EDITORIAL

Anticholinergics in the Management of COPD

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In recent years our attitude towards chronic obstructive pulmonary disease (COPD) has changed dramatically from defeatist to one of hope. COPD is no longer considered an irreversible bronchial obstruction but a multifactorial disease that includes a partially reversible obstructive component. In fact, depending on the evaluation criterion used, between 23% and 42% of patients present some degree of bronchodilator responsiveness, and this reversibility can be clinically noteworthy in patients with severe obstruction. There are numerous mechanisms that can cause chronic airflow limitation in COPD. The thickness of airway smooth muscle is almost normal and the strength of this muscle is hardly influenced by the degree of airflow obstruction. Such obstruction is therefore believed to be caused primarily by airway wall thickening and loss of elastic load owing to destruction of lung parenchyma and parenchymal attachments surrounding the airways. These irreversible structural changes enhance the effect of changes in airway muscle tone, which is regulated mainly by cholinergic activity. Overstimulation of muscarinic receptors M<sub>1</sub> and M<sub>3</sub> with acetylcholine leads to airway narrowing. Airways of patients with COPD present increased cholinergic tone, as reflected by the stronger bronchodilator effect of anticholinergic drugs. Cholinergic tone increases with the severity of obstruction; therefore the increase in airway caliber depends not only on the degree of smooth muscle relaxation but also on geometric factors. The obstruction produced by structural changes, such as thickening of the airway wall, increases the relaxation–contraction effect of the smooth muscle on the diameter of the airway, a factor which can be especially apparent in patients with greater airflow obstruction.

Anticholinergics act by producing a competitive blockade of acetylcholine at the muscarinic cholinergic receptors, thus inhibiting bronchoconstriction and bronchial hypersecretion, thereby increasing airflow. Two such drugs are currently available: ipratropium bromide and tiotropium. Tiotropium is a new anticholinergic bronchodilator that is administered once daily and, unlike other anticholinergics, acts through prolonged antagonism of M<sub>3</sub>, thus sustaining airway patency for 24 hours. In patients with COPD, functional improvement after administration of bronchodilators is not always reflected in changes in forced expiratory volume in 1 second (FEV<sub>1</sub>); in fact, it is noteworthy that FEV<sub>1</sub> is only weakly related to patient-reported variables such as dyspnea, exercise tolerance, and health-related quality of life (HRQL). These 3 variables are the ones that have the most impact on patients’ perception of their disease and the resulting limitations; therefore, evaluation of other parameters—such as forced vital capacity, lung volume, or inspiratory capacity—may be necessary to document physiological improvement.

In view of the above, continuous 24-hour cholinergic blockade in the airways has important repercussions on functional, clinical, and evolution parameters of patients with COPD.

Casaburi et al<sup>10</sup> showed that tiotropium had superior bronchodilator efficacy compared to placebo and ipratropium—the other available anticholinergic—by measuring increased FEV<sub>1</sub>. Furthermore, the improvement with tiotropium was sustained for the following 12 months with no tachyphylaxis. Tiotropium was also more effective compared with a placebo and ipratropium at improving dyspnea, exercise tolerance, dynamic and static hyperinflation, inspiratory capacity, and HRQL. Other authors such as Dusser et al<sup>11</sup> and Niewoehner et al<sup>12</sup> compared tiotropium with a placebo and found that treatment with tiotropium led to significant reduction in frequency of exacerbations and use of health care services among patients with moderate and severe COPD. The Cochrane Airways Group<sup>13</sup> recently prepared a meta-analysis to determine the efficacy of tiotropium, other bronchodilators used to treat stable COPD, and a placebo on the principal variables of clinical evaluation, such as exacerbations, hospitalizations, symptom scales, and lung function. The results of 9 randomized controlled trials (a total of 6584 patients) were included in the meta-analysis. According to the findings, compared with placebo or ipratropium bromide, tiotropium reduced the odds of a COPD exacerbation (odds ratio [OR], 0.74; 95% confidence interval [CI], 0.66-0.83) and related hospitalization (OR, 0.64; 95% CI, 0.51-0.82). When tiotropium was administered to patients with an annual baseline risk of exacerbations of 45% and related hospitalization of 10%, the number of patients needed to treat for 1 year with tiotropium, compared to placebo and ipratropium, was 14

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Manuscript received December 27, 2006. Accepted for publication January 9, 2007.
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