The role of ipratropium bromide in the emergency management of acute asthma exacerbation; a metaanalysis of randomized clinical trials

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Authors' objectives
To determine whether the addition of inhaled ipratropium to inhaled beta-agonist therapy is effective in the treatment of adults with acute asthma exacerbation.

Searching
Searches were conducted of the following databases for articles published in English, French or Italian: MEDLINE (1966 to January 1997); EMBASE (1980 to 1997); CINAHL (1982 to 1997); Biological Abstracts 1990 to 1997; Cochrane register of controlled trials; and Current Contents (1996 to August 1997). Bibliographies from identified studies and review articles were manually searched. Search terms included 'asthma', 'bronchial hyperreactivity', 'clinical trial', 'randomised' combined with 'ipratropium'. Full details of the search strategy were given. A list of published or unpublished trials was sought from the manufacturer of ipratropium.

Study selection
Study designs of evaluations included in the review
Randomised placebo-controlled trials (RCTs).

Specific interventions included in the review
Ipratropium bromide given as an adjunct to beta 2-agonists and delivered by metered dose inhaler (with or without spacer device) or wet nebulizer. In the review, 5 mg ipratropium was delivered by wet nebulizer in adjunct to salbutamol (2.5 mg to 10mg) or fenoterol (1 mg to 1.25 mg). Concomitant treatment included intravenous steroids (hydrocortisone or methylprednisolone).

Participants included in the review
Adults presenting to hospital emergency departments or similar acute care setting with acute asthma exacerbations. Patients included those who met the American Thoracic Society definition for the diagnosis of asthma. The mean age of participants ranged from 29.5 years to 53.2 years across treatment groups. Patients with exacerbation of chronic obstructive airways disease were excluded from the analysis. Trials that exclusively studied paediatric patients (< 18 years) were excluded.

Outcomes assessed in the review
The primary outcome was the change observed in measures of airflow obstruction assessed as peak expiratory flow rates (PEFR) or forced expiratory volumes in one second (FEV1) over the study period. Spirometry measurements collected 45 minutes or one hour after the first administered dose of ipratropium were used where available. Measures taken at 30 minutes and 90 minutes were also included. The risk of hospitalisation was also assessed.

How were decisions on the relevance of primary studies made?
Retrieved abstracts were assessed independently by two reviewers and classified as controlled trials, clearly not a controlled trials or unclear. Citations classified as controlled trials or unclear were retrieved for a more thorough assessment according to inclusion criteria.

Assessment of study quality
Validity was assessed and scored using the Jadad criteria which assess quality of randomisation, double-blinding, and drop-outs and withdrawals (see Other Publications of Related Interest no.1). Possible scores ranged from a 0 (poor) to 5 (high quality). Two reviewers scored validity, with disagreements resolved by consensus.
Data extraction
Two reviewers independently extracted the following data: trial design; drug treatments; dosages; time intervals; patient characteristics; and baseline and post treatment spirometry or peak flow measures with standard deviations. To standardise reported measures, the relative improvement in respiratory function, the percentage change from baseline in mean peak expiratory flow rates or forced expiratory volumes in one second was calculated and the overall percentage difference between the control and treatment groups were calculated for each trial.

Methods of synthesis
How were the studies combined?
The net percentages improvements in flow rates of the intervention versus the placebo were pooled using weighted averages with weights equal to the inverse of the variance of the observed effect. PEFR and FEV1 data were converted to effect size data and the net effect of the intervention versus placebo was pooled using weighted averages. For dichotomous outcomes such as hospitalisation rates, the DerSimonian and Laird random-effects model was used to estimate the pooled relative risk (RR). A funnel plot was used to assess publication bias.

How were differences between studies investigated?
Between-trial heterogeneity was assessed using the Cochran Q test. Sensitivity analyses were conducted by restricting the analysis to studies with higher validity scores, and investigating the influence of baseline expiratory flow rate and age on the results.

Results of the review
Ten RCTs were included (1377 patients).

FEV1 (n = 5 RCTs): Compared to placebo the use of ipratropium/ Beta-agonist was associated with a pooled improvement in FEV1 of 7.3% (95% CI: 3.8%, 10.9%) corresponding to an absolute improvement of 100 ml (95% CI: 50 ml, 149 ml) above that seen for the group receiving only Beta-agonist. PEFR (n = 5 RCTs): Compared to placebo the use of ipratropium/ Beta-agonist was associated with a pooled improvement in PEFR of 22.1% (95% CI: 11.0%, 33.2%) corresponding to an absolute improvement of 32 L/min (95% CI: 16 L/min, 47 L/min) above that seen for the group receiving only Beta-agonist. After combining the data to give an effect size, the use of ipratropium/ Beta-agonist was associated with a summary effect size of 0.38 (95% CI: 0.27, 0.48). Cochran Q test suggested heterogeneity (P = 0.047). After removal of one trial reporting lower baseline PEFR values in both treatment and control groups statistical heterogeneity was no longer significant (P = 0.37) and effect size was slightly smaller = 0.35 (95% CI: 0.24, 0.47). Limiting the analysis to studies with quality scores of four or five (n = 6), gave a summary effect size = 0.33 (95% CI: 0.22, 0.44). There was no evidence of statistical heterogeneity (P = 0.29). Studies enrolling patients with more severe airway obstruction at baseline appeared to show greater absolute positive effects of ipratropium/Beta-agonist therapy. Mean baseline expiratory flows and study effect sizes were negatively correlated r = -0.74, P = 0.05 for PEFR and r = -0.75, P = 0.05 for FEV1). Effect size was not strongly related to the mean age of the patients enrolled r = 0.58, P = 0.08), or the Beta-agonist dose used r = 0.38, P = 0.27). Trials in which intravenous steroids were administered gave an effect size not significantly different from the overall effect size (4 RCTs): effect size = 0.25 (95% CI: 0.10, 0.40). Rates of hospitalisation were statistically significantly less (though just reaching significance) in patients receiving ipratropium/ Beta-agonist (3 RCTs, 1064 patients): RR = 0.73 (95% CI: 0.53, 0.99). None of the trials reported length of hospital stay or effect of treatment on the use of concomitant medicines. None of the trials reported serious adverse effects attributable to either of the treatments. The 10 included RCTs were independently selected by two reviewers. There was agreement between the two reviewers quality scores for 7 of the 10 trials (Kappa = 0.87). The funnel plot showed no evidence of publication bias.

Cost information
No actual costs were reported though mention was made of items to consider when costing the intervention studied.

Authors' conclusions
There is a modest statistical improvement in air flow obstruction when ipratropium is used as an adjunctive treatment to
Beta 2 antagonists for the treatment of acute asthma exacerbation. Although the clinical significance of this improvement in airflow obstruction remains unclear, it would appear reasonable to recommend the use of combination ipratropium/Beta-agonist therapy in acute asthma exacerbations since the addition of ipratropium seemed to provide physiologic evidence of benefit without risk of adverse effects.

**CRD commentary**
This thorough review was clearly presented. The aims and inclusion criteria were clearly defined. Full details of the search strategy were reported. Attempts were made to locate unpublished studies. Publication bias was assessed. Methods used to select primary studies assess validity and extract data were described. Sensitivity analysis was conducted to investigate the influence of various factors on the results. The discussion includes consideration of the uncertainty of the clinical significance of the improvement found, greater improvement found in studies reporting PEFR compared to FEV1, and the limitations of the review (potential for publication bias and use of effect size). Limiting the search to studies published in English, French, or Italian may result in important studies being missed. Although the authors state that heterogeneity was investigated, the results of heterogeneity tests were only presented for the effect size pooling. Forest plots were presented for the FEV1 and PEFR outcomes which suggest there may have been some heterogeneity in the FEV1 studies. Therefore it is not clear whether pooling was appropriate for these studies. The evidence supports the authors conclusions, though as the authors state, the clinical significance of the improvement found is not clear.

**Implications of the review for practice and research**
Practice: The authors state that it would appear reasonable to recommend the use of combination ipratropium/beta-agonist therapy in acute asthma exacerbations. The authors refer to a review of the efficacy of ipratropium bromide in acute childhood asthma (see Other Publications of Related Interest no.2).

Research: The authors state that research is required to determine the optimal dose of ipratropium and to test metered-dose inhaler preparations of ipratropium combined with salbutamol.

**Bibliographic details**

**PubMedID**
10381989

**Other publications of related interest**


**Indexing Status**
Subject indexing assigned by NLM

**MeSH**
Acute Disease; Administration, Inhalation; Adrenergic beta-Agonists /therapeutic use; Adult; Asthma /drug therapy; Bronchodilator Agents /pharmacology /therapeutic use; Double-Blind Method; Drug Therapy, Combination; Effect Modifier, Epidemiologic; Emergency Treatment /methods; Forced Expiratory Volume /drug effects; Hospitalization /statistics & numerical data; Humans; Ipratropium /pharmacology /therapeutic use; Peak Expiratory Flow Rate /drug
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Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.