Review: Ipratropium is not more effective than β_2-agonists for acute exacerbations of chronic obstructive pulmonary disease

McCrory DC, Brown CD. **Anti-cholinergic bronchodilators versus beta2-sympathomimetic agents for acute exacerbations of chronic obstructive pulmonary disease.** Cochrane Database Syst Rev 2002;(4):CD003900 (latest version 8 Mar 2002).

QUESTION

In patients with acute exacerbations of chronic obstructive pulmonary disease (COPD), are anticholinergic agents more effective than placebo or β_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 randomized controlled trials (RCTs) comparing anticholinergic agents (ipratropium or oxitropium bromide, given by inhalation by nebulizer or metered-dose inhaler) with an appropriate control (e.g., 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 (e.g., lung function measurements, arterial blood gas measurements, and symptom scores).

MAIN RESULTS

9 RCTs were included. 4 studies compared ipratropium with an inhaled β_2-agonist, and 5 studies compared ipratropium plus a short-acting β_2-agonist with a β_2-agonist alone. The most common outcome reported was FEV_1. Four studies that compared ipratropium bromide with a β_2-agonist showed no difference between groups for change in FEV_1 at 90 minutes (weighted mean difference [WMD] 0 L, 95% CI −0.19 to 0.19). 5 studies that compared ipratropium plus a β_2-agonist with a β_2-agonist alone also showed no difference between groups for change in FEV_1 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 β_2-agonist showed no difference between groups for hypoxia (PaO_2), 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 β_2-agonist does not increase the degree of bronchodilation more than a short-acting β_2-agonist used alone.

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COMMENTARY

Current guidelines recommend that an anticholinergic agent be combined with a β_2-adrenergic agonist when inhaled bronchodilator therapy is prescribed for patients with severe or exacerbated COPD. Short-acting anticholinergics and short-acting β_2-agonists produce similar bronchodilation in patients with stable COPD (1). Combined therapy produces larger FEV_1 increases than does either agent alone, but the additive effect is modest and the clinical benefit remains uncertain (1).

The meta-analysis by McCrory and Brown shows that anticholinergics and short-acting β_2-agonists are similar also when given alone to patients hospitalized for COPD exacerbations. However, combined therapy seems to provide no additive bronchodilation during exacerbation, either short- (90 min) 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 FEV_1 differences as large as 100 mL might not have been detected, and changes of this magnitude during exacerbation seem to be clinically meaningful (2).

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 β_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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References

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2. **Niewoehner DE, Collins D, Erbland ML.** Relation of FEV(1) to clinical outcomes during exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. Am J Respir Crit Care Med. 2000;161:1201-5.