Ergogenic Effects of Inhaled β2-Agonists in Non-Asthmatic Athletes

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KEYWORDS

• β2-agonists • Asthma • Ergogenic potential
• Performance • Competitive athletes

Asthma is defined as a chronic inflammatory disorder of the airways with bronchial hyperresponsiveness and variable bronchoconstriction.[1] It is well recognized that physical exercise itself may cause asthmatic symptoms, described by the term exercise-induced asthma (EIA).[2] Numerous athletes suffer from EIA. The pharmacologic treatment is based on antiinflammatory drugs (eg, inhaled glucocorticosteroids [GCS]) and bronchodilators (eg, β2-agonists). These drugs are preferably administered by inhalation. Short-acting, inhaled β2-agonists are used prophylactically before exercise, when bronchoconstriction occurs with exercise, or other conditions. Long-acting β2-agonists are often used in combination with inhaled GCS as a basic treatment for severe cases.[3]

The use of β2-agonists is forbidden in athletes according to the ''Prohibited List of the World Anti-Doping Agency'' (WADA).[4] However, EIA in athletes is common and requires, in some cases, the use of inhaled β2-agonists before exercise. The proof of asthma by means of lung function and provocation tests requires a special medical examination to obtain a therapeutic use exemption (TUE).[5] The TUE process includes a complicated administrative process for the athletes and for the physicians who are responsible for the treatment. In addition, the responsibility to cover the cost for these additional tests remains unclear. Based on these considerations, the purpose of this article, as a follow-up of a recent review from 2007,[6] is to clarify whether inhaled β2-agonists have a performance-enhancing effect justifying the prohibition of these substances from the ergogenic point of view.

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EPIDEMIOLOGY OF ASTHMA IN ATHLETES

Exercise-induced asthma is common in highly trained athletes. More than 10% of competitive athletes suffer from EIA. More elite athletes suffer from asthma, compared with the general population.[7] A maximum prevalence for EIA of 45% was reported in cyclists.[8] Up to 22% of Olympic athletes from the United States and Italy (Olympic Games 1996, 1998, and 2000) had asthma.[8–11] The prevalence of asthma in other highly trained athletes was reported to be between 10% to 23%,[12–14] and in adolescent athletes between 12% and 38%.[15,16] The prevalence of EIA is high in summer and winter sports. Studies show a high prevalence of EIA especially in cross-country skiers, other so-called cold-weather-athletes,[17,18] and summer endurance athletes.[14,19] Asthma also seems more common among female athletes.[8,11,14] However, this has not been entirely confirmed in other studies.[9]

Since 1984, the percentage of athletes using inhaled β2-agonists at the Olympic Games has slightly risen.[20–24] The percentage of German Olympic athletes using β2-agonists varied between 5.1% in Athens, 12.4% in Torino, and 8% in Beijing.[25–27] The question of whether this is a real increase because of EIA or a misuse because of potential ergogenic effects remains open. The increase in the use of inhaled β2-agonists has led to more stringent anti-doping rules regarding these substances.[4]

The type of training and the kind of sport can influence the prevalence of asthma.[28] The risk for developing asthmatic symptoms is higher in endurance athletes and swimmers than in other athletes.[8–12,14,19,29–34] Asthma is particularly more common in winter-sport athletes.[10,11,31,32,35] A remarkably high prevalence of asthma was reported in Swedish cross-country skiers.[31,32] Furthermore, asthma was also more frequent in athletes who participated in Nordic-combined events, short-track events,[10,11] figure skating,[36,37] and ice hockey.[37]

The highly increased ventilation during exercise and inhalation of cold, dry air are thought to be important triggers for EIA.[38] The risk for asthma seems to be higher in athletes training more than 20 hours per week when compared with training levels below 10 hours per week.[14] Atopic disposition and exposure to pollutants are risk factors for a marked bronchoconstriction during exercise.[12,34,37,39] Finally, respiratory tract infections transiently increase the bronchial hyperresponsiveness in athletes compared with non-active subjects during exercise.[40]

The more common occurrence of asthma in swimmers[19,29,30] can be explained by a number of sport-specific issues. For example, 36% of the swimmers in the 2008 German Olympic team had asthmatic symptoms and applied for a TUE to use β2-agonists by inhalation.[27] The water in swimming pools is usually chlorinated for disinfection purposes. Because of the inhalation of air floating just above the water surface, swimmers are exposed to high concentrations of chlorine.[29] In athletes with preexisting bronchial hyperreactivity, a bronchoconstriction is the logical result of chloride-gas inhalation. Furthermore, it is assumed that the repeated exposure to chlorine gas may promote the development of asthma. Based on the results of recent studies,[41–44] it was assumed that chlorination products may provoke an increase in lung-epithelium permeability in susceptible swimmers, so that the risk for developing asthma seems to be elevated.

RECOMMENDATIONS FOR THE TREATMENT OF EXERCISE-INDUCED ASTHMA

According to the guidelines,[3,45,46] baseline therapy for asthma in athletes should be anti-inflammatory, preferably with inhaled corticosteroids. Short-acting β2-agonists should be given before exercise to prevent attacks of EIA. In athletes with only rare episodes of EIA, the prophylactical application of inhaled short-acting β2-agonists may be

sufficient. In all other athletes, a combined therapy with inhaled corticosteroids and long-acting β2-agonists is recommended.[3,45,46] Surprisingly there is no study published showing a positive effect of inhalative corticosteroids preventing EIA in elite athletes.

The efficiency of inhaled β2-agonists was demonstrated with several substances.[47,48] The positive effects for long-term acting β2-agonists, such as salmeterol and formoterol, were also shown.[49,50] Formoterol had a significant protective effect against EIA, compared with placebo, and a long duration of its effect was obtained.

Randomized and controlled studies for other substances, such as cromoglycate and nedocromil sodium, have not been conducted concerning the effects of inhaled β2-agonists on EIA in elite athletes, although there is evidence of a benefit in preventing EIA with leukotriene antagonists.[51–55]

RELEVANT SIDE EFFECTS OF INHALED β2-AGONISTS

Athletes can have fatal asthma exacerbations during and immediately after participating in sport activities, especially high-intensity training sessions or competition.[56] Therefore, sufficient diagnosis and therapy are necessary. On the other hand, adverse effects of β2-agonists can occur. The most frequent adverse effects from inhalation of β2-agonists are tachycardia and muscle fascillation/tremor, which are more pronounced with short-acting agents.[57] Further possible and relevant adverse effects are headaches and irritability, and at very high doses, hyperglycemia and hypokalemia.[57] Furthermore, the regular administration of β2-agonists may be associated with the development of tolerance to their effects and increased airway inflammation.[50,58–60] Tachyphylaxis develops with short- and long-acting β2-agonists, and the daily use of long-acting β2-agonists attenuates the bronchodilator effect of short-acting substances.[58,59,61] A combination with inhaled corticosteroids does not necessarily reduce tolerance.

TOLERANCE AGAINST INHALED β2-AGONISTS

The development of tolerance could influence the success of rescue therapy for severe EIA.[58–60] The increased tolerance is associated with downregulation of peripheral β2-receptors and desensitization of the receptors.[59] Tachyphylaxis to β2-agonists could be modulated by β2-adrenoceptor gene polymorphisms.[62]

In a recent review of the problems of inhaled long-acting β2-agonists,[63] a minor degree of tolerance to the bronchodilator activity was seen with formoterol, but not with salmeterol. However, there is a partial loss of protection against exercise-induced bronchoconstriction with regular use of either of these long-acting β2-agonists. Cardiac risks were not documented. In the same review, it was pointed out that the frequent administration of short-acting β2-agonists induces some loss of bronchodilatation and decrease in bronchoprotective action. However, it is the consensus, and scientifically proven, that the regular use of inhaled GCS and inhaled β2-agonists is state-of-the-art in the prevention of the bronchial system from chronic damage related to asthma.[45,46]

LEUKOTRIENE ANTAGONISTS

Leukotriene antagonists and cromolyn compounds (sodium cromoglycate and nedocromil) may provide an additional benefit and could be useful for athletes with asthma.[51–55] Leukotriene antagonists reduce asthma-related bronchoconstriction and inflammation. No relevant adverse effects have been reported.[52,53] Effects in the prevention of EIA in athletes were demonstrated for montelukast[52,53] and nedocromil.[54,55] On the other hand, montelukast was also shown to be of no benefit in the treatment of asthma like symptoms in elite ice-hockey players.[64] The performance

Table 1
Effects of inhaled β2-agonists on performance in elite athletes

Authors	Year	Subjects	Substance	Performance
McKenzie et al[69]	1983	Middle/long distance runners, 9 M, 10 F	Salbutamol	Performance unchanged
Bedi et al[68]	1988	Cyclists and triathletes, 14 M,1 F	Salbutamol	Endurance performance unchanged, final sprint improved
Meeuwisse et al[79]	1992	Cyclists, 7 M	Salbutamol	Performance unchanged
Morton et al[89]	1992	Middle/long distance runners, 16 M, 1 F	Salbutamol	Performance unchanged
Signorile et al[67]	1992	Recreational athletes, 8 M, 7 F	Salbutamol	Increased peak power in Wingate test
Fleck et al[90]	1993	Cyclists, 21 M	Salbutamol	Performance unchanged
Morton et al[91]	1993	Power athletes, 17 M	Salbutamol	Performance unchanged
Heir and Stemshaug[77]	1995	Cross-country skiers, marathon runners, orienteers, 17 M	Salbutamol	Running time until exhaustion decreased
Lemmer et al[92]	1995	Cyclists, 14 M	Salbutamol	Performance unchanged
Norris et al[93]	1996	Cyclists, 15 M	Salbutamol	Performance unchanged
Morton et al[94]	1996	Cyclists and triathletes, 16 M	Salmeterol	Performance unchanged
Carlsen et al[70]	1997	Cross-country skiers, biathletes, long dist. runners, 18 M	Salbutamol/salmeterol	Running time until exhaustion decreased

McDowell et al[95]	1997	Cyclists, 11 M	Salmeterol	Performance unchanged
Larsson et al[78]	1997	Cross-country skiers, middle/long distance runners, cyclists, 20 M	Terbutaline	Performance unchanged
Sandsund et al[72]	1998	Cross-country skiers, 8 M	Salbutamol	Performance unchanged
Sue-Chu et al[76]	1999	Cross-country skiers, 8 M	Salmeterol	Performance unchanged
Carlsen et al[96]	2001	Cross-country skiers, orienteers, others, 24 M	Formoterol	Performance unchanged
Goubault et al[71]	2001	Triathletes, 12 M	Salbutamol	Performance unchanged
Stewart et al[97]	2002	Highly trained athletes, 10 M	Salbutamol/formoterol	Performance unchanged
van Baak et al[73]	2004	Cyclists and triathletes, 16 M	Salbutamol	Time trial performance increased (+1.9%)
Riiser et al[74]	2006	Cross-country skiers, 20 M	Formoterol	Performance unchanged
Tjörhom et al[75]	2007	Cross-country skiers, 20 M	Formoterol	Performance unchanged
Sporer et al[98]	2008	Cyclists and triathletes, 37 M	Salbutamol	Performance unchanged

Abbreviations: F, female; M, male.

of highly trained non-asthmatic athletes is not affected by montelukast.[65] Different testing methods could have contributed to these varying results. In the study of Rundell and colleagues,[52] eucapnic voluntary hyperventilation was used for the identification of EIA, whereas other authors tested only baseline lung function or clinical aspects. In conclusion, cromolyn was less effective than β2-agonists.[66]

EFFECTS OF β2-AGONISTS ON PERFORMANCE IN ATHLETES

All studies investigating the effects of inhaled β2-agonists on physical performance in highly trained athletes are summarized in **Table 1**. The athletes were tested in randomized, double-blind, and mostly crossover placebo-controlled design. The studies by Signorile and colleagues[67] and Bedi and colleagues[68] are included, although these studies investigated recreational athletes and elite athletes in mixed cohorts. These studies are the only two published so far demonstrating a positive effect of therapeutic doses of inhaled β2-agonists on performance in athletes. All subjects were non-asthmatic, competitive athletes and had normal pulmonary function. The subjects were mainly endurance athletes such as cyclists, middle- and long-distance runners, cross-country skiers, and triathletes; in one study, power athletes were the subjects.

Differing test results, mainly ergometer and treadmill trials, were conducted by assessing, in numerous studies, the performance time until exhaustion, total exercise time, and time-trial performances. Also, sport-specific tests in ambient environments were conducted proving the laboratory results.

In most of the studies, the β2-agonists were inhaled 15 to 30 minutes before exercise. In one study, salbutamol was administered four times per day for 1 week.[69] The inhaled substances were salbutamol, salmeterol, formoterol, and terbutaline. High doses of salbutamol (800–1200μg) were given in four studies.[70–73] Proving the effects of extreme ambient conditions, five studies were conducted at an ambient temperature of −10 °C, −15°C,and −20°C and one study was conducted under hypobaric conditions.[72,74–76] In the presented studies, inhaled β2-agonists were without effect on VO2max, anaerobic threshold, alactic and lactic anaerobic power, strength performance, blood lactate, rate of perceived exertion, and psychomotor performance. In two studies, the performance in running time until exhaustion was even reduced under salbutamol[70,77] and salmeterol.[70] Even high doses of salbutamol had no ergogenic effect in four of five studies.[70–72] Furthermore, inhaled β2-agonists did not change physical performance under the stress of cold temperatures or hypobaric conditions.[72,76,78]

On the other hand, ergogenic effects were demonstrated in three studies.[67,68,73] Bedi and colleagues[68] found an increased performance in ride time in an exhaustive final sprint after salbutamol inhalation. However, two recreational cyclists were included in their study. In a subsequent study, with a similar study design, these results could not be confirmed.[79] In the study by van Baak and colleagues,[73] the inhalation of a supratherapeutic dose of salbutamol (800μg) improved the cycling performance in a time trial by 2%. The largest improvements were found in those subjects with lower performance. After inhalation of salbutamol, a better performance was seen in 11 of 16 subjects; however, this effect was minimal in five of these subjects. In the frequently cited study by Signorile, an increase in peak power during a 15 second Wingate test was observed after inhalation of salbutamol before performance. In contrast to all other studies cited here, Signorile and colleagues[67] observed only recreational athletes assuming that there might be an ergogenic effect of β2-agonists in recreational athletes.

Despite unchanged performance-related variables, the lung function was improved after inhalation of β2-agonists in most studies (measured by an increase in the forced expiratory volume in 1 second [FEV1]). Apparently, inhaled β2-agonists also induce

a small bronchodilation in healthy athletes. However, the increase in lung function does not induce enhancement in performance.

In contrast to inhaled β2-agonists, oral administration of salbutamol can induce ergogenic effects.[80–86] Oral administration of salbutamol can improve muscle strength,[80,85,86] anaerobic power,[83,84] and endurance performance in men.[81] In addition, concomitant hormonal and metabolic changes were demonstrated.[82,83] The dose needed to obtain this effect is higher than that used for therapeutic purposes in asthma. The oral administration dose of salbutamol is 10- to 20-fold greater than the dose used by inhalation.

In conclusion, inhaled β2-agonists seem to be without relevant effect on physical performance in highly trained non-asthmatic athletes. The improved lung function, as demonstrated in the majority of studies, cannot be regarded as ergogenic. The ventilation is generally considered as non-limiting during maximal exercise in young non-asthmatic subjects.[87] During maximal exercise, pulmonary ventilation is not as high as the maximal achievable ventilation. Specific inspiratory muscle training does not improve aerobic capacity.[88] There is no evidence for anabolic effects of inhaled β2-agonists.

WORLD ANTI-DOPING CODE AND THERAPEUTIC USE EXEMPTIONS

The so-called ''Prohibited List'' was first published in 1963 under the leadership of the International Olympic Committee (IOC). Since 2004, as mandated by the World Anti-Doping Code (WADA Code), WADA is responsible for the preparation and publication of this list.[4] In the current WADA list (2009), all β2-agonists are prohibited, in and out of competition. As an exception, formoterol, salbutamol, salmeterol, and terbutaline are permitted by inhalation to prevent or treat asthma and EIA. In these cases, a TUE is necessary. A specific form for this must be completed and signed by the physician and the athlete. A clinical history of the athlete and results of lung-function tests are mandatory. The complete form package, including the signed forms and the medical file, has to be sent to the responsible anti-doping organization (eg, National Anti Doping Organization [NADO], International Federation [IF]). Each anti-doping organization has to establish a TUE committee (TUEC) of at least three people experienced in sports medicine who are in charge to review the applications and to decide whether an approval for the use of β2-agonists will be granted or not.[5]

The IOC was the first anti-doping body who established concrete limits for diagnostic methods aimed to prove EIA and asthma for the 2002 Salt Lake City Olympic Winter Games in the United States. The following tests were accepted[20]: (1) bronchodilator test (increase in FEV1 of at least 12% from baseline FEV1 after the administration of a β2-agonist by inhalation); (2) bronchial provocation with either exercise challenge in the laboratory or field, or eucapnic voluntary hyperpnea test ($\geq$10% fall in FEV1, respectively); or (3) bronchial provocation with methacholine (diagnostic limits: Provocative Concentration (PC20) FEV1 <4 mg/ml or Provocative Dose (PD20) $\leq$400μg in steroid naive subjects. If subjects inhaled steroids >3 months: PC20 FEV1 $\leq$16mg/ml or PD20 $\leq$1600μg).

At the printing time of this article WADA released new regulations becoming effective from January 2010. The new reglament allows the use of two β2-agonists (salbutamol and salmeterol) by inhalation without the need for a full TUE. In these cases a so called declaration of use is sufficient. However, for the use of other inhalative substances like formoterol or terbutaline the formerly described TUE process remains the same.

SUMMARY

Empiric data suggests that some non-asthmatic athletes use β2-agonists believing this could potentially enhance their performance. However, on the basis of scientific evidence, inhaled β2-agonists do not have a relevant performance-enhancing effect in non-asthmatic competitive athletes. To prevent an overuse of non-performance–enhancing medication in general, education and prevention programs seem to be more appropriate compared to prohibition and sanctioning. For these reasons and from the ergogenic point of view, inhaled β2-agonists should not be prohibited for athletes. Considering the possibility for quantitative analysis of salbutamol, the recently implemented threshold regulation is sufficient to detect misuse of this substance. From this point of view, it would make sense to include the β2-agonists in the so-called monitoring list of the WADA anti-doping program. This inclusion would enable the anti-doping bodies to control for a possible increase in the use of β2-agonists, and in this case to bring back the substance to the list without greater efforts, if needed. On the other hand, it would significantly reduce the administrative expenses for the handling of these substances. With the announced changes of the WADA list 2010, the first step in that direction is done. Considering the limited financial and personal resources, the fight against doping should concentrate on substances and methods that have performance-enhancing effects, and therefore, lead to unfair competition conditions.

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