SUPPLEMENT

Inhaled β_2 agonists and performance in competitive athletes

W Kindermann, T Meyer

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See end of article for authors' affiliations

Correspondence to: Professor Dr W Kindermann, Institute of Sports and Preventive Medicine, University of Saarland Campus, Bldg. B 8-2, 66123 Saarbrücken, Germany; w.kindermann@mx.uni-saarland.de

Objectives: To provide an overview of the current literature on the use of inhaled β_2 agonists in non-asthmatic competitive athletes, and to assess the performance enhancing effect of inhaled β_2 agonists.
Methods: Review of the literature.
Results: Twenty randomised, placebo controlled studies (19 double blind, one single blind) were located. Only three studies reported a performance enhancing effect of inhaled β_2 agonists. However, methodological shortcomings were most likely responsible for these findings (for example, non-elite athletes, inconsistent results in different tests, subgroups with above-average responsiveness).
Conclusions: This review reveals that there is no ergogenic potential of inhaled β_2 agonists in non-asthmatic athletes. In view of the epidemiology of asthma in athletes and the considerable workload involved in provision of therapeutic use exemptions the inclusion of inhaled β_2 agonists on the list of prohibited substances should be reconsidered.

Asthma is a chronic inflammatory airway disorder. Some external stimuli, mainly pollutants and air dust, can lead to bronchial hyperresponsiveness and bronchoconstriction. In addition, there exists a genetic predisposition. Asthma is one of the most frequently occurring chronic diseases, and its prevalence in the adult population is about 5%. Among athletes, however, it is assumed to be 10–20%.[1 2]

A number of factors can induce an acute asthmatic attack, including exposure to pollen or dust, contact with animals or chemical substances, the intake of certain drugs (for example, non-steroidal anti-inflammatory drugs), viral infections, and psychological stress.[3–6] Also, it is well recognised that acute physical exercise may give rise to asthmatic symptoms—described by the term ''exercise induced asthma'' (EIA).[1 7] Inhalation of large volumes of cold, dry air with the subsequent development of a bronchial edema seems to play a substantial role, thus athletes participating in winter sports are more frequently affected than those competing in other disciplines.[2 7–11] Endurance athletes experience EIA more frequently than other sportspeople. Despite the somewhat favourable humid conditions during swimming, the frequency of EIA is particularly high in this discipline[12–14]—presumably due to the inhalation of chlorine gas, a known provocative agent.[12 15]

Inhaled β_2 agonists, which are among the drugs of choice for treatment of asthma, are prohibited for non-asthmatic athletes according to the most recent list of prohibited substances released by the World Anti-Doping Agency (WADA).[16] This means that an athlete with asthma or EIA has to prove the presence of the disease to a medical committee of their national or an international ruling body and wait for grant of a therapeutic use exemption (TUE) before they can start β_2 agonist treatment.

The main reason for prohibition of the use of inhaled β_2 agonists in non-asthmatic athletes is its claimed ergogenic potential. This article critically examines the scientific basis of this assumption.

DIAGNOSING ASTHMA

Asthma is suspected when typical respiratory/expiratory symptoms are present, but the diagnosis is usually confirmed by means of additional (technical) investigations. Respiratory symptoms can have many causes. Often the reason for shortness of breath, and even wheezing during exercise in poorly conditioned individuals, is lack of fitness, sometimes leading to a misdiagnosis of asthma. For a reliable diagnosis, lung function tests are necessary. In severe cases, simple resting spirometry with measurement of forced expiratory volume in one second (FEV_1) is sufficient. If FEV_1 is reduced or increases after inhalation of a β_2 agonist by at least 12%, the presence of asthma can be assumed.[17] For most cases of EIA or a hyperresponsive bronchial system, provocation tests are necessary, such as ergometric tests measuring lung function before the onset of exercise and after its cessation. If such procedures are not conclusive for establishing the diagnosis, field tests under sport specific conditions could be an alternative. A test is considered positive if the FEV_1 drops by more than 10% after exercise. Other lung function tests involve the inhalation of test substances such as methacholine, which can induce bronchoconstriction. When an allergy against particular substances/pollen is suspected to be the underlying cause (recurring seasonal variation of complaints), diagnostic allergy tests are necessary.

For documentation of asthma, and/or EIA, or exercise induced bronchoconstriction the following tests are considered appropriate by the International Olympic Committee (IOC):[17]

- bronchodilator test—increase in FEV_1 of at least 12% of the baseline FEV_1 after the administration of a β_2 agonist by inhalation
- bronchial provocation tests—eucapnic voluntary hyperpnea test, exercise challenge in the laboratory or in the field, hypertonic aerosol, methacholine test.

A urine salbutamol concentration of >1000 ng/ml is considered as positive doping test because this concentration cannot be achieved by inhalation alone.

THERAPEUTIC MANAGEMENT OF ASTHMA IN ATHLETES

There is no difference in the basic medical treatment of asthma in athletes and the general population. According to current guidelines the baseline therapy of asthma should be

Abbreviations: EIA, exercise-induced asthma; TUE, therapeutic use exemption; WADA, World Anti-Doping Agency

anti-inflammatory in nature, preferably inhaled corticosteroids. Shortly before the onset of exercise, inhalation of a short acting β_2 agonist is useful in preventing an EIA attack. Prophylactic administration of inhaled short acting β_2 agonists alone may be sufficient in athletes with infrequent episodes of EIA. In all other athletes, a combination of inhaled corticosteroids and long acting β_2 agonists is recommended. Overdose of inhaled[2] β_2 agonists may lead to side effects such as heart palpitations, tachycardia, tremor or ectopic beats. Somewhat surprisingly, apart from formoterol,[18] no randomised controlled studies have been conducted concerning the effects of inhaled β_2 agonists on EIA in athletes.

Athletes with asthma on long term treatment may obtain additional symptom relief with leukotrienes and cromolyn compounds (sodium cromoglycate and nedocromil). Montelukast[19] as well as nedocromil[20 21] have been shown to be effective in the prevention of EIA in athletes. Both drugs have a favourable effect on bronchoconstriction as well as on the inflammatory reaction. Adverse effects have not been reported so far. However, montelukast remained without benefit in the treatment of asthma-like symptoms in elite ice hockey players[22] for unknown reasons. Overall, there is evidence that sodium cromoglycate and nedocromil are less effective than β_2 agonists.[23]

DO INHALED β_2 AGONISTS AFFECT ATHLETIC PERFORMANCE?

We found 20 randomised, placebo controlled studies (19 double blind, 1 single blind) that addressed the effect of inhaled β_2 agonists on physical performance in non-asthmatic athletes with documented normal resting pulmonary function. Eighteen of these included endurance athletes such as cyclists, middle and long distance runners, cross-country skiers, and triathletes, one study was in power athletes,[24] and one in recreational subjects.[25] In most of the studies, β_2 agonists were inhaled between 15 and 30 minutes prior to the onset of exercise. High doses, between 800 μg and 1200 μg, of salbutamol were given in four studies.[26–29] Moreover, three studies were performed in cross-country skiers at ambient temperatures of −10°C and −15°C,[28 30 31] which closely resembled a typical situation for the onset of EIA. In 15 studies salbutamol was the substance investigated and salmeterol in 4, formoterol in 2, and terbutaline in 1; two investigations compared two different β_2 agonists (salbutamol/formoterol, salbutamol/salmeterol, both studies appear in tables 1 and 2). Details of the ergometric testing procedures as well as other study variables are given in tables 1 and 2.

Ergogenic effects were demonstrated in three studies only.[25 29 32] Signorile *et al*,[25] in a frequently cited investigation,

Table 1 Effects of inhaled β_2 agonists on performance of non-asthmatic competitive athletes (studies using salbutamol)

Authors	Study type	Subjects	Dosage	Bronchoprovocation	Performance and other findings
Bedi *et al*, 1988[32]	Crossover	Cyclists and triathletes 14 M, 1 F	180 μg	Histamine	= One hour ride (70–75% VO_2 max) ↑ Exhaustive final sprint (~3 min)
Carlsen *et al*, 1997[26]	Crossover	10 Cross-country skiers 2 Biathlon 6 Long distance runners 18 M	800 μg	–	= VO_2 max = Anaerobic threshold ↓ Running time until exhaustion (~ 4 min)
Fleck *et al*, 1993[35]	Crossover	Cyclists 21 M	360 μg	Methacholine	= VO_2 max, maximal workload = Maximal lactate = RPE
Goubault *et al*, 2001[27]	Crossover	Triathletes 12 M	200 μg 800 μg	–	= Cycling time until exhaustion (85% VO_2 max; ~ 23 min) = Maximal lactate = Psychomotor performance
Heir and Stemshaug 1995[34]	Crossover	9 Cross-country skiers 5 Marathon runners 3 Orienteers 17 M	0.05 mg/kg	–	= VO_2 max ↓ Running time to exhaustion (110% VO_2 max; ~ 6 min)
Lemmer *et al*, 1995[36]	Crossover	Cyclists 14 M	360 μg	Methacholine	= Anaerobic performance = Maximal lactate
McKenzie *et al*, 1983[37]	Independent samples	Middle and long distance runners 9 M,10 F	4 × 200 μg daily (1 week)	–	= VO_2max = Ventilatory threshold
Meeuwisse *et al*, 1992[33]	Crossover	Cyclists 7 M	200 μg	–	= VO_2 max = Exhaustive final sprint = Anaerobic capacity
Morton *et al*, 1992[38]	Crossover	Middle and long distance runners 16 M, 1 F	200 μg	Histamine	= VO_2 max = Anaerobic performance = Maximal lactate = RPE
Morton *et al*, 1993[24]	Crossover	Power athletes 17 M	200 μg	–	= Anaerobic performance = Strength performance
Norris *et al*, 1996[39]		Cyclists 15 M	400 μg	–	= VO_2 max = 20 km time trial = Anaerobic performance
Sandsund *et al*, 1998[28]	Crossover	Cross-country skiers 8 M	1200 μg	Methacholine	= VO_2 max = Running time until exhaustion (~ 6.5 min) = Lactate performance curve
Signorile *et al*, 1992[25]	Crossover	Recreational athletes 8 M,7 F	180 μg	–	↑ Peak power during 15 s Wingate test
Stewart *et al*, 2002[40]	Crossover	Highly trained athletes 10 M	400 μg	Methacholine	= VO_2max = Anaerobic performance
van Baak *et al*, 2004[29]	Crossover	Cyclists and triathletes 16 M	800 μg	–	↑ Time trial (~ 67 min), performance +1.9% = Lactate during trials

= Unchanged, ↑ increase, ↓ decrease.
M, males; F, females; RPE, rate of perceived exertion.

Table 2 Effects of inhaled β_2 agonists on performance of non-asthmatic competitive athletes (studies using salmeterol, formoterol, orterbutaline)

Authors	Study type	Subjects	Substance	Dosage	Bronchoprovocation	Performance and other findings
Carlsen *et al*, 1997[26]	Crossover	10 Cross-country skiers 2 Biathlon 6 Long distance runners 18 M	Salmeterol	50 μg	–	= V_{O_2} max = Anaerobic threshold ↓ Running time until exhaustion (~ 4 min)
Morton *et al*, 1996[41]	Crossover	Cyclists and triathletes 16 M	Salmeterol	50 μg	Methacholine	= Anaerobic performance = Strength performance = Fine motor control = Reaction time
McDowell *et al*, 1997[42]	Crossover	Cyclists 11 M	Salmeterol	42 μg	Methacholine	= Anaerobic performance = Maximal lactate
Sue-Chu *et al*, 1999[31]	Crossover	Cross-country skiers 8 M	Salmeterol	50 μg	Methacholine	= V_{O_2} max = Running time until exhaustion (~ 6.5 min) = Lactate performance curve
Carlsen *et al*, 2001[43]	Crossover	11 Cross-country skiers 5 Orienteers 8 Other athletes 24 M	Formoterol	9 μg	–	= V_{O_2} max = Running time until exhaustion (105% V_{O_2} max; ~ 5 min)
Stewart *et al*, 2002[40]	Crossover	Highly trained athletes 10 M	Formoterol	12 μg	Methacholine	= V_{O_2} max = Anaerobic performance
Larsson *et al*, 1997[30]	Crossover (single blind)	8 Cross-country skiers 8 Middle long distance runners 4 Cyclists 20 M	Terbutaline	3 mg	Methacholine	= V_{O_2} max = Total exercise time (~ 25 min) = RPE

= Unchanged, ↓ decrease.
M, male; RPE, rate of perceived exertion.

observed increased peak power outputs during repeated 15 s Wingate tests. However, their subjects were not competitive but recreational athletes. This lower fitness status might be linked to different exercise limitations during repetitive anaerobic exercise bouts that can be overcome by bronchodilation. Bedi *et al*[32] found cycling time increased after the inhalation of 180 μg salbutamol during a trial including an exhaustive final sprint. However, they included two recreational cyclists in their study. In a subsequent study of similar design, these results could not be confirmed.[33] van Baak *et al*[29] found that the inhalation of a supratherapeutic dose of 800 μg salbutamol improved cycling time trial performance by 2%. The largest improvements, however, were found in the subjects with the worst performance. Of 16 subjects, performance in 11 improved after inhalation of salbutamol, but the effect remained rather small in 5 of them. In contrast, in two studies running time until exhaustion was reduced under salbutamol and salmeterol.[26 34] Even high doses of salbutamol had no ergogenic effect in three of four studies.[26–28] Furthermore, inhaled β_2 agonists did not influence physical performance under cold conditions.[28 30 31] In contrast with inhalation of β_2 agonists, oral administration of salbutamol can improve muscle strength[44–46] and endurance performance.[47 48] However, the dose needed to obtain such an effect is 10–20-fold greater than the dose used for inhalation.

Altogether, inhaled β_2 agonists do not seem to affect physical performance in non-asthmatic competitive athletes. In addition, there is no evidence for anabolic effects of inhaled β_2 agonists. It is noteworthy that after inhalation of β_2 agonists, lung function improved in most studies (typically measured by an increase in FEV_1). Apparently, inhaled β_2 agonists also induce some degree of bronchodilation in healthy athletes. This improved lung function, however, does not lead to performance enhancement in competitive athletes, perhaps because the ease of ventilation is generally not a limiting factor during maximal exercise in young non-asthmatic subjects.[49] During maximal exercise pulmonary ventilation is not as high as the maximal achievable ventilation during clinical tests of ventilation.

β_2 AGONISTS AND ANTI-DOPING REGULATIONS

WADA publishes an updated list of prohibited substances and methods (Prohibited List) every year as an international standard. Currently, all β_2 agonists are prohibited in and out of competition[16] with the exception of only formoterol, salbutamol, salmeterol and terbutaline when they are used for inhalation to prevent and/or treat asthma and EIA. An abbreviated TUE is necessary for an athlete to be able to receive such treatment. The application for a TUE is sent to the responsible national association which then submits it to the international association for international-level athletes and to the respective national anti-doping agency for national-level athletes. The association is required to fill out an application form which has to be signed by both the physician and the athlete. Results of lung function tests must be submitted with the application. A TUE is not issued before approval by an independent medical panel. The time needed to make a decision can be up to several weeks, but the Fédération Internationale de Football Association (FIFA) and the Union of European Football Associations (UEFA) have established the practice of temporary immediate approval

What is known about this topic

Inhaled β_2 agonists are included in the list of prohibited substances for non-asthmatic athletes because they are considered performance enhancing.

What this study adds

This review of twenty original articles about the effects of inhaled β_2 agonists on athletic performance, suggests that they do not have ergogenic potential. In view of the epidemiology of asthma in athletes as well as the considerable administrative workload involved in issuing a TUE, we recommend that inclusion of inhaled β_2 agonists on the list of prohibited substances should be reconsidered.

and request for the substantiated clinical diagnosis later, if required.

Obviously, the administrative burden for acquiring permission to use inhaled β_2 agonists is substantial. For many athletes, the proof of presence of asthma by means of lung function tests and provocation tests requires specialised medical investigation. This can have considerable costs. In contrast with glucocorticosteroids, inhaled β_2 agonists, or asthma sprays, are not only banned for competition but also for training, which further magnifies the problem.

PRACTICAL IMPLICATIONS

A number of non-asthmatic athletes consider inhaled β_2 agonists ergogenic although scientific evidence clearly disregards a performance enhancing effect. Drug intake by these athletes, thus, can be labelled ''misuse''. However, several other (permitted) substances such as acetylsalicylic acid and other analgesics (for example, diclofenac) with well known side effects are used much more frequently without indication.[50] It is therefore questionable if the documented misuse of inhaled β_2 agonists is a sufficient argument to prohibit their use.

The prevalence of asthma in athletes has been demonstrated to be higher than in the non-athletic population, which implies a more frequent indication for the use of β_2 agonists. The requirement for TUEs obviously leads to considerable administrative workload for athletes, physicians, and associations. This may even interfere with appropriate drug therapy in some althletes. It is highly questionable if such expenditures are necessary and if they really promote the fight against doping. Campaigns to educate athletes and coaches about the appropriate use of asthma sprays and their lack of performance enhancing efficacy seem more promising.

In summary, the inclusion of β_2 agonists on the Prohibited List should be newly discussed becaused of their lacking ergogenic effects. Furthermore, the limited financial and human resources of the fight against doping may be better focused on substances and methods which have a proved performance enhancing effect and, therefore, a much larger potential to elicit unfair competition—anabolic steroids, erythropoietin, human growth hormone, insulin-like growth factor, blood doping, and similar substances and methods.

Authors' affiliations

W Kindermann, T Meyer, Institute of Sports and Preventive Medicine, Faculty of Clinical Medicine, University of Saarland, Saarbrücken, Germany

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