

Exercise-induced asthma in children: a marker of airway inflammation

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EXERCISE-INDUCED ASTHMA (EIA) is the term used to describe the transient reduction in lung function that occurs after vigorous exercise.¹ A reduction in FEV₁ of 13.2% or more after exercise is diagnostic of EIA.² A prevalence of EIA of between 19.3% and 23.4% has been reported in Australian schoolchildren.^{3,4} While severity of EIA was found to be associated with the number of wheeze attacks per year, 40% of children identified with EIA had not been diagnosed with asthma by a doctor.³

Exercise is the most common stimulus for inducing an attack in asthmatic children. Recognition of EIA is important, because full participation in sporting activities is a goal in the management of childhood asthma.

Failure to recognise EIA

EIA is not predicted by risk factors, including positive answers to items about asthma in questionnaires,⁵ nor is it excluded by failure to report symptoms. In a child with undiagnosed EIA, the enquiry that has the most potential to elicit a positive response and thus identify EIA is "Do you feel *more* breathless/wheezy/symptomatic five to ten minutes *after* you stop exercise than *during* exercise."

There are many reasons why EIA is not recognised. Firstly, it occurs most commonly after exercise, so it may not limit performance unless the child has moderate to severe asthma. Secondly, children may fail to notice the symptoms of EIA until they take part in organised or competitive sport. Thirdly, 50% of children become refractory to the bronchoconstricting effects of exercise when exercise is repeated within an hour or warm-up occurs before exercise. This refractoriness means that the association of exercise and "asthma" symptoms does not occur on all occasions when exercise is performed.

EIA as a marker of airway inflammation: the role of steroids

Most children with well-controlled asthma do not need medication before exercise.⁶ Thus, taking 400 µg of budesonide for 4 weeks reduced the severity of EIA to such an extent that less than 10% of the standard dose of terbutaline was required for complete prevention of EIA.

ABSTRACT

What we know

- Exercise-induced asthma (EIA) occurs in up to 23% of schoolchildren.
- In 40% of children with demonstrable EIA, no clinical diagnosis of asthma has been made.
- Children with asthma and EIA have eosinophils in their sputum, consistent with active asthma.
- EIA is well controlled in 50%–65% of children with moderate to severe asthma, so that only a minority will need prophylactic therapy immediately before exercise.
- β₂-Agonists are not the most suitable therapy for preventing EIA if they need to be used on a daily basis.
- The severity of EIA appears to be an indirect index of the severity of airway inflammation.

What we need to know

- Do non-symptomatic children with EIA require treatment for asthma?
- Does failure to identify and treat children unaware of their airways narrowing after exercise lead to airflow limitation in the long term, particularly in the small airways?
- Can exercise, or surrogate tests used to identify EIA, also be used to assess children with asthma?
- What is the minimum dose of steroid required to inhibit EIA, as high doses of steroids may be inappropriate in children?
- What is the best prophylactic treatment for EIA in children whose asthma is otherwise well controlled by inhaled steroids?
- What is the best prophylactic treatment for EIA in children with frequent episodic asthma or mild persistent asthma?
- Are leukotriene antagonists alone better than β₂-agonists alone in preventing EIA throughout the day?
- How many children taking long-acting β₂-agonists twice daily, either alone or in combination with an inhaled steroid, experience breakthrough EIA during school and require rescue medication?

MJA 2002; 177: S61-S63

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In a recent study of 57 children with asthma and mild EIA (25% fall in forced expiratory volume in one second [FEV₁] after exercise) and a normal FEV₁ % predicted, low doses of budesonide for 12 weeks significantly reduced the severity of EIA (Box 1).⁷ A study in children with moderate EIA (34% fall in FEV₁ after exercise) showed that treatment with 100 µg or 250 µg of fluticasone for three weeks was equally

effective in reducing severity of EIA.⁸ In a study of 19 children with severe EIA (55% fall in FEV₁ after exercise), 100 µg budesonide daily for four weeks stabilised symptoms and peak flow variability, but EIA still occurred at this low dose.⁹ In this double-blind crossover study, in which each child received the active medication in a random sequence for four weeks, the severity of the EIA diminished with increasing doses of budesonide. Thus, the mean percentage fall in FEV₁ was 55.4% after placebo, 25.7% after 100 µg/day, 20.1% after 200 µg/day, and 9.9% after 400 µg/day.⁹

These studies clearly show that children with normal spirometry can still have EIA,⁷ and that lack of symptoms or variability of peak expiratory flow at rest does not reflect control of the airways in response to exercise.⁹ Furthermore, these studies support the long-held impression that EIA is one of the last problems to disappear after treatment with steroids, and that it is likely to indicate that the inflammation of asthma is active.

The role of inflammatory cells

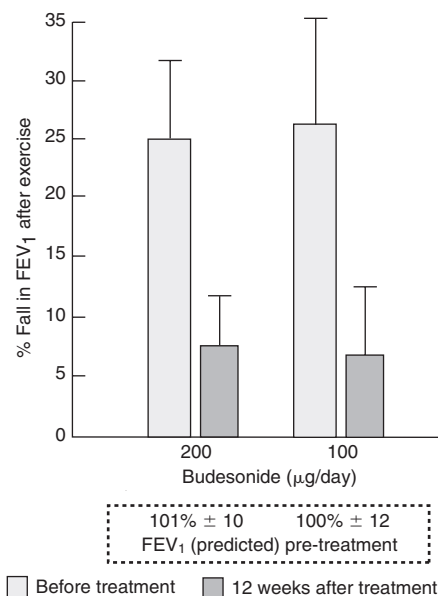
Eosinophils are one of the major inflammatory cells present in asthma, and studies show that there are more eosinophils in the sputum of children with asthma and EIA compared with children with asthma without EIA (Box 2).¹⁰ Furthermore, a recent study reported an acute increase in the proportion of eosinophils in sputum in asthma patients with EIA, but not in those without EIA.¹¹

The inflammatory cells most likely to be important in EIA are mast cells and eosinophils. The mediators potentially released by these cells include histamine, leukotrienes and prostaglandins. EIA is most commonly associated with positive skin tests and raised IgE levels.

Medications, mediators and EIA

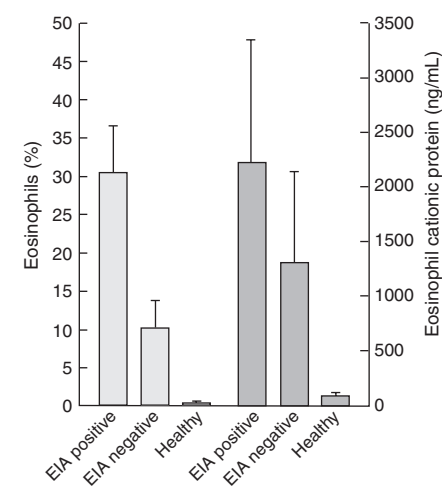
Histamine antagonists modify the severity of EIA in children, but the effect is small compared with the protective effects of a β₂-agonist, sodium cromoglycate, and nedocromil sodium. Daily use of long-acting β₂-

1: The role of steroids in exercise-induced asthma



The mean (SD) fall in forced expiratory volume in one second (FEV₁), expressed as a percentage of the pre-exercise value, after six minutes of running on a treadmill, before and 12 weeks after treatment with one dose daily of budesonide. There were 14 different children with exercise-induced asthma in each treatment group. The FEV₁ measured before the start of treatment showed good lung function. (From Jonasson G, Carlsen KH, Hultquist C.⁷ Reproduced with permission from Blackwell Publishing.)

2: Increase in eosinophils in sputum of children with exercise-induced asthma (EIA)



Proportion of eosinophils in induced sputum and eosinophil cationic protein content of sputum from 21 children with asthma with and without EIA (defined as > 20% fall in FEV₁ after six minutes of running exercise), and nine healthy subjects. (Redrawn from Yoshikawa T, Shoji S, Fujii T, et al.¹⁰)

agonists in the management of EIA in children has recently been questioned,¹² and reversal of a provoked attack of asthma, such as EIA, is slower when short-acting β₂-agonists are used daily.¹³ Therefore, we need to know about alternative treatments for EIA.

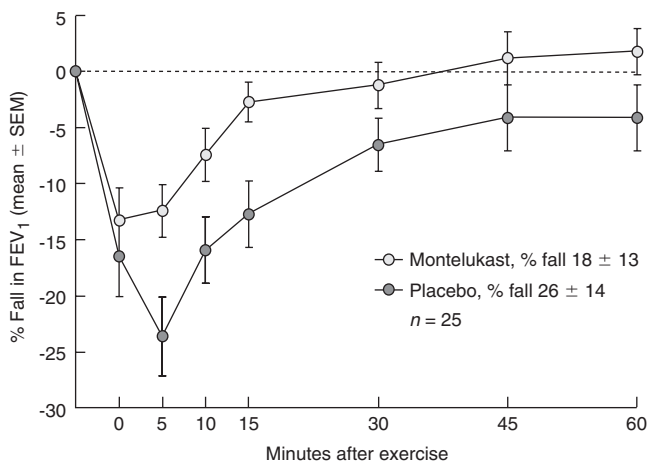
Leukotrienes are important in sustaining the airway response to exercise,¹⁴ and leukotriene antagonists have been shown to be effective in reducing EIA. For example, although immediately after exercise FEV₁ fell somewhat, the time to return to pre-exercise FEV₁ was significantly shorter in children taking the leukotriene antagonist montelukast compared with those taking placebo (Box 3).¹⁴ Leukotriene antagonists have the advantage of being administered as tablets and are effective in protecting against EIA in children when given once daily,¹⁴ or even as a single dose. The duration of their protective effect is maintained with daily use, and this gives them an advantage over the long-acting β₂-agonists¹⁵ and other less expensive medications used to prevent EIA.

Leukotrienes are generated by eosinophils as well as mast cells, and are more potent in causing the human airways to narrow than histamine. Thus, a thousandth of the dose of leukotriene is required to induce the same degree of airway narrowing as histamine. This potency difference may be important in understanding why some children with significant EIA are not hyperresponsive to inhaled histamine.⁵ Leukotrienes are released from eosinophils in response to an increase in osmolarity and could feasibly cause transient migration of eosinophils to the airways. While treatment with inhaled steroids decreases eosinophil number, steroids do not prevent the contractile effects of leukotrienes. Thus, EIA may still occur if there are sufficient cells left containing this potent mediator.

Towards a new definition of EIA

The importance of EIA as a marker of airway inflammation and active asthma may be better appreciated if EIA is described as follows:

3: Effect of leukotriene antagonists in reducing exercise-induced asthma



The mean (SEM) fall in forced expiratory volume in one second (FEV₁) in 27 children, expressed as a percentage of the pre-exercise value after six minutes running on a treadmill. In this double-blind crossover trial, placebo or 5 mg montelukast was taken in the two evenings before the challenge. (From Kemp JP, Dockhorn RJ, Shapiro GG, et al.¹⁴ Reproduced with permission from Mosby Inc.)

Exercise-induced asthma (EIA) reflects active inflammation of the airways, and is usually associated with atopy and sputum eosinophilia. EIA is modified or prevented by long-term treatment with inhaled steroids. EIA is characterised by variable severity over time and in response to treatment. Intensity and duration of exercise, and the water content and temperature of the air, determine the potential for EIA. EIA reverses spontaneously, but it reverses more rapidly after inhalation of a β_2 -agonist. Airway smooth-muscle contraction in response to the osmotic release of mediators is the likely cause of EIA. The severity and duration of EIA is markedly reduced by premedication with drugs that prevent

the release of, or block the action of, these mediators. EIA is commonly associated with chest tightness, shortness of breath, wheeze and cough 5–10 min after exercise, but it can also occur in the absence of symptoms.

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