Review: ipratropium is not more effective than $\beta_2$ agonists for acute exacerbations of chronic obstructive pulmonary disease


QUESTION: In patients with acute exacerbations of chronic obstructive pulmonary disease (COPD), are anticholinergic agents more effective than placebo or $\beta_2$ agonists?

Data sources
Studies were identified by searching Medline, EMBASE/Excerpta Medica, CINAHL, and the Cochrane COPD Trials Register, using the terms bronchodilator, ipratropium, and oxitropium; and by scanning bibliographies of relevant studies.

Study selection
Studies were selected if they were randomised controlled trials (RCTs) comparing anticholinergic agents (ipratropium or oxitropium bromide, given by inhalation by nebuliser or metered dose inhaler) with an appropriate control (eg, placebo, other bronchodilating agents, or combination therapies) and assessed adults with a diagnosis of COPD having symptoms of acute exacerbation of COPD. Studies of patients with acute asthma or those receiving ventilation were excluded.

Data extraction
Data were extracted on study quality and methods, participants, interventions, and outcomes (eg, lung function measurements, arterial blood gas measurements, and symptom scores).

Main results
9 RCTs were included. 4 studies compared ipratropium with an inhaled $\beta_2$ agonist, and 5 studies compared ipratropium plus a shortacting $\beta_2$ agonist with a $\beta_2$ agonist alone. The most common outcome reported was FEV1. 4 studies that compared ipratropium bromide with a $\beta_2$ agonist showed no difference between groups for change in FEV1 at 90 minutes (weighted mean difference [WMD] 0.1, 95% CI −0.19 to 0.19). 5 studies that compared ipratropium plus a $\beta_2$ agonist with a $\beta_2$ agonist alone also showed no difference between groups for change in FEV1, at 90 minutes (WMD 0.02 l, CI −0.08 to 0.12) and at 24 hours (WMD −0.05 l, CI −0.14 to 0.05). 2 studies that compared ipratropium with a $\beta_2$ agonist showed no difference between groups for hypoxia (PaO2), either in the short or long term.

Conclusion
In patients with acute exacerbations of chronic obstructive pulmonary disease, ipratropium alone or combined with a short acting $\beta_2$ agonist does not increase the degree of bronchodilation more than a short acting $\beta_2$ agonist used alone.

COMMENTARY
Current guidelines recommend that an anticholinergic agent be combined with a $\beta_2$ adrenergic agonist when inhaled bronchodilator treatment is prescribed for patients with severe or exacerbated COPD. Short acting anticholinergics and short acting $\beta_2$ agonists produce similar bronchodilation in patients with stable COPD. Combined treatment produces larger FEV1 increases than does either agent alone, but the additive effect is modest and the clinical benefit remains uncertain.

The meta-analysis by McCrory and Brown shows that anticholinergics and short acting $\beta_2$ agonists are similar also when given alone to patients admitted to hospital for COPD exacerbations. However, combined treatment seems to provide no additive bronchodilation during exacerbation, either short (90 mins) or longer term (24 h).

Several reasons are possible for this seeming disparity, although none are readily apparent. Chance can never be fully excluded. Although several hundred patients are included in the meta-analysis, there is a small possibility that FEV1 differences as large as 100 ml might not have been detected, and changes of this magnitude during exacerbation seem to be clinically meaningful.

None of the trials included in the meta-analysis attempted to evaluate clinical outcomes. McCrory and Brown suggest the need for a very large trial to better evaluate patient oriented endpoints, but it is doubtful that support will ever be found for such a large, expensive project. Hence, treatment recommendations will continue to be made from the available evidence, which provides little justification for combining an anticholinergic with a $\beta_2$ agonist in the treatment of COPD exacerbations. As monotherapy, the 2 drug classes seem to be equally effective, and because both have excellent safety profiles, individual patient preference or cost should dictate the choice.

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