a good measure of response to bronchodilators in these patients. I believe that this work extends our understanding of the role that these very widely prescribed, but little studied, medications can play in patients with cystic fibrosis.

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