Aim: To determine if the addition of ipratropium bromide (IB) by metered-dose inhaler in moderate acute asthma in children affects hospital admission rates when compared with inhaled salbutamol and oral prednisolone alone.

Methods: A prospective, single-blinded, randomised, controlled, equivalence trial in a tertiary paediatric emergency department. Patients aged 2–15 years with acute, moderate asthma were randomised to two groups, one receiving salbutamol, prednisolone and IB, the other receiving only salbutamol and prednisolone. The managing doctor was blinded to treatment. Admission rates were compared, and less than 15% difference was accepted as statistically equivalent.

Results: Recruitment ran from June 2007 until January 2011. Three hundred forty-seven subjects were analysed. The admission rate in the IB group was 70.1% (122/174) compared with 64.2% (111/173) in the non-IB group. The absolute difference of +5.9% (95% confidence interval −4.0% to 15.8%) is not statistically equivalent but does not show a statistically significant decrease in admission rates when IB was given. Adverse effects were more prevalent in the IB group, at 13.2% (23/174), compared with 4.6% (8/173) in the non-IB group, a relative risk of 2.86 (95% confidence interval 1.31–6.21).

Conclusion: In children with acute asthma of moderate severity who are treated with adequate doses of salbutamol and prednisolone, the addition of IB is not significantly associated with a reduction in admission rates. There is a significantly higher rate of adverse effects if IB is given. IB should be reserved for children with severe asthma exacerbations.

Key words: asthma; child; emergency service; hospital; ipratropium.

What is already known on this topic
1 Ipratropium bromide is frequently used in the management of moderate and severe acute exacerbations of asthma in childhood.
2 Ipratropium bromide is an effective addition to the management of severe asthma exacerbations in children.
3 In moderate exacerbations of asthma, results are variable, and it is uncertain whether the addition of ipratropium bromide decreases admission rates.

What this paper adds
1 This is the first study examining the use of metered-dose inhaler ipratropium bromide with oral corticosteroids and optimised doses of inhaled salbutamol in the management of moderate acute childhood asthma.
2 There is no significant decrease in admissions when ipratropium bromide is given.
3 There is an increased risk of adverse effects when ipratropium bromide is given.

Asthma is a common respiratory illness, accounting for over 3% of our facility’s emergency department (ED) presentations, mirroring presentation rates of 3.6–4.1% in other developed nations.1 Traditional asthma management includes inhaled beta₂-agonists and oral corticosteroids.2 Additional agents include inhaled anticholinergics, oral leukotriene receptor antagonists and intravenous (IV) beta₂-agonists, methylxanthines, corticosteroids, and magnesium sulphate.2 In paediatric hospitals, moderately severe exacerbations are traditionally treated with multiple doses of inhaled salbutamol and ipratropium bromide (IB), and oral corticosteroids.1-3

Anticholinergic agents, such as IB, act on the muscarinic receptor of the bronchial smooth muscle resulting in bronchodilation and possibly decreased mucosal oedema and secretion.6,7 Therefore, the addition of inhaled anticholinergics to beta₂-agonists could theoretically result in improved bronchodilation.7
We hypothesised that the addition of inhaled IB to the treatment of asthma of moderate severity does not alter the need for hospital admission. Thus, the primary aim of this study was to discover whether, with the administration of adequate doses of inhaled beta₂-agonists and oral corticosteroids, the addition of inhaled IB conferred a difference in hospital admission rates in children with acute moderate asthma exacerbations. Children were admitted if they required more than 4 h of in-hospital care. Secondary outcomes examined were admission destination and adverse effects in each group.

Methods

The study design was a prospective single-blinded randomised controlled trial. Patients presenting with acute asthma or wheezing of moderate severity to the Princess Margaret Hospital for Children (PMH) ED were recruited. PMH is the sole tertiary paediatric ED in Western Australia, seeing over 65,000 children annually. Since 2009, there were more than 2000 presentations annually of asthma or wheeze in children aged over 24 months, accounting for 3.5% of all presentations. Approximately 50% of these children were admitted, predominantly to the 24-h ED observation ward (_EDOW_) but also to inpatient medical wards (IPWs) or the paediatric intensive care unit (PICU).

Subjects aged 2–15 years inclusive, presenting with an acute wheezing illness of moderate severity, were eligible for inclusion. Children below 2 years were excluded to avoid overlap with bronchiolitis. Adolescents 16 and older were excluded as this is the upper limit for acceptance to our ED. Eligible subjects included children with a previous history of asthma or wheezing and those with a first presentation of viral induced wheeze. The classification of moderate severity was based on the criteria suggested by the National Asthma Council Australia and included patients with one or more of the following: oxygen saturations of 90–94% inclusive, speaking in phrases and moderate to loud wheeze. Subjects were excluded if they exhibited any markers of severe asthma: oxygen saturations less than 90%, cyanosis, inability to speak secondary to breathlessness, silent chest or abnormal conscious state. Subjects were also excluded if they had another chronic respiratory illness or had IB in the preceding 6 h.

The parents of eligible children were approached by the treating ED doctor and provided with a detailed information sheet prior to consenting. Baseline data were obtained including demographics (age, sex, weight), oxygen saturations and severity data. Severity was measured using the pulmonary score, an independently validated asthma severity score, quantifying respiratory rate, wheeze and accessory muscle use (range 0–9), Treatment prior to presentation to the ED and use of preventative medication was documented.

The subjects were randomised into two groups, using blocked (n = 6) computerised random number generation, and allocated in numerical order. The individual allocations were concealed in opaque envelopes that were opened by the ED nurse prior to initiating treatment. Nursing staff treated the patient as per these instructions. The doctor managing the patient was not present during the administration of treatment and thereby remained blinded to which group the patient was allocated to and which treatment they received. Additionally, to maintain the single blind, the exact treatment given was not documented in the patient record. A double-blind methodology was unable to be used, as placebo metered-dose inhalers (MDIs) are unlicensed for use in children.

Both groups received salbutamol by MDI (100 μg per actuation) with a spacer (with or without mask and available in two sizes depending on age), three times at 20-min intervals (six actuations per dose if 2–5 years, 12 actuations per dose if 6–15 years, with five breaths between each actuation, consistent with usual practice) and oral prednisolone 1 mg/kg to a maximum of 50 mg. Additionally, the IB group received IB by MDI (21 μg per actuation) with appropriate-sized spacer, three times at 20-min intervals (four actuations per dose if 2–5 years, eight actuations per dose if 6–15 years, with five breaths between each actuation).

From 2009, a change in ED practice resulting from new evidence evaluating the benefit of oral corticosteroids in pre-school children with viral wheeze meant that some patients with viral-induced wheeze did not receive prednisolone routinely. As this was likely to affect both IB and non-IB groups equally, these children were not excluded from analysis.

Following the first hour of treatment, the managing doctor determined ongoing management and need for admission, in consultation with a senior ED doctor. Patients requiring admission were admitted either to the EDOW or IPW. Adverse events were also noted by the managing doctor within the same time frame, both by direct observation and patient or parent reporting.

Ethical approval was granted by the PMH Ethics Committee, and the trial was registered with the Australian New Zealand Clinical Trials Registry (No. ACTRN12607000383460).

Statistical methods

Sample size

The study design was an equivalence trial with a 15% margin of equivalence, analysing the primary outcome of rate of admission to hospital. An equivalence design was chosen as we wished to assess whether a simplified treatment protocol of salbutamol and prednisolone would be of equal effectiveness as the standard treatment of salbutamol, prednisolone and IB. A 15% margin of equivalence was chosen by consensus of PMH consultant staff as there was no available published evidence as to what constitutes a significant difference in admission rates. Sample size calculations used 5% statistical significance and 80% power, assuming an admission rate of 40–44%. This rate used data from the PMH Emergency Department Information System, examining the 5 years prior to 2006. Calculated sample size was 173 subjects per arm.

Statistical analysis

The study is reported in accordance with the CONSORT Statement (www.consort-statement.org/consort-2010/). Flow of patients within the study is summarised in the CONSORT flow diagram.

The primary outcome measure was rate of admission to hospital. Secondary outcomes measured were admission rates to IPW versus EDOW, need for transfer to an IPW following a 24-h
stay in the EDOW and occurrence of adverse effects in both groups. Patients were admitted to an IPW if they required oxygen, needed more than 24 h of inpatient treatment or were unable to be discharged from the EDOW within 24 h.

As the objective of the study was to decide whether it was safe to discontinue the use of IB in children with asthma exacerbations of moderate severity, statistical analysis was aimed at determining equivalence between the two groups. We used a 15% equivalence range and 95% confidence interval (CI) to examine difference in admission rates. Secondary outcomes relating to disposition had small numbers, so only totals and percentages have been presented. The secondary outcome relating to adverse effects has been analyzed using the \( \chi^2 \) test.

Data were analyzed on an intention-to-treat basis using SPSS v.21, Chicago, IL, USA.

**Results**

Patients were recruited from 7 June 2007 to 30 January 2011. From January 2008, recruitment was on alternating weeks, on a strict, published schedule, due to a concurrent asthma study in our ED.

During recruitment weeks, 2735 patients aged 2–15 years presented with wheezing. Of these, 436 were recruited, 418 randomized and 347 were suitable for analysis (Fig. 1).

The baseline data showed no significant differences (Table 1). One hundred twenty-two of 174 (70.1%) patients in the IB group were admitted to hospital, compared with 111/173 (64.2%) in the non-IB group. The total risk difference is +5.9% (95% CI −4.0% to 15.8%) (Table 2). True equivalence cannot be concluded due to a trend towards a higher admission rate in patients receiving IB; thus, the 95% CI just exceeds 15%.

Planned secondary analyses were performed on disposition data and adverse effects (Table 3). Most patients presenting with asthma exacerbations requiring admission were admitted to the EDOW.

Provision was made to withdraw patients if they deteriorated and needed nebuliser or IV treatment. However, no study patients fulfilled these criteria or required PICU admission. Numbers relating to disposition were too small to reach statistical significance, so only totals and percentages have been included.

Adverse effects were recorded in both groups. Twenty-three patients in the IB group had adverse effects, compared with eight in the non-IB group (Table 4). Despite the study not being powered to reveal a difference, this relative risk of 2.86 (95% CI 1.31–6.21) for all adverse effects reached statistical significance. Individually, the relative risk for the specific adverse effect of tremor was also statistically significant at 4.97 (95% CI 1.11–22.36). Adverse effects noted are consistent with known adverse effects of IB, noted to be headache, nausea, dry mouth, tachycardia, palpitations and dizziness.6

**Discussion**

We hypothesised that the use of multiple doses of IB by MDI in moderate acute exacerbations of asthma would not reduce admission rates when adequate doses of salbutamol and prednisolone were given. While equivalence was not reached due to the higher admission rates in the IB group, the lower 95% CI of −4.0% suggests administering inhaled salbutamol and oral prednisolone alone is unlikely to be inferior to the combination of inhaled salbutamol, inhaled IB and oral prednisolone, though further research is needed to confirm this.

We chose to examine MDIs over nebulisation as this is routine practice in paediatric EDs in Australia.3 Administration of bronchodilators via MDI and spacer has been shown to be at least as effective and better tolerated than via nebulisation.11,12

Our results show a 2.86 times relative risk of adverse effects with IB. These adverse effects are not severe, with tremor and vomiting being most common, but could impact on the perception of treatment by the child and family. Twenty of 23 (87.0%) patients with documented adverse effects in the IB group were admitted, suggesting the possibility that an increase in adverse effects may have contributed to a non-significant increase in admissions in this group. Anecdotally, many ED nursing and medical staff observe that younger children can become uncooperative with treatment following IB as the taste of inhaled IB can be unpleasant, though in our trial, we did not specifically examine this.

The primary aim of our study was to determine whether the standard treatment of IB could be withheld when treating moderate asthma exacerbations. Dankner et al. describe in a retrospective study the complete removal of IB from a large tertiary adult hospital's ED. They had no significant increase in combined negative outcomes in young adults (17–35 years) with acute asthma exacerbations of all severities.13

The evidence supporting the use of multiple dose inhaled anticholinergics by nebuliser in acute severe exacerbations of asthma is well established and has been documented in a Cochrane Review, showing in the studied group seven children needed to be treated to prevent one admission.7 In our facility’s ED, this had been extrapolated to the use of multiple doses of MDI IB in the treatment of acute asthma of moderate severity. This is a common practice among paediatric and adult EDs throughout Australia.5,4

Despite this common practice, there is little evidence to suggest that using IB in moderate asthma improves outcomes or prevents admissions. The above Cochrane Review showed no significant reduction in admission rate in children with mild, moderate or moderate to severe exacerbations, although a protective trend was noted.7 Several trials investigating the treatment of moderate asthma with inhaled anticholinergics have been conducted, with results trending towards no difference in outcomes.14–20 Sharma and Madaan demonstrated an improvement in peak expiratory flow rates in children over 6 years.14

Iramain et al. investigated the use of nebulised IB in moderate and severe exacerbations of asthma in children and found improvements in SaO₂, pulmonary score, hospital admissions, FEV₁ and PEF. However, when they analysed the moderate and severe groups separately, only improvements in SaO₂ and FEV₁ were sustained in the group with moderate asthma.21 In contrast to our study, all of the above trials examined nebulised anticholinergics rather than MDI, and two of the trials examining nebulised IB used non-maximal doses of beta-agonist.15,16

There has been one trial examining the use of MDI IB in the treatment of acute asthma of moderate severity. Chakraborti et al. compared spirometric parameters and clinical asthma...
During recruitment period, presented with acute wheeze and aged 2–15 yrs  
\(n = 2735\)

**Not approached for enrolment**  
Reasons include:  
- Mild exacerbation  
- Severe exacerbation  
- Already in trial in same illness  
- Wheezing better accounted for by another diagnosis  
- Other cardiac or respiratory condition  
- Enrolled in another asthma trial  
- IB used in last 6 hours  
- Language difficulties  
- Missed (due to high departmental workload, staff turnover)

**Enrolment**  
\(n = 436\)

**Randomisation**  
\(n = 416\)

**Allocated to intervention**  
Ipratropium bromide (IB)  
\(n = 209\)
  
- Received allocated intervention (\(n = 205\))  
- Did not receive allocated intervention (\(n = 4\))  
  - Consent withdrawn after randomisation (\(n = 3\))  
  - Withdrawn due to ineligibility (reason not documented) (\(n = 1\))

- Lost to follow-up (\(n = 10\))  
  - Data collection sheet missing or blank (\(n = 10\))

- Excluded from analysis (\(n = 21\))  
  - Too mild (\(n = 1\))  
  - Too severe (\(n = 6\))  
  - Outside nominated age range (< 2 years) (\(n = 8\))  
  - Inappropriate consent (not legal guardian) (\(n = 1\))  
  - No documentation of appropriate consent (\(n = 5\))

**Analysed**  
\(n = 174^*\)

**Allocated to intervention**  
No ipratropium bromide (non-IB)  
\(n = 207\)
  
- Received allocated intervention (\(n = 205\))  
- Did not receive allocated intervention (\(n = 2\))  
  - Consent withdrawn after randomisation (\(n = 2\))

- Lost to follow-up (\(n = 10\))  
  - Data collection sheet missing or blank (\(n = 10\))

- Discontinued intervention (\(n = 0\))

- Excluded from analysis (\(n = 22\))  
  - Too mild (\(n = 1\))  
  - Too severe (\(n = 5\))  
  - Outside nominated age range (< 2 years) (\(n = 8\))  
  - No documentation of appropriate consent (\(n = 7\))  
  - Final diagnosis pneumonia, not asthma (\(n = 1\))

**Analysed**  
\(n = 173^{**}\)

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**Fig. 1** Consolidated Standards of Reporting Trials-style flow diagram. *One patient discontinued intervention at parents’ request due to side effects but was included for an intention-to-treat analysis; **One patient inadvertently received the wrong intervention but was included on their original arm for an intention-to-treat analysis.*
scores in children aged 5–15 years with acute exacerbations of moderate severity and showed an improvement in PEFR and FEF 25–75%. However, none of these children were admitted, suggesting they examined children with milder asthma than those in our study. They also used sub-maximal doses of beta2-agonist, and it is not noted whether oral corticosteroids were given.22

The literature suggests that when lower doses of beta2-agonists are used, a benefit is conveyed by adding an inhaled anticholinergic. Our trial shows that when higher doses of inhaled salbutamol and an oral corticosteroid are given, that benefit is no longer evident. This is amplified by the higher raw admission rate in the group receiving IB, though this was not statistically significant.

The cost of IB is $A33.84 per 21 µg 200 dose CFC-free inhaler.6 Thus a small potential cost saving can be made by reserving IB for those with severe asthma exacerbations.

### Limitations

A major limitation of this study is the difficulty in enrolling all eligible patients. A total of 2735 patients presented to the ED with a wheezing illness during the recruitment weeks for this trial, but only 436 were approached for enrolment. Many would have been ineligible, most commonly due to having either mild or severe disease; however, surveys of Australian paediatric EDs suggest that exacerbations of moderate severity account for 49% of all presentations, leaving approximately 1340 eligible patients. Likely explanations for the failure to enrol these patients include the principal investigator working overseas for 18 months of the recruitment period; a high turnover of junior medical staff in the ED, resulting in a lack of awareness of ongoing departmental research; high workloads in the department; and the absence of a dedicated research assistant.
The study was an equivalence trial aimed at showing that using salbutamol and prednisolone was equivalent to previous standard practice of salbutamol, prednisolone and IB. Due to a lack of evidence as to what constitutes a significant difference in admission rates, an equivalence margin needed to be chosen by consensus. It is arguable that as the upper 95% CI was greater than 15%, statistical equivalence was not reached. However, given that the lower 95% CI was just −4.0%, it can be postulated that withholding IB is unlikely to be inferior to giving it. The higher admission rates in the IB group were unexpected, and further research would be needed to prove that administering IB actually increases the risk of admission.

The trial was not double blinded or placebo controlled. Despite attempts to obtain placebo MDIs from the pharmaceutical company that supplies such inhalers, permission was refused by the company as placebo inhalers were not licensed for use in children due to a lack of testing in this population. As the managing ED doctor was responsible for admission decisions, we determined that blinding the doctor to allocation allowed the trial to remain single blinded. Nursing staff administering the treatment did not contribute to the decision to admit.

The admission rate seen in this trial was much higher than predicted, with a total admission rate of 233/347 (67.1%) compared with a pre-trial predicted rate of 40–44%. The admission rate for all presentations with asthma during the recruitment period was also higher than previous years at 50.3%. These rates were for all presentations to the ED with asthma; therefore, the exclusion of children with milder exacerbations of asthma, who have a very low admission rate, would have contributed to the high rate of admission seen in this trial. The Hawthorne effect may also have contributed to the higher admission rate. This rate is also considerably higher than the usually seen in research into moderate asthma, typically around 10–35%. A likely explanation for this is the presence of the EDOW. At PMH, any patient not needing inpatient care who is expected to remain in the ED for more than 4 h after triage is transferred to the EDOW, admitted under the care of the consultant emergency physician. In other departments, these children may remain in the ED. This could have been clarified by examining length of stay. However, in the original study design, we chose to analyse admission as a binary variable, thereby avoiding other length of stay confounders, such as timing of doctors’ rounds, social variables including transport issues and discharge at night.

Conclusion

This is the first trial examining the use of multiple dose MDI anticholinergic therapy in acute exacerbations of asthma in the context of adequate doses of beta2-agonist and oral corticosteroids. The results of our trial suggest that using salbutamol and prednisolone in adequate doses does not result in an increase in admission rates over using IB, salbutamol and prednisolone. Additionally, there is a higher risk of adverse effects, particularly tremor, with IB. While further research is needed to clarify our results further, we feel that based on these results, the recommendation can be made to withhold IB in children with acute exacerbations of moderate severity, treating with adequate doses of salbutamol and oral prednisolone and reserving IB for children with severe exacerbations.

Acknowledgements

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References


Table 4 Secondary outcomes: adverse effects

<table>
<thead>
<tr>
<th></th>
<th>IB (n = 174)</th>
<th>Non-IB (n = 173)</th>
<th>P value</th>
<th>Number†</th>
<th>Percentage ± 95% CI</th>
<th>Number†</th>
<th>Percentage ± 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adverse effects</td>
<td>23 (13.2 ±5.0%)</td>
<td>8 (4.6 ±3.1%)</td>
<td>0.005</td>
<td>95% CI</td>
<td></td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (1.7)</td>
<td>4 (2.3)</td>
<td>NA</td>
<td>95% CI</td>
<td></td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td>9 (5.2)</td>
<td>2 (1.2)</td>
<td>NA</td>
<td>95% CI</td>
<td></td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>Tremor</td>
<td>10§ (5.7)</td>
<td>1 (0.06)</td>
<td>NA</td>
<td>95% CI</td>
<td></td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>Hyperactivity</td>
<td>3 (1.7)</td>
<td>1 (0.06)</td>
<td>NA</td>
<td>95% CI</td>
<td></td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (0.06)</td>
<td>0 (0)</td>
<td>NA</td>
<td>95% CI</td>
<td></td>
<td>95% CI</td>
<td></td>
</tr>
<tr>
<td>Presyncope</td>
<td>1 (0.06)</td>
<td>0 (0)</td>
<td>NA</td>
<td>95% CI</td>
<td></td>
<td>95% CI</td>
<td></td>
</tr>
</tbody>
</table>

†Totals add to more than 23 as more than one side effect could be listed per subject. §Chi-squared test. One subject had a significant subjective feeling of tremor, without outward signs. NA, not analysed.


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