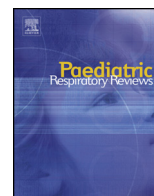




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Cochrane Corner



Combined inhaled anticholinergics and short-acting beta₂-agonists for initial treatment of acute asthma in children

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There are several treatment options for managing acute asthma exacerbations. Guidelines advocate the use of inhaled short acting beta₂-agonists (SABA) in children experiencing an asthma exacerbation.^{1,2} Anticholinergic agents, such as ipratropium bromide and atropine sulfate, are also used in asthma management but have a slower onset of action and weaker bronchodilating effect, but may specifically relieve cholinergic bronchomotor tone and decrease mucosal oedema and secretions.³ Therefore, the combination of inhaled anticholinergics with SABAs may yield enhanced and prolonged bronchodilation and provide more effective treatment for acute asthma exacerbations.

This Cochrane review looked at the evidence for adding anticholinergic drugs to SABAs in acute asthma attacks in children.⁴ We also aimed to identify patient characteristics and delivery protocols that may be most effective.

Admission to hospital was the primary outcome but data was also collected for secondary outcomes that included spirometric data, oxygen saturations, relapses and adverse events.

RESULTS

The review identified 20 trials with 24 comparisons randomising 2697 children to receive a SABA (which in all but one trial was salbutamol) plus placebo or SABA plus anticholinergic agent (which in all but one trial was ipratropium bromide). Potential biases were identified in five out of the 20 included studies. One study used consecutive assignment to randomise subjects (possible selection bias), one study failed to provide data for 10 patients enrolled in the study, one study collected hospital admission data but did not publish it, one study only provided data at 30 minutes post treatment (possible selective reporting),

one study did not blind the study medications (possible performance bias). However, removing these studies with potential bias did not change the direction or significance of the results for the primary outcome.

Reviewing the study population characteristics revealed that most studies included children experiencing moderate to severe asthma attacks. Most studies included pre-school and school age children. The doses of ipratropium bromide varied from 120 mcg to 500 mcg (with the majority using 3 doses of 250 mcg or two doses 500 mcg) and delivering the drug with a nebuliser device. The number of doses ranged between one to six over 30 - 90 minutes and the majority were delivered at fixed pre-determined time points.

The combination of ipratropium bromide and SABA significantly reduced the risk of hospital admission compared to SABA alone, the primary outcome of this review (RR 0.73; 95%CI 0.63 to 0.85, [figure 1](#)). This result was derived from 15 studies (19 comparisons) and 2497 children. We found that the children receiving SABA and anticholinergic were 27% less likely to be admitted to hospital than those receiving SABA and placebo.

In the group receiving only SABA, 23 out of 100 children with acute asthma were admitted to hospital compared to 17 (95% CI 15 to 20) out of 100 children treated with SABA plus anticholinergics. This represents an overall number needed to treat (NNT) of 16 children (95% CI: 12 to 29).

Examining the secondary outcomes, statistically significant group differences favouring anticholinergic use were observed for lung function, clinical score at 120 minutes, oxygen saturation at 60 minutes, and the need for repeat use of bronchodilators prior to discharge from the emergency department. No significant group difference was seen in relapse rates.

We explore a possible differential effect (effect modifier) between children experiencing severe, moderate and mild asthma attacks, both by subgrouping according to control group event rate and using the trialists' own assessment of severity. We found that

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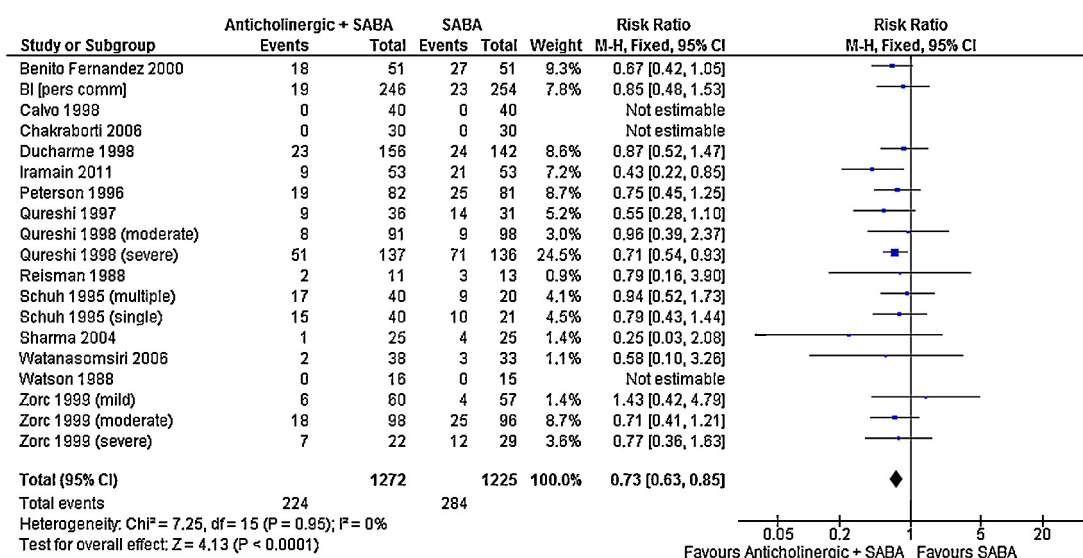


Figure 1. Hospital admissions.

although there was a greater effect in the children with the most severe attacks, the difference between the groups was not statistically significant.

We also looked at the manner in which the anticholinergic was delivered in the trial to try and inform best practice. Ipratropium bromide was administered as a single dose, multiple doses according to a fixed protocol, or a flexible dosing regimen, where the ipratropium bromide was systematically added to every SABA treatment until sufficient clinical improvement for discharge. Most of the data came from trials using a multiple dose fixed protocol. Three studies gave a single dose of anticholinergic and two studies used a multiple dose flexible regime but did not provide hospital admission data. There was a statistically significant reduction in hospital admissions for the multiple dose fixed protocols. The single dose studies did not show a definite effect as there was no statistically significant difference between the groups.

In absence of significant group difference in this analysis and the absence of head-to-head comparison between treatment protocols, there was insufficient information to judge how these different treatment protocols compare with each other.

CONCLUSIONS

The findings of this Cochrane review support the use of anticholinergics in addition to SABAs over SABAs alone in the management of moderate to severe acute asthma in children.

The absence of statistically significant differences in treatment response between studies grouped by severity or those receiving

different treatment intensity (multiple doses vs. single doses) prevented firm conclusions regarding a possible effect modification associated with treatment intensity and asthma severity.

Yet, given the large weight of the trials pertaining to children with moderate or severe asthma (with an under representation of those with mild asthma), it seems prudent to recommend the systematic use of anticholinergics in children with moderate or severe asthma only. Similarly, as most of the evidence is derived from trials giving multiple doses of ipratropium at fixed time points using three doses of 250 mcg or two doses of 500 mcg of ipratropium bromide administered by nebulizer over 60 - 90 minutes, in combination with a SABA, we would recommend this treatment strategy and duration.

The addition of anticholinergic to SABAs was associated with significantly less tremor and nausea than SABAs alone.

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