Indirect bronchial provocation tests in childhood asthma
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Chapter 6

Effect of an Intranasal Corticosteroid on Exercise Induced Bronchoconstriction in Asthmatic Children

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ABSTRACT

Rationale
Allergic rhinitis and exercise induced bronchoconstriction (EIB) are common in asthmatic children. The aim of this study was to investigate whether treatment of allergic rhinitis with an intranasal corticosteroid protects against EIB in asthmatic children.

Methods
This was a double-blind, randomized, placebo-controlled, parallel group study. Subjects aged 12-17 years, with mild-to-moderate asthma, intermittent allergic rhinitis and ≥ 10% fall in FEV₁ at a screening exercise challenge were randomized to 22 ± 3 days treatment with intranasal fluticasone furoate or placebo. The primary outcome was change in exercise induced fall in FEV₁. Secondary outcomes were changes in the area under the curve (AUC), asthma control questionnaire (ACQ), pediatric asthma quality of life questionnaire (PAQLQ) and exhaled nitric oxide (FeNO).

Results
Twenty-five children completed the study. Mean exercise induced fall in FEV₁ (± SD) decreased significantly (95% CI: 0.7 to 18.2%, \( P = 0.04 \)) in the fluticasone furoate group from 28.4 ± 15.8% to 19.0 ± 13.8%, compared to the placebo group (27.4 ± 16.0% to 27.4 ± 19.2%). The change in AUC was not significantly different between treatment groups. However, within the fluticasone furoate group the AUC decreased significantly (\( P = 0.01 \)). Although total PAQLQ score did not improve, the activity limitation domain score improved significantly within the fluticasone furoate group (\( P = 0.03 \)). No significant changes were observed in FeNO and ACQ.

Conclusion
Treatment of allergic rhinitis in asthmatic children with an intranasal corticosteroid reduces EIB and tends to improve quality of life.
INTRODUCTION

Asthma is a chronic disorder of the lower airways, characterized by inflammation and bronchial hyperresponsiveness (BHR), leading to recurrent episodes of wheezing, chest tightness, shortness of breath and coughing. Childhood asthma is often allergy induced. Allergy frequently induces inflammation in the upper airways as well, resulting in episodes with symptoms of allergic rhinitis (AR). Although AR is very common in asthmatic children, it often remains unrecognized and undertreated. AR and asthma are recognized as manifestations of a single “united airways” syndrome and a combined treatment strategy therefore seems appropriate.

Intranasal corticosteroids (INCS) provide a safe and effective treatment of AR. Treatment of AR with INCS tends to improve asthma symptom scores and measures of lung function. The effect of treatment with INCS on BHR is controversial. The effect of INCS on BHR to direct stimuli, such as methacholine and histamine, has been studied in a large number of studies. Some have shown that INCS reduce BHR in adult patients with seasonal or perennial AR and asthma. Others, however, could not confirm this effect. The effect of INCS on BHR to indirect stimuli, such as exercise, has been studied in only one study, which was inconclusive. Direct stimuli act directly on airway smooth muscle cells, without involving inflammatory pathways. Indirect stimuli act on inflammatory cells, such as mast cells, which release mediators interacting with smooth muscle cells. Indirect stimuli are therefore more specific for asthma, as they employ inflammatory cells resident in the asthmatic airway wall.

Exercise is used as an indirect bronchial provocation test to diagnose and monitor exercise induced bronchoconstriction (EIB) in children. EIB is defined as an acute, reversible bronchial obstruction induced by physical exercise and is a disabling characteristic of asthma, affecting 80-90% of asthmatic children. Exercise induced hyperpnoea leading to evaporative water loss and an increase in osmolarity of the airway surface liquid is considered an essential determinant to provoke EIB. A shift of water from the epithelial cells to the airway surface induces the release of mediators from inflammatory cells that cause bronchoconstriction. The severity of EIB is augmented by exercise in cold and dry air. In this study, we investigated the effect of intranasal fluticasone furoate on BHR to exercise in cold air in asthmatic children with intermittent AR.

MATERIALS AND METHODS

Subjects
Children were recruited from the outpatient clinic of the pediatric department of the Medisch Spectrum Twente, Enschede. Thirty-two children aged 12-17 years, with
mild-to-moderate asthma, doctor diagnosed intermittent AR and allergy (defined as a positive specific immunoglobulin E test to ≥ 1 inhalation allergen) were included after a screening exercise challenge. Children were included if they had an exercise induced fall in FEV₁ ≥ 10%. Other inclusion criteria were the ability to perform reproducible pulmonary function tests (i.e., variation of percentage of the predicted value of FEV₁ in 3 of 5 consecutive measurements < 5%) and clinically stable (i.e., no hospital admissions or use of systemic corticosteroids 4 weeks prior to the study), partly or well controlled asthma (as measured by the asthma control questionnaire). Exclusion criteria were pulmonary or cardiac co-morbidity and use of intranasal corticosteroids 4 weeks prior to the study. Both steroid-naïve, as well as children on anti-inflammatory treatment were included. Children were not allowed to use short-acting β2-agonists within 8h and long-acting β2-agonists within 36h prior to testing. Children were excluded if their baseline FEV₁ before and after treatment with INCS differed >12%. The study was approved by the Medical Ethics Committee, Enschede. All children and parents gave written informed consent.

The study was registered online in the ISRCTN register under number ISRCTN90761040.

**Study design**

The study had a double-blind, randomized, placebo-controlled, parallel group design. The study was conducted out of the main grass pollen season, from October 2009 to January 2010 and subjects were (based on a pre-test interview) asymptomatic for AR. Subjects were allocated fluticasone furoate 27.5 µg/dose or matching placebo nasal spray. Subjects were instructed to administer the nasal spray once daily; the first week 2 puffs into each nostril, and 1 puff into each nostril afterwards, as per guideline. Subjects were treated for 22 ± 3 days. Before and after treatment, subjects underwent an exercise challenge and filled out the asthma control questionnaire¹⁸ (ACQ) and the paediatric asthma quality of life questionnaire (PAQLQ). Prior to both exercise challenges, exhaled nitric oxide (FeNO) was measured.

The primary end point was the change in exercise induced fall in FEV₁ after treatment. Secondary end points were changes in the area under the FEV₁ curve, asthma control score (ACQ), quality of life (PAQLQ) and FeNO.

**Randomization and allocation concealment**

Randomization was performed using a computer-generated randomization list, which was maintained by an independent pharmacy. All study medications were packaged and labeled by an independent pharmacy (European Packaging Centre, Heerenveen, the Netherlands). Treatment allocation was concealed from the investigators and participants. Placebo nasal spray was identical in appearance and labeling to fluticasone furoate nasal spray, 27.5 µg per dose. Both were supplied by Glaxo Smith Kline (GSK Pharmaceuticals, Zeist, the Netherlands). Adherence to medication was determined by
weighing study medication before and after the treatment period. The total number of administered puffs of nasal spray was calculated by the loss in weight divided by the weight of one puff. Adherence was calculated as a percentage of prescribed puffs that were used.

**Spirometry**

Pulmonary function tests were performed before (baseline) and after exercise using a standardized protocol according to international guidelines. A Microloop® MK8 Spirometer (Micromedical, Quayside, United Kingdom) with Spida5® software was used to measure flow-volume loops. The calibration of the spirometer was checked before testing. The expiratory flow-volume loop was recorded by one trained assistant in duplicate by instructing the children to perform a maximal expiratory effort from inspiratory vital capacity to residual volume. Best spirometry values were used for analysis. Baseline values of FEV₁ were expressed as percentage of the predicted value.

**Exercise challenge**

Exercise challenges were performed by running with nose clipped on a treadmill (Horizon® fitness Ti22, Cottage Grove, Wisconsin, United States) with an incline of 10% using the standardized ATS protocol. Exercise challenges were performed in the local skating rink, where air temperature is kept constant at 9.5-10.0°C and relative humidity at 56% (absolute humidity 4.2 g/kg). During exercise, heart rate was continuously monitored by a radiographic device (Inventum SH 40®, Veenendaal, the Netherlands). The running speed of the treadmill was increased, raising the heart rate to approximately 90% of the predicted maximum (220-age). This speed was maintained for a total duration of 6 min. Spirometry was performed before exercise (baseline value) and 1, 3, 6, 9, 12, 15, 20, 25 and 30 min after exercise. Thirty minutes after exercise, or at request, children received 100 µg salbutamol, after which spirometry was repeated until FEV₁ was recovered to >95% of baseline. Recovery to baseline FEV₁ was measured as the total area under the curve from 0 to 30 min post-exercise (AUC₀-30min).

**Fraction of exhaled Nitric Oxide**

FeNO was measured before any forced expiratory maneuvers according to current guidelines, using the single-breath online measurement method. Children were asked to exhale to residual volume and then inhale through a hand-held nitric oxide analyzer (Niox Mino®, Aerocrine, Stockholm, Sweden). Children inhaled gas with a low NO concentration to near to total lung capacity and immediately exhaled at a constant flow rate of 50 mL/sec. FeNO was measured in the expired air by its reaction with ozone, which is detected by chemiluminescence.
Questionnaires

The ACQ has 7 questions, scoring 5 symptoms, baseline FEV\(_1\) % predicted and daily rescue bronchodilator use.\(^1\) Children can respond to these questions on a 7-point scale. Baseline FEV\(_1\) % predicted is also scored on a 7-point scale. The questions are equally weighted. The ACQ score is calculated as the mean of the 7 questions and ranges between 0 (totally controlled) and 6 (severely uncontrolled).

The PAQLQ has 23 questions in 3 domains; symptoms, activity limitation and emotional function.\(^2\) Children can respond on a 7-point scale. The total PAQLQ score is calculated as the mean of all 23 questions and domain scores are calculated as the means of the items in those domains. Scores range from 1 (maximal impairment in quality of life) to 7 (no impairment in quality of life).

Statistical analysis

Exercise induced fall in FEV\(_1\) was expressed as percentage fall from baseline. Continuous variables were tested for normality with a Shapiro-Wilk test. Differences between groups were analyzed with a chi-square test (for proportions), independent samples \(t\)-test (for normally distributed variables) or Wilcoxon-rank sum test (for variables with a skewed distribution). Within group changes were analyzed with a paired \(t\)-test or Wilcoxon-signed rank test, as appropriate. FeNO was analyzed before and after natural log transformation. SPSS\(^®\) 17.0 for Windows\(^®\) was used for statistical analysis. The sample size estimated to detect a 10% change in fall in FEV\(_1\) (with a 2-sided significance level of 5% and 95% power), was set at 10 subjects for each treatment group, on the assumption that variability was similar to that observed in previous studies by our study group.

RESULTS

Subjects

Thirty-two children were randomized (17 placebo group, 15 fluticasone furoate group), of which 25 completed the study. Five children were excluded because of exclusion criteria (3 in the placebo group and 2 in the fluticasone furoate group) and 2 children dropped out (one in each treatment group). Patient characteristics are presented in Table 1. None of the variables presented in Table 1 was significantly different between treatment groups (all \(P\) values > 0.10). An overview of changes in all outcome parameters is shown in Table 2.

In both treatment groups, 8 children were using inhaled corticosteroids (ICS), with a mean ± SD dose of 356 ± 124 µg/day in the placebo group and 320 ± 145 µg/day in the fluticasone furoate group (\(P = 0.30\)). Mean ± SD adherence was 82.5 ± 20.5% in the placebo group and 84.3 ± 24.4% in the fluticasone furoate group (\(P = 0.85\)). All children
used > 60% of prescribed study medication, except for one patient in the fluticasone furoate group who had used only 32% of the prescribed medication.

**Table 1.** Patient characteristics (n = 25)

<table>
<thead>
<tr>
<th></th>
<th>Placebo (n=13)</th>
<th>Fluticasone Furoate (n=12)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>14.6 ± 2.1</td>
<td>13.8 ± 1.8</td>
</tr>
<tr>
<td>Male (%)</td>
<td>38.5</td>
<td>66.7</td>
</tr>
<tr>
<td>Duration asthma (years)</td>
<td>11.1 ± 3.9</td>
<td>12.0 ± 3.1</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.67 ± 0.06</td>
<td>1.66 ± 0.12</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>55.9 ± 11.0</td>
<td>57.6 ± 11.7</td>
</tr>
<tr>
<td>LABA (%)</td>
<td>53.8</td>
<td>33.3</td>
</tr>
<tr>
<td>ICS (%)</td>
<td>61.5</td>
<td>66.7</td>
</tr>
<tr>
<td>Leukotriene antagonist</td>
<td>30.8</td>
<td>16.7</td>
</tr>
<tr>
<td>Antihistamine (%)</td>
<td>23.1</td>
<td>16.7</td>
</tr>
<tr>
<td>Sensitization to any inhalant allergen (%)</td>
<td>100.0</td>
<td>100.0</td>
</tr>
<tr>
<td>House dust mite allergy (%)</td>
<td>84.6</td>
<td>75.0</td>
</tr>
<tr>
<td>Pollen allergy (%)</td>
<td>61.5</td>
<td>75.0</td>
</tr>
<tr>
<td>Animal dander allergy</td>
<td>61.5</td>
<td>50.0</td>
</tr>
</tbody>
</table>

Data expressed as mean ± standard deviation (SD) or percentage of patients. ICS = inhaled corticosteroid, LABA = long acting β2-agonist.

**Exercise induced bronchoconstriction**

Mean exercise induced fall in FEV₁ (± SD) decreased significantly in the fluticasone furoate group from 28.4 ± 15.8% to 19.0 ± 13.8%, compared to the placebo group (27.4 ± 16.0% to 27.4 ± 19.2%). The mean difference in decrease in exercise induced fall in FEV₁ between the two groups was 9.5% (95% CI: 0.7 to 18.2 %, P = 0.04); Fig. 1. The exercise induced fall in FEV₁ decreased in all children in the fluticasone furoate group, except for the patient who had used 32% of study medication. Intranasal fluticasone furoate provided 33% protection against EIB compared to placebo.

**Area under the curve**

There was a non-significant difference in decrease in the AUC₀-₃₀min between placebo and treatment groups (95% CI: -41 to 366%.min; P = 0.11). Within the fluticasone furoate group, AUC₀-₃₀min decreased significantly from 620 ± 363%.min to 404 ± 249%.min (mean decrease 216%.min; 95% CI: 54 to 378%.min; P = 0.01). Recovery curves are shown in Fig. 2.

**Spirometry**

Baseline FEV₁ before the first exercise challenge was 88.5 ± 8.6% predicted in the fluticasone furoate group and 88.0 ± 13.2% predicted in the placebo group (P = 0.91). Baseline FEV₁ after treatment was not significantly different in the fluticasone furoate group (88.2
Table 2. Outcome parameters before and after treatment

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Fluticasone Furoate</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>FEV₁ % predicted</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>88.0 ± 13.2</td>
<td>88.5 ± 8.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>after treatment</td>
<td>86.6 ± 13.4</td>
<td>88.2 ± 12.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>change</td>
<td>-1.4 ± 3.8</td>
<td>-0.3 ± 5.6</td>
<td>-2.9 to 5.0</td>
<td>0.59</td>
</tr>
<tr>
<td>Exercise induced fall in FEV₁ (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>27.4 ± 16.0</td>
<td>28.4 ± 15.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>after treatment</td>
<td>27.4 ± 19.2</td>
<td>19.0 ± 13.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>change</td>
<td>0.0 ± 0.5</td>
<td>-9.5 ± 10.0</td>
<td>-18.2 to -0.7</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>AUC₀⁻₃₀min (%.min)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>592 ± 361</td>
<td>620 ± 363</td>
<td></td>
<td></td>
</tr>
<tr>
<td>after treatment</td>
<td>538 ± 394</td>
<td>404 ± 249</td>
<td></td>
<td></td>
</tr>
<tr>
<td>change</td>
<td>-53 ± 237</td>
<td>-216 ± 255</td>
<td>-366 to 41</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>ACQ</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>1.1 ± 0.6</td>
<td>1.2 ± 0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>after treatment</td>
<td>1.1 ± 0.6</td>
<td>1.2 ± 0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>change</td>
<td>0.0 ± 0.6</td>
<td>0.0 ± 0.8</td>
<td>-0.5 to 0.5</td>
<td>0.84</td>
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<tr>
<td><strong>PAQLQ -total-</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>baseline</td>
<td>6.0 ± 0.8</td>
<td>6.0 ± 0.8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>after treatment</td>
<td>5.9 ± 1.0</td>
<td>6.2 ± 0.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>change</td>
<td>0.0 ± 0.5</td>
<td>0.2 ± 0.5</td>
<td>-0.2 to 0.7</td>
<td>0.28</td>
</tr>
<tr>
<td><strong>PAQLQ -symptoms-</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>5.8 ± 1.0</td>
<td>5.7 ± 1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>after treatment</td>
<td>5.7 ± 1.0</td>
<td>5.7 ± 1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>change</td>
<td>-0.1 ± 0.6</td>
<td>0.0 ± 0.7</td>
<td>-0.4 to 0.6</td>
<td>0.72</td>
</tr>
<tr>
<td><strong>PAQLQ -activity limitation-</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>5.5 ± 1.2</td>
<td>5.6 ± 1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>after treatment</td>
<td>5.5 ± 1.4</td>
<td>6.0 ± 0.9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>change</td>
<td>-0.1 ± 0.7</td>
<td>0.4 ± 0.5</td>
<td>-0.1 to 0.9</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>PAQLQ -emotional function-</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>baseline</td>
<td>6.5 ± 0.6</td>
<td>6.5 ± 0.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>after treatment</td>
<td>6.5 ± 0.8</td>
<td>6.8 ± 0.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>change</td>
<td>0.0 ± 0.5</td>
<td>0.3 ± 0.6</td>
<td>-0.1 to 0.7</td>
<td>0.17</td>
</tr>
<tr>
<td><strong>FeNO (ppb)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>baseline</td>
<td>36.8 ± 26.2</td>
<td>47.0 ± 50.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>after treatment</td>
<td>30.6 ± 25.2</td>
<td>36.5 ± 37.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>change</td>
<td>-6.2 ± 17.3</td>
<td>-10.4 ± 32.6</td>
<td>-25.6 to 17.1</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Data expressed as mean ± standard deviation (SD). ACQ = asthma control questionnaire, \( \text{AUC}_{0-30\text{min}} \) = total area under the curve from 0-30 min post-exercise, CI = confidence interval, FeNO = fraction of exhaled nitric oxide, FEV₁ = forced expiratory volume in 1 s, PAQLQ = pediatric asthma quality of life questionnaire, ppb = parts per billion.
± 12.5% pred., $P = 0.84$) or the placebo group (86.6 ± 13.4% pred., $P = 0.22$). Change in baseline FEV₁ did not differ between treatment groups ($P = 0.59$).

**Quality of Life and Asthma Control**

There was no significant difference in total PAQLQ scores or domain scores between the two study groups (all $P$ values > 0.10). However, mean activity limitation score increased 0.4 units (95% CI: 0.0 to 0.7; $P = 0.03$) in the fluticasone furoate group, whilst no change was observed in the placebo group (95% CI: -0.5 to 0.4; $P = 0.71$). No change was observed in other PAQLQ domains, however, in the fluticasone furoate group a trend towards an increase in quality of life in emotional function was seen (95% CI: -0.1 to 0.7; $P = 0.08$).

There was no change in mean ACQ scores after treatment with fluticasone furoate or placebo. There was no difference in change in ACQ scores between treatment groups (95% CI: -0.5 to 0.5; $P = 0.84$).

**Fraction of exhaled Nitric Oxide**

Baseline FeNO was 36.8 ± 26.2 ppb in the placebo group and 47.0 ± 50.0 ppb in the fluticasone furoate group, which was not significantly different (95% CI: -42.8 to 22.5; $P = 0.53$). In the fluticasone furoate group, FeNO decreased 10.4 ± 32.6 ppb after treatment, which was not significantly different (95% CI: -17.1 to 25.6; $P = 0.68$) from the decrease in FeNO in the placebo group (6.2 ± 17.3 ppb). There was also no significant difference in the decrease in FeNO between treatment groups after natural log transformation ($P = 0.93$).

Children on ICS had a non-significant lower baseline FeNO compared to steroid-naïve children (34.2 ± 34.0 ppb vs. 55.1 ± 42.8 ppb, $P = 0.21$). Steroid-naïve children had a

![Fig. 1. Exercise induced fall in FEV₁ (%)](image-url) before and after treatment with placebo or fluticasone furoate. Data expressed as individual fall in FEV₁ and mean fall in FEV₁. **FEV₁** = *forced expiratory volume in 1s.*
non-significant greater decrease in FeNO than children on ICS with fluticasone furoate (28.8 ± 55.8 ppb vs. 1.25 ± 7.0 ppb; 95% CI: -15.0 to 70.0; \( P = 0.18 \)). However, steroid naïve children also had a greater decrease in FeNO compared to children on ICS with placebo (17.4 ± 24.7 ppb vs. -0.9 ± 4.1 ppb; 95% CI: -0.8 to 37.4; \( P = 0.06 \)) and there was no difference in decrease in FeNO between treatment groups (95% CI: -76.4 to 53.7; \( P = 0.69 \)).

**Adverse events**

There were no significant differences in the prevalence of reported adverse events between the two groups (\( P = 0.79 \)). All reported adverse events were mild. Two children complained of epistaxis (1 in each group). Six children reported flu like symptoms (3 in each group) and respiratory tract infections were reported in 4 (2 in each group). One patient in the placebo group was treated for a urinary tract infection with nitrofurantoin for 7 days.

**Fig. 2.** Mean fall in FEV\(_1\) at each time point after exercise. (A) Before and after treatment with placebo. (B) Before and after treatment with fluticasone furoate. Patients received 100 µg salbutamol at \( t = 30 \) min. \( FEV_1 = \) forced expiratory volume in 1s.
DISCUSSION

The results of this study demonstrate that treatment with an INCS (fluticasone furoate) significantly reduces exercise induced fall in FEV₁ in children with mild to moderate asthma, intermittent AR and EIB. In addition, there was a significant within group decrease in AUC₀⁻₃₀min and a trend towards an improvement in the activity limitation domain of quality of life in the fluticasone furoate group.

To our knowledge, this study is the first to investigate the effect of an INCS on EIB in cold air in asthmatic children. Henriksen and Wenzel investigated the effect of intranasal budesonide on EIB in room temperature in allergic asthmatic children with chronic nasal obstruction and found a trend towards a reduction in EIB after 4 weeks treatment.¹⁴ There were important differences between the study by Henriksen and our study. Firstly, we included children with intermittent symptoms of AR whereas Henriksen selected children with a persistently blocked nose and mouth breathing. Secondly, we used cold, dry air, which amplifies EIB¹⁷ and may explain the greater difference between groups in our study. Furthermore, Henriksen used a different device to deliver INCS, a pressurized aerosol and a different, but equipotent INCS, i.e., budesonide.

This study, using an indirect bronchial provocation test, showed a clinically significant attenuation of BHR to exercise by INCS that is similar to the attenuation provided by a low dose of inhaled corticosteroids.²³ Studies assessing the effect of INCS on BHR to direct bronchial provocation tests, such as methacholine and histamine, were inconclusive.⁶⁻¹³ Some studies demonstrated an attenuation of the increase in BHR during seasonal allergy exposure.⁸⁻⁹ Studies that did find a decrease in BHR to direct stimuli had a longer duration of treatment with INCS and showed a small, statistically significant, though not clinically relevant improvement.⁶⁻⁷ We hypothesized that the short-term effects of INCS on the lower airways may be better demonstrated with an indirect bronchial provocation test. The response to an indirect stimulus reflects the actual inflammatory state of the airways and the presence and activity of inflammatory cells.²⁴ BHR to a direct stimulus is more closely related to airway smooth muscle function and airway caliber¹⁵ and is therefore a reflection of functional and anatomic airway remodeling as a result of chronic inflammation.

Several methodological issues of our study design need to be addressed. Firstly, in our study duration of treatment (22 ± 3 days) was rather short compared to other studies, treating for 4-6 weeks.⁷⁻⁹,¹⁴ We hypothesized that this treatment period was long enough as BHR to indirect stimuli responds more rapidly to anti-inflammatory treatment than BHR to direct stimuli.²⁵ Furthermore, fluticasone furoate is a modern, potent corticosteroid, with an onset of action against nasal symptoms within the first 24h of treatment.²⁶
Fluticasone furoate reaches its maximal effect on nasal symptoms after 2-3 weeks of treatment.\textsuperscript{26}

The size of our study population was small, yet we found a clinically relevant improvement in EIB. However, a larger study population might have provided statistically significant changes in secondary outcome measures that showed a trend in our study.

Our study population was non-homogeneous in relation to asthma severity, upper airway symptoms and atopic sensitization. The study was intended as a ‘proof of principle’ study and we chose to include a cross section of the mainstream of asthmatic children in a general pediatric outpatient clinic. The improvement in EIB was seen in all children in the fluticasone furoate group, both with mild or more severe EIB, partly or well controlled asthma and with or without concomitant treatment with ICS, except for one child who had used only 32\% of study medication.

As we did not perform additional tests to objectify symptoms of AR on inclusion we cannot clearly distinguish whether our patients had asymptomatic upper airway inflammation or undiagnosed perennial AR. It is therefore uncertain from this study if INCS would be more effective against EIB in subgroups of patients with more severe or persistent AR.

The effect of INCS on asthma control in asthmatic children, as measured with an ACQ, has not been described before. In our study, no change in ACQ was observed after treatment with fluticasone furoate, which is in agreement with results of Nathan et al. who found no improvement on asthma symptoms scores and rescue albuterol use with INCS in asthmatic adults on ICS.\textsuperscript{27} In our study the ACQ score was already low at baseline leaving little room for improvement. Several other studies did show a beneficial effect of INCS on asthma symptom scores\textsuperscript{6,10} and the asthma control test\textsuperscript{28} in adults, suggesting an improvement in asthma control. However, the effect of INCS on symptoms of AR could confound asthma symptoms scores, as symptoms of AR and asthma overlap.

The PAQLQ showed a within group reduction in activity limitation after treatment with INCS, which could be a result of the reduction in EIB. Although this result was statistically significant, its mean increase was 0.4 units, which is just below the clinically relevant difference of 0.5 units.\textsuperscript{22} Nair et al. found no additional improvement in asthma quality of life score (AQLQ) in adults treated with both intranasal and inhaled fluticasone compared to treatment with inhaled fluticasone alone.\textsuperscript{12}

In this study, we found no significant reduction in FeNO after treatment with intranasal fluticasone furoate. However, steroid-naïve children tended to have a greater decrease in FeNO after treatment with fluticasone furoate than children on ICS. As in our study, Pedroletti et al. described unchanged levels of FeNO after treatment of asthmatic children on ICSs with mild to moderate AR with intranasal mometasone furoate.\textsuperscript{29} A study
In steroid-naïve asthmatic adults did find a significant decrease in FeNO after treatment of AR with triamcinolone. \(^\text{30}\)

The results of this study confirm the existence of an important physiologic relation between the upper and lower airways. Several mechanisms have previously been proposed as putative underlying mechanisms, such as the existence of a neural nasobronchial reflex and/or systemic inflammatory response from upper to lower airways.\(^\text{4,31}\) An improvement of nasal breathing can reduce epithelial injury and chronic inflammation of the lower airways, as the nose warms, humidifies and filters the inspired air.\(^\text{8,14}\) Improved nasal breathing during the exercise challenges cannot explain the protective effect of fluticasone furoate on EIB, as patients wore a nose clip during both challenges. A systemic effect of nasal corticosteroids is also unlikely, since nasal and gastro-intestinal absorption of fluticasone furoate after intra-nasal administration is low.\(^\text{32}\) Furthermore, a protective effect due to intrapulmonary deposition of fluticasone furoate also seems unlikely, as less than 2% of nasal medication reaches the lower airways.\(^\text{7}\)

In conclusion, this study shows that anti-inflammatory treatment of AR improves EIB in children with mild to moderate asthma and intermittent AR. Although AR is very common in asthmatic children, it often remains unrecognized and undertreated.\(^\text{2,3}\) This study shows that in the general pediatric outpatient clinic, many asthmatic children could benefit from intranasal anti-inflammatory treatment. Therefore, in children with EIB, clinicians should actively inquire about symptoms of AR. In the presence of such symptoms, even when only intermittently, INCS can improve EIB, which may improve quality of life. Studies in larger populations are required to corroborate our findings and to look further into the mechanism by which upper airway inflammation affects lower airway inflammation.

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Intranasal corticosteroid and EIB
