Dose-Responses Over Time to Inhaled Fluticasone Propionate Treatment of Exercise- and Methacholine-Induced Bronchoconstriction in Children With Asthma

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Summary. When treating bronchial hyperresponsiveness to so-called direct and indirect stimuli, distinct pathophysiological mechanisms might require differences in dose and duration of inhaled corticosteroid therapy. To test this hypothesis in children with asthma, we investigated the time- and dose-dependent effects of 2 doses of fluticasone propionate (FP, 100 or 250 µg bid.) in improving exercise- (EIB) and methacholine-induced bronchoconstriction during 6 months of treatment, using a placebo-controlled parallel group study design. Thirty-seven children with asthma (aged 6 to 14 years; forced expired volume in 1 sec (FEV1) ≥70% predicted; EIB ≥20% fall in FEV1 from baseline; no inhaled steroids during the past 4 months) participated in a double-blind, placebo-controlled, 3-arm parallel study. Children receiving placebo were re-randomized to active treatment after 6 weeks. Standardized dry air treadmill exercise testing (EIB expressed as %fall in FEV1 from baseline) and methacholine challenge using a dosimetric technique (expressed as PD20) were performed repeatedly during the study.

During FP-treatment, the severity of EIB decreased significantly as compared to placebo within 3 weeks, the geometric mean % fall in FEV1 being reduced from 34.1% to 9.9% for 100 µg FP bid, and from 35.9% to 7.6% for 250 µg FP bid (P < 0.05). These reductions in EIB did not differ between the 2 doses and were sustained throughout the treatment period. PD20 methacholine improved significantly during the first 6 weeks as compared to placebo (P < 0.04) and steadily increased with time in both treatment limbs (P = 0.04), the difference in improvement between doses (100 µg FP bid, 1.6 dose steps; 250 µg FP bid, 3.3 dose steps) approaching significance after 24 weeks (P = 0.06).

We conclude that in childhood asthma, the protection afforded by inhaled fluticasone propionate against methacholine-induced bronchoconstriction is time- and dose-dependent, whereas protection against EIB is not. This suggests different modes of action of inhaled steroids in protecting against these pharmacological and physiological stimuli. This has to be taken into account when monitoring asthma treatment.


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Key words: exercise-induced asthma; bronchial hyperresponsiveness; inhaled corticosteroids; fluticasone propionate; eosinophil cationic protein; randomized clinical trial; children.

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INTRODUCTION

Asthma is a chronic inflammatory disorder of the airways, characterized by variable airways obstruction over time.1 Episodic bronchoconstriction can occur either spontaneously or in response to bronchoconstrictor stimuli. The sensitivity to such stimuli is a measure of the severity of the underlying bronchial hyperresponsiveness (BHR),2 the latter being associated with an inflammatory cellular infiltrate, especially eosinophils, in and around the airway.3,4 Some of the bronchoconstrictor stimuli act directly through stimulation of the bronchial smooth muscle in the airway wall (for example, methacholine). Other stimuli (such as exercise) act indirectly through infiltrative or resident pulmonary cells or neural pathways.5 Exercise, especially in childhood, is a common trigger of acute, usually short-lived asthma attacks. This is referred to as exercise-induced bronchoconstriction (EIB).6 The current understanding regarding mechanisms suggests that inflammatory mediators are released in response to airway cooling and/or drying triggered by hyperventilation of exercise.7 An association between the severity of EIB and eosinophilic inflammation has been reported in adult asthma patients.8,9

At present, inhaled corticosteroids are the most effective drugs for treatment of asthma and BHR,10,11 acting presumably through a suppressive effect on airway inflammation.2,3,12 Short-term treatment with inhaled steroids resulted in decreased severity of EIB in asthmatic children.13 Conflicting results have been published regarding dose-response effects of inhaled steroids on EIB14,15 as well as on bronchial responsiveness to methacholine.15,16 Similar reductions in the degree of histamine- and exercise-induced bronchoconstriction were achieved during short-term treatment with inhaled steroids in adult asthma patients.17 In asthmatic children, however, an ongoing improvement in bronchial hyperresponsiveness to histamine was reported, using maintenance treatment with inhaled steroids over a 22-month period,18 whereas maximal inhibition of EIB reached a plateau within 2 months of therapy.19 These data suggest that the effects of inhaled steroids against bronchial responsiveness to directly acting pharmacological and physiological stimuli are time- and dose-dependent, the difference in response to treatment reflecting differences in the underlying pathophysiology of asthma.

To test this hypothesis, we simultaneously investigated within the same study population of asthmatic children the time- and dose-dependent effects of fluticasone propionate (FP) 100 µg bid and 250 µg bid in reducing EIB and bronchial hyperresponsiveness to methacholine during 24 weeks of treatment, using a placebo-controlled parallel group study design. To evaluate a potential role of sECP in monitoring treatment efficacy20 the association between the changes in EIB and concomitant changes in serum eosinophil cationic protein (sECP), were also investigated.

METHODS

Patients

Thirty-seven children (23 male, 14 female) with a mean age of 10.3 years and clinically diagnosed as having asthma1 participated in the study. Their baseline FEV₁ was >70% of predicted values (Table 1);21 all children showed a >20% fall in FEV₁ from baseline after a standardized screening exercise test. They were clinically stable, i.e., had no history of viral infections during the two weeks before screening, and no hospital admissions or use of oral steroids during the 4 weeks before entry into the study. Thirty-two children were atopic to at least one inhalant allergen, as shown by a positive RAST class >2. Thirteen children had used inhaled steroids previously, but not during the 4 months prior to entry into the study. Five children used sodium cromoglycate or nedocromil as maintenance treatment, which was stopped at least 2 weeks before screening, and no hospital admissions or use of oral steroids during the 4 weeks prior to entry. Six children used sodium cromoglycate or nedocromil as maintenance treatment, which was stopped at the screening visit. Use of intranasal and dermatological steroids, as well as ophthalmological cromones, were allowed, provided dose and frequency were not changed during the study period.

### Table 1.—Baseline Characteristics of Treatment Groups at Entry

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>100 FP</th>
<th>250 FP</th>
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<tbody>
<tr>
<td>Number</td>
<td>12</td>
<td>11</td>
<td>14</td>
</tr>
<tr>
<td>Age (years)</td>
<td>9.8 ± 2.4</td>
<td>9.9 ± 1.6</td>
<td>11.1 ± 2.4</td>
</tr>
<tr>
<td>Duration of asthma</td>
<td>5.2 ± 4.3</td>
<td>5.8 ± 3.6</td>
<td>7.5 ± 3.9</td>
</tr>
<tr>
<td>FEV₁ % predicted</td>
<td>92.1 ± 12.5</td>
<td>96.6 ± 6.9</td>
<td>93.2 ± 13.3</td>
</tr>
<tr>
<td>Reversibility (%)</td>
<td>8.0 (3–23)</td>
<td>7.0 (0–29)</td>
<td>9.0 (3–27)</td>
</tr>
<tr>
<td>EIB: % fall (%)</td>
<td>33.2 ± e^30.53</td>
<td>34.1 ± e^30.37</td>
<td>35.9 e^30.35</td>
</tr>
<tr>
<td>PD20 methacholine</td>
<td>26.4 ± e^21.5</td>
<td>26.6 ± e^21.0</td>
<td>24.7 ± e^21.5</td>
</tr>
<tr>
<td>sECP (µg/L)</td>
<td>12.5 ± e^20.96</td>
<td>17.1 ± e^20.53</td>
<td>17.7 ± e^20.95</td>
</tr>
</tbody>
</table>

1 100 FP, 100 µg fluticasone propionate bid; 250 FP, 250 µg fluticasone propionate bid.
2 Median (range).
3 Geometric mean ± e^SD.
4 Geometric mean ± 2×doubling dose.

### Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>AUC</td>
<td>Area-under-the-curve</td>
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<tr>
<td>BHR</td>
<td>Bronchial hyperresponsiveness</td>
</tr>
<tr>
<td>EIB</td>
<td>Exercise-induced bronchoconstriction</td>
</tr>
<tr>
<td>sECP</td>
<td>Serum eosinophil cationic protein</td>
</tr>
<tr>
<td>%fall</td>
<td>%fall in FEV₁ from baseline</td>
</tr>
<tr>
<td>FEV₁</td>
<td>Forced expiratory volume in 1 second</td>
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<tr>
<td>PEF</td>
<td>Peak expiratory flow</td>
</tr>
<tr>
<td>PD₂₀</td>
<td>Provocative dose causing 20% fall in FEV₁ from baseline</td>
</tr>
<tr>
<td>p.r.n.</td>
<td>As needed</td>
</tr>
</tbody>
</table>
The study was approved by the Medical Ethics Committees of the two participating hospitals, and written informed consent was obtained from all children and their parents.

Study Design

The study had a double-blind, placebo-controlled, 3-arm parallel design with a treatment period of 24 weeks. After a run-in period of 2 weeks using inhaled salbutamol as-needed (p.r.n.) only, the children were randomly allocated into 3 treatment groups to receive either fluticasone propionate 100 $\mu$g bid (100 FP), fluticasone propionate 250 $\mu$g bid (250 FP), or placebo, using a metered-dose inhaler attached to a Volumatic™ spacer. Six weeks after randomization, the placebo group was randomly re-allocated to the 2 active treatment arms for the remaining 18 weeks of the study. The children repeatedly attended the lung function laboratory every 3 to 6 weeks according to protocol (Fig. 1), to perform a standardized exercise challenge test, or a methacholine inhalation challenge test. Exercise and methacholine challenges were separated by no more than 7 days. Venous blood for measurement of sECP was drawn before each exercise provocation, except at screening and 12 weeks after randomization. During the whole study period, asthma symptoms and peak expiratory flow (PEF) measurements and the use of rescue bronchodilator medication (inhaled salbutamol on demand, maximal allowed dose of 200 $\mu$g 8 times a day) were recorded on diary cards.

In addition, at each clinic visit, height, body weight, heart rate, and blood pressure were measured. Furthermore, the patients were asked for adverse events. Treatment compliance was checked after the study without the subjects’ knowledge, by dividing the actual weight loss of the canisters by the expected weight loss.

Lung Function Measurements

Salbutamol was withheld for at least 8 hr before each visit. Spirometric measurements were made using a pneumotachograph (Masterscreen®, Jaeger, Germany), with baseline lung function determined as the highest forced expired volume in 1 sec (FEV1) obtained from three forced expiratory maneuvers. At screening, the postbronchodilator FEV1 was also measured. Thirty minutes after exercise provocation, 800 $\mu$g salbutamol were administered by MDI attached to a Volumatic™ spacer. FEV1 (best of 3) was measured after 20 min, with reversibility expressed as: \( \frac{\text{FEV1}_{\text{postbronchodilator}} - \text{FEV1}_{\text{prechallenge}}}{\text{FEV1}_{\text{prechallenge}}} \times 100\% \).

Exercise Challenge

Challenges were performed only if pre-exercise FEV1 was >70% of predicted values and >80% of a patient’s baseline FEV1 at entry. Exercise testing for measuring severity of EIB was performed using a standardized protocol, previously shown to provide reproducible results. A motor-driven treadmill was used for running (LE 2000, Jaeger, Germany or Tunturi J880, Finland), with heart rate continuously monitored. According to recent recommendations, dry air (relative humidity <10%, obtained from compressed air medical tanks and stored in a Douglas bag), was inhaled by the child during running, using a face mask (Hans-Rudolph) with an inspiratory and expiratory port, and with the nose in a separate compartment. The incline of the treadmill was set at 5–10%, depending on the physical condition of the child. After a 1-min walk at slow pace, the children started running, and the speed of the treadmill was subsequently adjusted to induce a heart rate >90% of the predicted maximum (approximately 210-age) by the third minute of the test. Having reached the target heart rate, the children were coached to run for another 3 min, unless discomfort due to dyspnea made further running impossible. FEV1 was measured in duplicate at 1, 3, 5, 7.5, 10, 15, 20, and 30 min post-exercise, with the best FEV1 at each time point retained for analysis. The severity of EIB was expressed as maximal % fall in FEV1 from baseline (% fall), and as area-under-the-curve (AUC) of the time-response curve (0–30 min).

Methacholine Challenge

Methacholine challenge was performed using a standardised dosimetric technique. A DeVillbiss® nebulizer type 646, connected to a Rosenthal-French dosimeter, was triggered by compressed air at 140 kPa, with the
timing adjustment of the dosimeter set at 0.6 sec. The dosimeter delivered its dose of methacholine during slow inhalation (3–4 sec) from functional residual capacity to total lung capacity. Doubling doses of methacholine bromide in 0.9% saline were inhaled at 5-min intervals (dose range, 3–3200 µg). FEV1 was measured as the response 30 and 90 sec after inhalation, the lowest, technically satisfactory FEV1 used for analysis.25

When FEV1 had fallen by more than 20% from baseline value, the induced bronchoconstriction was reversed by inhalation of 400 µg salbutamol (children aged <8 years) or 800 µg salbutamol (children aged >8 years) MDI, connected to a Volumatic™ spacer. Bronchial responsiveness to methacholine was expressed as PD20 methacholine, which was determined by linear interpolation between two data points on the noncumulative log dose-response curve.27

Measurement of sECP

Before exercise testing, 4 ml of venous blood were drawn, with blood dripping into the glass tube (SST Becton-Dickinson). Thereafter, it was allowed to clot for 60 ± 10 min at room temperature. After centrifugation, serum samples were stored by −20°C until analysis of sECP, according to the manufacturer’s instructions (Pharmacia Upjohn28).

Diary Cards

During the entire study period, absence (−) or presence (+) of symptoms was recorded on the diary cards for both nocturnal and daytime cough, wheeze, and shortness of breath, with symptoms related to exercise recorded for daytime only. Use of rescue salbutamol was noted as well. Peak flow measurements were performed in triplicate without using a bronchodilator after rising in the morning and in the evening.

Analysis

FEV1 and PEF values were expressed as percentage of predicted values (%pred).21 Values of PD20 methacholine were used after logarithmic transformation (base 2). Because the data for % fall, AUC, and sECP were non-Gaussian distributed, (natural) log-transformation was applied before using parametric tests, or, when using the raw data, nonparametric tests were applied. Each of the four different daily symptom scores were divided into yes or no answers, averaged over a 6-week treatment period, and expressed as percentage of symptom-free days. We then performed a logit transformation of the data.

Baseline variables were compared between treatment groups at entry into the study. Deterioration of asthma while using placebo treatment was evaluated by within-group comparison of variables at entry and after 6 weeks of treatment, using the Wilcoxon signed rank sum test. Provided baseline variables did not differ at entry and after 6 weeks of placebo treatment, the data of the placebo group were pooled with the data of the two active treatment groups (Fig. 1). By increasing the number of subjects per treatment group, the power of the study in detecting dose-related differences in effects during active treatment was enhanced.

To compare the efficacy of treatment versus placebo, ANCOVA was used to analyze the data of the first 6 weeks of treatment, with therapy as a between-patient grouping factor, and baseline measurement of the outcome variable as a covariate. Thereafter, dose-related differences in the protective effect of inhaled steroids on exercise- and methacholine-induced bronchoconstriction within each treatment group during these first 6 weeks were evaluated, using an analysis previously described in adults.17 In this analysis, the reduction in % fall in FEV1 following exercise and to a single dose of methacholine was compared before and after treatment. The dose of methacholine was thus chosen for each child to match the % fall after exercise to within 10% fall in FEV1 in that particular child. The differences in effect of inhaled steroids on both stimuli were analyzed non-parametrically, using the Wilcoxon signed rank sum test.

Subsequently, 24 weeks of active treatment were evaluated for dose-response related differences in treatment efficacy during long-term treatment. To that end, a potential difference in efficacy between the two active treatment groups was explored by repeated measures ANOVA. Therapy was again taken as the between-patient grouping factor, and baseline measurement of the outcome variable as a covariate, while time was added as within-patient factor, as well as the interaction effect of time and therapy.

To evaluate a potential role of sECP in monitoring disease severity, the level of sECP at each visit was related to the concomitant degree of EIB, as well as peak flow values and symptoms during the 2 following weeks, using multiple regression analysis.

For all analyses, P > 0.05 was considered statistically significant.

RESULTS

At entry, the three treatment groups did not differ with respect to age, gender distribution, duration of asthma, lung function parameters, level of bronchial responsiveness, and sECP levels (Table 1). These variables did not change significantly during placebo treatment (Table 2), allowing data of the placebo group after reallocation to active treatment to be pooled with baseline data of the active treatment groups. One subject in the placebo group was withdrawn after 12 weeks of treatment because of
noncompliance. In the analysis, this subject was included up to the visit prior to withdrawal.

**Bronchial Responsiveness to Exercise and Methacholine**

Three weeks after starting active treatment, EIB (%fall FEV₁; Fig. 2) was significantly \( P < 0.05 \) reduced when compared to placebo treatment; the geometric mean % fall in FEV₁ decreased from 34.1 (%) to 9.9 (%) on 100 FP, and from 35.9 (%) to 7.6 (%) on 250 FP (Table 2). Reductions in the AUC of similar magnitude were observed (Table 2). These improvements in EIB were sustained throughout the 24 weeks of treatment, the protective effect of the two doses of FP not differing significantly (Fig. 2).

Bronchial responsiveness to methacholine lessened during the first 6 weeks as compared to placebo for both 100 FP \( P = 0.035 \), and 250 FP \( P = 0.0037 \) treatment groups (Table 2; Fig. 3). PD\(_{20}\) methacholine progressively improved over time in both treatment limbs \( P = 0.04 \), with a mean increase of 1.6 dose steps for children using 100 \( \mu \)g FP bid, and a mean increase of 3.3 dose steps for children using 250 \( \mu \)g FP bid after 24 weeks of treatment, the difference in PD\(_{20}\) methacholine approaching significance at that time point \( P = 0.06 \).

Within-group analysis of the effects of steroids on the two different challenges was performed. At baseline in the 100 FP group, the median %fall in FEV₁ to methacholine was 33.1%, and the median %fall in FEV₁ to exercise was 32.0%. In the 250 FP group, these values were 40.3% (methacholine) and 37.0% (exercise), respectively. For children using 100 \( \mu \)g FP bid, the median changes in %fall in FEV₁ to methacholine and 22% (exercise), after 6 weeks of treatment (Fig. 4A), the difference in effect being statistically significant \( P = 0.04 \). Median changes in %fall in FEV₁ for the group using 250 \( \mu \)g FP bid were 17.2% (methacholine) and \( 9.7 \times 10^{-2} \text{ mg} \).
Lung Function and Symptoms

Treatment with 250 µg FP twice daily significantly improved FEV₁ %predicted values (Table 2) in the first 3 weeks of therapy as compared to placebo (mean change: +7.8 % points; \( P = 0.0031 \)), while the change in FEV₁ %predicted in the 100 µg bid FP group just failed to reach significance (mean improvement: +4.9 % points; \( P = 0.06 \)). This difference in effectiveness between the two doses was sustained throughout the treatment period (\( P = 0.046 \)).

The level of inflammatory mediators as measured by sECP in the blood did not change significantly during treatment (Fig. 5). At randomization, the level of sECP (log-transformed) correlated well with the severity of EIB (%fall in FEV₁; \( r = 0.64, P < 0.0001 \); AUC: \( r = -0.63, P < 0.0001 \)). Once treatment had started, a correlation was no longer evident.

When evaluating the data on the diary cards, it appeared that significantly more days and nights were without wheeze when using active treatment compared to placebo (\( P < 0.05 \)). No effect of fluticasone propionate was found on symptoms scores of cough, shortness of breath, and exercise-related symptoms. Peak flow values as recorded on the diary cards did not change significantly over time during active or placebo treatment. Neither were the levels of sECP related to peak flow values or symptoms score.

Adverse Effects

During the treatment period, no clinically significant abnormalities in heart rate and blood pressure were observed. Most adverse events were related to respiratory infections, or contacts with allergen. No candidiasis or hoarseness of the throat was reported by the children.

DISCUSSION

We have shown that the two doses of fluticasone propionate (200 µg daily and 500 µg daily) were equally effective in producing early and sustained protection against EIB in childhood asthma. In contrast, the reduction of bronchial hyperresponsiveness to methacholine was dose-dependent, with a progressive improvement over the 6-month treatment period. Within-group comparison showed the lower dose of fluticasone (100 µg bid) to be significantly better in reducing EIB as compared to a matched level of methacholine-induced bronchoconstriction. In contrast, the higher dose (250 µg bid) was equally effective in reducing the responses to either challenge. This suggests that steroids protect against pharmacological and physiological acting bronchoconstrictor stimuli by different mechanisms.29 We speculate that the steroid-induced decrease in EIB is likely due to a rapidly achieved reduction in cellular activity, whereas the time-related improvement in PD₂₀ methacholine might predominantly be due to relatively slow resolution of airway remodeling.

To the best of our knowledge, this study is the first to describe the time- and dose-dependency of the protective effects of inhaled steroids against pharmacological and physiological bronchoconstrictor stimuli within the same study population. Our results confirm and extend previous observations from studies in asthmatic children 18 and adults 16,30 on lessening the bronchial responsiveness to...
directly acting pharmacological stimuli during long-term treatment. The fast reduction in EIB, followed by a sustained time-independent protection, is in agreement with earlier studies.\(^\text{13,19}\) The absence of a dose-dependent effect, however, is contrary to observations with budesonide during short-term treatment.\(^\text{16}\)

When comparing our results to those previously reported, a number of methodological points need to be addressed. Firstly, study populations may differ in terms of severity of asthma. This is illustrated by two studies that reported dose-response effects of budesonide on EIB in childhood asthma. A dose-dependent reduction in EIB was observed in children with severe asthma,\(^\text{14}\) but not in those with mild asthma.\(^\text{15}\) Our study population included children diagnosed with mild to moderate asthma and a mean exercise-induced \%fall in FEV\(_1\) from baseline of approximately 35%. Secondly, different outcome variables used to assess the effect of steroid treatment may account for variability of results, as illustrated by a faster improvement in \%fall in FEV\(_1\) after exercise compared to the observed improvement in \(\text{PE}_{25-75}\) in one study.\(^\text{13}\) Thirdly, when comparing dose-effects of inhaled steroids, the inhalation device used should be taken into account, because the effect is dependent upon the actual dose deposited in the lungs, and not the dose prescribed.\(^\text{31}\) In addition, different formulations of inhaled steroids may have different effects when used at the same dosage.\(^\text{32}\) Finally, dose-related effects could be masked in clinical trials by the heterogeneity of the response to inhaled steroids in individual asthmatics.\(^\text{33}\)

How should the present findings be interpreted? It is becoming clear that corticosteroids are capable of reducing the numbers of mast cells and eosinophils in the bronchial (sub)mucosa,\(^\text{12,34}\) cells that might be relevant in EIB.\(^\text{8,9}\) Corticosteroids also interfere with cellular protein synthesis, leading to inhibition of pro-inflammatory cytokine and mediator synthesis.\(^\text{10}\) Thus, it can be postulated that inhaled steroids protect against EIB by reducing cell numbers and levels of mediators thought to be important in the pathogenesis of EIB. However, the use of a biomarker in the blood to monitor airway inflammation and disease severity was disappointing in this study. Although a cross-sectional relationship between the severity of EIB and the level of sECP was found before starting steroid therapy, this relationship disappeared during treatment,\(^\text{8}\) rendering sECP less suitable for monitoring disease severity.\(^\text{20}\)

Reduced cell numbers might also be an important feature in protection against methacholine-induced bronchoconstriction, as evidenced by the relationship between the severity of bronchial hyperresponsiveness to methacholine and the numbers of mast cells and eosinophils in the lamina propria in steroid-treated asthmatics.\(^\text{3,34,35}\) It is still unknown how steroid-induced reduction in the number and/or activity of cells could lead to improvement of BHR to methacholine. The beneficial effect is believed to be the result of reductions in mucosal and peribronchial thickness, potentially restoring the forces of interdependence between airway wall and lung parenchyma.\(^\text{36}\) These effects may have a relatively short time-course,\(^\text{37}\) and could also explain the relatively acute effect seen on airway patency. In addition to this acute effect, inhaled steroids have been reported to reduce the thickening of the subepithelial reticular layer in asthma during long-term treatment, showing the potential of reversing long-term fibrosis.\(^\text{12,34,38}\) Thus, the presently observed time-related improvement in \(\text{PD}_{20}\) methacholine is likely to reflect an improvement in airway remodeling associated with chronic asthma.

What is the clinical significance of our findings? Firstly, these data indicate that monitoring exercise- and methacholine-induced bronchoconstriction provides information on different aspects of the pathophysiologic mechanisms involved in asthma.\(^\text{3}\) This is supported by the results from allergen avoidance studies in asthmatic children.\(^\text{39}\) Secondly, in children with mild to moderate asthma, EIB is reduced in most patients within 3 weeks after starting steroid treatment, allowing the children to better engage in daily exercise with their peers. Such behavior not only improves physical fitness, but more importantly may result in improved self-esteem.\(^\text{40}\) Thirdly, low dose steroid therapy may be sufficient for treatment of EIB, a relevant finding in view of the risk of systemic side effects of these drugs.\(^\text{41}\) However, when treatment is aimed at reversing chronic inflammation, as reflected by improvements in \(\text{PD}_{20}\) methacholine, it can be argued that high dose levels of steroids should be used to obtain the maximal effect.\(^\text{10}\) Such a view is supported by the larger improvement in \(\text{PD}_{20}\) methacholine with 500 \(\mu\)g FP daily in our study. Indeed, recent investigations have shown that treatment with inhaled steroids, aimed at attenuating bronchial hyperresponsiveness on top of improving symptoms, leads to more effective control of asthma whilst alleviating chronic airways inflammation.\(^\text{38}\) On the other hand, it cannot be excluded that the improvement in the low-dose steroid group would have equalled this effect with prolonged follow-up. Hence, further studies are needed to investigate the effect of early use of inhaled steroids in children with asthma,\(^\text{41}\) as well as studies evaluating the efficacy of a combination of treatment modalities to circumvent the use of high dose inhaled steroids.

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