

Evidence-based Pharmacy Practice (EBPP): **EXERCISE-INDUCED ASTHMA**

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Abstract

Exercise-induced asthma (EIA) is a common condition that is frequently unrecognised, especially in school children and competitive athletes. Confirmation of EIA requires the use of an exercise test. Diagnosis cannot rely on self-reported symptoms alone. Cooling and drying of the airways play prominent roles in the mechanism of EIA. Inflammatory mediators also play a role. Both non-pharmacological and pharmacological approaches are often necessary to minimise the effects of EIA. Non-pharmacological approaches to treatment include warming up before exercise, nasal breathing, wearing a mask in cold environments, and avoidance of triggers. Dietary salt restriction and fish oil supplementation may also play a role in reducing the severity of EIA. Inhaled corticosteroids are the most effective drugs for managing asthma and preventing EIA. Short-acting β_2 agonists are the most commonly used prophylactic agents for EIA. Long-acting β_2 agonists and leukotriene receptor antagonists are also now used in the management of EIA. Pharmacists are well positioned to advise patients about proper medication use and proper inhaler technique. They can also educate patients about the non-pharmacological measures that can reduce or prevent EIA.

Definitions

The terms EIA (exercise-induced asthma) and EIB (exercise-induced bronchoconstriction) are often used interchangeably.¹ Both of these terms are used to describe acute narrowing of the airway triggered by vigorous physical activity in people with bronchial hyper-responsiveness.² To differentiate between the two, EIA denotes symptoms of asthma and reduction of lung function after physical exercise, while EIB denotes the reduction in lung function (objectively defined as a $\geq 10\%$ decline in FEV₁ [forced expiratory volume in one second]) after standardised exercise tests.^{1,3}

EIB is 'self-limiting' meaning that the reductions in pulmonary function, which can be severe, dissipate over 30 minutes to an hour.⁴ This is in contrast to antigen-induced asthma which often requires medication in order to limit the attack.⁴

Epidemiology

The prevalence of EIB in the general population is unknown.⁴ It is generally considered that EIB occurs in 80 to 90% of individuals with asthma, 40% of those with allergic rhinitis and 12 to 15% of the general population experience EIB with moderate exercise.⁴ It is likely that all individuals that suffer with asthma will experience EIB if the exercise intensity and duration is sufficient.⁴

Exercise is one of the most common triggers of bronchospasm in known asthmatics, second only to viral respiratory tract infections.^{2,5} The degree of exertion that can induce bronchoconstriction differs between individuals. It may vary between carrying bags of shopping up a flight of stairs to

running a 10 km race.⁵ This means that some asthmatic patients may only be able to perform limited exercise whereas some may become elite athletes and perform in the Olympics.⁵

There is a group of asthma patients who only have EIA and not chronic daily asthma.⁵ These patients are usually recreational athletes (school students and adults who like to jog, swim, and bike etc.) who only have asthma symptoms with exercise.⁵

EIA in children

Epidemiological studies have determined that the prevalence of EIA in children from the general population ranges from 3.1% to 16%.² Some of these studies have observed a slightly higher incidence in girls and in children living in urban areas.² These observations suggest that social and environmental factors such as wealth, lifestyle and housing environment are important determinants of EIA.²

Children's lifestyles are active, and they spontaneously and intermittently engage in strenuous activity during play, without using premedication to prevent bronchoconstriction.⁶ EIA limits the daily activities of asthmatic children.⁶ Children with asthma who do not receive anti-inflammatory treatment are especially predisposed to EIA.⁶

EIA in athletes

The prevalence rates of bronchospasm related to exercise in athletes ranges from 11 to 50%.³ It is especially prevalent in endurance events such as cross-country skiing, swimming and long-distance running in which ventilation is increased for long periods of time during training and competition,

allowing for relatively more evaporative water loss and subsequent airway narrowing.³ Athletes that train and compete in environments in which there are environmental pollutants are at increased risk for the development of EIB.³ Examples of this include the chlorine compounds in swimming pools and chemicals related to ice-resurfacing machinery in ice rinks which may act as allergic “triggers” and may exacerbate bronchospasm in athletes who are predisposed to EIA.³ Drug treatment in athletes should follow standard treatment guidelines (both national⁷ and international⁸) and be individualised to achieve asthma control.⁹ Effects of treatment should be monitored (as it should be in all asthmatics). Any medications prescribed must comply with World Anti-Doping Agency (WADA) regulations.^{9,10,11} All oral β_2 agonists are prohibited.⁹ Inhaled corticosteroids and some inhaled β_2 agonists can be used in accordance with the relevant section of the International Standard for Therapeutic Use Exemption (TUE).^{9,12} Systemic corticosteroids are prohibited and require a standard TUE.⁹

Aetiology/pathophysiology

There are two main theories that can explain how physical activity may cause EIA.¹ One relates to increased water loss from the respiratory tract during exercise (the hyperosmolarity theory⁵) and the other focuses upon cooling of the airways caused by increased ventilation during exercise (the airway rewarming theory⁵).¹ The underlying mechanisms of EIA are not thought to be the same as chronic persistent asthma, in which inflammation of the airways is the primary underlying pathologic event.⁵

The hyperosmolarity theory states that water loss occurs during the hyperventilation of exercise and that this water comes from the airway surface liquid of the bronchi.⁵ Then there is hypertonicity and hyperosmolarity within the airway cells due to this water loss.⁵ This is then thought to lead to the release of mediators such as histamine, prostaglandins and leukotrienes, which cause bronchoconstriction.⁵ If this water loss occurs in a patient who has chronic persistent asthma and underlying airway inflammation, this may aggravate the postexercise bronchospasm caused by the exercise-related hyperosmolarity.⁵

The airway rewarming theory states that the hyperventilation of exercise leads to cooling of the airway.⁵ After completion of the exercise, there is rewarming of the airway because of the small bronchiolar vessels that wrap around the bronchial tree.⁵ The influx of warm blood into these vessels leads to congested vessels, fluid exudation from the blood vessels into the submucosa of the airway wall, and mediator release resulting in bronchoconstriction.⁵

Neither of these theories considers inflammation as an underlying pathophysiology of EIA.⁵ However, there is some evidence that inflammation may be involved in some patients with EIA.⁵ Data available on inflammation suggests that individuals that exercise frequently, especially in cold air,

may develop chronic inflammatory changes in the airways similar to the type of inflammation seen in chronic persistent asthma.⁵ This may not apply to those individuals that have EIA only with no evidence of chronic persistent asthma.⁵

Inflammation also plays an important role in the pathogenesis of EIB in asthmatic subjects.³ Asthma results from a chronic inflammatory cascade that results in airway inflammation, mucous production, smooth muscle hypertrophy, and bronchospasm.³ Increased levels of inflammatory mediators such as prostaglandins, leukotrienes and histamine in the airway may produce bronchoconstriction during exercise, resulting in an asthma attack.² A significant correlation has been reported between the severity of EIA and the degree of peripheral blood eosinophilia and eosinophilic inflammation in induced sputum in asthmatics.³ However, the role or significance of inflammation in the pathogenesis of EIA in individuals without asthma is unclear.³

Clinical manifestations

The clinical presentations of EIA include cough, wheezing, chest tightness, unusual shortness of breath and/or excess mucous after a burst of strenuous and continuous aerobic exercise.² Usually the severity of the symptoms correlates with the intensity of the exercise.² The symptoms of EIA may differ from one person to another.

Non-specific symptoms (see Table 1) may also be suggestive of EIA.² These symptoms can worsen after exposure to certain triggers during exercise, such as animal dander, house dust mites, mould, cigarette smoke, pollen, pollution, airborne chemical, or changes in weather.²

Patients with EIA typically have initial bronchodilation during the first six to eight minutes of exercise.¹³ This initial bronchodilation is followed by bronchoconstriction, which begins within three minutes after exercise, and generally peaks within 10 to 15 minutes and resolves by 60 minutes.¹³

Table 1: Symptoms of EIA after continuous exercise²

Typical symptoms

- Cough
- Wheezing
- Chest tightness
- Unusual shortness of breath
- Excess mucus

Nonspecific symptoms

- Poor performance
- Chest pain
- Prolonged upper respiratory illness
- Difficulty in sleeping due to nocturnal symptoms
- Avoidance of activity
- Inability to keep up with peers

In most patients with EIA, bronchoconstriction is followed by a refractory period, during which repeated exercise causes less bronchoconstriction.¹³ This refractory period is usually less than four hours. It is thought that inhibitory prostaglandins such as prostaglandin E₂ that are released during this period are the protective factors against further EIB.¹³

Diagnosis

EIA can be diagnosed in several ways.¹ The best method is to use a standardised exercise test and measure lung function before and after the exercise.¹ Standardisation is especially important with the follow-up of EIA over time.¹ A diagnosis based on self-reported symptoms alone may not be a good predictor for EIA. Initially, an important distinction must be made to determine whether the individual has chronic persistent asthma or solitary EIB.⁴ Most individuals with asthma will have EIB.⁴ However, those with solitary EIB do not usually have respiratory distress related to a non-exercise stimulant.⁴

A thorough history must be obtained that includes a family and occupational history.³ A complete physical examination should be performed including an ENT examination looking for allergic rhinitis, sinusitis, otitis media, a cardiac examination to evaluate for possible murmurs or arrhythmias, and a chest examination to check for wheezes, rhonchi or rales.⁵ The physical examination is normal in most patients with EIA.⁵ Abnormal findings should be investigated and treated accordingly.⁵ If allergic rhinitis or chronic sinusitis is found this may aggravate EIA and treatment will be required to improve the EIA.⁵ Other causes of exercise-induced dyspnoea include central airway obstruction, vocal cord dysfunction, laryngotracheomalacia, parenchymal pulmonary disease, gastroesophageal reflux, cardiac arrhythmias, and pulmonary and cardiac shunts.^{3,13}

Challenge testing may be necessary in some patients to help confirm the diagnosis of EIA, especially if the usual therapy has failed to give relief.⁵ The International Olympic Committee Medical Commission requires challenge testing for the proof of diagnosis of EIA so that the athletes may take anti-asthma medications while competing.⁵ There are a number of different challenge tests that can be performed to confirm the diagnosis of EIA.^{2,5} The standard treadmill or ergometer exercise challenge being the most common.⁵ The International Olympic Committee adopted the eucapnic voluntary hyperventilation (EVH) challenge as the test recommended to document EIB in Olympians.³

Clinical approaches to exercise-induced asthma by the pharmacist

The pharmacist can advise the patient on non-pharmacological methods to prevent EIA such as choice of sport, warming-up before exercise, wearing a mask while exercising and avoiding training on cold days or days when the pollen count is high.

The pharmacist can also advise the patient on proper medi-

cation use which includes adherence to the dosing schedule (so the pharmacist can make sure the patient understands the instructions) and proper inhaler technique.⁵ It is important that the patient demonstrates their inhaler technique in person⁵ even if the patient has been using inhalers for many years they may have been using them incorrectly all that time. When metered-dose inhalers are used, it may be beneficial to use a spacer device along with the inhaler to improve coordination and drug deposition.⁵

The pharmacist can also advise the patient to avoid training during ongoing respiratory infections since a long-lasting increase in bronchial responsiveness may occur.¹

Therapeutic objectives

EIA is a complex pathophysiological phenomenon, and therapeutic responses are difficult to predict. Normal or better-than-normal lung function (as in trained athletes) does not guarantee the absence of severe EIA.² Weather conditions, air quality, personal fitness, physical effort, the duration of symptoms and the underlying bronchial hyper-reactivity all influence the development of EIA.² Management of EIA should start with non-pharmacological treatment and follow the general asthma treatment principles, such as making use of short acting β_2 agonists, inhaled steroids and leukotriene receptor antagonists, and individually tailored treatment.² If the patient with EIA fails to respond to the usual treatment then other causes need to be investigated.²

Available treatment options

The treatment of EIA involves:⁵

1. education of the patient, including types of exercise to choose and how to warm-up before exercise
2. treatment with pharmacological agents
3. treatment assessment at a follow-up visit
4. follow-up evaluations to monitor changes in the EIA

Management of exercise-induced asthma

Each patient with EIA is an individual and may respond differently to various medications. Treatment trials are essential and combinations of non-pharmacological interventions and medications may be needed to adequately control EIA.

Non-pharmacological treatments

The first step of non-pharmacological treatment for EIA involves advising the patient on the types of exercise that are least likely to induce an asthma attack, such as swimming, intermittent exercise, team games and exercise in warm and humid air.² If the patient has to exercise in a cold environment, breathing through the nose rather than the mouth (by allowing cool dry air to be humidified and warmed), or wearing a mask reduces the loss of heat and moisture and has been shown to minimise EIA.² Underlying allergic and environmental nasal conditions should be treated to allow for nasal breathing.¹⁴ Avoidance of known triggers e.g. freshly cut grass, high pollen days, pollution and chemicals is important when exercising.³

Exercise is the only natural trigger of asthma that induces tachyphylaxis.^{2,15} When repetitive tasks are performed within 40 minutes of one another, bronchial narrowing progressively decreases.² Certain warm-up routines may reduce EIA if done before exercise.⁵ Athletes should try to warm up at 80 to 90% of their maximum workload before they exercise or compete.⁵ This type of warm-up before the exercise reduces the severity of EIA.⁵ This phenomenon is referred to as the 'refractory period' of protection against EIA by an intense warm-up and has been shown to last as long as two hours.⁵ This effect has been shown to be different between individuals and in the same individual on different days so cannot be relied upon as the sole therapy for preventing or minimising EIA.⁵

Dietary salt restriction reduces airway inflammation in individuals with asthma following exercise, while increasing salt intake enhances inflammation.² Dietary salt intake also increases plasma volume, weight gain and urinary output volumes in asthmatic individuals.² This suggests that airway obstruction may be partly related to increased blood flow to the lungs, which could affect airway narrowing via capillary engorgement, airway wall oedema and direct mechanical compression with an accompanying decrease in forced expiratory flow rates.²

Diets rich in fish oil (which contain omega-3 fatty acids) may be helpful in asthmatic individuals with EIB.^{13,16} Pulmonary function can be improved to below the EIA diagnostic threshold by inducing a 10% decrease in postexercise FEV₁ and by alleviating the decrease in FEV₁ by approximately 64% (15 minutes after exercise).¹⁶

Table 2: Non-pharmacological treatments for EIA²

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|-------------------------------------|
| Warm-up |
| Nasal breathing |
| Avoidance of triggers |
| Wearing a mask in cold environments |
| Dietary salt restriction |
| Fish oil supplementation |

Pharmacological treatments

There are two main medical treatment principles for managing EIA.¹ The first one being prophylactic treatment (anti-inflammatory) and the second being premedication prior to physical activity.¹

Anti-inflammatory treatment using inhaled corticosteroids is the most important and effective management for asthma and for the control of EIA.¹

The most common group of drugs taken as premedication are the inhaled β_2 agonists. Other drugs which are rarely used include disodium cromoglycate and nedocromil sodium.¹

Table 3: Pharmacological treatments for EIA²

| |
|---|
| Short-acting β_2 agonists |
| Long-acting β_2 agonists |
| Inhaled corticosteroids |
| Leukotriene receptor antagonists |
| Disodium cromoglycate/nedocromil sodium |
| Ipratropium bromide |

Short-acting β_2 agonists

The most common method of minimising or preventing EIA is the prophylactic use of short-acting β_2 agonists e.g. salbutamol shortly before undertaking exercise.² Short-acting β_2 agonists are used as initial therapies for individuals with pure EIA who do not have persistent asthma.² Inhaled β_2 agonists have better effect than when taken orally.¹ The recommended dose of inhaled salbutamol is 0.2–0.4 mg corresponding to an inhaled dose of 0.25–0.5 mg terbutaline.¹ Treatment with two puffs of a short-acting β_2 agonist about 15 minutes before exercise provides peak bronchodilation in 15 to 60 minutes and protection from EIB for at least three hours in most patients.³ Regular use of β_2 agonists may decrease expression of the β_2 receptor and lead to the development of tolerance.² After regular use for just one week the protective effects of salbutamol was decreased when compared to individuals who only used the drug when needed.²

Long-acting β_2 agonists

The two long-acting β_2 agonists, salmeterol and formoterol, both protect against EIA.¹ Children with EIA may benefit from a long-acting bronchodilator since they do not plan their physical activity during the day.¹ In general, long-acting β_2 agonists are not rescue medications and should not be used more than twice a day.² The regular use of long-acting β_2 agonists reduces their protective effects and can build tolerance. With regular salmeterol treatment tolerance can occur after four to eight weeks.² The therapeutic effects of salmeterol can decrease from 12 hours to less than three to four hours after one month of daily use.² Tolerance does not seem to develop when salmeterol is used three or fewer times a week.²

Inhaled corticosteroids

Inhaled corticosteroids are currently the most effective treatment for managing asthma and preventing EIA.² This is especially the case when poor asthma control is the cause of refractory EIB.¹³ Inhaled corticosteroids do not improve EIB in the short-term but they do improve airway hyper-responsiveness and, over weeks to months, decrease the amount of bronchoconstriction that occurs with a given workload.¹³

Leukotriene receptor antagonists

Leukotriene receptor antagonists (LTRAs) have been shown to have a protective effect upon EIA and reduce the symptoms.¹ The magnitude of EIA is reduced after two to three days' treatment, but not completely abolished.¹

Protection from EIA is apparent by two hours after a single dose of montelukast, and post-exercise recovery is accelerated.¹³ The long half-life of montelukast allows once-daily dosing with protection from EIB for up to 12 hours.¹³ LTRAs are an effective treatment for EIA in children as they are given orally and are taken daily so offer good prophylaxis against EIB, as children often neglect to premedicate with an inhaled β_2 agonist. LTRAs appear to be superior to long-acting β_2 agonists when treating asthmatics with EIB.¹³ In one blinded multicentre trial, asthmatics with EIB were randomly assigned to either salmeterol or montelukast for eight weeks.¹³ Both therapies were protective within three days; however tolerance to salmeterol developed, and by eight weeks, the bronchoprotective effect of montelukast was significantly better. Unfortunately, LTRAs are not effective in all patients.¹³

Disodium cromoglycate/nedocromil sodium

Both disodium cromoglycate and nedocromil sodium are useful in the pre-treatment of EIA.¹ Disodium cromoglycate also reduces ventilatory work and energy consumption during running in children suffering from EIA but not in healthy children.¹ This suggests that energy consumption during exercise is higher in untreated than in treated asthmatic children.¹ These drugs are mast cell stabilisers which prevent mast cell degranulation and the subsequent release of histamine.² They can be used many times a day, without the fear of side effects or the development of tolerance. Disodium cromoglycate needs to be taken in adequately high doses.¹ A dose of 20 mg is recommended.¹ This high dose may make the treatment impractical and both drugs have shorter durations of action and lower efficacy than β_2 agonists which are now the preferred agents.^{1,2}

Inhaled disodium cromoglycate and nedocromil sodium are no longer available in South Africa.

Ipratropium bromide

Ipratropium bromide may be effective against EIA in individual patients but is less useful than inhaled β_2 agonists.¹ Sometimes an additional protective effect may be obtained when ipratropium bromide is added to an inhaled β_2 agonist.¹ This drug is not used frequently due to the wide variability in airway responses among individuals.²

Other therapies

Other asthma therapy such as theophylline and oral β_2 agonists are marginally effective or ineffective in almost all patients.¹³

Several other drugs have been tested as possible prophylactic agents against EIA.¹³ Inhaled furosemide, prostaglandin E₂, indomethacin and heparin may protect against EIA.¹³ The role of these drugs in the treatment of EIB is unclear as there have been insufficient studies comparing them to the long-term use of inhaled β_2 agonists as prophylactic agents in the management of EIA.¹³

Evidence based guidelines/recommendations

The treatment and management of asthma should follow local⁷ and international⁹ guidelines. In the management of EIA non-pharmacological interventions should be initiated first after a confirmed diagnosis. These should be continued even if not solely effective in preventing or minimising EIA. In patients with chronic persistent asthma, EIA may be a manifestation of poor asthma control.¹⁴ In these patients it is important to assess overall treatment strategies to maximise therapy and improve asthma control.¹⁴ Whereas in patients solely with EIA it is important to determine that there is no underlying chronic asthma.¹⁴

Inhaled short-acting β_2 agonists are the most effective drugs for immediate inhibition of EIA and for relieving intermittent symptoms of asthma.⁹ They are considered first-line treatments.

Long-acting β_2 agonists are also effective. The onset of action of formoterol is similar to salbutamol and can be used shortly before exercise.¹⁴ The onset of salmeterol is delayed and it may take 90 minutes before it gives full exercise protection.¹⁴ Long-acting β_2 agonists should not be used as monotherapy.⁹

Inhaled corticosteroids are the most effective drugs for the long-term control of asthma and the prevention of EIA.⁹ Leukotriene receptor antagonists (LRTAs) can also be effective in EIA when used prophylactically.¹⁴ Unlike the β_2 agonists, the benefits of the LRTAs are not reduced over time when they are used on a regular basis as monotherapy.¹⁴

Theophylline and anticholinergics are third-line treatments and are rarely required or suggested.¹⁴

If the above medications are ineffective, the diagnosis of EIA should be reconsidered.²

Breakthrough symptoms can occur if the patient has forgotten to take prophylactic therapy for EIA, bronchoconstriction should be treated with two to four puffs of an inhaled β_2 agonist.¹³ Disodium cromoglycate and nedocromil sodium are not effective in this situation.¹³

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Contd from p 17

EBPP: Asthma

Conclusion

Patients with EIA or EIB should be diagnosed using a specific test so that they can be managed according to their individual needs and to ascertain whether it is indeed EIA. The patient should be educated about their condition regarding their environment and non-pharmacological measures that can be undertaken to prevent or minimise bronchoconstriction occurring as the result of exercise.

The combination of non-pharmacological and pharmacological intervention can prevent EIB in most asthmatics. It is well documented that the incidence of EIB after proper medical prophylaxis is extremely low.¹⁷ Avoidance of exercise by asthmatics should not be recommended but it is important to prevent EIB by educating asthmatic patients and treating them according to their individual needs. Asthmatics can improve their cardiopulmonary fitness with exercise conditioning and the benefits are both subjective and objective for the patient.¹⁷ Asthmatics should exercise as much as desired and be encouraged and motivated by the fact that athletes who have symptomatic asthma have won Olympic medals and have become professional sportsman. □

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