Efficacy of ipratropium bromide in acute childhood asthma: a meta-analysis

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Authors' objectives
To establish if ipratropium bromide, when given in conjunction with beta2-agonists, is beneficial to the health of children suffering with acute asthma.

Searching
MEDLINE was searched from 1966 to 1992 for articles published in the English language using the following MeSH terms: 'N-isopropylatropine' and (explode) 'child', and 'asthma' and (explode) 'child'. The reference lists of all available primary and review articles were searched for relevant literature, and the two oldest studies included were searched forward in time using the Science Citation Index. The authors of all the selected studies were contacted for additional material.

Study selection

Study designs of evaluations included in the review
Randomised, double-blind, placebo-controlled trials were included.

Specific interventions included in the review
Inhaled ipratropium bromide and placebo in conjunction with inhaled beta2-agonists (fenoterol or salbutamol).

Participants included in the review
Children under 18 years who had an acute unprovoked asthma attack (by reasonable definition) were included.

Outcomes assessed in the review
Any of the following clinical or physiological outcomes were measured: change in vital signs, length of admission, peak expiratory flow rate (PEFR), clinical rating scores of asthma severity, number of admissions to hospital and the forced expiratory volume in 1 second (FEV1).

How were decisions on the relevance of primary studies made?
Agreement regarding the relevance of studies was determined by calculating weighted kappa values with quadratic weights for the first 218 titles. There was 92% agreement giving a weighted kappa of 0.67.

Assessment of study quality
Validity was assessed using: study population (appropriateness of diagnostic criteria for asthma and well-defined inclusion/exclusion criteria for patients); baseline characteristics (age, gender, previous medication and clinical spirometry score), description of treatment regime, and adequacy of outcome measure. All of the identified studies were reviewed independently by two reviewers using the validity criteria described. A final quality score was reached by consensus.

Data extraction
The data were extracted by a single reviewer then checked by a second reviewer for accuracy; differences were resolved by consensus. If important data were missing the authors of the study were contacted.

Methods of synthesis
How were the studies combined?
The fixed-effect model was used to estimate the weighted mean difference and pooled effect size. Differences in mean values between control and treatment groups and their 95% confidence intervals (CIs) were calculated according to the
method of Bracken (see Other Publications of Related Interest no 1), as was the weighted mean difference and its 95% CI. Effect size and 95% CIs, along with the pooled effect size and 95% CI, were determined as described by Hedges and Olkin (see Other Publications of Related Interest no 2).

How were differences between studies investigated?
Homogeneity of effect sizes between the pooled studies was tested as described by Hedges and Olkins, with p<0.10 as the significance level.

Results of the review
Six studies with 285 patients were included.

None of the 6 studies reported a significant difference between the treatment and control group for the following outcomes: clinical rating score, admission rate and length of stay in hospital. Three studies of the highest methodological validity were combined to determine the pooled effect size for the percentage change in predicted FEV1 from baseline to 60 minutes. The pooled value was 0.88 (95% CI: 0.42, 1.34). An improvement over the control group of 12.5% (95% CI: 6.6, 18.4) was found. The test for homogeneity was not significant. In one study with a subset of 23 children who had severe airway obstruction, the PEFR responded better to a beta2-agonist alone (p=0.007).

Authors' conclusions
Ipratropium bromide when used in conjunction with a beta2-agonist offers a significant improvement in percentage predicted FEV1 although there is no evidence for a clinical improvement. Ipratropium bromide may also result in a deterioration in the PEFR in severely asthmatic children. Further research is required to clarify these findings.

CRD commentary
This is a very well-written and structured review. However, the study is limited by the quality of the primary studies, which the authors acknowledge. The results of the meta-analysis are based on only 3 studies (n=80). This is a relatively small sample size on which to base global recommendations, and should be considered when evaluating the significance of the authors' conclusions.

Implications of the review for practice and research
The use of ipratropium bromide for the treatment of acute childhood asthma requires further research to establish the clinical significance of spirometric changes. The authors found 80 studies which they considered to be relevant, but only 6 were considered to be of sufficient quality for inclusion. This suggests that research in this field is of a particularly poor standard, although one must remember that the inclusion criteria for the analysis were quite strict (double-blind randomised controlled trials).

Bibliographic details

PubMedID
8521214

Other publications of related interest
Indexing Status
Subject indexing assigned by NLM

MeSH
Acute Disease; Administration. Inhalation; Adolescent; Asthma /drug therapy; Bronchodilator Agents /administration & dosage /therapeutic use; Child; Child, Preschool; Clinical Trials as Topic; Female; Humans; Ipratropium /administration & dosage /therapeutic use; Male; Respiratory Function Tests; Treatment Outcome

AccessionNumber
11995001713

Date bibliographic record published
28/02/1997

Date abstract record published
28/02/1997

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.