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The effect of an inhaled corticosteroid (budesonide) on exercise-induced asthma in children

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ABSTRACT: The effect of long-term treatment with inhaled corticosteroid on exercise-induced asthma (EIA) was studied in 55 children, aged 7–18 yrs (mean 12 yrs). We also compared the time course of stabilization of EIA to that of other indicators of airway responsiveness, such as peak expiratory flow (PEF) variation and the provocation dose of histamine causing a 20% fall in forced expiratory volume in one second (FEV_1).

All children participated in an ongoing multicentre study to compare the effects of long-term treatment either with the β_2-agonist salbutamol (600 $\mu g \cdot day^{-1}$) plus the inhaled corticosteroid budesonide (600 $\mu g \cdot day^{-1}$) (BA+CS), or salbutamol plus placebo (BA+PL), on airway calibre, airway responsiveness and symptoms. After a median follow-up of 22 months, the study design had to be changed, because of the high number of drop-outs on BA+PL. At that time, the treatment regimen of all children who had not withdrawn was changed into BA+CS. At the moment of change, and after 2 and 8 months of treatment, a treadmill exercise test was performed in two centres.

Eighteen of the 22 children (82%) who were treated with BA+PL from the beginning had EIA, compared to 18 of the 33 children (55%) who were treated with BA-CS ($p<0.05$). After 2 and 8 months of treatment with BA+CS in the patients previously on BA+PL this percentage decreased to 59 and 55%, respectively, and was not significantly different between both groups. In the patients previously on BA+PL the mean fall in PEF after exercise decreased from 33 to 16% after 2 months, and to 18% after 8 months. It was unchanged in patients on BA+CS from the beginning, being, respectively, 16, 15, and 15%. The time course of stabilization of EIA (2 months) was shorter than that of PEF variation (8 months) and PD_{20} histamine (20 months).

We conclude that long-term treatment with inhaled corticosteroid reduced the prevalence of EIA by about 33% and the severity by about 50%, and, furthermore, that the various stimuli of airway hyperresponsiveness act through different bronchoconstricting mechanisms.

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Exercise-induced asthma (EIA) is known to occur in 70–80% of children with asthma [1–4]. EIA is defined as a reduction of 10% or more in peak expiratory flow (PEF) or forced expiratory volume in one second (FEV_1) after exercise [5]. The major fall in lung function occurs 5–10 min after exercise, and spontaneous recovery is usually complete within 1–3 h [6].

The mechanism of EIA is not completely understood. The trigger is thought to be respiratory heat loss [7, 8], respiratory water loss [8, 9], or an interaction between the two. [10]. There is growing evidence that cooling or drying induces a change in osmolarity of the airways, which subsequently causes the release of inflammatory mediators and narrowing of the airways [11].

EIA can be prevented in the majority of patients by inhalation of a beta$_2$-agonist or sodium cromoglycate shortly before exercise [12]. Usually the duration of action of these drugs is less than 2 h, and the protective effect is often incomplete [12]. Inhaled corticosteroid has been shown to be ineffective in diminishing EIA when given shortly before exercise [13–15]. Earlier studies on the prolonged treatment of inhaled corticosteroid have failed to find a significant effect [15, 16], while more recent studies have shown a reduction of EIA after 1–8 weeks of treatment [17–20]. However, it is unknown whether EIA further decreased after much longer treatment with inhaled corticosteroid. In our long-term study we have shown that stabilization of airway calibre

occurred at 2–4 months, of peak expiratory flow rate (PEFR) variation at 8 months, and of provocative dose of histamine producing a 20% fall in FEV_1 (PD_{20}) more than 20 months after the beginning of treatment with inhaled corticosteroid plus inhaled $beta_2$-agonist [21].

The aim of this study was to investigate the time course to stabilization of EIA in children who changed regular medication from inhaled $beta_2$-agonist to inhaled corticosteroid and inhaled $beta_2$-agonist. Furthermore, we compared the time course to stabilization of EIA, which is often regarded as an indicator of airway hyperresponsiveness with that of PEF variation and PD_{20} histamine. We also compared the prevalence and severity of EIA in children previously treated with inhaled corticosteroid plus an inhaled $beta_2$-agonist with those who were on an inhaled $beta_2$-agonist only.

Patients

The children, aged 7–18 yrs, were participants in an ongoing, double-blind, randomized, multicentre study, in which the effect of long-term treatment with inhaled bronchodilator (salbutamol, 200 μg *t.i.d.*) plus inhaled corticosteroid (budesonide, 200 μg *t.i.d.*) (BA+CS) was compared to that of long-term bronchodilator treatment plus placebo (BA+PL) on symptoms, airway calibre and airway responsiveness (first treatment period) [21]. Criteria for entering the long-term intervention study were a history of episodic shortness of breath and/or wheeze, a baseline FEV_1 between 55–90% of predicted, and/or a ratio of FEV_1/forced vital capacity (FVC) of 50–75%, as well as airway hyperresponsiveness (AHR), defined as a PD_{20} of ≤150 μg (this being more than two standard deviations below the mean value in healthy children [22]). The children had a positive skin test response or specific immunoglobulin E (IgE) against one or more common allergens.

After a median follow-up time of 22 months (range 10–28 months), the study design had to be changed because of the high number of withdrawals: 26 on BA+PL *versus* three on BA+CS. From that time, treatment of the children (n=87) who were still participants was changed into BA+CS in such a way that both patients and doctors remained unaware of the previous treatment regimen (second treatment period). Fifty five children (45 boys) with moderate asthma participated in the present study, of whom 22 were treated with BA+CS and 33 with BA+CS in the first treatment period.

Informed consent was obtained from both children and parents, and the study was approved by the Medical Ethics Committees of the participating centres.

Methods

The exercise challenge consisted of 6 min of continuous running on an inclined treadmill (10°) with a constant work load adjusted to produce a heart rate of at least 170 beats·min^{-1} [2, 23]. Heart rate was recorded before, during, and immediately after exercise. The children wore a noseclip during exercise. Room temperature and relative humidity were recorded. Individual tests were performed at the same time of day, and the same setting and duration was used for each test. An exercise test was performed as soon as a patient entered the second treatment period, and after 2 and 8 months in the children of 2 centres (n=55). All medication was withheld at least 8 h before exercise testing. During exercise the children were in a clinically stable phase of their asthma.

PEF (best of three readings) was measured with a Wright peak flow meter (Airmed, Harlow, UK) before (=baseline), immediately after, and 3, 5, 7.5, 10, 15, 20 and 30 min after exercise. FEV_1 and FVC were measured according to the recommendations of the European Community for Coal and Steel [24] by water-sealed or dry rolling spirometer, at least one hour after the exercise test, and when post-exercise PEF values came within 5% of the pre-exercise PEF values.

Airway responsiveness was measured by inhalation of histamine diphosphate in increasing dosages to a standardized protocol [21]. Histamine was nebulized with a deVilbiss 646 nebulizer and a Rosenthal-French dosimeter. A total of 20 μl of aerolised solution was delivered to the mouth in four consecutive breaths.

Children kept a diary for 14 consecutive days prior to the exercise test. They were asked to record symptoms of dyspnoea, wheeze and cough daily on a scale from 0 to 3 (0=no symptoms, to 3=severe symptoms). In the same period, they used a mini Wright peak flow meter to record PEF values at home, before taking any medication in the morning (directly after rising), and evening (before the evening meal), as the best of three attempts.

Table 1. – Baseline characteristics of the children at entry into the second treatment period

	BA+PL	BA+CS
n	22	33
Sex M/F	18/4	27/6
Age yrs mean (SD)	12.2 (2.2)	12.3 (1.9)
FEV_1 % pred mean (95% CI)	76.7 (70–83)	85.0 (81–89)*
PEF variation mean (95% CI)	10.6 (7–15)	6.3 (4–8)*
Symptom score median (range)	0.21 (0–1.5)	0.0 (0–1.6)*

BA+PL: inhaled $beta_2$-agonist and placebo; BA+CS: inhaled $beta_2$-agonist and inhaled corticosteroid; FEV_1; forced expiratory volume in one second; PEF: peak expiratory flow; 95% CI: 95% confidence intervals; *: $p<0.05$ BA+PL *versus* BA+CS.

Statistical analysis

The exercise-induced changes in PEF were expressed as percentage fall from baseline ((PEF pre-exercise -lowest recorded PEF post-exercise)/PEF pre-exercise) × 100%) and as the absolute fall (PEF pre-exercise -lowest recorded PEF post-exercise). Diurnal PEF variation was determined on the 14 days prior to the tests from the difference between the daily highest and lowest PEF, and expressed as a percentage of the mean of these two readings (amplitude % mean) [25].

Table 2. – Mean (95% CI) percentage fall in PEF, absolute fall in PEF heart rate and test conditions before and after 2 and 8 months of treatment with BA+CS in children who were treated with BA+PL or BA+CS in the preceding 10 months

	Baseline	After 2 months	After 8 months
Initial BA+PL group (n=22)			
Fall in PEF ≥10% n (%)	18 (82)	13 (59)	12 (55)
Absolute PEF fall $l \cdot min^{-1}$	104 (79–129)	60 (36–84)**	67 (41–92)**
% PEF fall	33 (25–41)	16 (10–23)***	18 (11–24)**
Heart rate before exercise bpm	94 (89–99)	85 (81–90)**	84 (81–87)**
Heart rate after exercise bpm	191 (185–197)	187 (182–192)*	188 (185–191)
Relative humidity %	54 (51–56)	55 (54–57)	57 (54–60)
Temperature °C	22 (21–22)	22 (22–23)	22 (21–22)
Initial BA+CS group (n=33)			
Fall in PEF ≥10% n (%)	18 (55)#	18 (55)	20 (61)
Absolute PEF fall $l \cdot min^{-1}$	56 (41–70)†	52 (36–69)	54 (41–67)
% PEF fall	16 (11–20)†	15 (11–19)	15 (11–19)
Heart rate before exercise bpm	87 (83–91)#	86 (82–91)	85 (81–89)
Heart rate after exercise bpm	186 (182–191)	187 (184–191)	184 (181–187)
Relative humidity %	54 (52–56)	55 (54–57)	61 (59–64)*#
Temperature °C	21 (21–22)	22 (22–23)*	22 (21–22)

*: p<0.05; **: p<0.01; ***: p<0.001; *versus* baseline; #: p<0.05; †: p<0.01; initial BA+CS *versus* initial BA+PL. For abbreviations see legend to table 1.

The relationship between diurnal PEF variation, FEV_1 % pred and symptoms on the severity of EIA was studied using least squares linear regression. The numbers of children with EIA at the three visits were compared with Fisher's exact or Chi-squared test. Student's t-test for paired data was used for comparing group means within groups. Comparison of initial lung function and mean fall in PEF between the two groups was calculated by means of Student's t-test for unpaired data. The 5% level was considered as significant.

Results

Fifty five children (45 boys), mean (SD) age 12.2 (2) yrs, were admitted to the exercise study. Twentytwo had been treated with BA+PL and 33 with BA+CS for at least 10 months in the preceding period. Baseline characteristics of the children at the first exercise test are presented in table 1. FEV_1 % pred, diurnal PEF variation, and symptoms differed significantly between both groups due to treatment with inhaled corticosteroid in the first treatment period. Results of the exercise tests, heart rate (HR), relative humidity and room temperature are shown in table 2.

Eighteen children (82%) who were on BA+PL in the first treatment period and 18 (55%) on BA+CS from the start had EIA, defined as a fall in PEF of at least 10% from baseline (table 2). This difference was significant (p<0.05). After 2 and 8 months of treatment with BA+CS the number of children with EIA did not differ between those who had been on BA+PL and those who had been on BA+CS in the first treatment period. Also, the initial mean fall in PEF was significantly lower in the children who had been treated with BA+CS in the first treatment period in comparison with those who had been treated with BA+PL (p=0.001). This difference had disappeared after 2 months (p=0.67), and 8 months (p=0.53).

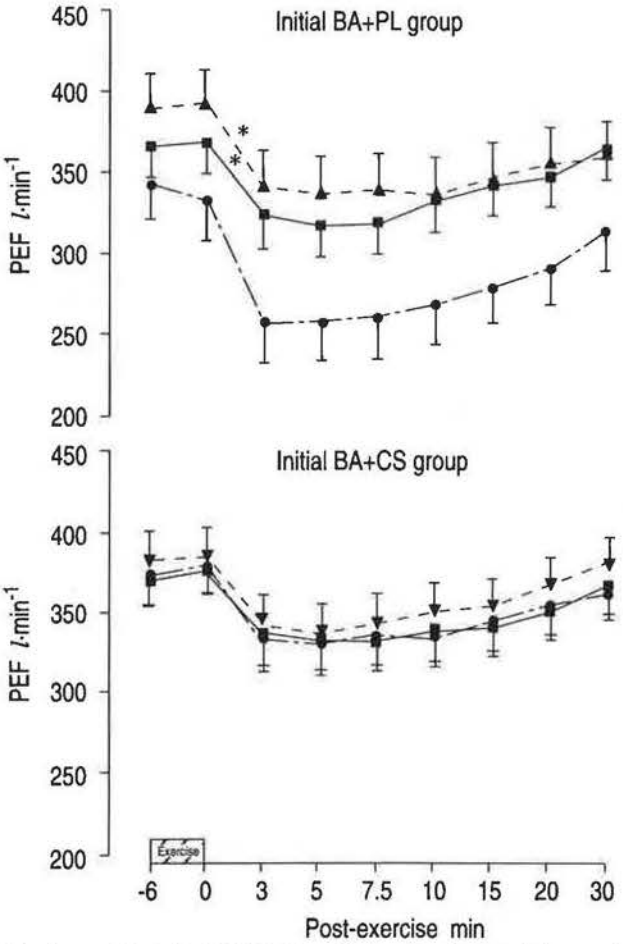

Fig. 1. – Mean (SEM) PEF values during exercise test before and after 2 and 8 months of treatment with BA+CS in children who were on BA+PL or BA+CS in the first treatment period. *: p<0.05 change in fall in PEF after 2 and 8 months *versus* baseline. BA+PL: inhaled $beta_2$-agonist and placebo; BA+CS: inhaled $beta_2$-agonist and inhaled corticosteroid; PEF: peak expiratory flow. ●—●: baseline; ■—■: after 2 months BA+CS; ▼- -▼: after 8 months BA+CS.

In the children who were on BA+PL in the first treatment period, baseline PEF before exercise increased significantly after 2 and 8 months of treatment in the second treatment period (both $p<0.001$) (fig. 1). The small additional increase from 2 to 8 months was also significant ($p<0.01$). The mean absolute and mean percentage fall in PEF after exercise was significantly reduced after 2 and 8 months of treatment with BA+CS compared to the first exercise test (both $p<0.001$) (table 2). The fall in PEF between 2 and 8 months did not differ significantly.

Heart rate before exercise was significantly lower at 2 and 8 months, and heart rate after exercise was significantly lower after 2 months in comparison to the baseline values in the BA+PL group. No differences in heart rate before and after exercise were observed in the BA+CS group.

In patients who were already treated with BA+CS for at least 10 months in the first treatment period, PEF before exercise, mean percentage and absolute fall in PEF did not differ significantly between tests at the start of the second treatment period and after 2 and 8 months of treatment with BA+CS (fig. 1).

There was a weak relationship between the percentage fall in PEF after exercise and FEV_1 % pred ($r=-0.40$; $p=0.002$); a stronger association was found with diurnal PEF variation ($r=0.50$; $p<0.001$). There was no relationship between symptoms and the percentage fall in PEF ($r=0.03$; $p=0.42$).

Discussion

In the present study we found that treatment with inhaled corticosteroid reduced the prevalence and severity of EIA. This improvement could be observed after 2 months, and was maintained at 8 months, indicating that stabilization of EIA occurred within 2 months. However, the majority of children still had EIA despite long-term treatment with inhaled corticosteroid.

The design of this study needs some consideration. The children participated in an ongoing long-term study, in which we compared the effect of treatment with inhaled corticosteroid plus inhaled $beta_2$-agonist to that of an inhaled $beta_2$-agonist alone [21]. Because of the high rate of withdrawals in the children who were on BA+PL in the first treatment period and the clinical and functional improvement of those who were on BA+CS baseline characteristics of both groups differed significantly (table 1). No data exist on the prevalence of EIA in children in whom anti-inflammatory drugs were added to inhaled bronchodilators. In this study, we were able to assess the effect of addition of inhaled corticosteroid to regular inhaled $beta_2$-agonist on the prevalence and severity of EIA, and we could study the time course to stabilization. Controls were patients with minor symptoms and stable airway calibre and PEF variation as a result of treatment with inhaled corticosteroid and inhaled $beta_2$-agonist for at least 10 months [21]. It might be argued that, in our study, the prevalence and severity of EIA is underestimated in the children who were on BA+PL, due to selection bias, since more withdrawals from the long-term study were found among those who had more severe asthma [21]. Nevertheless, the prevalence of EIA was high (82%) in the children who were on BA+PL, and comparable with data from the literature [1–4].

Studies on the prolonged administration (1–8 weeks) of inhaled corticosteroid have yielded conflicting results with respect to EIA; some did find an effect [15, 17–20], whilst others did not [13, 16]. HODGSON *et al.* [15] found that the inhibitory effect on EIA was dose-related; the percentage of children with EIA, as well as the mean fall in PEF after exercise, was lower in those who were treated with the higher dose. HENRIKSEN and DAHL [18] found an additive protective effect of inhaled corticosteroid and inhaled $beta_2$-agonist, and they also showed that adequate protection of inhaled corticosteroid was present after 4 weeks but not after 1 week of treatment. These data indicate that the protective effect of inhaled corticosteroid on EIA depends not only on dose, but also on duration of therapy. Our findings indicate that stabilization of EIA had been achieved within 2 months. We found that the time course to stabilization of EIA differs with that of other indicators of airway responsiveness, such as PEF variation, which stabilized at 8 months [21], and PD_{20} histamine, which stabilized at 20 months of treatment with inhaled corticosteroid [26]. This indicates that the various stimuli of airway hyperresponsiveness act through different bronchoconstricting mechanisms, which is in agreement with other reports [27, 28].

The underlying mechanisms which determine airway responsiveness and the reaction of airways to triggers are complex [29]. Exercise is likely to have its primary point of action at the epithelial level [11], histamine on neural control and smooth muscle [30], and methacholine on smooth muscle [30], whereas PEF variation is the expression of the spontaneous changes in smooth muscle contractility as the result of these interacting factors. This may explain the different modes of action of inhaled corticosteroid on the various indicators of airway responsiveness. Although this study shows that treatment with inhaled corticosteroid nearly halves the severity of EIA, we found that the prevalence of EIA had only reduced from approximately 80 to 55% in asthmatic children treated with a dose of inhaled corticosteroid, which is at the upper limit of the recommended conventional range [31]. Thus, long-term treatment with inhaled corticosteroid gave partial protection against EIA, and EIA appeared to be present in slightly more than 50% of the children.

In summary, we conclude that inhaled corticosteroid reduced the prevalence and severity of EIA, and this effect was achieved within 2 months. Complete protection was not possible in the majority of the children.

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