The Role of Tiotropium in the Hospital Management of Exacerbation of Chronic Obstructive Pulmonary Disease

According to current guidelines regarding the hospital management of exacerbations of chronic obstructive pulmonary disease (COPD), short-acting inhaled β_2 agonists are generally the preferred bronchodilators (evidence grade A).[1] In the absence of a prompt response to those drugs, addition of a short-acting anticholinergic bronchodilator is recommended, although the effectiveness of this combination in the hospital setting has not been firmly established, in contrast to the well-known additive effects of combined therapy in stable COPD.[2,3] The role of methylxanthines when there is an inadequate response to short-acting bronchodilators also remains controversial. On the other hand, there is grade A evidence in support of the addition of oral or intravenous corticosteroids to other therapies.[1,4] Despite the established efficacy of long-acting inhaled bronchodilators (the anticholinergic tiotropium, and the β_2 agonists salmeterol and formoterol) in the management of stable COPD,[5] little evidence exists concerning the efficacy of long-acting inhaled bronchodilators during an exacerbation.

A recent 3-way crossover study evaluated the bronchodilator effects of a single-day treatment with either tiotropium, formoterol, or their combination in patients with mild-to-moderate COPD exacerbations managed at home.[6] The duration of bronchodilation with tiotropium and formoterol was shorter than that in stable COPD. The difference in the time course of the effects of these agents in acute and stable COPD could be due to several factors, including (1) less effective respiratory delivery of the inhaled medication during an exacerbation, due to the associated increase in airways obstruction from increased inflammation, airway mucus, and bronchospasm, and (2) possibly greater functional antagonism by bronchoconstrictor mediators associated with the acute-on-chronic inflammation. Interestingly, while the bronchodilator effect of tiotropium and formoterol as single agents administered during an exacerbation did not extend as long as the 24-hour and 12-hour durations, respectively, observed with these agents in stable COPD, the co-administration of the 2 classes of long-acting inhaled bronchodilator did result in an additive bronchodilator effect that was still evident at 24 hours.

A clinical implication of the above-cited study is that the combination of 2 different long-acting inhaled bronchodilators might have benefits over each agent alone even during an exacerbation, although supplementation with a short-acting β_2 agonist might still be required. The latter study therefore provides a useful extension to the acute setting of other information from studies with patients with stable COPD concerning the additive bronchodilation from combining long-acting inhaled anticholinergic and β-adrenergic bronchodilators,[7-10] including nebulized formoterol.[11]

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The paper by Drescher et al in this issue of RESPIRATORY CARE[12] provides new information on the possible benefits of incorporating long-acting inhaled bronchodilators into the hospital management of severe COPD exacerbations. Drescher et al retrospectively examined the impact on patient care and costs of a respiratory-therapist-directed program in one medical center, in which they routinely incorporated maintenance therapy with a long-acting anticholinergic bronchodilator, tiotropium once daily, into the bronchodilator regimen of non-intubated and non-tracheostomized patients hospitalized with COPD exacerbation.

The same group had previously incorporated maintenance twice-daily treatment with the long-acting β_2 agonist formoterol into their in-patient program for managing COPD exacerbations.[13] Consequently, the addition of tiotropium to this pre-existing program equated to in-hospital combination long-acting inhaled bronchodilator therapy. In addition to the long-acting inhaled bronchodilators, patients received short-acting agents, mostly via nebulization, as needed. The total number and type (β_2 agonist, anticholinergic) of such treatments per patient per admission since the new bronchodilator protocol was implemented in 2006, in comparison to similar data collected in 2004, were the primary outcomes for assessing health care resource use. The in-patient bronchodilator protocol during the historical comparison period included twice-daily formoterol via powder inhaler, so that differences between the 2 periods reflected primarily the novel addition of tiotropium to the pre-existing bronchodilator regimen. Drescher et al found that adding tiotropium significantly reduced the number of short-acting bronchodilator treatments

per admission (largely in the form of combination short-acting β_2 agonist and anticholinergic) and hospital stay (by approximately 1 d), compared to an appropriately matched control group who had been treated during the same season of the year (winter months) in the historical comparison period. Consequently, the costs for medications, supplies, and respiratory-therapist labor (taking into account inflation in health care costs) were also reduced. In their retrospective analysis, Drescher et al also found that, in the in-hospital setting, tiotropium was well-tolerated, without adverse events, despite the occasional concomitant use of ipratropium in combination with a short-acting inhaled β_2 agonist.

The major limitations of the Drescher et al study[12] are its retrospective design, the use of historical controls, and the relatively small sample sizes (n = 174 and 181), although the groups appear to have been well-matched on baseline disease severity, comorbidities, and medication use, and the study design controlled for seasonal variation. Clearly, the findings need to be replicated in a controlled, prospective, multi-institution study, randomized by either institution or subject, and with a larger sample size, before the results can be generalized to the general population of patients hospitalized for COPD exacerbation but who do not require intubation.

With the above-noted caveat, the potential clinical implications of these preliminary findings are important, because, if replicated, they could lead to clinically meaningful and cost-effective changes in current recommendations on in-patient management of COPD exacerbations. Presumably, in patients hospitalized for a COPD exacerbation, the benefits of a regimen that includes regular (once or twice daily) administration of 2 long-acting inhaled bronchodilators with complementary mechanisms of action are due to the prolonged, as well as additive, improvement in airway patency, which minimizes the need for additional as-needed therapy with short-acting agents and the associated costs.

According to the data in Table 3 in the Drescher et al paper[12] the combination of a short-acting β_2 agonist and ipratropium was occasionally administered as part of the respiratory-therapist-directed bronchodilator protocol in the patients who received maintenance tiotropium and formoterol. The use of rescue treatment with an as-needed short-acting β_2 agonist superimposed on a maintenance regimen of a long-acting bronchodilator (β_2 agonist and/or tiotropium) is consistent with the current guidelines of the Global Initiative for Chronic Obstructive Lung Disease (GOLD).[1] Moreover, the addition of quarterly administration of a short-acting anticholinergic (ipratropium) to maintenance therapy with a long-acting β_2 agonist in the in-patient setting is a not-uncommon practice. On the other hand, the efficacy and safety of adding ipratropium to the in-patient treatment of a COPD exacerbation that includes once-daily tiotropium have not been systematically studied. However, a recent randomized controlled trial with patients with stable COPD revealed a slightly but significantly greater peak bronchodilator response (52-mL increase in forced expiratory volume in the first second [FEV_1]) when a single 40-μg dose of ipratropium was added to maintenance once-daily tiotropium, compared to the addition of placebo; however, the peak add-on placebo-adjusted FEV_1 response was significantly greater with a short-acting β_2 agonist (137 mL) than with ipratropium.[14] Since Di Marco et al[6] found that the duration of action of tiotropium is curtailed when used in the outpatient treatment of a mild-to-moderate COPD exacerbation, the efficacy and safety of the as-needed addition of ipratropium, along with that of a short-acting β_2 agonist, to maintenance therapy with tiotropium in the hospitalized patient with a severe COPD exacerbation warrant investigation.

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