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Pharmaceutical Treatment of Asthma Symptoms in Elite Athletes – Doping or Therapy

Jimmi Elers and Vibeke Backer
Copenhagen University, Denmark

1. Introduction

According to the World Health Organization (WHO), 300 million people suffer from asthma, a disease which is increasing in western societies, and furthermore asthma is the most common chronic disease among children, adolescents and young adults. A steady increase in the prevalence of asthma, has been seen in most countries in recent decades (Thomsen et al 2011) and the higher frequency of asthma in young people may partly explain the high frequency found in elite athletes – although both frequency of asthma symptoms and use of anti-asthmatic medication are different than expected. Moreover, the frequency of airway hyperresponsiveness (AHR) in elite athletes is higher than expected as well as the frequency of asthma-like symptoms (cough, wheeze, shortness of breath and chest tightness) which might be caused by exhaustive ventilation, but the pathogenesis is still unknown.

The frequency of asthma among the general population is around 7-10%; whereas the frequency of asthma among elite athletes is found to be higher, especially among endurance athletes (Pedersen et al 2008b). It seems as asthma is something they gain, as only one third of Olympic athletes had childhood asthma. Although asthma among the general public is a permanent phenomenon, it seems to be different in elite athletes, as asthma apparently disappeared after retiring from the sport (Fitch et al 2008).

2. Asthma among athletes

Asthma is a chronic respiratory condition classically characterised by airway inflammation and airway hyperresponsiveness (AHR) to multiple stimuli (Anderson et al 2009). AHR is defined as a pathological bronchoconstrictive response to a given stimulus . AHR to a direct stimulus (e.g. methacholine) acts through airway smooth muscles and the response is thought to be independent of airway inflammation. Whereas response to an indirect stimulus (e.g. exercise, hyperventilation, mannitol) acts through a release of inflammatory mediators, such as histamine, prostaglandins, and leukotrienes, which causes contraction of the airway smooth muscle cells. Airway inflammation in asthma is characterised by inflammatory cells, such as eosinophils, mast cells, and macrophages. The inflammation causes remodelling of the basal membrane, enlargement of the mass of smooth muscles, and disturbance of the surface area. Permanent use of controller therapy with inhaled steroids (ICS) is needed in asthma, as well as relief therapy with short-acting $beta_2$-agonists (SABA), long-acting $beta_2$-agonists (LABA) or others.

Elite athletes, with or without asthma, have asthma-like symptoms during their training season, especially cough, phlegm and shortness of breath is a dominant complain among athletes (Lund et al 2009). Furthermore, athletes are more often found with AHR to direct stimuli and less to direct stimuli than found in normal subjects thus suggesting a respiratory illness. Variation in action of the different provocative agents is related to the fact that response to an indirect challenge would reflect an ongoing inflammation better than would direct tests, and perhaps thus reflect the presence of classical asthma, whereas AHR to direct agents indicates airway smooth muscle dysfunction and, in some cases, asthma (Pedersen et al 2008a, Sue-Chu et al 2010).

The definition of asthma includes respiratory symptoms, variable airway obstruction and airway hyperresponsiveness to multiple agents. The respiratory symptoms in patients with common asthma and the elite athletes with or without asthma are similar, which leave a diagnostic problem in these cases where symptoms are the single diagnostic parameter available. Whereas, the differences between common asthma and asthma among elite athletes are predominantly related to the airway responsiveness to inhaled agents, the day-to-day variability of lung function as well as the content of the inflammatory cells which predominantly are neutrophilic cells and not eosinophilic.

3. Exercise-induced asthma and bronchoconstriction in elite athletes

Exercise-induced bronchoconstriction (EIB) is an acute, transient narrowing of the airway that occurs during and particularly after exercise. In most scientific papers, exercise-induced asthma (EIA) are defined as respiratory symptoms and a significant reduction in FEV1 after exercise, i.e. Δ $FEV_1 \geq 10\%$, whereas EIB is a significant reduction in FEV1 (≥10%) when tested, independent of symptoms or not. In population samples, the prevalence of EIB (16%) is the same as the findings of AHR to histamine (16%), although only 6% had responsiveness to both test (Backer et al 1992). EIB is believed to be more specific to asthma, but less sensitive, as the number of false negative results is a problem when research and clinical situations settings are evaluated (Anderson & Kippelen 2005). The frequency of AHR is frequently found above 40%, which is higher than the frequency of asthma. Elite athletes claim that exercise is the most prominent trigger of asthma symptoms, as they very seldom complain of respiratory symptoms at rest or during the night.

The pathogenesis of asthma-like symptoms in elite athletes is multifactorial, and is not completely understood. However, deep, exhaustive ventilation during exercise brings atmospheric air which is cold and dry and this manoeuvre overcomes the ability of the upper airways to warm up and humidify the air reaching the smaller airways(Anderson & Kippelen 2005). This brings about airway narrowing due to osmotic and thermal evaporative water loss, and some vascular involvement. These airway differences, together with some degree of inflammation, lead to a respiratory condition described as EIB or sports asthma. This abnormal response is most often found in endurance sports, such as cross-country skiing , swimming, rowing, cycling, fast-track skating and long distance running.

The symptoms of exercise-induced bronchoconstriction range from mild impairment of performance with minor reduction in lung function after exercise to severe bronchospasm with large reduction in FEV_1. In athletes, however, the most common symptoms include cough, wheezing, chest tightness, dyspnoea, and fatigue. These symptoms are frequently found in healthy subjects, subjects with asthma, subjects who are not in good condition and

sometimes in subjects suffering from an extrathoracal disorder such as vocal cord dysfunction (VCD).
In conclusion, the most frequent complaint among healthy and diseased athletes is respiratory symptoms during exercise. Furthermore, healthy elite athletes often have AHR with a pattern which differ from the general asthma patient. Lastly, the types of cells involved in the inflammation are different from those in normal asthmatics.

4. Diseases mimicking exercise-induced asthma

Not all that wheezes is asthma. When the diagnosis of asthma is based on respiratory symptoms alone, misdiagnosis may occur. Patients may present with respiratory distress, such as wheezy, when experiencing a low level of fitness, a psychological condition, inhalation of airborne irritants, rhinosinusitis, or gastroesophageal reflux disease. Moreover, exercise-induced symptoms can occur as periodic occurance of laryngeal obstruction (POLO) or exercise induced laryngeal obstruction (EILO) and present with asthma like symptoms. These diseases include conditions such as vocal cord dysfunction (VCD), exercise-induced paradoxical arytenoid motion (EPAM), exercise-induced laryngomalacia (EIL), exercise-induced laryngochalasia, angioedema, vocal cord tumours, and vocal cord paralysis. There seems to be a substantial overlap between EILO and EIA, at least in elite athletes. It could be of minor importance, but it could also have a major influence on the diagnostic procedure in the daily care settings of those with asthma-like symptoms. When POLO/EILO is misdiagnosed as asthma, patient are erroneously treated with anti-asthma therapy, even high doses because of "resistant disease".
These diseases are easily recognized by performing a Flow/Volume curve where a classical cutoff of the inspiratory loop is apparent. On the other hand, a specific diagnose of the actual pathology need laryngeal examination during exercise. The definitive diagnosis of laryngeal obstruction might require laryngoscopy during strenuous exercise. Heimdal et al (Heimdal et al 2006) recently published a paper describing a model for use when performing the continuous laryngoscopy exercise test (CLE). Patients with asthma should start asthma medication, and for those with satisfactory adherence who do not achieve well-controlled disease, other reasons for persistent respiratory symptoms should be explored. In such cases CLE should be performed.

5. Treatment

Treatment of elite athletes with asthma can be divided into non-pharmacological and pharmacological treatment. During the last decades the International Olympic Committee (IOC) increased their focus on the increasing use of anti-asthmatic medication by Olympic and other elite athletes. At the 1996 Olympic Games in Atlanta 3.7% of the athletes used beta2-agonists, 5.6% at the 1998 Winter Games in Nagano, and 5.7% at the Sydney Games 2000. The IOC and the World Anti Doping Agency (WADA) have had many changes in the anti-doping regulations on beta2-agonists through the years, partly due to concerns regarding ergogenic effects and partly because of health risk concerns. Due to the increased use of beta2-agonists as mentioned above the IOC introduced a criterion of demonstration of asthma by an objective measure of reversibility or bronchial airway hyperresponsiveness in order approved use of beta2-agonist. This resulted in a 27% reduction in the use of beta2-agonists in the 2004 Games in Athen.

5.1 Pharmacological treatment

Treatment of asthma and exercise-induced bronchoconstriction (EIB) in elite athletes should follow international asthma treatment guidelines like the Global Initiative for Asthma (GINA), see Figure 1 (Bateman et al 2008). The main purpose of pharmacotherapy is control of asthma symptoms, reducing airway inflammation and airway hyperresponsiveness, achieving normal lung function, and prevent exacerbations

Step1	Step2	Step3	Step4	Step5
	Asthma education	and	Environmental control	
Short-acting beta2-agonist as needed		Short-acting beta2-agonist as needed		
	Select one	Select one	Select one	Select one
	Low-dose inhaled corticosteroid	Low-dose inhaled corticosteroid + Long acting beta2-agonist	Medium or high-dose inhaled corticosteroid + Long acting beta2-agonist	Oral glucocorticosteroid
	Leukotriene modifier	Medium or high-dose inhaled corticosteroid	Leukotriene modifier	Anti-IgE treatment
		Low-dose inhaled corticosteroid + Leukotriene modifier	Theophylline	
		Low-dose inhaled corticosteroid + Theophylline		

Fig. 1. Management approach. Adapted from GINA.

5.2 Beta2-agonists

Inhaled short acting beta2-agonists (SABA), e.g. salbutamol and terbutaline, are first choice therapy for fast relief of EIB. Moreover, SABA is useful in preventing EIB if taken 15 minutes before exercise. Frequent and increased use indicates uncontrolled asthma and should result in reassessment of treatment strategies. Side effects are tremor, tachycardia, palpitations and headache, which increase in frequency and intensity with higher doses. With high systemic doses hypopotassemia and muscle convulsions can occur. Systemic use of beta2-agonists by elite athletes is entirely prohibited according to the Prohibited List, see Table 1.

Inhaled long acting beta2-agonists (LABA), e.g. salmeterol and formoterol, are used in management of uncontrolled asthma treated with inhaled corticosteroid alone. LABA is used as add-on therapy to inhaled corticosteroids, either as fixed combination or in two separate devices. LABA should never be used as monotherapy in asthma due to risk of serious adverse events with increased risk of mortality in case of exacerbation. In a review from 2005 it was concluded that combined fluticasone and salmeterol was superior to fluticasone as monotherapy in preventing EIA. Furthermore, in a randomized, double-blinded study combined budesonide/formoterol was compared with budesonide alone, asthma control was better with reduced symptoms when treated with combination of budesonide/formoterol. A new study from 2010 confirms previous findings with more efficacy when inhaled budesonide is combined with formoterol among adults and adolescents with moderate to severe asthma. These findings indicate that it is not an effect related to the specific drug, but a class effect of the combination.

I SUBSTANCES AND METHODS PROHIBITED AT ALL TIMES (IN- AND OUT-OF-COMPETITION):
S0. Non-approved substances
S1. Anabolic agents
S2. Peptide hormones, growth factors and related substances
S3. Beta2-agonists
S4. Hormone antagonists and modulators
S5. Diuretics and other masking agents
M1. Enhancement of oxygen transfer
M2. Chemical and physical manipulation
M3. Gene doping
II SUBSTANCES AND METHODS PROHIBITED IN-COMPETITION:
S0-5 and M1-3 defined above
S6. Stimulants
S7. Narcotics
S8. Cannabinoids
S9. Glucocorticosterooids
III SUBSTANCES PROHIBITED IN PARTICULAR SPORTS:
P1. Alcohol
P2. Beta-Blockers

Table 1. The 2011 Prohibited List by World Anti-Doping Agency.

It is well known that regular use of beta2-agonist could lead to development of tolerance to bronchodilation (i.e. reduced bronchodilator response during acute asthma) and bronchoprotection (i.e. reduced ability to prevent exercise-induced bronchoconstriction). Tolerance to bronchodilator develops rapidly, after only few doses, and regardless of ongoing treatment with inhaled corticosteroid. Tolerance to bronchoprotection develops after few weeks of treatment and regardless of ongoing treatment with inhaled corticosteroids. The decreased bronchoprotection might result in increased use of beta2-

agonist and higher risk of side effects. Though theoretical concerns that regular beta2-agonist treatment may lead to tolerance and failure to respond to emergency asthma treatment, there is little evidence that this is a clinical problem. However, as elite athletes exercise daily and often several times a day, use of beta2-agonists, either before exercise to prevent bronchoconstriction or during/after due to bronchoconstriction, would exceed the maximal recommend weekly use in the GINA guidelines, indicating that other treatment strategies than SABA in case of EIB are needed.

5.3 Inhaled corticosteroids

Inhaled corticosteroids (ICS) are the most used and most effective inhaled anti-inflammatory drug available. ICS improves asthma symptoms, self-reported quality of life and lung function, reduces airway inflammation and airway hyperresponsiveness and furthermore, ICS has been found to reduce number and severity of exacerbations and asthma mortality (Jeffery et al 1992, Suissa et al 2000). GINA guidelines recommend ICS when asthma is uncontrolled with non-pharmacological interventions and rescue therapy alone. Effects are observed after 7-14 days, while full effects are seen after eight weeks of treatment.

Our current knowledge about effects of ICS on exercise-induced bronchoconstriction is based on adults and children with asthma. Existing studies ranges from three weeks to two years duration of treatment, mostly conducted in a parallel design. A study with 40 adult asthmatic subjects randomized to 6 weeks treatment with placebo or 800 micrograms budesonide twice a day showed a post-exercise fall in FEV_1 of 7% in the budesonide group and to 22% in the placebo group. Similar findings are reported in asthmatic children.

5.4 Leukotriene modifiers

Leukotriene modifiers have anti-inflammatory and bronchodilatory effects. Leukotriene modifiers are administered orally and once daily for montelukast and twice daily for zileuton. Montelukast is used as add-on treatment in case of uncontrolled asthma with medium dose ICS as monotherapy(Lofdahl et al 1999). Prevention of EIA is another indication in elite athletes with asthma. Studies report a reduced post-exercise fall in FEV_1 and a reduced period of bronchoconstriction after exercise when treated with montelukast compared to placebo in non-smoking asthmatic subjects. No studies have reported development of tolerance during regular use.

5.5 Cromoglycate

In a study from 2010 treatment with sodium cromoglycate decreased the FEV_1 fall after a eucapnic voluntary hyperpnoea (EVH) challenge in elite athletes with EIB (Anderson et al 2010). This finding support that release of mast cell mediators is an important factor for the severity of EIB. However, use of cromones in asthmatic elite athletes is limited.

6. Non-pharmacological interventions

Asthmatic athletes with pollen allergy should avoid prolonged outdoor endurance exercise in areas with high pollen counts. Exercise in temperatures below minus 15 degrees Celsius should be avoided, particularly in areas with air pollution or other airway irritants.

Few studies have investigated correlation between physical warm-up and degree of EIA in asthmatic athletes and a warm-up period has been shown to induce refractoriness to

EIA without itself inducing significant bronchoconstriction. The protective effect of different types of warm-up has been compared in controlled studies, but no consensus is found. Different study protocols and designs make it difficult to compare the existing studies, but physical warm-up in some form and extent seems generally to have a protective effect on EIA, and physical warm-up should be advised for all athletes with asthma. Breathing filters may reduce EIB among those exercising in cold conditions. A study from 2000 compared response to exercise in cold air (decrease in FEV_1) in nine patients with EIA when given no treatment, given premedication with a beta2-agonist, wearing a heat-and-moisture-exchanging facemask, and given both premedication and facemask. The mean maximal change in FEV_1 was 27% with no treatment, 12% with facemask, 7% with premedication, and no change with the combination of premedication and facemask. Another study from 2006 examined effects of a heat exchanger mask, placebo mask, and premedication with a beta2-agonist. Five patients with EIA performed a treadmill exercise test while breathing cold air. It was concluded that a heat exchanger mask prevented cold exercise-induced fall in lung function as effectively as treatment with beta2 agonist before exercise in cold air.

During the last decade some research has focused on nutritional factors, especially omega-3-polyunsaturated fatty acids' influence on airway inflammation and exercise-induced bronchoconstriction. A review from 2005 concluded that omega-3-polyunsaturated fatty acid supplementation reduces the degree of exercise-induced bronchoconstriction compared with placebo in patients with EIA. The review was based on a small number of studies with limited range of clinically important outcomes. Further controlled and well-designed research is needed to establish any evidence-based recommendations.

7. Treatment or doping

As mentioned above the IOC and WADA have increased their attention on the status of beta2-agonists on the "The 2010 Prohibited List" (www.wada-ama.org). Until the end of 2009 granting of a Therapeutic Use Exemption (TUE) was necessary for use of inhaled salbutamol, terbutaline, salmeterol and formoterol. From 2010 use of inhaled salbutamol and salmeterol in therapeutic doses are allowed. From 2010 use of inhaled terbutaline and formoterol is still prohibited and requires a TUE and a reasonable explanation of why these drugs are prescribed when other equal drugs are permitted. Use of inhaled corticosteroids in therapeutic doses is permitted, except when used in a fixed combination with formoterol, which requires a TUE. Use of oral or topical antihistamines or leukotriene modifiers is permitted. Use of systemic corticosteroids is prohibited during competition. Systemic intake of beta2-agonist and clenbuterol is strictly prohibited in elite athletes. The criteria for granting a TUE, the "Prohibited List", and guidelines are available on WADA's website (www.wada-ama.org). As the anti-doping legislation and the prohibited list are continually updated, it is important to be familiar with the current regulations before prescribing asthma medication to an elite athlete with asthma. The 2011 Prohibited List is shown in Table 2. For details visit WADA´s website.

In the academic societies of sports and pulmonary medicine it is discussed whether or not beta2-agonists have any ergogenic, i.e. performance enhancing effects, and if it should be considered doping or not. According to the World Anti-Doping Agency (WADA) minimum

two of three criteria must be met in order to consider a substance or method for inclusion on the Prohibited List:

1. The substance or method can be performance enhancing
2. The use of the substance or the method can endanger the athlete´s health
3. The use of the substance or method is against the spirit of sport

As it appears a substance or method can be listed without being performance enhancing. Due to health issues the IOC considers inhaled use of beta2-agonist without need unacceptable. Beta2-agonists have received much attention the last decades because of side effects, and few studies have reported and the US Food and Drug Administration have issued some concerns about beta2-agonists and side effects/serious adverse events. Regarding health issues in elite athletes using beta2-agonists the IOC is concerned about athletes using beta2-agonists without need and in supratherapeutic doses. Studies in asthmatic children have shown both significant raised and normal blood levels of myocardial stress markers after inhalation of beta2-agonists in ten times prophylactic doses. Studies with unrestrained rats have documented dose-response myocyte apoptosis after administration of the beta2-agonists formoterol and clenbuterol. Significant changes in human cardiac electrophysiological properties is seen after administration of salbutamol 5 mg as a single dose.

Several studies have investigated the ergogenic effects of inhaled and oral beta2-agonists conducted with healthy well-trained men, most studies in therapeutic doses. The extensive research on therapeutic doses of inhaled beta2-agonsits clearly rules out any ergogenic effects. Only few studies have shown ergogenic effects of inhaled salbutamol, but these are limited by enrolment of recreational subjects. It is now a common opinion that inhaled beta2-agonists in therapeutic doses has no advantageous effects in healthy athletes. However, animal and human studies, where beta2-agonists are given in systemic supra-therapeutic doses daily for few weeks, have shown evidence of improvement of muscle strength and endurance performance. Pluim et al. concluded in a systematic review and meta-analyses of randomized controlled trials on beta2-agonists and physical performance published in 2011 that there is some evidence indicating that systemic beta2-agonists may have a positive effect on physical performance in healthy subjects(Pluim et al 2011). Clenbuterol, another beta2-agonist used in veterinary medicine via prescription as a bronchodilator, cardiotonic and tocolytic agent. However used in supratherapeutic doses in animals and humans it is misused as a growth promotor with anabolic and lipolytic effects.

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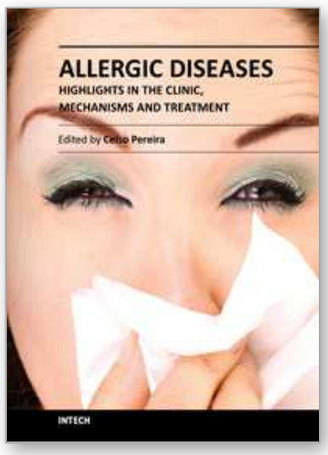

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中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
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