

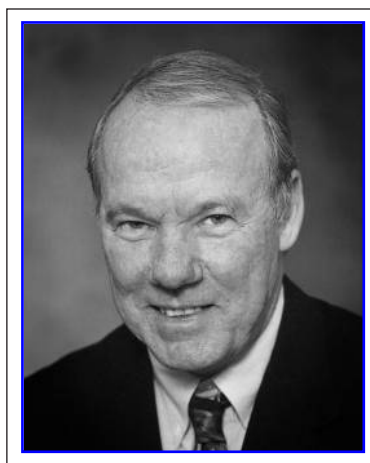
Pharmacotherapy Update

What Is New in the Prevention of Exercise-Induced Bronchospasm (EIB) in Children?

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EXERCISE-INDUCED BRONCHOSPASM (EIB) is common in children with asthma, and exercise limitation is a primary complaint in children with mild to moderate asthma.^{1,2} The exact prevalence of EIB in children with asthma is unknown but has been reported to occur in 50%–90% of patients with asthma. Some have argued that it is universal provided a sufficient intensity and duration of exercise is provided. Much of the disparity may also be a result of lack

of a consistent definition of what constitutes EIB.² The National Asthma Education and Prevention Program Expert Panel Report 3 (EPR-3) states that a 15% drop in forced expiratory volume in one second (FEV₁) following exercise establishes the diagnosis. However, a recent report of a working group of the American Academy of Allergy, Asthma & Immunology stated that a drop in FEV₁ of only 10% with accompanying symptoms would make the diagnosis. This difference has been further exacerbated by the U.S. Food and Drug Administration's (FDA's) requiring that patients have at least a 20% drop in FEV₁ following a standard exercise test prior to enrollment in studies to determine the efficacy of various therapies in EIB.³⁻⁵

Although EIB has a discrete pathophysiology which remains poorly understood, it is clear that it is associated with the increased ventilatory rate associated with exercise.² The cooling and drying of the airway epithelium have both been proposed as the primary event that then results in the release of pro-inflammatory mediators, including substances that can induce bronchospasm. In patients with mild intermittent asthma, EIB may be the only asthma symptom for some patients; however, in many it results from an overall lack of asthma control and increased bronchial responsiveness.^{1,2} In support of the latter, studies have shown that baseline values of fraction of exhaled nitric oxide (FeNO) correlate with the severity of EIB in children.^{6,7} In addition, the cysteinyl leukotrienes (Cys-LTs: LTC₄, LTD₄, and LTE₄) have been detected in exhaled breath condensate (EBC) in children with persistent asthma⁸⁻¹⁰ and have been reported to be higher in those with EIB.¹¹ As a result, the degree of EIB can be modified by the environment in which the exercise is performed and can be improved with the use of chronic anti-inflammatories.^{2,12-15} Thus, improving overall asthma control should be considered for patients with frequent complaints of EIB and who are not elite athletes.^{1,2}

Currently recommended prophylactic therapy for EIB is inhalation of a short-acting β_2 agonist 10 to 15 minutes prior to exercise known to induce bronchospasm.¹ An advantage of this strategy is that if the EIB is not completely prevented, the patient can use the bronchodilator again to reverse the residual bronchospasm. Other agents also have FDA-approved labeling for prevention of EIB in children. These include cromolyn down to 5 years, the long-acting inhaled β_2 agonists, salmeterol down to 4 years, and formoterol down to 5 years. In addition, ipratropium bromide and nedocromil have shown activity in EIB. In April 2007, montelukast gained FDA-approved labeling as a single dose for prevention of EIB in patients 15 years of age and older. Each of these alternative agents has disadvantages that make them less desirable than the short-acting inhaled β_2 agonists.

Both mast cell stabilizers are effective in the prophylaxis of EIB when administered within 15 to 30 minutes prior to exercise.¹⁶ A large meta-analysis by the Cochrane Library reported that they completely protect (defined as an FEV₁ decrease less than 15%) 66% to 73% of patients but are less effective than inhaled β_2 agonists.¹⁶ However, they are not effective for reversing EIB once it occurs. Salmeterol and formoterol inhibit EIB for up to between 8 to 12 hours after a single dose; however, after chronic therapy the duration of protection is only about 4 hours due to tolerance.^{1,2} Frequent use of long-acting inhaled β_2 agonists as monotherapy is now discouraged due to concerns of increased life-threatening exacerbations.¹ Although regular administration of any β_2 agonists will induce tolerance, administration of short-acting β_2 agonists prior to exercise will still produce complete protection in the vast majority of patients. Inman and O'Byrne reported that the mean exercise-induced drop in FEV₁ after two inhalations of albuterol was 5% following chronic albuterol use compared to 2% following chronic placebo use.¹⁷

Leukotriene receptor antagonists attenuate but rarely completely protect against EIB. Chronic treatment with montelukast reduces EIB by 20%–50%; however, up to 50% of patients may not respond.¹⁸⁻²⁰ Comparisons of montelukast and salmeterol on EIB have been performed; however, the exercise challenges were completed 12 hours after the last dose of montelukast or salmeterol.^{18,21} As expected, after 3 days of therapy the two drugs provide similar protection, but then at 4 to 8 weeks of chronic therapy, the salmeterol is less effective than montelukast for attenuation of the EIB due to the tolerance that shortens the duration of action.^{21,22} A recent study in children compared montelukast alone with budesonide alone, budesonide plus formoterol, and budesonide plus montelukast each for 4 weeks on EIB in children 6 to 18 years.²² Challenges were performed prior to therapy and at the end of 4 weeks. Both the budesonide and budesonide plus formoterol groups attenuated EIB similarly, and the montelukast and montelukast plus budesonide groups produced similar attenuation that was numerically greater than the non-montelukast groups but not statistically significant. The authors suggested that montelukast produced superior efficacy for EIB in children compared to inhaled corticosteroid or combination formoterol and inhaled corticosteroid. However, they provided no indication as to when the last dose of formoterol was administered in relation to the exercise challenge. Patients were on a mix of long-term controllers prior to run-in to the study that were stopped for 4 weeks. Patients unable to control asthma just on as-needed albuterol were excluded. The effect of inhaled corticosteroid was significantly less than that reported in other studies.¹²⁻¹⁴ The dose of budesonide 200 μ g/day was less than that used in a crossover study comparing budesonide

PHARMACOTHERAPY UPDATE

400 $\mu\text{g/day}$ to montelukast in patients down to 8 years old.²³ In this study budesonide was superior to montelukast for reducing EIB. The disparity may be due to dosage, as there appears to be a dose-response for inhaled corticosteroids reducing EIB.¹² The montelukast effect was similar to that seen in other studies in children.^{19,24} It is unclear why there was no effect of formoterol, unless the challenges were performed 4 or more hours since the last dose, in which case no effect would be anticipated.

The recent approval of montelukast for acute protection against EIB in children 15 and older and adults is interesting. It is based upon studies showing attenuation of EIB at 2 hours following a single dose of montelukast.^{4,5} Although numerically greater attenuation was seen at 12 and 24 hours post dose, the differences were not significant. These studies also reported a significantly greater protection against EIB for montelukast compared to placebo. However, they used a maximum fall of $\leq 20\%$ in FEV_1 to show 83% and 96% protection, but 69% and 50% of patients receiving placebo also were protected using that criteria.^{4,5} These results call into question the use of a $>20\%$ fall as a clinical meaningful cut point, if over 50% of patients appear to respond to placebo. In the study by Pearlman and colleagues using a 15% drop in FEV_1 as cut point, the numbers protected were 35% for placebo and 69% for montelukast, and using a 10% drop were 20% for placebo and 47% for montelukast.⁵ These latter values emphasize that the leukotriene receptor antagonists generally attenuate but do not completely protect against EIB except in about 50% of patients.

The onset and the duration of effect on EIB after one dose of montelukast has been evaluated in children.²⁴ Children 7 to 13 years old performed an exercise challenge 2, 12, and 24 hours after a single dose of montelukast. Montelukast produced a significant protection against EIB compared to placebo only at 12 hours post dose, percent fall in FEV_1 (9.78 ± 1.85 vs. 18.69 ± 2.83 , respectively). A significant difference was seen in the percentage of patients on montelukast (50%) compared to placebo (31%) with EIB protection defined as $<15\%$ fall in maximum FEV_1 only at 12 hours post dose. These results again suggest more attenuation than complete protection. More recently montelukast was compared to standard therapy of 2 inhalations of albuterol in a crossover study in children 7 to 17 years of age.²⁵ Using 15% drop in FEV_1 as the endpoint, 100% of the patients receiving albuterol and 55% of patients receiving montelukast were protected. In this study patients continued to use albuterol as needed so that any tolerance to albuterol would not be washed out and the exercise challenge was performed at 12 hours post montelukast dose, the time of maximum effect.

In conclusion, the short-acting inhaled β_2 agonists continue to be the preferred and most effective therapy for the prevention of EIB in children. The mast cell stabilizers, leukotriene receptor antagonists, and anticholinergics are significantly less effective. The long-acting inhaled β_2 agonists should not be used, although they are as effective as the short-acting β_2 agonists, because with regular use their duration is not much more than that of short-acting β_2 agonists. Despite recent labeling approval of montelukast for prevention of EIB, it appears to only protect about 50% of patients and primarily moderates the degree of bronchospasm. Studies of chronic inhaled corticosteroid suggest that they produce similar to better control of EIB than leukotriene receptor antagonists.

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PHARMACOTHERAPY UPDATE

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