
Research question
Does adding inhaled ipratropium bromide to inhaled β-agonist therapy improve respiratory function and lower hospitalization rates of adults with acute asthma?

Type of article and design
Meta-analysis of multinational randomized, double-blind, controlled trials.

Relevance to family physicians
Family physicians frequently see adults with asthma, a chronic inflammatory disorder that is increasing in Canada and the United States. In Canada¹ the 2-year incidence rate for people 12 years and older is two to three new cases per 100 people. In the United States, 13.7 million people reported having asthma in 1994,² an increase in prevalence of 75% from 1980 to 1994. Acute exacerbations of asthma result in reduced respiratory function and hospitalizations. Even mild improvement in respiratory function can substantially reduce morbidity and cost of care.

When an acute episode occurs, patients are treated aggressively in offices or emergency departments with inhaled β-agonists, intravenous steroids, and oxygen for hypoxia. Whether adding an inhaled anticholinergic drug, such as ipratropium, is beneficial for these acute exacerbations has been controversial. National Heart, Lung, and Blood Institute guidelines³ do not include ipratropium for acute treatment of asthma.

A recent study⁴ considered addition of ipratropium to β-agonists and oral steroids for children. Large clinical trials have not been conducted on adults.

Overview of study and outcomes
The study reviewed the literature from 1978 to April 1999. Only randomized controlled clinical trials were analyzed; studies on children 16 years and younger were excluded. Outcome measures were improvement in pulmonary function and hospital admission rates.

Two reviewers blinded to author and location examined the search results. Studies were excluded if they were of hospitalized patients, were not randomized, used ipratropium therapy alone, or studied patients with chronic obstructive pulmonary disease. The reviewers found 10 articles that met their inclusion criteria. The articles were from five countries (two from Canada and three from the United States) and involved 1483 patients (36% were men) with an average age of 32 years (± 13 years).

The articles were scored for quality based on randomization method, demographic characteristics, inclusion and exclusion criteria, asthma definition, sample size, and withdrawal of subjects. Agreement between the two reviewers was calculated. The primary outcome measured was effect on pulmonary function at 90 minutes after treatment. A secondary measure was the effect on hospital admissions.

Results
The pooled population showed a substantial benefit for ipratropium, with a 10% (95% confidence interval [CI] 0.02 to 0.18) improvement in FEV₁ (forced expiratory volume in 1 second) compared with controls. A fail-safe number was calculated at 36.4, indicating approximately 37 similarly sized studies, each showing no effect, would be necessary to negate these results.

Differences in baseline spirometric measures between study and control groups were corrected (difference between FEV₁ in treatment group and FEV₁ in control group) before outcome was assessed. When the five lowest-quality studies were excluded, overall effect and confidence levels were unchanged.

Five studies showed improvement in hospital admission rates. Pooled results revealed significantly reduced admission rates (odds ratio 0.62, 95% CI 0.50 to 0.78).

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0.44 to 0.88, \( P = .007 \)). Number needed to treat (NNT) to prevent one hospital admission was 18 (95% CI 0.11 to 0.77).

No differences in side effects were noted for the two groups, as measured by heart rate, anxiety, respiratory rate, blood pressure level, dry mouth, or oxygen saturation.

**Analysis of methodology**

There were no apparent weaknesses in the study’s methods or analysis. It was a multinational meta-analysis. Two reviewers, blinded to authors and location, simultaneously reviewed and analyzed the studies.

Most patients in the meta-analysis received care in emergency rooms, not primary care offices. Applicability to busy family practice offices is unclear.

Only five of the studies (80% of the study sample) reported admission rates. Factors used to admit these patients were not reported, limiting the ability to analyze admission rates.

The study had some limitations. The number of patients in the pool was reduced by excluding studies that were not randomized, were pooled analyses, were conducted on hospitalized patients, administered ipratropium alone, or were done on patients who were not acutely ill. Method of randomization was indicated in only 5 of the 10 studies.

**Application to clinical practice**

Relevance to primary care practice is unclear. Many physicians are already providing acute asthma care in their offices, primarily using inhaled \( \beta \)-agonists. Addition of anticholinergic inhaled medication has a good chance of improving pulmonary function and reducing hospitalizations with minimal risk to patients.

**Bottom line**

- Addition of inhaled ipratropium to \( \beta \)-agonists can improve pulmonary function and reduce hospitalizations in adults. The effect was small (10%).
- No studies have been done in family practice offices.
- Side effects from this treatment are minimal, and it is easy to administer. It should be considered, especially for patients who are difficult to treat, because treatment might lead to lower hospitalization rates for refractory patients.

**Points saillants**

- L’ajout d’ipratropium par inhalation aux \( \beta \)-agonistes peut améliorer la fonction pulmonaire et réduire l’hospitalisation chez les adultes. L’effet était faible (10%).
- Aucune étude n’a été réalisée dans des cabinets de pratique familiale.
- Les effets secondaires de cette thérapie sont minimes et elle est facile à administrer. Elle devrait être envisagée en particulier chez les patients difficiles à traiter, car elle peut se traduire par un taux d’hospitalisation moins élevé chez les patients réfractaires.

**References**