

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

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Summary. 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 $\geq 10\%$ fall in FEV₁ at a screening exercise challenge were randomized to 22 \pm 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 (\pm SD) decreased significantly (95% CI: 0.7–18.2%, $P = 0.04$) in the fluticasone furoate group from 28.4 \pm 15.8% to 19.0 \pm 13.8%, compared to the placebo group (27.4 \pm 16.0% to 27.4 \pm 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. **Pediatr Pulmonol.** 2012; 47:27–35. © 2011 Wiley Periodicals, Inc.

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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.¹ Childhood asthma is often allergy induced.² 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.^{2,3} AR and asthma are recognized as manifestations of a single “united airways” syndrome^{2,4} and a combined treatment strategy therefore seems appropriate.

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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.⁵ 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.^{6–13} Some have shown that INCS reduce BHR in adult patients with seasonal or perennial AR and asthma.^{6–9} Others, however, could not confirm this effect.^{10–13} The effect of INCS on BHR to indirect stimuli, such as exercise, has been studied in only one study, which was inconclusive.¹⁴ 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.¹⁵

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.¹⁶ 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.

ABBREVIATIONS:

ACQ	Asthma control questionnaire
AR	Allergic rhinitis
AUC	Area under the curve, 0–30 min post-exercise
BHR	Bronchial hyperresponsiveness
CI	Confidence interval
EIB	Exercise induced bronchoconstriction
FeNO	Fraction of exhaled nitric oxide
FEV ₁	Forced expiratory volume in 1 sec
ICS	Inhaled corticosteroids
INCS	Intranasal corticosteroids
PAQLQ	Pediatric asthma quality of life questionnaire
SD	Standard deviation

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 $\geq 10\%$.¹⁷ 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 bronchodilators within 8 hr and long acting bronchodilators within 36 hr 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 $\mu\text{g}/\text{dose}$ 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 pediatric 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, Heereveen, 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.¹⁹ 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.²⁰

Exercise Challenge

Exercise challenges were performed by running with nose clipped on a treadmill (Horizon[®] fitness Ti22, Cottage Grove, WI) with an incline of 10% using the standardized ATS protocol.¹⁷ 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 (AUC_{0–30 min}).

Exhaled Nitric Oxide

FeNO was measured before any forced expiratory maneuvers according to current guidelines, using the single-breath online measurement method.²¹ 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 FEV₁ % predicted and daily rescue bronchodilator use.¹⁸ Children can respond to these questions on a 7-point scale. Baseline FEV₁ % 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.²² 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 FEV₁ 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 sum 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 FEV₁ (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 \pm SD dose of 356 ± 124 μ g/day in the placebo group and 320 ± 145 μ g/day in the fluticasone furoate group (*P* = 0.30). Mean \pm SD adherence was $82.5 \pm 20.5\%$ in the placebo group and $84.3 \pm 24.4\%$ 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.

Exercise Induced Bronchoconstriction

Mean exercise induced fall in FEV₁ (\pm SD) decreased significantly in the fluticasone furoate group from $28.4 \pm 15.8\%$ to $19.0 \pm 13.8\%$, compared to the placebo group ($27.4 \pm 16.0\%$ to $27.4 \pm 19.2\%$). The mean difference in decrease in exercise induced fall in FEV₁ between the two groups was 9.5% (95% CI: 0.7–18.2%, *P* = 0.04); Figure 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 AUC_{0–30 min} between placebo and treatment groups (95% CI: –41% to 366%·min; *P* = 0.11). Within the fluticasone furoate group, AUC_{0–30 min} decreased significantly from $620 \pm 363\%$ min to $404 \pm 249\%$ min (mean decrease 216% min; 95% CI: 54–378% min; *P* = 0.01). Recovery curves are shown in Figure 2.

Spirometry

Baseline FEV₁ before the first exercise challenge was $88.5 \pm 8.6\%$ predicted in the fluticasone furoate group and $88.0 \pm 13.2\%$ predicted in the placebo group (*P* = 0.91). Baseline FEV₁ after treatment was not significantly different in the fluticasone furoate group ($88.2 \pm 12.5\%$ pred., *P* = 0.84) or the placebo group ($86.6 \pm 13.4\%$ 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: 0.0–0.7; *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).

FeNO

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).

TABLE 1—Patient Characteristics (N = 25)

	Placebo (N = 13)	Fluticasone furoate (N = 12)
Age (years)	14.6 \pm 2.1	13.8 \pm 1.8
Male (%)	38.5	66.7
Duration asthma (years)	11.1 \pm 3.9	12.0 \pm 3.1
Height (m)	1.67 \pm 0.06	1.66 \pm 0.12
Weight (kg)	55.9 \pm 11.0	57.6 \pm 11.7
LABA (%)	53.8	33.3
ICS (%)	61.5	66.7
Leukotriene antagonist (%)	30.8	16.7
Antihistamine (%)	23.1	16.7
Sensitization to any inhalant allergen (%)	100.0	100.0
House dust mite allergy (%)	84.6	75.0
Pollen allergy (%)	61.5	75.0
Animal dander allergy (%)	61.5	50.0

Data expressed as mean \pm standard deviation (SD) or percentage of patients.

LABA, long acting beta2 agonist; ICS, inhaled corticosteroid.

TABLE 2—Outcome Parameters Before and After Treatment

	Placebo	Fluticasone furoate	95% CI	<i>P</i> -value
FEV ₁ (% predicted)				
Baseline	88.0 ± 13.2	88.5 ± 8.6		
After treatment	86.6 ± 13.4	88.2 ± 12.5		
Change	−1.4 ± 3.8	−0.3 ± 5.6	−2.9 to 5.0	0.59
Exercise induced fall in FEV ₁ (%)				
Baseline	27.4 ± 16.0	28.4 ± 15.8		
After treatment	27.4 ± 19.2	19.0 ± 13.8		
Change	0.0 ± 0.5	−9.5 ± 10.0	−18.2 to −0.7	0.04
AUC _{0–30 min} (% min)				
Baseline	592 ± 361	620 ± 363		
After treatment	538 ± 394	404 ± 249		
Change	−53 ± 237	−216 ± 255	−366 to 41	0.11
ACQ				
Baseline	1.1 ± 0.6	1.2 ± 0.8		
After treatment	1.1 ± 0.6	1.2 ± 0.7		
Change	0.0 ± 0.6	0.0 ± 0.8	−0.5 to 0.5	0.84
PAQLQ-total				
Baseline	6.0 ± 0.8	6.0 ± 0.8		
After treatment	5.9 ± 1.0	6.2 ± 0.7		
Change	0.0 ± 0.5	0.2 ± 0.5	−0.2 to 0.7	0.28
PAQLQ-symptoms				
Baseline	5.8 ± 1.0	5.7 ± 1.0		
After treatment	5.7 ± 1.0	5.7 ± 1.0		
Change	−0.1 ± 0.6	0.0 ± 0.7	−0.4 to 0.6	0.72
PAQLQ-activity limitation				
Baseline	5.5 ± 1.2	5.6 ± 1.0		
After treatment	5.5 ± 1.4	6.0 ± 0.9		
Change	−0.1 ± 0.7	0.4 ± 0.5	−0.1 to 0.9	0.11
PAQLQ-emotional function				
Baseline	6.5 ± 0.6	6.5 ± 0.6		
After treatment	6.5 ± 0.8	6.8 ± 0.3		
Change	0.0 ± 0.5	0.3 ± 0.6	−0.1 to 0.7	0.17
FeNO (ppb)				
Baseline	36.8 ± 26.2	47.0 ± 50.0		
After treatment	30.6 ± 25.2	36.5 ± 37.0		
Change	−6.2 ± 17.3	−10.4 ± 32.6	−25.6 to 17.1	0.68

Data expressed as mean ± standard deviation (SD).

FEV₁, forced expiratory volume in 1 sec; AUC_{0–30 min}, total area under the curve from 0–30 min post-exercise; ACQ, asthma control questionnaire; PAQLQ, pediatric asthma quality of life questionnaire; FeNO, fraction of exhaled nitric oxide; ppb, parts per billion; CI, confidence interval

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 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.

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 AUC_{0–30 min} and a trend towards an improvement in the

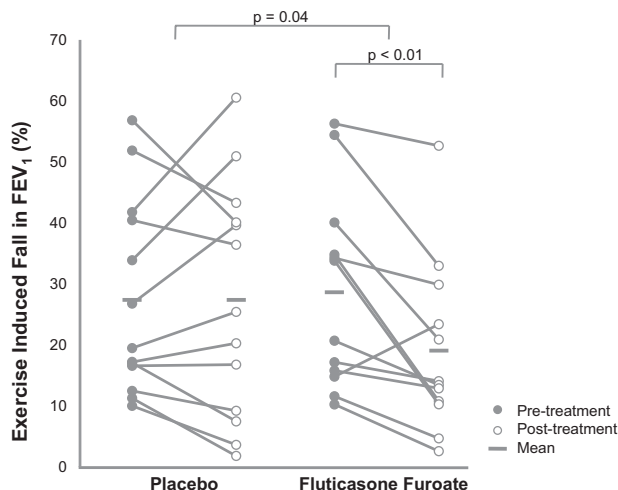


Fig 1. Exercise induced fall in FEV₁ (%) before and after treatment with placebo or fluticasone furoate. Data expressed as individual fall in FEV₁ and mean fall in FEV₁. FEV₁, forced expiratory volume in 1 sec.

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

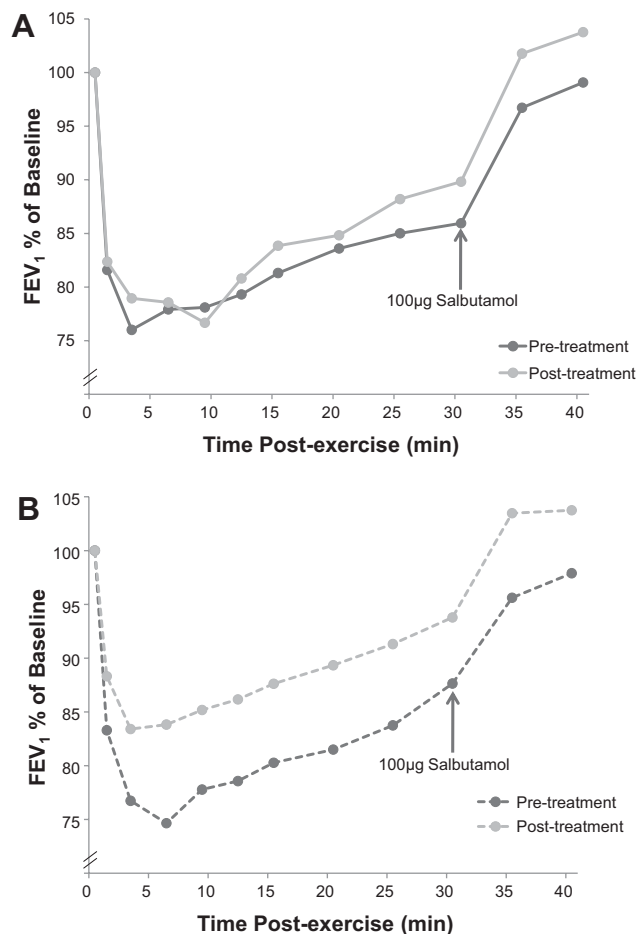


Fig 2. Mean fall in FEV₁ at each time point after exercise. (A) Before and after treatment with placebo. (B) Before and after treatment with fluticasone furoate. Patients received 100 µg salbutamol at t = 30 min. FEV₁, forced expiratory volume in 1 sec.

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 24 hr of treatment.²⁶ Fluticasone furoate reaches its maximal effect on nasal symptoms after 2–3 weeks of treatment.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.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^{6,10} and the asthma control test²⁸ 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 partly 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.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.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.²⁹ A study in steroid-naïve asthmatic adults did find a significant decrease in FeNO after treatment of AR with triamcinolone.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.^{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.^{4,14} 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.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.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.^{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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REFERENCES

1. Global Initiative for Asthma. GINA Report, Global Strategy for Asthma Management and Prevention. Update 2009 [accessed June 20, 2010]. Available from <http://www.ginasthma.com/>.

2. Bousquet J, Khaltaev N, Cruz AA, Denburg J, Fokkens WJ, Togias A, Zuberbier T, Baena-Cagnani CE, Canonica GW, van Weel C, Agache I, Ait-Khaled N, Bachert C, Blaiss MS, Bonini S, Boulet LP, Bousquet PJ, Camargos P, Carlsen KH, Chen Y, Custovic A, Dahl R, Demoly P, Douagui H, Durham SR, van Wijk RG, Kalayci O, Kaliner MA, Kim YY, Kowalski ML, Kuna P, Le LT, Lemiere C, Li J, Lockey RF, Mavale-Manuel S, Meltzer EO, Mohammad Y, Mullol J, Naclerio R, O'Hehir RE, Ohta K, Ouedraogo S, Palkonen S, Papadopoulos N, Passalacqua G, Pawankar R, Popov TA, Rabe KF, Rosado-Pinto J, Scadding GK, Simons FE, Toskala E, Valovirta E, van Couwenberge P, Wang DY, Wickman M, Yawn BP, Yorgancioglu A, Yusuf OM, Zar H, Annesi-Maesano I, Bateman ED, Ben KA, Boakye DA, Bouchard J, Burney P, Busse WW, Chan-Yeung M, Chavannes NH, Chuchalin A, Dolen LK, Emuzyte R, Grouse L, Humbert M, Jackson C, Johnston SL, Keith PK, Kemp JP, Klossek JM, Larenas-Linnemann D, Lipworth B, Malo JL, Marshall GD, Naspitz C, Nekam K, Niggemann B, Nizankowska-Mogilnicka E, Okamoto Y, Orru MP, Potter P, Price D, Stoloff SW, Vandenplas O, Viegi G, Williams D. Allergic rhinitis and its impact on asthma (ARIA) 2008 update (in collaboration with the World Health Organization, GA(2)LEN and AllerGen). *Allergy* 2008;63:8–160.
3. Stewart MG. Identification and management of undiagnosed and undertreated allergic rhinitis in adults and children. *Clin Exp Allergy* 2008;38:751–760.
4. Braunstahl GJ. United airways concept: what does it teach us about systemic inflammation in airways disease? *Proc Am Thorac Soc* 2009;6:652–654.
5. Taramarcaz P, Gibson PG. Intranasal corticosteroids for asthma control in people with coexisting asthma and rhinitis. *Cochrane Database Syst Rev* 2003;4:CD003570.
6. Agondi RC, Machado ML, Kalil J, Giavina-Bianchi P. Intranasal corticosteroid administration reduces nonspecific bronchial hyperresponsiveness and improves asthma symptoms. *J Asthma* 2008;45:754–757.
7. Watson WT, Becker AB, Simons FE. Treatment of allergic rhinitis with intranasal corticosteroids in patients with mild asthma: effect on lower airway responsiveness. *J Allergy Clin Immunol* 1993;91:97–101.
8. Corren J, Adinoff AD, Buchmeier AD, Irvin CG. Nasal beclomethasone prevents the seasonal increase in bronchial responsiveness in patients with allergic rhinitis and asthma. *J Allergy Clin Immunol* 1992;90:250–256.
9. Foresi A, Pelucchi A, Gherson G, Mastropasqua B, Chiapparino A, Testi R. Once daily intranasal fluticasone propionate (200 micrograms) reduces nasal symptoms and inflammation but also attenuates the increase in bronchial responsiveness during the pollen season in allergic rhinitis. *J Allergy Clin Immunol* 1996;98:274–282.
10. Stelmach R, do Patrocinio TN, Ribeiro M, Cukier A. Effect of treating allergic rhinitis with corticosteroids in patients with mild-to-moderate persistent asthma. *Chest* 2005;128:3140–3147.
11. Dahl R, Nielsen LP, Kips J, Foresi A, Cauwenberge P, Tudoric N, Howarth P, Richards DH, Williams M, Pauwels R. Intranasal and inhaled fluticasone propionate for pollen-induced rhinitis and asthma. *Allergy* 2005;60:875–881.
12. Nair A, Vaidyanathan S, Clearie K, Williamson P, Meldrum K, Lipworth BJ. Steroid sparing effects of intranasal corticosteroids in asthma and allergic rhinitis. *Allergy* 2010;65:359–367.
13. Rak S, Heinrich C, Jacobsen L, Scheynius A, Venge P. A double-blinded, comparative study of the effects of short pre-season specific immunotherapy and topical steroids in patients with allergic rhinoconjunctivitis and asthma. *J Allergy Clin Immunol* 2001;108:921–928.
14. Henriksen JM, Wenzel A. Effect of an intranasally administered corticosteroid (budesonide) on nasal obstruction, mouth breathing, and asthma. *Am Rev Respir Dis* 1984;130:1014–1018.
15. Cockcroft D, Davis B. Direct and indirect challenges in the clinical assessment of asthma. *Ann Allergy Asthma Immunol* 2009;103:363–369.
16. Merikallio VJ, Mustalahti K, Remes ST, Valovirta EJ, Kaila M. Comparison of quality of life between asthmatic and healthy school children. *Pediatr Allergy Immunol* 2005;16:332–340.
17. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, MacIntyre NR, McKay RT, Wanger JS, Anderson SD, Cockcroft DW, Fish JE, Sterk PJ. Guidelines for methacholine and exercise challenge testing-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 2000;161:309–329.
18. Juniper EF, O'Byrne PM, Guyatt GH, Ferrie PJ, King DR. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902–907.
19. Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, Crapo R, Enright P, van der Grinten CP, Gustafsson P, Jensen R, Johnson DC, MacIntyre N, McKay R, Navajas D, Pedersen OF, Pellegrino R, Viegi G, Wanger J. Standardisation of spirometry. *Eur Respir J* 2005;26:319–338.
20. Quanjer PH, Borsboom GJ, Brunekreef B, Zach M, Forche G, Cotes JE, Sanchis J, Paoletti P. Spirometric reference values for white European children and adolescents: Polgar revisited. *Pediatr Pulmonol* 1995;19:135–142.
21. ATS/ERS recommendations for standardized procedures for the online and offline measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide, 2005. *Am J Respir Crit Care Med* 2005;171:912–930.
22. Juniper EF, Guyatt GH, Feeny DH, Ferrie PJ, Griffith LE, Townsend M. Measuring quality of life in children with asthma. *Qual Life Res* 1996;5:35–46.
23. Stelmach I, Grzelewski T, Majak P, Jerzynska J, Stelmach W, Kuna P. Effect of different antiasthmatic treatments on exercise-induced bronchoconstriction in children with asthma. *J Allergy Clin Immunol* 2008;121:383–389.
24. Brannan JD. Bronchial hyperresponsiveness in the assessment of asthma control: airway hyperresponsiveness in asthma: its measurement and clinical significance. *Chest* 2010;138:11S–17S.
25. Doull J, Sandall D, Smith S, Schreiber J, Freezer NJ, Holgate ST. Differential inhibitory effect of regular inhaled corticosteroid on airway responsiveness to adenosine 5' monophosphate, methacholine, and bradykinin in symptomatic children with recurrent wheeze. *Pediatr Pulmonol* 1997;23:404–411.
26. Scadding GK, Keith PK. Fluticasone furoate nasal spray consistently and significantly improves both the nasal and ocular symptoms of seasonal allergic rhinitis: a review of the clinical data. *Expert Opin Pharmacother* 2008;9:2707–2715.
27. Nathan RA, Yancey SW, Waitkus-Edwards K, Prillaman BA, Stauffer JL, Philpot E, Dorinsky PM, Nelson HS. Fluticasone propionate nasal spray is superior to montelukast for allergic rhinitis while neither affects overall asthma control. *Chest* 2005;128:1910–1920.
28. Scichilone N, Arrigo R, Paterno A, Santagata R, Impellitteri S, Braido F, Baiardini I, Battaglia S, Walter CG, Bellia V. The effect of intranasal corticosteroids on asthma control and quality of life in allergic rhinitis with mild asthma. *J Asthma* 2011;48:41–47.
29. Pedroletti C, Lundahl J, Alving K, Hedlin G. Effect of nasal steroid treatment on airway inflammation determined by

- exhaled nitric oxide in allergic schoolchildren with perennial rhinitis and asthma. *Pediatr Allergy Immunol* 2008;19:219–226.
30. Sandrini A, Ferreira IM, Jardim JR, Zamel N, Chapman KR. Effect of nasal triamcinolone acetonide on lower airway inflammatory markers in patients with allergic rhinitis. *J Allergy Clin Immunol* 2003;111:313–320.
 31. Kleinjan A, Willart M, van Nimwegen M, Leman K, Hoogsteden HC, Hendriks RW, Lambrecht BN. United airways: circulating Th2 effector cells in an allergic rhinitis model are responsible for promoting lower airways inflammation. *Clin Exp Allergy* 2010;40:494–504.
 32. McCormack PL, Scott LJ. Fluticasone furoate: intranasal use in allergic rhinitis. *Drugs* 2007;67:1905–1915.