The Asthmatic Athlete: Inhaled Beta-2 Agonists, Sport Performance, and Doping

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Abstract: The asthmatic athlete has a long history in competitive sport in terms of success in performance and issues related to doping. Well documented are detailed objective tests used to evaluate the athlete with symptoms of asthma or airway hyperresponsiveness and the medical management. Initiated at the 2002 Salt Lake City Games, the International Olympic Committee's Independent Asthma Panel required testing to justify the use of inhaled beta-2 agonists (IBAs) in Olympic athletes and has provided valuable guidelines to the practicing physician. This program was educational and documented the variability in prevalence of asthma and/or airway hyperresponsiveness and IBA use between different sports and different countries. It provided a standard of care for the athlete with respiratory symptoms and led to the discovery that asthmatic Olympic athletes outperformed their peers at both Summer and Winter Olympic Games from 2002 to 2010. Changes to the World Anti-Doping Agency's Prohibited List in 2010 permitted the use of 2 IBA produced by the same pharmaceutical company. All others remain prohibited. However, there is no pharmacological difference between the permitted and prohibited IBAs. As a result of these changes, asthmatic athletes are being managed differently based on a World Anti-Doping Agency directive that has no foundation in pharmacological science or in clinical practice.

Key Words: asthma, airway hyperresponsiveness, inhaled beta-2 agonists, WADA, Olympic Games performance

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INTRODUCTION

The asthmatic athlete is commonly encountered in elite competitive sport and has attracted considerable attention as a result of their prevalence, performance at major games, and issues related to doping. Although there is extensive literature on asthma, there is surprisingly little information on the elite athlete with this condition. The descriptive physiological data are scant, and clinical studies in this population are rare. This article will cover the important clinical aspects of asthma in this population, with an emphasis on the controversy surrounding the regulations and use of inhaled beta-2 agonists (IBAs).

PREVALENCE

The recent substantial increase in the reported prevalence of asthma worldwide has led to numerous studies of the prevalence and characteristics of this condition.[1,2] Although genetic predisposition is evident, gene-by-environment interaction is responsible for much of the variation in prevalence rates. A wide variation exists, from a low prevalence (2%-4%) in Asia to that (15%-20%) in the United Kingdom, Australia, New Zealand, Canada and other developing countries.[3,4]

At major sporting events where the prevalence of asthma has been documented with pre-competition pulmonary function testing, the number of athletes with asthma is in the range of 7% to 8% but with a large variation based on sport.[5,6] Asthma is most commonly seen in endurance events, with fewer athletes in the shorter duration high-intensity intermittent activities such as judo, wrestling, and weightlifting and fewer still in the non–physically demanding skill sports such as archery and shooting. Sports that require high minute ventilation for extended periods expose athletes to environmental factors that may damage the airways and result in a high prevalence of airway hyperresponsiveness (AHR).[7] Cold dry air, particulate matter, and by-products of chlorine are the 3 factors known to injure the airways and increase AHR. Consequently, cycling, triathlon, swimming, endurance snow, and some ice sports have been those with the highest percentage of athletes approved for IBA use.[8] Some clinicians have coined the phrase "sports asthma" implying that participation in sport may actually "cause" asthma, and there is increasing evidence that this may be so and explain the late development of asthma in many elite endurance athletes.[9,10] Fortunately, there is some evidence that this condition may be partially reversible once their competitive career is finished.[11]

CLINICAL PRESENTATION AND DIAGNOSIS

Participation in strenuous sports can result in symptoms that may suggest asthma or AHR. The athlete may present with the classic symptoms of dyspnea, wheezing, chest tightness, sputum production, and cough. Frequently, the clinical picture is atypical, and the predominant symptoms are dyspnea out of proportion to the exercise task, a transient post-exercise cough, and poor performance.[12] Wheezing and waking with shortness of breath are less prevalent in athletes than in the general

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population.[13] In many athletes, the relationship between asthma symptoms and documented AHR is poor.[14,15] Thus, it is medically responsible to confirm the presence of asthma and/or AHR before commencing treatment with pharmaceutical agents that could be life long.

In addition to a clinical history and examination, the diagnosis should be confirmed by either a bronchodilator test (a simple procedure that can be performed in a consulting room) or a direct or indirect bronchial provocation test that requires a pulmonary function laboratory (Table). It is important to test these athletes; justification to require a confirmed diagnosis was contained in the report of 266 athletes in the 2004 British Olympic team. Asthma had been misdiagnosed in 21% but undiagnosed in 2.6%.[16]

Currently, exercise challenge, which for several decades was the preferred indirect test, has been largely superseded by the eucapnic voluntary hyperpnea (EVH) test. Recently, the use of mannitol as a provocation agent has become available in an increasing number of countries, although it has not yet achieved approval globally.[8,17] At the Beijing Olympic Games, a breakdown of the 650 new applications from athletes to inhale a beta-2 agonist (IBA) revealed that EVH testing comprised 28.8%, exercise 6.5%, mannitol 4.6%, and hypertonic saline 1.5%, whereas bronchodilator tests comprised 22.5% and methacholine 36.1%. Of the National Olympic Committees with the greatest number of applications, EVH testing was preferred in Great Britain, Canada, and Australia; methacholine in the Netherlands, Germany, Switzerland, and France; exercise in the United States; and bronchodilator tests in Japan and Italy (International Olympic Committee Independent Asthma Panel, unpublished data, 2010).

MANAGEMENT

The management of the athlete with asthma is not appreciably different than for the nonathlete and should follow current consensus guidelines, such as the Global Initiative for Asthma[18] and the Canadian Guidelines that provide specific recommendations.[19] Recent task forces have summarized the current knowledge regarding highly trained athletes.[8,20] Education, environmental control, identification of triggers, and comorbid conditions are essential components of an action plan for the asthmatic athlete.[7] Adequate warm-up can induce a refractory period and reduce the likelihood of exercise-induced bronchoconstriction (EIB) for several hours.[21]

Inhaled corticosteroids represent the basis for treatment with rapid-acting IBAs used to optimize airway control, relieve acute intermittent symptoms, and prevent EIB. It is important to recognize that regular use of IBAs leads quickly to tolerance (tachyphylaxis) and their bronchoprotective effect is rapidly diminished.[22] For this reason, the minimum dose and frequency of IBAs to protect against EIB and to manage symptoms are recommended to minimize this loss of therapeutic effect. Monotherapy with a long-acting IBA must be avoided; such treatment can trigger severe asthma events and result in other serious medical consequences.[19]

DOPING VERSUS HEALTH

The World Anti-Doping Agency (WADA) is "the world leader on health, medical, and research issues related to drug-free sport." Their programs have changed the landscape of doping control, and indeed sport, and they are providing valuable and necessary leadership in this domain. In terms of doping, each year, WADA creates a Prohibited List that identifies the substances and methods not allowed in sport. Substances are included on the Prohibited List if they meet 2 of 3 criteria: (1) medical or scientific evidence that the substance has the potential to enhance or enhances sport performance; (2) the substance represents an actual or potential risk to the health of the athlete; and (3) the substance violates the "spirit of sport" as identified in the WADA code. Inhaled beta-2 agonists do not enhance performance but do represent a health risk. As nonasthmatic athletes may take this medication in the belief that it will improve their performance, the nonintended use of IBAs violates the spirit of sport and

TABLE. Tests to Confirm Asthma and/or Airway Hyperresponsiveness

Type of Test	Test and Description	Criteria for Positive
Bronchodilator		
Bronchodilator	Inhale a rapid-acting beta-2 agonist	≥12% or greater increase in baseline FEV_1
Provocation tests	Exercise challenge in the laboratory or	≥10% reduction in baseline FEV_1
Indirect tests	sport specific in the field of 6-minute to 8-minute	
Exercise	duration achieving 85% to 95% of maximum heart rate	
Eucapnic voluntary hyperpnea	Ventilate at 30 × FEV_1 for 6 minutes breathing dry air containing 5% carbon dioxide at room temperature	≥10% reduction in baseline FEV_1
Hypertonic saline	While tidal breathing, inhale nebulized 4.5% hypertonic saline for increasing periods	≥15% reduction in baseline FEV_1
Mannitol	Inhale increasing doses of dry powdered mannitol to a maximum cumulative dose of 635 mg	≥15% reduction in baseline FEV_1
Direct tests	Increasing concentrations of aerosol methacholine are	≥20% reduction in FEV_1 to a PC_{20} ≥4 mg/mL
Methacholine	delivered either via tidal breathing (preferred) or dosimeter methods	or if glucocorticosteroids have been inhaled ≥1 month, a PC_{20} ≥16 mg/mL

Other direct tests such as histamine, carbachol, and AMP have been used but are not recommended.
FEV_1, forced expiratory volume in 1 second (L); PC_{20}, provocative concentration of methacholine causing a 20% fall in FEV_1; AMP, adenosine monophosphate.
AMP, adenosine monophosphate; FEV_1, forced expiratory volume in 1 second (L); PC_{20}, provocative concentration of methacholine causing a 20% fall in FEV_1.

thus the inclusion of these substances on the Prohibited List is justified.

Although there were concerns that IBAs might confer a competitive advantage to the asthmatic athlete, there is extensive literature that demonstrates that when inhaled, even in supramaximal doses, beta-2 agonists do not possess ergogenic properties.[23–28] This is not the case with oral preparations.[29]

It is very clear that asthma is a health issue, and there are compelling data that document the health risks associated with asthma and the pharmacological treatment of this condition. Inhaled beta-2 agonists are not benign medications. The US Food and Drug Administration recently (2010) announced new safety controls and labeling requirements for long-acting IBAs for the treatment of asthma in the United States.[30] The safety concerns were related to an increased risk of severe asthma exacerbations requiring hospitalization and an increased risk of death in some patients with asthma. These concerns continue to be expressed in the lay and medical literature.[19,31]

BETA-2 AGONISTS AT THE OLYMPIC GAMES

Inhaled beta-2 agonists became available shortly before the 1972 Olympic Games, where the International Olympic Committee's (IOC's) Medical Commission prohibited them. In 1975, the IOC permitted IBA subject to prior notification, and this persisted until 2002 except for 1986-1993 when IBAs were permitted unrestrictedly in sports.[32] However, because of a major increase in notifications of IBA use from Atlanta 1996 to Sydney 2000, a symposium was convened in May 2001 and the IOC resolved to require athletes to demonstrate the presence of asthma and/or AHR to be permitted to use IBAs at the Olympic Games. An Independent Expert Panel (IP) was established to implement and oversee this program, the outcomes of which were published after Salt Lake City 2002[5] and Athens 2004.[6] Approvals, although not termed a Therapeutic Use Exemption (TUE), were, in fact, a TUE and were valid for 4 years including the next games of the same type.

In January 2008, after 3 Olympics and pressure from WADA, the IOC convened a consensus conference to examine its policy and invited acknowledged experts including one chosen by WADA. The outcome was that the policy was deemed to be appropriate, and the athletes were to continue to justify their need for IBAs and did so for Beijing 2008.[8]

At the last 3 Olympic Games 2006-2010, the percentage of athletes applying for and meeting the criteria to use IBAs has been stable: 7.1% to 7.7%. This percentage probably understates the prevalence of asthma because an additional 0.5% of athletes in 2006 and 1.1% in 2008 managed their asthma with inhaled corticosteroids (ICS) without IBAs. No data on ICS were available in 2010. Thus, approximately 8.2% (2006) and 8.3% (2008) of athletes had asthma/AHR, making it the most common medical condition affecting Olympic athletes.

PERFORMANCE

An unexpected outcome of the IP program requiring documentation of asthma was that Olympic athletes with asthma have consistently outperformed their nonasthmatic peers (Figure).[8,33] At the Beijing Olympic Games, where 7.2% were approved for IBA use, data were available on only 2 sports with many individual medals and a high prevalence of IBA use. In 2008, 19.1% of swimmers were approved for IBA use and won 32.9% of the individual medals awarded, whereas 17.3% of cyclists were permitted to use IBAs and won 28.9% of individual medals (International Olympic Committee Independent Asthma Panel, unpublished data, 2010).

The Figure demonstrates that Winter Olympic athletes with asthma are relatively more successful than their Summer Olympic counterparts, and this is considered to be related, in part, to the number of individual medals awarded in endurance or nonendurance sports. Many individual medals are awarded in nonendurance summer sports, such as boxing (33), gymnastics (45), judo (42), shooting (45), tae kwon do (24), weightlifting (45), and wrestling (54) with low prevalence of asthma, and many of these sports include a high proportion of elite competitors from countries known to have a low prevalence of asthma such as eastern Europe, Asia, and Africa. In contrast, very few individual medals are on offer in triathlon (6), rowing (6), and hockey (0), sports with some of the highest percentage of asthmatic competitors. In Winter Olympic Games, cross-country skiing, speed skating, and biathlon are the sports with a high prevalence of asthma and significant numbers of individual medals awarded.

To date, there is no satisfactory explanation for this observation that has been repeated at every Olympic Games since 2000. Is it the irritants, pollutants, and extremes of temperature in the air inspired during the high minute ventilation necessary while training and competing that leads to airway injury and remodeling? Do these physiological changes associated with asthma represent a training stimulus not available to the nonasthmatic athlete? Is there a unique genetic profile of the asthmatic athlete and their response to training and medication? It is accepted that the harder an athlete trains, the better he/she performs. But is it because of the increased frequency that such elite endurance athletes inhale large minute volumes of often potentially injurious air that they have a greater prevalence of asthma/AHR? These observations merit a well-funded, basic and applied, hypothesis-driven research program. Finally, it should be recognized

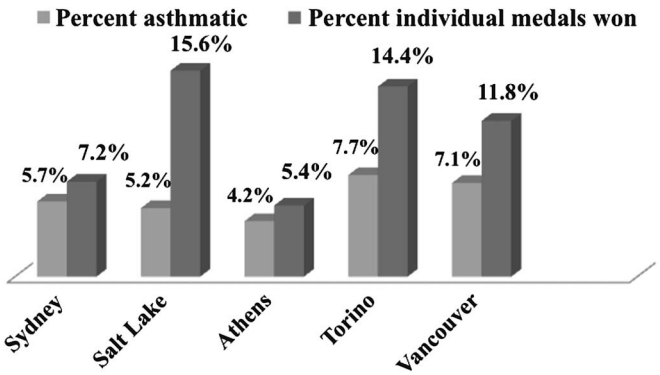

FIGURE. The percent of athletes with documented asthma/airway hyperresponsiveness, and the percent of medals they won at the Olympic Games in individual events.

that it was the IOC's IP program that provided these data that led to these important observations and underline the necessity of objective testing to identify athletes with AHR/asthma.

LESSONS FROM THE FIELD OF PLAY

In 2009, WADA introduced a TUE for athletes to use IBAs and established the same criteria and duration of approval as the IOC.[34] However, within 4 months, forces in and outside of WADA were pressing to rescind this decision[35] and did so in a way that was pharmacologically inexplicable. From 2010, salbutamol and salmeterol were permitted in sport—it was essential to declare use on the doping control form if tested. All other IBAs remained prohibited.[35] More perplexing and unreasonable is the requirement that to prescribe a prohibited IBA, it is necessary to provide an explanation why a permitted IBA is not being used. For athletes with newly diagnosed asthma, permitted IBAs are expected to be the primary treatment unless otherwise justified.

Thus, the 2010 WADA regulations determined what medications doctors could prescribe for the management of their elite athlete patients with asthma. However, there is no pharmacological difference between salbutamol (permitted) and terbutaline (prohibited) or indeed other short-acting IBAs,[36] although consensus guidelines, such as the Global Initiative for Asthma, indicate that long and rapidly acting formoterol (prohibited) has advantages over long and slowly acting salmeterol (permitted).[18]

Data obtained at the 2010 Olympic Games show that the decision to alter the regulations for the use of IBAs was premature. Of the 186 athletes who were approved for or declared IBAs at the 2010 Olympic Games in Vancouver, 181 had a valid TUE and yet 85 athletes used only permitted IBAs and thus did not require a TUE. Of the 5 without a valid TUE, 4 had TUEs that had expired in December 2009 and the fifth had been managed solely with ICS and, on the last possible day, declared the use of salbutamol (International Olympic Committee Independent Asthma Panel, unpublished data, 2010). Thus, as predicted, the increased workload associated with TUEs for IBAs occurred predominately in 2009, and with a 4-year approval, most athletes would not have required further testing until 2012-2013.

The athlete with cough and dyspnea deserves the same quality of medical care as the athlete with musculoskeletal symptoms. Competent sports physicians are expected to undertake suitable laboratory and imaging investigations to determine a finite diagnosis before instituting treatment in significant medical conditions and injuries in their athlete patients. One of the benefits of the requirement to document the presence of asthma/AHR before initiating treatment was the education of the primary care and sports physician. Rather than simply prescribing an inhaler, justification in terms of a diagnosis was required. Spirometry and challenge tests were required, and WADA and the IOC provided the details of these tests. A process was established that was in the best interest of the health of the asthmatic athlete.

The World Anti-Doping Agency should have no role in determining medical treatment, but this decision has resulted in changes to the management of athletes with asthma, and this is confirmed by the experiences of sport physicians and TUE committees from international federations. Athletes are not applying for renewal of the medication that has controlled their asthma successfully and are simply switching to the permitted drugs to avoid the expense of testing and the paperwork involved in applying for a TUE. As the British experience demonstrated, some may not have asthma.[16]

The "playing field" is not level. Athletes who wish to use or have been adequately managed with terbutaline or formoterol require specific testing and a letter explaining why they are not using the alternative "permitted" medication. Athletes wishing to use salmeterol or salbutamol simply declare their use. Athletes with AHR or asthma are treated differently based on a pharmaceutical bias that has no foundation in science or clinical practice.

In 2008, WADA decreed that all athletes wishing to use an IBA must complete an Abbreviated TUE application; in 2009, a Standard TUE was necessary, and in 2010, there is now a list of permitted and prohibited long-acting and short-acting IBAs. The disease has not changed, the drugs are pharmacologically identical, but the rules governing the use have changed each year. There is more at play than the well-being of the athlete.

THE FUTURE

With the substantial increase in the prevalence of asthma worldwide, the fact that asthma is the most common medical condition in the elite athlete and the recent warnings and concerns expressed about IBA, now is not the time to take a step back and allow the use of IBAs in athletes without objective data to justify their use. The health of the athlete must be the top priority and should not be forfeited for the sake or ease of bureaucracy.

The principles of standard clinical practice must be observed. For athletes with symptoms suggestive of asthma, there are well-established tests that can and should be used to document this condition. The management of athletes with asthma is also contained in the consensus statements produced by experts with extensive experience with this population.

Inhaled beta-2 agonists are not benign drugs, and there is a steady stream of controversy regarding their use, particularly the long-acting IBA. Although not ergogenic, they nevertheless pose a risk to the health of the athlete. The World Anti-Doping Agency and the IOC are correct in the need for these to be regulated.

Middle ground is a life-long TUE issued to athletes with objectively defined AHR/asthma. As noted, most of this work has been done on the existing pool of athletes.

The fact that in both summer and winter sports asthmatic athletes repeatedly outperform their peers requires prompt investigation and an explanation. Medical decisions to optimize treatment must be made by attending physicians based on empirical data and not be influenced by rules that are illogical and created simply to avoid the bureaucracy generated by regulatory agencies that are more interested in process than outcome. The 2011 version of the WADA list of Prohibited Drugs should level the playing field for all athletes with asthma.

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