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Effect of regular inhaled beclomethasone on exercise and methacholine airway responses in school children with recurrent wheeze

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Effect of regular inhaled beclomethasone on exercise and methacholine airway responses in school children with recurrent wheeze. N.J. Freezer, H. Croasdell, I.J.M. Doull, S.T. Holgate. ©ERS Journals Ltd 1995.

ABSTRACT: The role of airway inflammation in the pathogenesis of asthma in childhood is uncertain. In the present study, 27 atopic and nonatopic children aged 7–9 yrs who had ≥5 episodes of wheeze and symptoms of exercise-induced asthma (EIA) in the previous 12 months, performed a methacholine challenge and exercise test on separate days at monthly intervals. The subjects had not received oral or inhaled corticosteroids for 12 months prior to the study. The dose-response relationship to inhaled methacholine was expressed as the cumulative dose provoking a 20% decrease in forced expiratory volume in one second (PD_{20}). Forced expiratory volume in one second (FEV_1) and peak expiratory flow (PEF) were measured prior to the exercise test and at 0, 3, 5, 10, 15 and 20 min following maximal exercise. Following the first methacholine challenge and exercise test, the children were randomized in a double-blind manner to receive inhaled beclomethasone dipropionate (BDP) 200 µg *b.i.d.* or a placebo *b.i.d.* from a Diskhaler® for 3 months.

All children were asymptomatic at the time of testing, and there was no significant change in the baseline FEV_1 of any subject prior to either challenge throughout the study period. When compared to placebo, the bronchial responsiveness to exercise and methacholine was significantly attenuated in the children who had received inhaled BDP for at least 1 month. There was no relationship between the bronchial responsiveness to methacholine and exercise. There was no significant difference in the bronchial responsiveness to either stimulus in the atopic and nonatopic children.

The results of this study suggest that immunoglobulin E (IgE)- and non-IgE-mediated airway inflammation are important in exercise- and methacholine-induced bronchoconstriction in children with recurrent wheeze, although it is probable that different mechanisms are responsible.

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The pathogenesis of asthma is not well understood; however, evidence is accumulating that airway inflammation plays a central role [1]. Inflammation of the airways may increase bronchial responsiveness by lowering the threshold of many stimuli to induce bronchoconstriction. How the inflammatory response translates to airway hyperresponsiveness is a much debated topic; however, geometric factors, such as mucosal swelling [2] and uncoupling of the elastic retractile forces consequent upon inflammatory expansion of airway adventitia [3], are likely to be particularly relevant to the smaller airways of children with asthma.

Many exogenous stimuli may induce bronchoconstriction in asthmatic subjects. Methacholine induces bronchoconstriction by "nonspecific" stimulation of the bronchial smooth muscle in asthmatic and nonasthmatic subjects; whereas, exercise is a "specific" stimulus inducing bronchoconstriction only in asthmatics. The method by which exercise may induce bronchoconstriction is less well understood, however, the weight of evidence is in favour of exercise inducing hypertonicity of the airway lining fluid [1], thereby activating primed mast cells for autocoid secretion and triggering the early asthmatic reaction [4]. The release of short-acting inflammatory mediators may explain the persistence of bronchoconstriction after removal of the initial stimulus; and depletion of mediators has been advanced as one, but not the only, mechanism to explain the refractory period that often follows exercise-induced asthma (EIA) [5]. The stimulation of muscarinic receptors may also be important in the pathogenesis of EIA; however, the "muscarinic effect" varies among subjects and may be variable in the same subject [6]. EGGLESTON [7] reported a correlation between the bronchial responsiveness to exercise and methacholine; however, this has not been confirmed by other authors [8].

Recent bronchoalveolar lavage (BAL) [9] and bronchial biopsy studies [10] in adults have demonstrated a significant reduction in airway inflammation and bronchial reactivity to inhaled methacholine in adults with asthma following regular inhaled corticosteroids. Although BAL and bronchial biopsies have not been performed in children, inhaled corticosteroids have been reported to reduce bronchial responsiveness to inhaled methacholine in children [11–14]. The finding that topical beclomethasone dipropionate (BDP) can deplete the asthmatic airway mucosa of its mast cell content, possibly by inhibiting the production of cytokines from the T-cells [15], may also provide an explanation for the protective effect of this class of drugs against EIA.

The aim of the present prospective double-blind, placebo-controlled study was to determine whether inhaled corticosteroids significantly reduce airway responsiveness to "specific" and "nonspecific" exogenous stimuli in children with recurrent wheeze. The demonstration of significantly reduced bronchial responsiveness to inhaled methacholine and exercise in those receiving topical corticosteroids, would support the hypothesis that airway inflammation is important in the pathogenesis of airway responses to inhaled methacholine and exercise.

Patients and methods

Ninety five general practitioners at five health centres in the Southampton area were approached and permission sought to study the children in their care. The names and addresses of all children aged 7–9 yrs on 1st September 1991 on the practice lists of all participating practitioners were obtained, and a questionnaire was sent to each family for completion by the parents. The questionnaire was simple and enquired about the frequency of respiratory symptoms and treatment. If a reply was not received after 2 weeks, a reminder was sent.

The children were invited to participate in this study if they had ≥5 episodes of wheeze over the previous 12 months and they reported wheeze, cough, chest tightness and shortness of breath after exercise. The respiratory symptoms of each subject were confirmed by an interview with a physician at the time of enrolment. No children had received oral or inhaled corticosteroids over the 12 months prior to the study.

Following enrolment, the atopic status and bronchial responsiveness of each subject to methacholine and exercise was determined. Antihistamines were withheld for 14 days prior to allergen skin-prick testing. $Beta_2$-agonists were withheld for 6 h, sodium cromoglycate for 8 h, and theophylline for 12 h prior to the methacholine challenge or exercise test. The study was approved by the Southampton Joint Ethics Committee and informed consent was obtained from a parent or guardian.

Atopic status

Atopic status was assessed by skin-prick testing for *Dermatophagoides pteronyssinus,* mixed grass pollens and cat dander (Soluprick®, ALK, Denmark), with histamine dihydrochloride used as the positive control. A skin-prick test was considered to be positive if the diameter of induration was ≥3 mm greater than the saline control.

Methacholine challenge

Methacholine challenges were performed using handheld DeVilbiss No. 40 glass jet nebulizers (DeVilbiss Co., PA, USA) according to the method of YAN *et al.* [16]. Doubling doses of methacholine diluted with phosphate buffered saline from 0.025–6.4 µmol were inhaled until the forced expiratory volume in one second (FEV_1) 1 min post-inhalation fell to less than 80% of the post-saline value, or the highest concentration had been reached. If the FEV_1 was close to 80% of the post-saline value, the FEV_1 was repeated 3 min post-inhalation before the next dose was delivered. The dose-response relationship to methacholine was determined and the cumulative concentration proving a 20% decrease in FEV_1 (PD_{20}) was calculated by interpolation or extrapolation. Prior to randomization, bronchial challenges to methacholine were performed on two consecutive days to assess the repeatability of PD_{20} using this protocol.

Exercise testing.

A standardized exercise test [17] was performed on asymptomatic children if their baseline FEV_1 was ≥70% of the predicted value for their height [18]. They were studied at approximately the same time of day using a cycle ergometer (Jaeger ER900, Germany). A noseclip was worn and the children breathed dry air (water content ≤4 $mL \cdot L^{-1}$) at room temperature (20–24°C) from a Douglas bag. The workload was increased from 25 W in 20–25 W increments at 1 min intervals to a maximum of 150 W, depending on the age, sex and physical fitness of the child [19].

Heart rate was monitored with an electrocardiogram (S&W Medico Teknik A/S, Alertslund, Denmark) and oxygen consumption ($V'O_2$) was displayed in real time (Ametek Thermox Instruments Division, Pittsburgh, PA, USA). The test was conducted for at least 5 min and terminated when the child was exhausted, the heart rate was ≥170 $beats \cdot min^{-1}$ and the $V'O_2$ was ≥30 $mL \cdot kg^{-1} \cdot min^{-1}$ for at least 1 min [19]. The workload for each exercise test was determined by monitoring the patients heart rate and oxygen consumption in real time.

A dry wedge spirometer (Vitalograph®, Buckingham, UK) and a paediatric Wright peak flow meter were used to measure the FEV_1 before exercise and at 0, 3, 5, 10, 15 and 20 min following exercise. At each time-point, the highest of two FEV_1 values within 100 mL of each other was recorded. The repeatability of the post-exercise fall in FEV_1 was assessed prior to randomization.

Study protocol

Following the first exercise test and methacholine challenge, the subjects were randomized into groups of four

in a double-blind manner, to receive inhaled beclomethasone dipropionate (BDP) 200 µg *b.i.d.* or placebo *b.i.d. via* a dry powder delivery device (Diskhaler®). Following randomization, three further exercise tests and methacholine challenges were performed at monthly intervals on separate days. Compliance with the study medication was assessed by counting the returned used BDP and placebo Diskhaler® disks. Because of the known marked carry-over effect of corticosteroids in asthma, the study was conducted as a parallel group, rather than as a cross-over design.

Statistical analysis

Statistical analyses were performed using Minitab and SPSS-X statistical software. Analysis of variance was used to compare the fall in FEV_1 and peak expiratory flow (PEF) post-exercise and the log PC_{20} values of the methacholine challenge of the steroid and placebo groups. Student's t-test was used to compare the baseline FEV_1 and PEF of each subject prior to each exercise test or methacholine challenge. The null hypothesis was rejected if the value of p was less than 0.05. The repeatability of the post-exercise fall in FEV_1 and PD_{20} methacholine was assessed prior to randomization. The coefficient of repeatability for FEV_1 was calculated using the method of BLAND and ALTMAN [20], and the repeatability of PD_{20} methacholine was calculated using the method of CHINN [21].

Results

Of the 5,727 questionnaires distributed 4,830 (84%) were returned. One hundred and forty one children had not received corticosteroids and had ≥5 episodes of wheeze in the previous 12 months. Thirty five of these children also reported cough, wheeze, chest tightness and shortness of breath following exercise. Of the 31 children who were enrolled, 27 children completed the study (22 males and 5 females). Four were withdrawn at parental request following the first exercise test.

Table 1. – Demographic and pulmonary function data prerandomization

Variable		BDP	Placebo
Pts n		14	13
Sex M/F		13/1	9/4
Age months		99±11	101±10
Atopic n		6	9
Baseline FEV_1	L	1.59±0.33	1.57±0.31
	% pred	95	95
Baseline PEF	$L \cdot min^{-1}$	253.0±33.9	252.5±37.3
	% pred	97	97
Log PD_{20} methacholine		1.98±1.5	1.50±1.7
Max fall in FEV_1 post-exercise	%	7.7±6.8	6.5±9.1

Values are presented as mean±SD. Pts: patients; FEV_1: forced expiratory volume in one second; % pred: percentage of predicted value; PEF: peak expiratory flow; PD_{20}: dose provoking a 20% decrease in FEV_1; BDP: beclomethasone dipropionate. p>0.05 (NS) for all variables.

Table 2. – Other asthma medications

Asthma medication	Pts n Total	(BDP/placebo)
β_2-agonist, *p.r.n.*	16	(7/9)
β_2-agonist, regularly	4	(3/1)
Sodium cromoglycate	3	(2/1)
Theophylline	1	(0/1)

Note: a patient may be taking more than one medication. Pts: patients; BDP: beclomethasone dipropionate.

Fourteen children received inhaled BDP and 13 received placebo. The mean compliance with the study medication of the group receiving BDP was 86%. The subjects in the corticosteroid and placebo groups were well-matched for demographic data and indices of pulmonary function (table 1). Four children received other regular asthma medications and 16 children used inhaled salbutamol as required for the relief of asthma symptoms (table 2). These medications were not withheld during the study.

Bronchial hyperresponsiveness

Methacholine. For each subject, the baseline FEV_1 did not change significantly prior to each methacholine challenge. Prior to randomization, 21 subjects exhibited bronchial responsiveness to inhaled methacholine. Twelve of these children subsequently received BDP and nine received placebo. There was no significant difference in the mean PD_{20} of the two groups (p=0.5), or the incidence of atopy. The 95% confidence interval for the measurement of PD_{20} was two doubling dilutions.

The methacholine-induced bronchial responsiveness was significantly reduced in the group who received BDP for at least 4 weeks (p<0.05). This effect was maintained whilst the subjects were receiving the study medication (fig. 1).

Exercise. All patients achieved the criteria for maximal exercise during each exercise test, and for each subject,

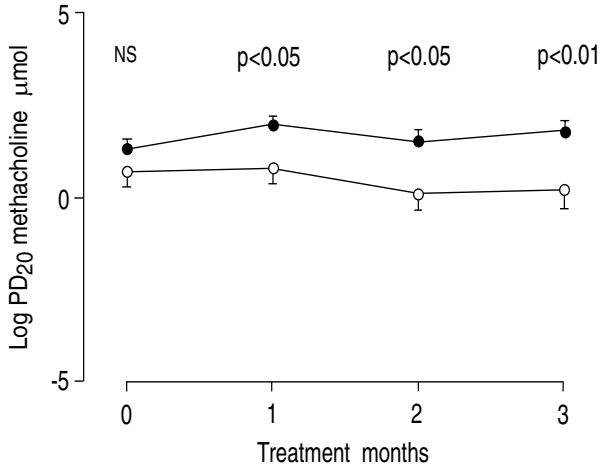

Fig. 1. – Cumulative log PD_{20} methacholine (µmol) *vs* duration of treatment. Values are presented as mean±SEM. PD_{20}: dose of methacholine provoking a 20% decrease in forced expiratory volume in one second; NS: nonsignificant. —●—: beclomethasone dipropionate; —○—: placebo.

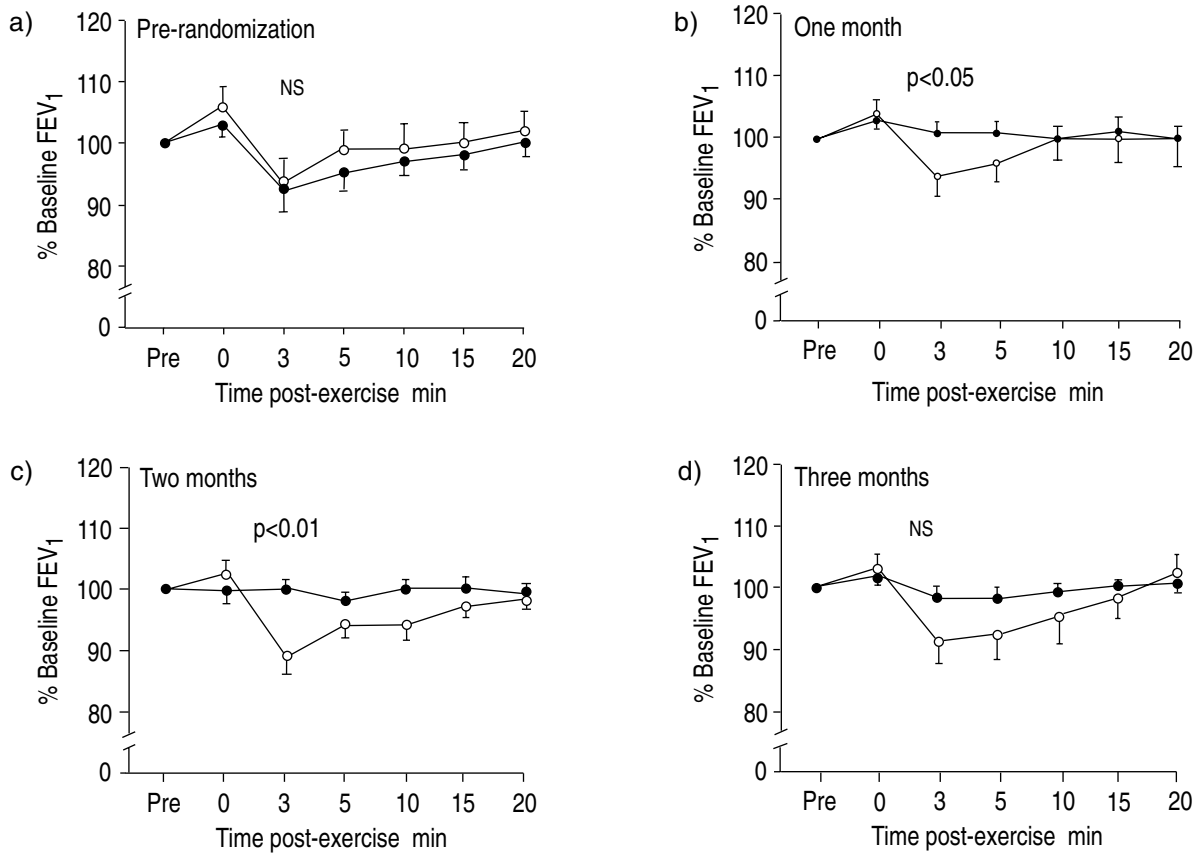

Fig. 2. – Post-exercise FEV1 pre-randomization and following treatment with BDP or placebo. Values are presented as mean±SEM. Note that the vertical axis are cut of from zero. FEV1: forced expiratory volume in one second; BDP: beclomethasone dipropionate; NS: nonsignificant. —●—: BDP; —○—: placebo.

the baseline FEV1 did not change significantly prior to each exercise test. The maximum fall in FEV1 was observed at 3 min post-exercise, and the coefficient of repeatability for FEV1 was 2.2%. Prior to randomization, no significant difference was found between the post-exercise fall in FEV1 when the corticosteroid and placebo treatment groups were compared (p=0.7) (fig. 2a). When analysed in terms of atopic status, there was no significant difference in the maximum post-exercise fall in FEV1 between the children who were skin test positive and those who were skin test negative (p=0.9). Eight out of 27 children experienced a >10% fall in FEV1 following exercise, five being atopic and three non-atopic (fig. 3).

Inhaled BDP had a marked effect in reducing the exercise-induced fall in pulmonary function. After 1 and 2 months of treatment with inhaled BDP, the maximum post-exercise fall in FEV1 was 0.0±1.7 (SD) and 0.0±1.6%, respectively, compared to 6.0±3.5 and 11.0±3.0% in the placebo group (analysis of variance (ANOVA) p<0.05) (fig. 2b and c). Following 3 months of treatment, a trend in protection against exercise-induced fall in spirometry persisted; however, it was no longer significantly different from the placebo group (p=0.09) (fig. 2d). Similar results were obtained using PEF as the measure of lung function.

No significant relationship could be established between the cumulative PD20 methacholine and the maximum fall in FEV1 post-exercise (r=-0.2; p=0.40) (fig. 3). The 3 children who were most responsive to methacholine (PD20 <0.1 µmol) had a ≤5% fall in FEV1 post-exercise.

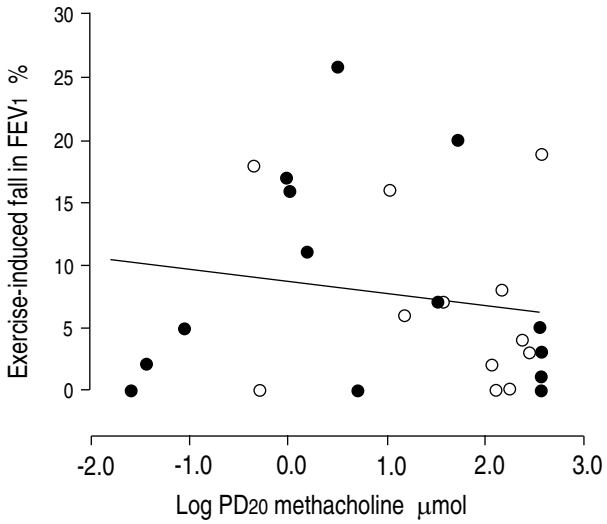

Fig. 3. – Individual patient data for post-exercise maximal fall in FEV1 *vs* log cumulative PD20 methacholine (µmol) in atopic and nonatopic subjects, at run-in into the study. For abbreviations see legends to figures 1 and 2. ●: atopic; ○: nonatopic

Discussion

The diagnosis of asthma in children is based on a clinical history and physical examination, and is not dependent on the demonstration of bronchial hyperreactivity to an inhaled exogenous agent or exercise test. The selection of the subjects for the present study was deliberately based on a history of recurrent wheeze (including wheeze following exercise) and not the PD_{20} methacholine or the degree of bronchoconstriction following a standardized exercise test. Most studies on asthma in childhood have been conducted on subjects selected from hospital clinics with severe disease, and, therefore, the results of this study may not be directly comparable.

As the diagnosis of asthma may be underestimated [22, 23] we deliberately selected children from the community on the basis of a positive response to a respiratory questionnaire, without making the prior assumption of a diagnosis of asthma. Although all of the children enrolled in this study had clinical asthma, only one third of those who entered the treatment phase had been diagnosed with asthma, further emphasising the under diagnosis and, therefore, undertreatment of asthma, originally highlighted by LEE *et al.* [22]. In order not to confound the interpretation of the therapeutic intervention, symptomatic children who had received oral or inhaled corticosteroids were deliberately excluded from the study.

In asthmatics, the attenuation of bronchial responsiveness to exogenous stimuli with the use of inhaled corticosteroids has been reported previously [11–14, 24–27]. These authors conclude that airway inflammation may be important in the pathogenesis of the increased bronchial responsiveness characteristic of asthma. The results of the present study confirm that regular inhaled corticosteroids attenuate methacholine- and exercise-induced bronchoconstriction in children with recurrent wheeze, supporting the hypothesis that airway inflammation may be important in the pathogenesis of bronchoconstriction in these children.

Although all of the children in the present study had symptoms consistent with exercise-induced bronchoconstriction, only 30% had unequivocal exercise-induced bronchoconstriction, with a fall in FEV_1 greater than 10% following maximal exercise. Despite the mild nature of EIA in many of the subjects, regular inhaled corticosteroids significantly attenuated exercise-induced bronchoconstriction. The effect of regular inhaled corticosteroids on exercise-induced bronchoconstriction appeared to be fully manifested after 1 month of treatment; however, the effect appeared to diminish after 3 months.

In the same subjects, BDP had a sustained inhibitory effect on methacholine-induced bronchial responsiveness. This suggests that a mild degree of tolerance may have developed when exercise was the stimulus used to provoke bronchoconstriction, and further long-term studies are required to establish whether tolerance to inhaled corticosteroids may occur. The discrepancy in the attenuation of bronchoconstriction following methacholine- and exercise-induced bronchoconstriction is unlikely to be due to lack of compliance with the study medication, as each subject performed both challenge tests, and a careful check of the number of empty BDP Diskhaler® blisters returned at each assessment showed no decrease in patient compliance. The possibility of a type 2 error cannot be excluded.

Of particular interest was the absence of any correlation between methacholine- and exercise-induced bronchial responsiveness. Indeed, the three children with the most responsive airways to inhaled methacholine (PD_{20} <0.1 µmol), had ≤5% falls in FEV_1 following exercise (fig. 3). Whilst in related populations of subjects with asthma, usually acquired from hospital clinics, methacholine and exercise have been positively correlated [7], a recent study on more representative symptomatic children [8] failed to confirm the association, suggesting that methacholine- and exercise-induced bronchoconstriction reflect independent components of the disordered airway function in asthma.

It has also been implied that most asthma (including exercise-induced asthma) in childhood is associated with atopy [28, 29]. In the present study, the response to exercise and inhaled methacholine did not differ in the atopic and nonatopic subjects (fig. 3), suggesting that bronchoconstriction in children with recurrent wheeze may occur in the absence of atopy.

In conclusion, the present study suggests that airway inflammation is important in the airway response to exercise and inhaled methacholine in children with recurrent wheeze. The marked efficacy of regular BDP in preventing bronchoconstriction induced by exercise and methacholine in children is an important clinical observation and has direct relevance to the recently published guidelines for the management of childhood asthma [23], where a strong emphasis is placed on preventative anti-inflammatory therapy. Whether children with relatively mild episodic disease should be treated with regular topical corticosteroids is a debatable issue in relation to compliance and systemic side-effects, but it would appear from this study that symptomatic school children who experience significant exercise-induced bronchoconstriction could benefit greatly from this form of treatment, thereby diminishing their need for the repeated use of symptom relieving bronchodilators.

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