Louisiana Drug Utilization Review (LADUR) Education

Asthma in Exercise and Sports

Bill Ross, BS Pharm.
Clinical Coordinator for Drug Information
Drug Information Service

Gregory W. Smith, R.Ph, AE-C, Asthma HELP Program
College of Pharmacy
University of Louisiana at Monroe

Issues

- Although numerous recent studies have demonstrated the value of exercise in promoting and maintaining good health, asthma patients are faced with additional challenges related to exercise.

- Between 14 and 15 million people in the United States are affected by asthma.

Overview

A primary therapeutic goal for all asthmatic patients is to live, as much as possible, a normal and productive life. Exercise is an essential aspect of a normal, healthy lifestyle. Although numerous recent studies have demonstrated the value of exercise in promoting and maintaining good health, asthma patients are faced with additional challenges related to exercise. This update will review the epidemiology, pathophysiology and management of exercise-induced asthma (EIA). The Guidelines for the Diagnosis and Management of Asthma define this disease as a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role, in particular, mast cells, esosinophils, T lymphocytes, neutrophils, and epithelial cells. Between 14 and 15 million people in the United States are affected by asthma. In addition, asthma is the most prevalent chronic disease of childhood, with an estimated 4.8 million patients in the United States.

Exercise-induced asthma is a condition in which vigorous physical activity triggers acute airway narrowing, with heightened airway reactivity, resulting in a reduction of greater than 10% in forced expiratory volume in one second (FEV1) compared to pre-exercise values. Exercise is the most common trigger of bronchospasm among those known to be asthmatic, and 40 - 90% of all these patients have airways that are hyper-reactive to exercise. EIA generally occurs about 5 to 15 minutes after intense exercise of variable duration and is characterized by respiratory symptoms, such as wheezing, dyspnea, chest tightness, and cough.

Prevalence
EIA may occur in up to 40 - 90% of patients with asthma, and approximately 10 - 15% of the general population without asthma. It is suggested that EIA occurs more frequently in children and young adults, possibly as a result of their more frequent and more vigorous levels of physical activity. Specific subpopulation groups may be at an increased risk. In a study of 80 pediatric subjects, it was determined that rates of EIA were significantly higher in children who were clinically obese. Limited data are available on the role of age and gender in the occurrence of EIA. A study of cross-country skiers with asthma failed to demonstrate a significant relationship between rates of EIA and either age or gender. Review data from various studies have shown the overall incidence of EIA in athletes to range from 11 - 50%. The incidence of an asthma history among athletes in the 1984 and 1997 Summer Olympics was 11% and 21.9%, respectively, while in the 1998 Winter Olympic Games, the prevalence among athletes was 21.9%.

Additional findings demonstrated a prevalence of EIA and airway hyper-reactivity (AHR), which ranged from 23 - 35% and 23 - 52%, respectively, among athletes exercising in cold air. In a study by Kukafka et al, which evaluated 238 football players, 10% of the athletes had a history of treated asthma while 15% exhibited EIA as demonstrated by a 15% decrease in peak expiratory flow post-exercise. Studies of participants in other sports including basketball players, long-distance runners, and sprinters documented EIA and AHR ranging from 8 to 21%. Contrary data come from a retrospective study of elite athletes in Finland who competed between 1925 and 1965. The conclusion was that asthma prevalence was no higher in subjects with a past history of athletic participation.

Efforts have been made to demonstrate a specific correlation between certain environmental factors and the occurrence of exercise-induced asthma. An earlier trial evaluated the effect of temperature and humidity changes on the incidence of exercise-induced bronchospasm (EIB). Results suggested a small but significant increase in EIB with decreased temperature and humidity. Another study investigated the influence of altitude on EIA. Conclusions were that patients with mild asthma generally experienced a significant reduction in peak expiratory flow at high altitudes. There was not, however, a significant additional decrease in peak expiratory flow after exercise in the asthmatic subjects at high altitude. Pernard-Morand et al studied 6,672 children to evaluate the relationship between EIB and background air pollution (nitrogen dioxide, sulfur dioxide, particulate matter <10 micron, and ozone). Results indicate that a moderate increase in long-term exposure to background ambient air pollution is associated with an increased prevalence of EIB in asthma patients.

Pathophysiology
The pathogenesis of exercise induced bronchoconstriction in asthma is only partially understood. One review suggests that EIA is not the direct result of exercise, but rather is secondary to cooling and/or drying of the airway caused by increased ventilation that accompanies exercise. When hyperventilation occurs secondary to exercise, bronchial mucosal cooling is associated with the concomitant warming and humidifying of the inhaled air. This cooling and re-warming phenomenon is thought to cause vasoconstriction and a reactive hyperemia of the bronchial microcirculation, together with edema of the airway wall, causing the airways to narrow after exercise. This combined heat and water loss from the mucosa appears to be the initial step in a series which leads to a bronchodilation response. Another general theory suggests a hyperosmolar hypothesis. As water evaporates from airway surface liquid during exercise, it becomes hyperosmolar and induces the osmotic movement of water from any nearby cells, resulting in cellular volume loss.

Consequently, the regulatory volume increase after cell shrinkage is thought to be a key event resulting in release of inflammatory mediators that cause airway smooth muscle to contract resulting in narrowing of asthmatic airways.

Eosinophils have an important role in asthma pathogenesis. Eosinophils are attracted to airways by different chemokines, with eotaxin being a principle one. In a recent small clinical trial, the role of chemokines in EIA was investigated. The authors concluded that exercise does not cause change in the systemic expression of eosinophilic chemokines. Peripheral eosinophils, however, may be a determinant of the exercise response in asthmatic patients.

Diagnosis
A recent investigation addressing the accuracy of diagnostic evaluation of EIA in children raised some question about the accuracy of methodology used for this diagnosis. This Canadian study evaluated the accuracy of clinically diagnosed EIA among students (n=52). Study results suggested that diagnosis of EIA was largely inaccurate among those in this study population, due principally to the unreliability of initial exercise-related complaints. Historically, evidence has documented a difference between physician generalists and specialists regarding the evaluation and management of asthma. A recent study addressed differences in the diagnosis and management of exercise-induced respiratory complaints among different physicians. Resulting data suggested that pulmonologists are much more likely to order bronchoprovocation testing than are family physicians and that family physicians predominantly begin with empiric therapy rather than bronchoprovocation when EIB is suspected. Definitive diagnosis of EIA is determined by the measurement of pre-and post-exercise expiratory flows documenting a fall of > 10% in forced expiratory volume in one second (FEV1) or a decrease of >15 - 20% in peak expiratory flow. Additionally, bronchial provocation tests, such as the mannitol osmotic aerosol test, have been used to diagnose EIA in olympic athletes.

Therapy
The majority of patients with EIA that receive appropriate therapy should be able to enjoy an active, healthy lifestyle. The variability in the individual degree of response to different treatment approaches suggests clinicians and patients work together to identify the most effective prophylactic therapy to achieve goals. Preventative pharmacological therapy is only one essential aspect of a successful treatment plan for these patients. For patients with EIA, establishing control for persistent symptoms, providing disease management cognitive services in the form of asthma education, and follow up assessments are all part of a successful comprehensive therapy plan. One of the most important elements of therapy for a patient with EIA is a regimen of regularly scheduled exercise. Unfortunately, noncompliance to an exercise schedule often occurs because of the physical challenge and ultimately may result in a deteriorated condition. Treating children with EIA is challenging because of the nature of their physical activity, which is often spontaneous and prolonged. The options to be considered for treatment depend on timing, frequency, and the duration of activity that induces the EIA. The therapy goals listed below outline a plan that can be implemented with long term success in caring for a patient with EIA.

Goals of Therapy
- Asthma Education
- Asthma Control
- Regular Assessments
- EIA Prevention

• Maintained Physical Activity

Asthma Education
Patients empowered with the knowledge of the asthma disease state and provided with instructions for self-managed therapy have been shown to have fewer exacerbations and improved long-term therapy outcomes. Periodic counseling sessions in an asthma education program can help the patient recognize environmental triggers that contribute to EIA and present additional opportunities to encourage the patient to meet therapy goals.

Asthma Control
If the asthma disease state is well controlled, the patient should be able to exercise without asthma symptoms. Current guidelines for the control of persistent asthma include the use of inhaled corticosteroids, long acting ß-2 agonists, and leukotriene modifiers. An important asthma management tool is the Baylor Health Care System Rules of Two® for Asthma, which states:

The asthma condition is not under control if the patient:

• Use a rescue inhaler more than two times a week
• Awakens at night with asthma symptoms more than two times a month
• Use more than two canisters of rescue medication in a year

Asthma controller medications should also be considered if over a course of a year, the patient receives a short course of oral steroid more than two times or has more than two unscheduled acute asthma care visits.

Since allergy symptoms often precipitate or worsen asthma symptoms, allergy control is often needed concomitant to asthma control. Appropriate therapy for allergy control and prevention includes medications such as antihistamines, nasal corticosteroids, mast cell stabilizers, and oral leukotriene modifiers.

Regular Assessments
Regular patient evaluations are necessary to monitor the progress of persistent EIA in addition to the patient's overall asthma condition between periods of exertion. Any indication of poorly controlled asthma should prompt a change in the patient's treatment plan.

Prevention of Exercise-Induced Asthma
The patient's treatment plan should be revised to include appropriate pre-exercise medications to prevent EIA.

Typically, bronchodilators are the first choice for preventative protection; however, other effective options or medication combinations could be warranted depending on individual needs.

Medications
• Short Acting ß-2 Agonists-
The most commonly used treatment for the prevention of EIA is inhaled short-acting beta-2 adrenergic receptor agonists (SABA).

    • Albuterol sulfate-

This SABA has a primary indication as prophylaxis for EIA and is typically given about
15 - 30 minutes prior to the onset of physical activity. Inhaled albuterol typically does not
demonstrate significant protection > 4 hours after dosing.
• Terbutaline sulfate-
Inhaled terbutaline has also been shown to be effective in the treatment of EIA for short
duration.

• Long Acting ß-2 Agonists-
Long-acting beta-2 adrenergic receptor agonists (LABA) currently are recommended as concomitant therapy for asthma control and are often used to attenuate predictable bronchoconstriction associated with exercise. The duration of the protective benefit of a LABA is typically 2-3 times that of a SABA.

• Formoterol Fumarate-
A single dose of formoterol has provided significant bronchoprotection against repeated exercise challenges as early as 15 minutes post dosing and for duration of benefit of up to 12 hours compared with placebo and from 4 hours onward compared with terbutaline.

• Salmeterol Xinafoate-
Salmeterol is also indicated for prophylaxis of EIA and like formoterol, it has a long duration of action, though the onset of protection is somewhat delayed.

One of the concerns of using LABA chronically is the issue of tolerance. When taken daily, there appears to be reduced duration of protection and a risk of EIA manifestation within the 12-hour therapy window. The chronic use of a LABA may attenuate the bronchodilator effect of SABA rescue medications, which can result in more severe bronchoconstriction. Tachyphylaxis developed resulting in a reduction of the bronchoprotective properties of formoterol after 4 weeks of standard dosing. Using these medications on an as needed basis for EIA should be a consideration to prevent loss of efficacy and reduced sensitivity to asthma rescue agents.

• Anticholinergics-
Some benefit in preventing EIA has been demonstrated in the use of the inhaled anticholinergic
medication ipratropium bromide, but it appeared to be less effective than the SABAs.

• Mast Cell Stabilizers -

• Cromolyn Sodium-
In a small, placebo-controlled study, cromolyn was more effective than ipratropium in preventing EIA. However, other studies have shown that salmeterol, a LABA, and albuterol, a SABA, provided better bronchoprotection for exercise-sensitive individuals.

• Leukotriene Modifiers-

One strong point of the leukotriene modifier therapy in patients with EIA appears to be the improved recovery of pulmonary function without the tolerance problems often seen with chronic
use of LABAs.

- Montelukast-
One study concluded that a single dose each of montelukast and salmeterol was comparable in efficacy. Another study revealed that, compared to placebo, montelukast provided significant protective effect at 12 hours after dosing, but no effect at 2 hours and 24 hours. The proper timing on single dose therapy should be considered to achieve the optimum protective effects.
- Zafirlukast and Zileuton-
These medications have also exhibited effective prophylaxis for EIA; however, montelukast has a distinct advantage in pediatric dosing for patients as young as 12 months of age.

• Alternative Therapies -

- Ascorbic Acid-
Data have suggested that high dose supplementation of ascorbic acid may reduce the severity of EIA by reducing the hyper-reactivity of airways.
- Fish Oil Supplements-
A possible contributing factor to the recent increase in prevalence and severity of asthma may be the consumption of a pro-inflammatory diet. An evaluation of clinical data has shown that omega-3 fatty acid supplementation, rich in n-3 PUFA, was beneficial to nonatopic elite athletes with EIB. The findings suggested that fish oil supplements may be of therapeutic benefit for asthma and EIB.

• Investigational Agents -

- Cilomilast-
This PDE-4-specific inhibitor is under review for maintenance of lung function in COPD patients, but has exhibited improvement in post exercise breathlessness as a secondary outcome.
- Fenoterol Hydrobromide-
This SABA is being investigated in the U.S. as a bronchodilating agent. Clinical trials have demonstrated efficacy for EIA.
- Ciclesonide-
In a study with the objective to evaluate EIB as a method of determining the dose and time responses of ICS therapy, the use of an investigational drug, ciclesonide, resulted in significant improvement in EIB for all doses used. Attenuation to exercise response was seen as early as 1 week at doses > 40 mcg and maximal attenuation continued to increase at doses > 200 mcg, even after 3 weeks of ciclesonide therapy.
- Roflumilast-
This selective phosphodiestrase (PDE)-4 inhibitor has anti-inflammatory and bronchodilator properties and has been shown to be effective in the reduction of EIA and AHR.

Physical Activity as Therapy

One aspect of therapy for EIA that is frequently overlooked is the promotion of physical activity to maintain and even enhance cardiopulmonary health in the asthmatic patient. There is a growing body of literature that implicates decreased physical activity as a contributor to the increase in asthma prevalence and severity. A common reason that EIA goes unnoticed is that the individual may choose to avoid activities that cause the symptoms, which often progressively leads to a sedentary lifestyle and ultimately deteriorated physical health. Every effort should be made to encourage the patient to maintain an active lifestyle that will be beneficial in the long term for the asthma condition and overall health of the individual. Promoting activities that may be less likely to cause EIA in the patient may improve the probability of compliance with an exercise regimen.

Sports that are less likely to trigger EIA include:
- Swimming
- Walking
- Leisure biking
- Hiking
- Downhill skiing
- Team sports that require short bursts of energy, including:
    - Baseball
    - Football
    - Wrestling
    - Golfing
    - Gymnastics

Swimming is often referred to as the exercise of choice for those individuals that experience EIA, because of the positive factors associated with it, such as its year-round availability and the horizontal position that may help mobilize mucous from the bottom of the lungs.

<u>The patient may take the following precautions to help prevent EIA:</u>

- Warm up period prior to exercise
- Cool down period after exertion
- Avoidance of exertion if a respiratory tract infection or bronchitis is present
- Smoking cessation
- Avoidance of environmental triggers especially during exercise such as:
    - Extremely cold temperatures
    - High humidity
    - High pollen count
    - Fresh cut grass
    - Any environmental triggers unique to the patient.

Examples of non-pharmacological therapy that have been attempted with mixed success to prevent or minimize EIA include:

- Facemask-

In cold weather, it may be possible to decrease symptoms by warming inspired air during exercising by wearing a scarf or surgical mask over the mouth and nose.

• Heat-exchanger mask-
Many asthma patients are limited in cold weather physical activities, in spite of appropriate pharmacological therapy. A study was conducted to determine the efficacy of a heat-exchanger mask in limiting cold air induced decline in pulmonary function in patients with EIA. The study determined that the mask blocks the decline in lung function induced by exercise at least as
effectively as an albuterol bronchodilator pretreatment.

• Dietary salt restriction-
Findings of one study suggested that individuals with EIA may benefit from a diet lower in salt. Other findings indicated that small salt-dependent changes in vascular volume and microvascular pressure may have significant effect on airway function following exercise.

• Laser acupuncture-
Results of a study involving the use of a single laser acupuncture therapy in pediatric and adolescent patients revealed that the treatment offered no protection against exercise-induced bronchoconstriction.

Conclusion
Exercise-induced asthma poses a number of specific challenges and opportunities to both the patient and health care professional. However, application of proactive evidence-based patient management and education has been demonstrated to achieve good outcomes in these patients. Participation in regular physical activity by asthma patients is both advantageous and achievable.

References Available Upon Request