# Cochrane Corner

## Does combining inhaled ipratropium bromide with beta2-agonists for initial treatment of acute asthma in children result in improved outcomes?

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The initial management of acute pediatric asthma exacerbations in children focuses on the rapid relief of bronchospasm using inhaled or nebulized bronchodilators. Anticholinergic agents, such as ipratropium bromide and atropine sulfate, have a slower onset of action and weaker bronchodilating effect, but may specifically relieve cholinergic bronchomotor tone and decrease mucosal edema and secretions. Thus, the combination of inhaled anticholinergics with beta2-agonists may yield enhanced and prolonged bronchodilation. This review included children aged 18 months to 17 years who presented to an accident and emergency department with acute unprovoked asthma. The interventions were single or repeated doses of nebulized or inhaled short acting anticholinergic agents with beta2-agonists and were compared with single or repeated doses of nebulized short acting beta2-agonists.

A total of 13 randomised controlled trials were selected for inclusion. With one exception (atropine) ipratropium bromide was used as the anticholinergic agent. The treatment protocol varied across trials with two to three doses of ipratropium bromide (250 to 500 ug per dose – New ethicals states that children can be given between 0.25mg and 0.5 mg three to four times daily a pediatric respule is 0.25 mg/2mL) being administered with multiple (two to seven) doses of ß2-agonists every 20 to 60 minutes. Most children received systemic corticosteroids as a co-intervention.

### Single Dose Protocols (five studies)

Five trials totalling 453 patients examined the efficacy of adding a single dose of 250ug ipratropium bromide to beta2-agonists. With regards to the primary endpoint, no reduction in hospital admission was observed when pooling the two trials reporting this outcome [RR=0.93 (95%CI 0.65, 1.32)] (RR= relative risk) and the fact that 1 lies between 0.65 and 1.32 shows that this is not statistically significant.

Four trials examined response to treatment using pulmonary function tests. In the two trials reporting the % change in FEV1 a significant difference of 16.10% [95% CI: 5.54, 26.66]% between group means was documented at 60 minutes and of 17.49% (95% CI 4.46, 30.53)% at 120 minutes after the inhalation of anticholinergics, both favouring anticholinergic use. However, when combining the three trials reporting change in lung function, either as change in % predicted FEV1 or % change from baseline FEV1, significant improvement was still apparent at 60 minutes and at 120 minutes after the dose of anticholinergics. In the single trial examining the intervention in the two strata of children with mild to moderate exacerbations, the absence of group difference observed at 60 and at 120 minutes confidently ruled out any important change in respiratory resistance due to treatment. There were no significant group differences in clinical score at 60 minutes or 120, in oxy-

gen saturation at 60 minutes or 120 minutes in the need for additional inhalation(s) after the standard protocol prior to disposition to admission or discharge and relapse to additional care. The addition of a single dose of anticholinergics was not associated with increased tremor.

### Multiple Doses, Fixed Protocols (seven studies)

Seven trials, totalling 1 045 children, examined the effect of multiple doses of combined ipratropium bromide and beta2-agonists in a fixed protocol. A 25% reduction in hospital admission rate was noted in favour of the combination therapy. Seven patients would need to be treated with a multiple dose-fixed protocol to prevent a single admission. However, baseline severity greatly influenced the reduction in hospital admission attributed to anticholinergics. A significant reduction was only observed in children with severe exacerbations.

The intensity of anticholinergic treatment protocol clearly influenced the extent of treatment response in terms of reduction in hospital admission. Whereas no group difference was observed in patients treated with a single dose of anticholinergics, a 25% reduction in hospital admission was observed in patients treated with multiple doses.

### Implications for practice

The addition of multiple doses of anticholinergics to beta2-agonist inhalations is indicated in the initial management of children with severe exacerbations of asthma (<=55% of predicted FEV1). This intensive protocol improves lung function, reduces by 25% the risk of hospital admission and by 19% the need for additional bronchodilator inhalations. In fact, only seven children with severe asthma need to be treated to prevent one admission. The use of anticholinergics was not associated with an increase in the following side effects, namely nausea, vomiting and tremor. There is insufficient evidence supporting the use of this protocol in children with mild to moderate exacerbations. Thus in New Zealand general practice we are likely to give those with severe asthma anticholinergics added to beta2-agonists with corticosteroids and refer them to hospital. Those with mild to moderate asthma probably do not require ipratropium when giving a beta2-agonist.

### References

References are available from B Arroll or from the Web http://www.cochrane.org/

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