

Treatment of Exercise-Induced Bronchoconstriction

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KEYWORDS

• Exercise • Asthma • Treatment • EIB

KEY POINTS

- Exercise-induced bronchoconstriction (EIB) frequently occurs in youngsters and young adults with asthma.
- Prevention of EIB is possible, either pharmacologically or nonpharmacologically.
- Some treatment modalities are best suited for infrequent EIB.
- Some treatment modalities are best suited for frequent EIB.
- Preventive treatment can be supplemented with short-acting reliever therapy when EIB occurs during exercise.
- Daily use of inhaled corticosteroid (ICS) should be initiated when control of EIB cannot be achieved with nonpharmacologic interventions and reliever therapy alone.
- Although low doses of ICS may have a modest effect on reducing EIB, higher doses are usually very effective in reducing severity of EIB.
- High-intensity warm-up is recommended.

INTRODUCTION

Treatment of exercise-induced bronchoconstriction (EIB) is currently based on the same principles as for asthma treatment in general, that is, a bronchodilating component and an antiinflammatory component. An important challenge in relation to EIB is that adjustment of treatment is based on the frequency of symptoms at rest. According to the Global Initiative for Asthma (GINA) guidelines,¹ those with daily symptoms have moderate persistent asthma and should be treated with inhaled corticosteroids (ICS).² Moreover, asthma patients should be able to perform unlimited activity. Currently, there is no entirely clear consensus in international guidelines on how to grade the severity of asthma in persons who complain of frequent asthma during exercise, but have few symptoms at rest. Furthermore, in asthma patients who report

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EIB-related symptoms, the frequency of symptoms may simply reflect the frequency of physical exercise. Active youngsters and young adults with asthma can experience EIB daily, for example, during sports activities or when cycling as a means of transport. These activities could lead to use of beta₂-agonist on a daily basis.³ The problem is that frequent use of a beta₂-agonist is a sign of partly controlled disease, which should logically lead to introduction of ICS treatment. However, tolerance may occur if ICS is prescribed in combination with a long-acting beta₂-agonist (LABA) on a daily basis.^{4,5} This tolerance manifests itself as a reduction in the duration of the protective effect of a beta₂-agonist against EIB and slower recovery of lung function in response to further treatment with a bronchodilator if relief is required after exercise or in an emergency.

EIB is an acute event with transient narrowing of the airways occurring during and particularly after exercise.⁶ The symptoms of EIB range from a slight feeling of chest tightness with a small reduction in lung function to severe bronchospasm and a large reduction in FEV₁ after exercise. Documenting EIB with a reduction in FEV₁ of at least 10% from the pre-exercise values is considered to be specific for asthma, but exercise itself is not a sensitive means of diagnosing asthma.^{7,8} Individuals with asthma who develop EIB generally report symptoms such as cough, wheeze, chest tightness, dyspnoea, and fatigue.⁶ These symptoms are also frequent in healthy individuals particularly while running, in nonasthmatic elite athletes, individuals who are not physically fit, and sometimes in those with extrathoracic disorders such as vocal cord dysfunction.⁹

EIB is most often a sign of eosinophilic airway inflammation and poor asthma control.¹⁰ The high ventilation required during intense exercise leads to airway narrowing because of the osmotic and thermal consequences of evaporative water loss from the airway surface.¹¹ The dehydration of the airway surface provides a favorable environment for release of mediators that cause airway smooth muscle contraction with or without edema.^{6,12,13} In a minority of individuals, primarily elite athletes, EIB can also develop without underlying eosinophilic airway inflammation⁴ and, in this group, probably reflects a different pathogenesis.^{5,14}

Another issue is the different inflammation associated with EIB.¹⁵ In most asthma patients the inflammation is due to eosinophils, whereas in elite athletes the inflammation may be due to neutrophils and macrophages.^{16–18} In the study in asthmatics by Duong and colleagues,¹⁹ a close association was found between number of sputum eosinophils and fall in FEV₁ after exercise when testing general asthma patients (Fig. 1). The relative contribution of these different types of inflammation or the precise mechanism for eosinophils in the development of EIB is currently unclear. For example, it is not known if some cases of EIB would benefit from medications targeting inflammatory pathways other than the classical type II pathway.

TREATMENT OF EIB

Short-acting beta₂-agonists (SABAs) or LABAs are established as preventive or acute treatment of EIB. For frequent respiratory symptoms, however, bronchodilator as needed might not be sufficient, necessitating the addition of daily therapy with an ICS. Antileukotrienes and mast cell stabilizing drugs, such as sodium cromoglycate and nedocromil sodium, are used either as a single drug or in combination with other drugs. Lastly, omega-3, vitamins, and other nonpharmacologic interventions such as vitamins are frequently used for EIB by elite athletes.²⁰

Beta₂-agonists

SABAs are the drugs of choice for prophylaxis of EIB and for treatment of bronchoconstriction developed during and after exercise.³ If taken at least 5 minutes before

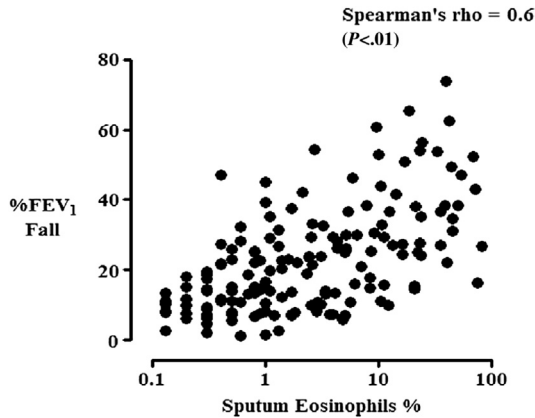


Fig. 1. The severity of EIB expressed as percentage fall in FEV₁ in relation to the percentage of eosinophils in sputum showing an association between sputum cell count and fall in FEV₁ after exercise. All visits were included in analysis. (Data from Duong M, Subbarao P, Adelroth E, et al. Sputum eosinophils and the response of exercise-induced bronchoconstriction to corticosteroid in asthma. *Chest* 2008;133:404–11.)

exercise,²¹ a SABA reduces the post-exercise fall in lung function by 70%.³ In a study by Küpper and colleagues,²² a mean standard deviation (SD) increase in FEV₁ of $5\% \pm 6$ after a SABA and decrease of $31\% \pm 11$ after placebo was documented in response to a standardized exercise challenge in a group of asthmatic patients (**Fig. 2**). These findings indicate that bronchodilator therapy not only prevents development of EIB but also induces an increase in FEV₁ in an asthmatic subject when used immediately before physical activity.

SABAs are frequently used as monotherapy, for prophylaxis and treatment of EIB, because of lack of awareness of asthma severity by both the patient and the doctor.²³ In a recent asthma survey as many as 22% of subjects reported taking a beta₂-agonist only before exercise, even though they were exercising every day.¹⁰ This figure was even higher (38%) in cases with doctor-diagnosed EIB, indicating that a substantial number of asthma patients frequently use a beta₂-agonist before exercise. Furthermore, 19% and 47% used a beta₂-agonist as rescue therapy during and after exercise, respectively (**Fig. 3**).¹⁰ These percentages indicate a substantial overuse of beta₂-agonist arising from asthma patients using the medication routinely pre-exercise, either from anxiety about an EIB attack to come, or simply because their asthma is undertreated. Daily use of a SABA usually indicates poor asthma control and warrants reassessment of asthma treatment.

The onset of action depends on the beta₂-agonist chosen: the onset of action of formoterol, an LABA is as rapid as that of a SABA, whereas salmeterol, another LABA, has a slower onset of action than salbutamol/albuterol.²⁴ However, the total period of protection is similar for both formoterol and salmeterol. In the study by Richter and colleagues,²⁵ equipotent doses of formoterol, salmeterol, and terbutaline prevented EIB with a comparable effect, even though the time to the maximal bronchodilating effect was different.

DEVELOPMENT OF TOLERANCE

Regular use of SABAs may lead to development of tolerance to their therapeutic effects. Tolerance to the bronchodilator effects of a beta₂-agonist develops rapidly after

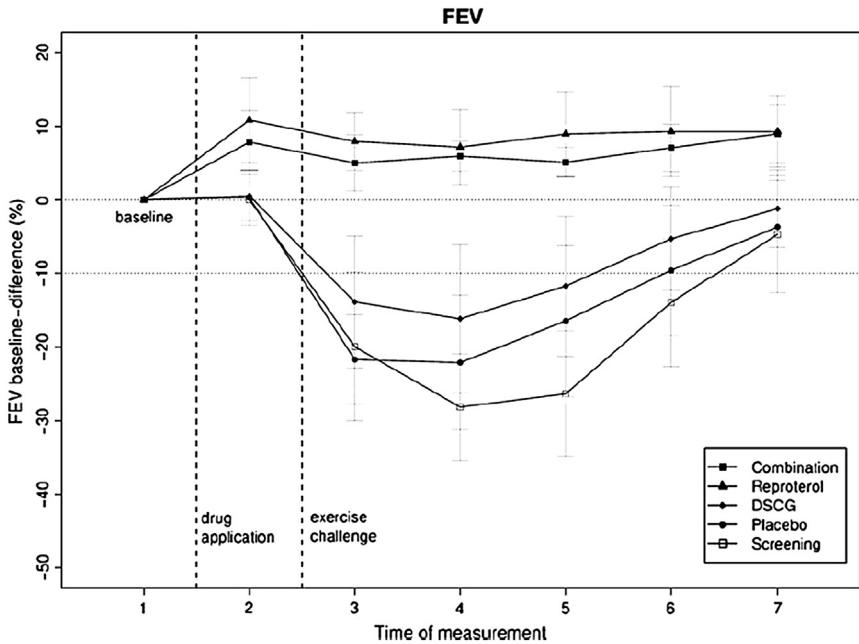


Fig. 2. Mean values (SD) for FEV₁ values for all subjects after sodium cromoglycate, after beta₂-agonist, and after both drugs were taken together. The figure illustrates a significantly better effect of beta₂-agonist compared with cromoglycate, but no additional effect when both drugs are taken together. (*Reproduced from Kupper T, Goebbels K, Kennes LN, et al. Cromoglycate, reproterol, or both-what's best for exercise-induced asthma? Sleep Breath 2012;16:1229–35.*)

only a few doses, and tolerance to the protective effect occurs irrespective of concomitant use with ICS. The former is of importance in respect of treatment of acute asthma, whereas the latter may lead to inability to prevent EIB.^{26–29} Several studies have shown development of tolerance after regular use of LABA, demonstrated by a reduction in the duration of the protective effect against EIB over time.^{30–33} Haney and Hancox²⁹ demonstrated that after 8 days of treatment with formoterol the effect of a SABA was reduced when given after an acute attack of bronchoconstriction, and the area under the salbutamol FEV₁ response curve was significantly reduced from 205 ± 63 SD %·time to 107 ± 53 SD $P < .001$ following treatment (**Fig. 4**).²⁹ These findings are supported by a study by Elers J and colleagues,²⁷ who showed a reduction in response of FEV₁ to beta₂-agonist of 0.5 L in absolute values compared with the response before LABA treatment. However, beta₂-agonist-induced tolerance is not found by all researchers,^{34–36} although this could be due to study design. The decrease in duration of protection by a beta₂-agonist^{30–33} might result in increased use of beta₂-agonist and a higher risk of side effects, such as tremor and palpitations, which are dose related, and maybe drug specific. LABA should never be used as monotherapy in asthma because of the potential risk of increased morbidity and mortality during an exacerbation,³⁷ although not shown by all.^{38,39}

There is very little clinical evidence that use of a SABA leads to failure to respond to emergency asthma treatment,^{26,40,41} whereas in the case of acute admission higher doses of beta₂-agonists are used.

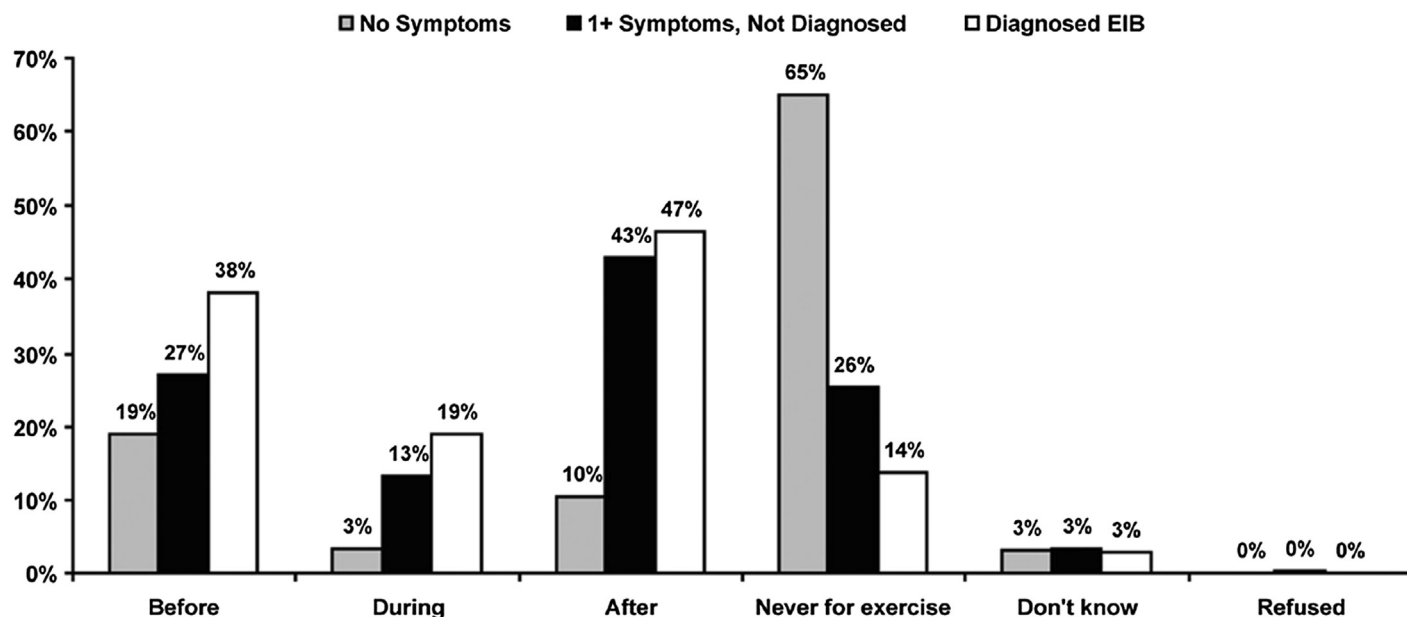


Fig. 3. Rescue medication use while exercising. The association is between the diagnosis of EIB and the use of bronchodilator before, during, or after exercise. Patients who knew that their shortness of breath developed during exercise used SABA more frequently than persons without this knowledge. (Reproduced from Parsons JP, Craig TJ, Stoloff SW, et al. Impact of exercise-related respiratory symptoms in adults with asthma: exercise-induced bronchospasm landmark national survey. *Allergy Asthma Proc* 2011;32:431–7.)

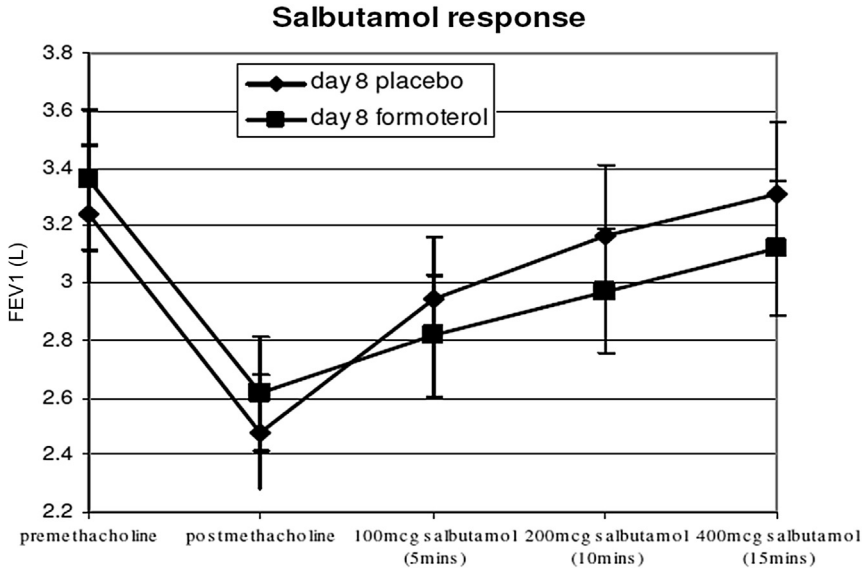


Fig. 4. The mean $\pm$ SE FEV₁ Liters (y axis) in response to salbutamol following a methacholine challenge. A reduced response to salbutamol was found after treatment with formoterol after 8 days. (*Reproduced from Haney S, Hancox RJ. Tolerance to bronchodilation during treatment with long-acting beta-agonists, a randomised controlled trial. Respir Res 2005;6:107.*)

Inhaled Corticosteroids

ICS are the most effective inhaled antiinflammatory therapy available. ICS reduce asthma symptoms, improve lung function, decrease airway inflammation, reduce airway hyperresponsiveness (AHR) and the number and severity of exacerbations, thereby improving quality of life and reducing asthma mortality.^{42,43} According to international guidelines, daily use of ICS should be initiated when asthma control cannot be achieved with nonpharmacologic interventions and reliever therapy alone. Although the beneficial effect of a single dose of ICS on EIB has been found,^{44,45} the effect increases over 7 to 14 days, and the maximum effect can be expected after at least 8 weeks of therapy. Most guidelines suggest use of low-dose ICS. Although this approach may be adequate to treat asthma patients without EIB, it is likely to be inadequate for those with frequent EIB. Subbarao and colleagues⁴⁶ showed a dose-response effect of ciclesonide, (40, 80, 160, and 320 μ g daily) ICS as well as a period (1 week and 3 weeks) effect of treatment on EIB (**Fig. 5**). The maximum fall in FEV₁ changed from 30%, 21%, 16% to 13%, respectively, after 3 weeks on 320 μ g daily of ciclesonide therapy. These findings suggest that, in those with persistent EIB, stepping up the ICS dose might be preferable to adding another type of anti-asthma treatment; this is in contrast to the GINA guideline, which recommends add-on therapy with inhaled LABAs to ICS for asthma that is uncontrolled when treated with ICS alone.

In a review from 2005, data showed that the combination therapy of fluticasone and salmeterol is superior to fluticasone alone in preventing EIB.^{47,48} Another study showed better asthma control with reduced symptoms when the disease was treated with budesonide and formoterol in combination compared with budesonide alone.⁴⁹ These findings suggest that combination therapy is a safe strategy for treating asthma,

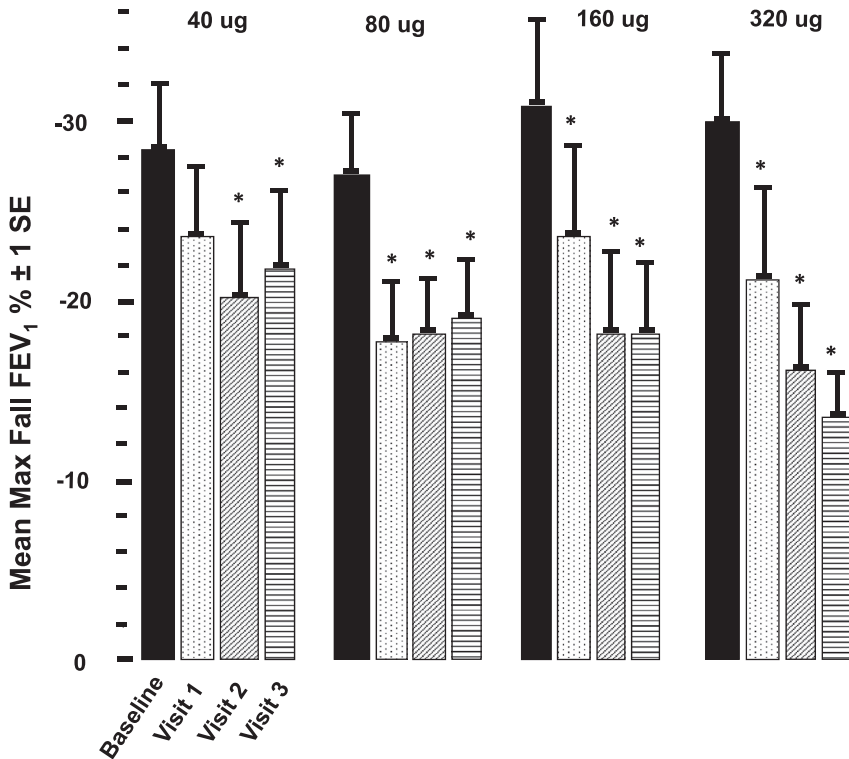


Fig. 5. Effect of increasing doses of inhaled steroid on the percentage fall in FEV₁ after exercise at baseline and at Visit 1 after 1 week, at Visit 2 after 2 weeks, and at Visit 3 after 3 weeks treatment with ciclesonide given by inhalation once daily in the evening. The higher doses of ICS – the lower fall in FEV₁ after exercise. (*Reproduced from Subbarao P, Duong M, Adelroth E, et al. Effect of ciclesonide dose and duration of therapy on exercise-induced bronchoconstriction in patients with asthma. J Allergy Clin Immunol 2006;117:1008–13.*)

but a problem being that the doses of ICS used might be too low to be effective in preventing EIB in all subjects.

Young adults with EIB, who do recreational sports of less than 10 hours per week, may have classic eosinophilic asthma and accordingly have good sensitivity to treatment with ICS. These asthma patients should, in accordance with the guidelines, be treated with daily doses of ICS either alone or in combination with LABA or an antileukotriene, although the use of ICS does not prevent the development of tolerance to beta₂-agonists.^{31,50} In the study by Duong and colleagues,¹⁹ it was shown that although low dose (400 and 800 µg daily) of ICS reduced severity EIB, it did not do so increasingly over time. This reduction in EIB severity at a low dose was independent of the cellular content of sputum being eosinophilic or neutrophilic (**Fig. 6**, left hand panel). However, when treating with the higher doses of ICS (160 or 320 µg daily) (see **Fig. 6**, right hand panel), a significant and continuous reduction was observed in the percentage fall in FEV₁ after exercise. These findings were even more pronounced in those with sputum eosinophilia compared with those with sputum neutrophilia, with a mean improvement in fall in FEV₁ of 24% versus 14%, $P < .01$. These findings suggest that stepping up the dose of ICS rather than adding on a LABA will lead to better control of EIB, and tolerance does not develop to ICS as it does to a

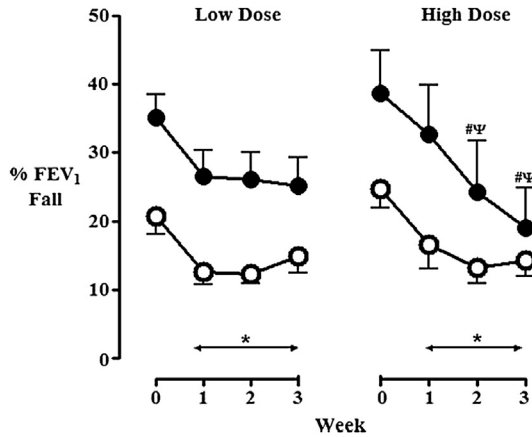


Fig. 6. Exercise response to low-dose and high-dose ciclesonide therapy according to base-line sputum eosinophil count. The data are presented as the mean $\pm$ SE noneosinophilic group (open circles), eosinophilic group (closed circles). The group of patients with eosinophilic asthma achieved a better effect with ICS on their EIB. (Reproduced from Duong M, Subbarao P, Adelroth E, et al. Sputum eosinophils and the response of exercise-induced bronchoconstriction to corticosteroid in asthma. *Chest* 2008;133:404–11.)

LABA. These findings are important for the clinicians, who seek objective measurements in clinical settings, to ensure that otherwise well-treated asthma patients can exercise without EIB.

Elite athletes and young adults who are training daily at the subelite level may have a different inflammatory phenotype.⁵¹ In elite athletes, the airway inflammation may not be of the eosinophilic type and ICS may be less effective, as has been found in skiers.⁵² In the daily clinical setting, both sports-active patients and elite athletes need treatment with ICS. The dose of ICS should be titrated so that exercise is possible without symptoms of asthma and without EIB; this may involve up or down titration of steroid dose with down titration being performed in accordance with response to an asthma challenge test, and not symptoms alone.^{19,52} Down titration of ICS following high doses of ICS is an issue by itself, and very few, if any, have reported findings in this area of interest.⁵² One way to assess asthma control in elite athletes could be by measuring AHR to indirect stimuli and adjusting doses until AHR is obliterated entirely.

Antileukotrienes

Antileukotrienes have antiinflammatory actions and prevent bronchoconstriction over time⁵³ and include the leukotriene synthesis inhibitors (eg, zileuton) and receptor antagonists (eg, montelukast). They do not have an acute bronchodilator effect and cannot reverse EIB. When compared with albuterol, montelukast was not as effective if taken immediately before exercise.⁵⁴ In addition, montelukast is less effective than low-dose ICS.⁵⁵ In contrast to beta₂-agonists however, daily use of montelukast does not lead to development of tolerance over time (Fig. 7).^{33,56,57}

Antileukotrienes are given orally and are administered once daily for montelukast and twice daily for zileuton.⁵⁸ Although the reduction in the mean overall symptom intensity score was significantly better with zileuton compared with montelukast [-5.0 ± 2.1 (4.6–5.4) vs -4.2 ± 2.3 (3.8–4.7) ($P < .05$)], the same reduction was not observed for the individual symptom scores. Although these findings suggest that

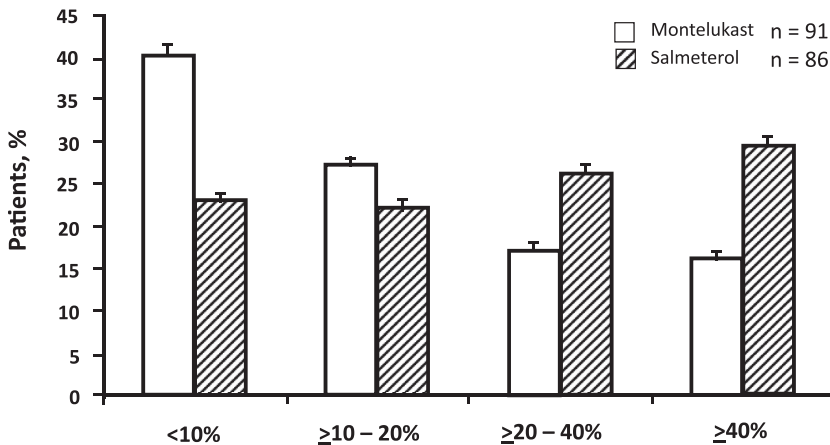


Fig. 7. The percentage fall in FEV₁ after exercise 8 weeks after daily treatment with salmeterol and montelukast. The bronchoprotective effect of montelukast was retained after 8 weeks with the most of the subjects having less than 10% fall in FEV₁ after exercise, whereas the protective effect of salmeterol decreased so that there were fewer subjects who had a less than 10% fall in FEV₁ after exercise and more with a fall greater than 40% compared with montelukast. (*Reproduced from Edelman JM, Turpin JA, Bronsky EA, et al. Oral montelukast compared with inhaled salmeterol to prevent exercise-induced bronchoconstriction. A randomized, double-blind trial. Exercise Study Group. Ann Intern Med 2000;132:97–104.*)

zileuton might be superior, serious side effects have led to removal of the drug from the lists of approved drugs for sport. Montelukast is also used as an add-on therapy when asthma is uncontrolled with medium-dose ICS alone.⁵⁹ Studies have reported a reduced fall in FEV₁ and a reduced period of bronchoconstriction after exercise when treated with montelukast, compared with placebo in asthmatic nonsmokers⁶⁰ as well as asthma patients in general.⁶¹ Montelukast is effective when given as a single dose 2 hours before exercise^{61–63} and would be a satisfactory choice as monotherapy in individuals with EIB who exercise a couple of times per week. However, the effect of montelukast is heterogeneous, being effective in some, and without effect in others.

Mast Cell Stabilizers

The airway narrowing from EIB is thought to be a consequence of the release of inflammatory mediators from the mast cell in response to an increase in osmolarity.^{64,65} The use of mast cell stabilizer treatment, such as nedocromil and cromoglycate, should theoretically have a beneficial effect on EIB. These mast cell stabilizers have been shown to be superior to placebo in pharmaceutical studies.⁶⁶ They also have an excellent safety profile, a dose-related response, which could be useful in EIB but are limited by their short duration of protection. Studies have shown that use of a SABA is superior to nedocromil.⁶⁷ In the study by Küpper and colleagues,²² the effect of cromoglycate was less than that found after use of a beta₂-agonist. The average fall in FEV₁ after placebo was 25% and only 15% after treatment with cromoglycate ($P<.01$), whereas an increase in FEV₁ was found after beta₂-agonist (see **Fig. 2**). No additional effect was found when combining the 2 treatments. Studies have shown a relatively lower protection against EIB when using mast cell stabilizer when compared with ICS, although the reason for this is unclear.⁶⁸ Although these mast

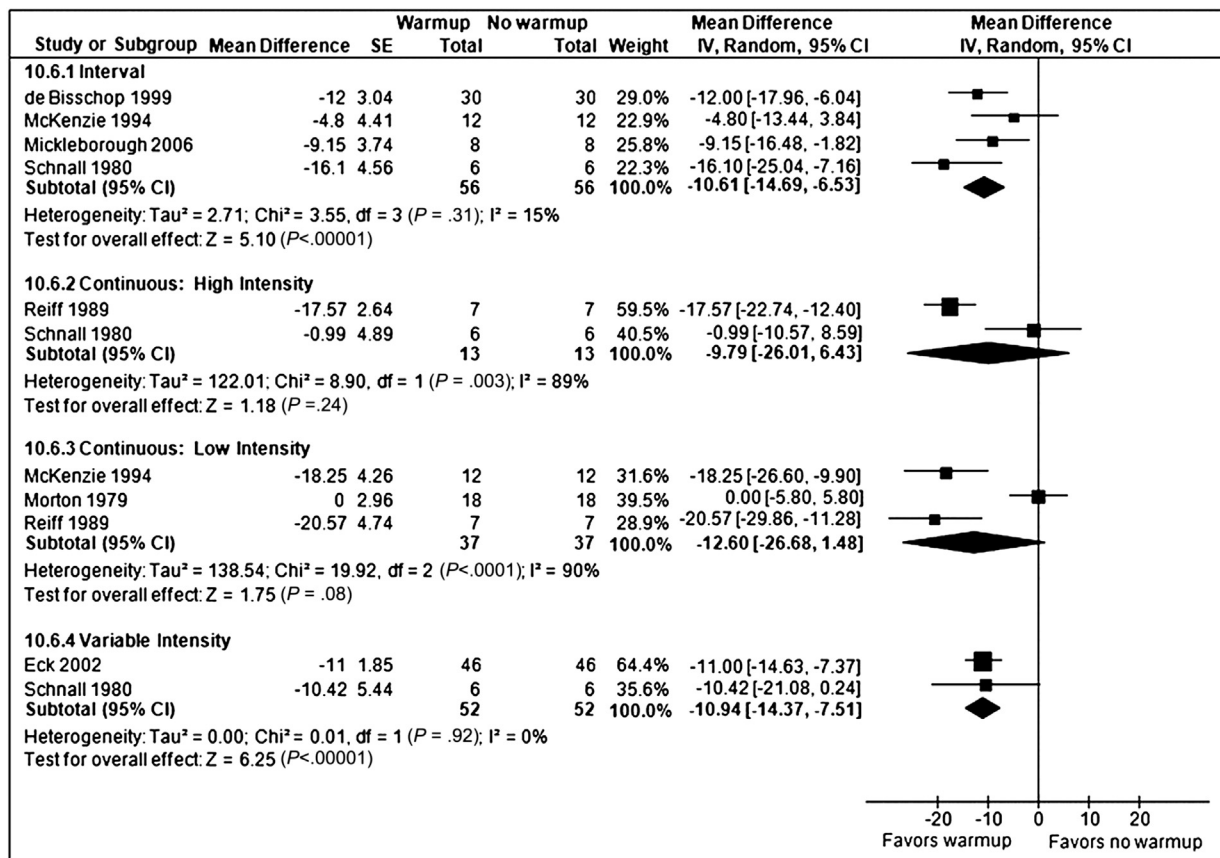


Fig. 8. Warm-up versus no warm-up in pre-exercise treatment of EIB: maximum percentage decrease in FEV_1 or peak expiratory flow rate. A meta-analysis showed a positive effect of warm-up on the development of EIB. (Reproduced from Stickland MK, Rowe BH, Spooner CH, et al. Effect of warm-up exercise on exercise-induced bronchoconstriction. *Med Sci Sports Exerc* 2012;44:383–91.)

cell stabilizers are effective against EIB, they are seldom used nowadays for treatment of asthma in general.

Omega-3, Fish Oil, and Vitamin

Several studies have examined the effect of fish oil in treating mild exercise-induced asthma and especially in some elite athletes in whom it has been shown that the fall in FEV₁ after exercise is reduced after 3 weeks' intake of fish oil capsules.^{69–73} Fish oil is rich in omega-3 fatty acids, which are thought to compete with proinflammatory mediators and cytokines in reducing EIB. Although both montelukast and fish oils have a protective effect on EIB, the combination of the 2 drugs did not have an additive effect,⁶⁹ suggesting that they work through the same pathways.^{74–76} In some patients with signs of exercise-induced asthma, the use of vitamin C might have a significant effect⁷⁴ and more reactivity to exercise was found in children with low levels of vitamin D.⁷⁷ It is not known however whether treatment with vitamin D would decrease the severity of EIB as no intervention studies have been performed.

NONPHARMACOLOGIC THERAPY

There is evidence that physical warm-up reduces EIB in asthmatic athletes. The most consistent and effective attenuation of EIB was observed with high-intensity interval and variable intensity pre-exercise warm-ups.⁷⁸ In a review including a meta-analysis concerning the same issue by the same research group,⁷⁸ these findings were further supported, as shown in **Fig. 8**. In conclusion, it seems likely that any form of pre-exercise warm-up is of significant importance for the reduction of EIB among asthmatic individuals. This is important information as most asthma patients have EIB and might well gain from doing pre-exercise warm-up.

Many winter-sport athletes, especially cross-country skiers, wear breathing filters for protection against cold air; few, if any, controlled studies exist in this area.^{79,80} Other issues of importance might be the number of environmental particles, where a high concentration of small particles is increasingly being associated with the presence of asthma.⁸¹

SUMMARY

EIB is the major complaint in asthma, and EIB should be treated in accordance with the general asthma guidelines. Given that EIB may relate to mechanisms other than the TH2 pathway in asthma, especially in elite athletes, it is possible that other types of medication could target EIB more specifically. An open question is whether EIB represents mild asthma that is revealed by intense physical exercise or whether different mechanisms are important in the more severe cases of EIB with large fall in FEV₁ as well as asthma symptoms. SABA as a preventer and reliever medication may be sufficient for most cases of EIB, but daily use of ICS should be initiated when asthma control cannot be achieved with nonpharmacologic interventions and reliever therapy alone. Add-on therapy with antileukotrienes, mast cell stabilizers, or omega-3 as well as vitamins should be considered, as they all reduce the fall in FEV₁ after exercise. However, none of these drugs can be used acutely when asthma develops during exercise and none can be used as reliever therapy in post-exercise EIB. Asthma symptoms with frequent use of SABA (>2 times per week) indicate the need to review asthma management. As frequent or daily use of LABA can lead to development of tolerance, ICS are the drug of choice. The dose of ICS should be increased from a low to high dose in cases with persistent EIB. From clinical experience, patients

with frequent EIB, such as elite athletes with asthma, often need high doses of ICS to achieve sufficient control.

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