

β_2 -Agonists at the Olympic Games

Kenneth D. Fitch*

School of Human Movement and Exercise Science, University of Western Australia, Nedlands WA, Australia. E-mail:kfitch@cyllene.uwa.edu.au

Abstract

The different approaches that the International Olympic Committee (IOC) had adopted to β_2 -agonists and the implications for athletes are reviewed by a former Olympic team physician who later became a member of the Medical Commission of the IOC (IOC-MC). Steadily increasing knowledge of the effects of inhaled β_2 -agonists on health, is concerned with the fact that oral β_2 -agonists may be anabolic, and rapid increased use of inhaled β_2 -agonists by elite athletes has contributed to the changes to the IOC rules. Since 2001, the necessity for athletes to meet IOC criteria (i.e., that they have asthma and/or exercise-induced asthma [EIA]) has resulted in improved management of athletes. The prevalence of β_2 -agonist use by athletes mirrors the known prevalence of asthma symptoms in each country, although athletes in endurance events have the highest prevalence. The age-of-onset of asthma/EIA in elite winter athletes may be atypical. Of the 193 athletes at the 2006 Winter Olympics who met the IOC's criteria, only 32.1% had childhood asthma and 48.7% of athletes reported onset at age 20 yr or older. These findings lead to speculation that years of intense endurance training may be a causative factor in bronchial hyperreactivity. The distinction between oral (prohibited in sports) and inhaled salbutamol is possible, but athletes must be warned that excessive use of inhaled salbutamol can lead to urinary concentrations similar to those observed after oral administration. This article provides justification that athletes should provide evidence of asthma or EIA before being permitted to use inhaled β_2 -agonists.

Index Entries

Asthma; β_2 -agonists; Olympics; doping; performance.

*Member of the Medical Commission of the International Olympic Committee since 1985.

Introduction

During the past three decades, the International Olympic Committee (IOC) has had many changes in its approach to the use of inhaled β_2 agonists by athletes. Contributing factors have included the developing knowledge of the effects of inhaled and oral β_2 -agonists on human physical performance, possible unnecessary use by some athletes, and concerns over unfavorable effects on the health of athletes.

The Availability of β_2 -Agonists for Athletes at the Olympic Games

The widespread introduction of selective β_2 -agonists into clinical medicine in the early 1970s coincided with the commencement of antidoping measures at the Olympic Games. At the 1972 Munich Games, inhaled salbutamol was not permitted because the IOC's Medical Commission (IOC-MC) considered it a stimulant. However, this decision was reversed prior to the 1976 Olympics, although team doctors were required to submit notification of intended use of an inhaled β_2 -agonist. Only salbutamol and terbutaline were permitted. A request for an athlete to continue to inhale fenoterol at the 1980 Olympic Games in Moscow was granted by the IOC-MC, and the athlete won a silver medal. However, this decision was rescinded in 1984, not because of clinical concerns relating to fenoterol (1), but because it was metabolized to p-hydroxyamphetamine (2) and this was detectable in urine. In 1985, the IOC-MC was persuaded to permit three other β_2 -agonists, biltolterol, isoprenaline (isoproterenol) and rimiterol, in competition, and in 1986, an article (3) convinced them to cease the necessity for doctors to notify the use of inhaled β_2 -agonists. Oral preparations remained prohibited.

The increasing use of clenbuterol, initially by body builders and later power athletes (4), resulted in the prohibition of this drug in 1992, and two athletes competing in field events at the Olympic Games in Barcelona were banned

because they had used this substance. In the same year, Martineau and her colleagues (5) demonstrated that 16 mg of oral sustained-release salbutamol taken daily for 3 wks had anabolic effects. In 1993, the IOC-MC re-introduced the notification requirement for inhaled β_2 -agonists and reverted to allowing only salbutamol and terbutaline. This decision resulted from reports of the high prevalence of asthmatic symptoms in cross-country skiers and the extent of their use of inhaled β_2 -agonists (6). Subsequently, to provide protection against exercise-induced asthma (EIA) for athletic events of longer duration, the IOC permitted inhaled salmeterol in 1996, and to minimize the use of two inhaled β_2 -agonists, formoterol was permitted in 2001 (Table 1).

Because of an increase of 212% in the notifications of β_2 -agonist use between the 1984 Olympic Games in Los Angeles and 1996 Olympic Games in Atlanta and a further increase of 151% in the 4 yr between the Olympic Games in Atlanta and those in Sydney in 2000, in 2001 the IOC-MC resolved that Olympic athletes who require an inhaled β_2 -agonist must submit evidence of current asthma or EIA. This decision was on the grounds of protecting the health of athletes and was not a doping issue. At that time, the IOC had relinquished the global responsibility of doping policy and standards to the newly established World Anti-Doping Agency (WADA).

In 2001, an Independent Asthma Panel was established by the IOC to oversee this regulation. The criteria established by this panel in 2001 have varied marginally. Hypertonic saline was added as an additional bronchial provocation test for the Games in 2004 and the PC_{20} forced expiratory volume in 1 s (FEV_1) and PD_{20} FEV_1 for methacholine were doubled for "corticosteroid-naïve" athletes prior to the Winter Games in 2006. Currently, the athlete must provide evidence of a positive response to one of the following (7):

- Positive bronchodilator response defined as a 12% or greater increase in baseline FEV_{1r} after inhaling a permitted β_2 -agonist.

Table 1
History of β_2 -Agonists and the Olympic Games

1972	Permission to administer inhaled <i>salbutamol</i> refused by IOC-MC.
1975	Inhaled <i>salbutamol</i> and <i>terbutaline</i> permitted with prior notification.
1976	Olympic team doctors notified IOC-MC of intended use <i>salbutamol</i> or <i>terbutaline</i> .
1980	Permission to use <i>fenoterol</i> by inhalation granted prior to the Moscow Olympics.
1984	<i>Fenoterol</i> prohibited at the Sarajevo Winter Games because of metabolism to p-hydroxyamphetamine.
1984	Because of concerns of the effect of air pollution on bronchial airways in Los Angeles, team doctors are permitted to notify β_2 -agonists postadministration.
1985	<i>Bitolterol</i> , <i>orciprenaline</i> (<i>isoproterenol</i>), and <i>rimiterol</i> added as permitted β_2 -agonists.
1986	Notification of administration of β_2 -agonists to IOC-MC no longer required; oral β_2 -agonists reconfirmed to be prohibited.
1992	<i>Clenbuterol</i> prohibited. Two athletes disqualified in Barcelona for using <i>clenbuterol</i> . β_2 -Agonists listed as anabolic agents when administered systemically (orally or by injection).
1993	<i>Bitolterol</i> , <i>orciprenaline</i> , and <i>rimiterol</i> no longer permitted β_2 -agonists. Notification of administration of permitted inhaled β_2 -agonists re-introduced.
1994	Permission to administer inhaled <i>salmeterol</i> refused by IOC-MC.
1996	<i>Salmeterol</i> permitted to provide prolonged protection from exercise-induced asthma.
2001	<i>Formoterol</i> permitted.
2001	Because of concerns at the large and increasing number of athletes inhaling β_2 -agonists, as a health measure, the IOC-MC introduces the necessity of demonstrating that an athlete had asthma and/or EIA.

IOC-MC, International Olympic Committee Medical Commission; EIA, exercise-induced asthma.

- Positive bronchoconstrictor response defined as a 10% or greater fall in FEV₁ within 30 min of ceasing either an exercise challenge in the laboratory or the field or eucapnic voluntary hyperpnea (EVH).
- Positive bronchoconstrictor response defined as a 15% or greater fall in FEV₁ after inhaling a hypertonic aerosol (e.g., 4.5% NaCl).
- After inhaling an aerosol of methacholine, a positive response is accepted if the PC₂₀ FEV₁ was equal to or less than 4 mg/mL or the PD₂₀ FEV₁ was equal to or less than a cumulative dose of 2 mmol or 400 mg or 40 breath units in "steroid-naïve" athletes. In athletes, treated with daily inhaled glucocorticosteroids (GCS) for more than 3 mo, a PC₂₀ FEV₁ ≤ 13.2 mg/mL or a PD₂₀ FEV₁ ≤ cumulative dose of 6.6 mmol or ≤ 1320 mg or 130 breath units is accepted.
- For athletes who are unable to provide evidence of any positive test, physicians are requested to submit the results of

negative tests and clinical information, including a detailed description of the athlete's asthma symptoms (both day and night), trigger factors, consultations for the treatment of asthma, hospital admission or emergency department attendance for acute asthma, treatment with oral GCS, other medications used, and results of radioallergosorbent test, and so forth.

The outcomes of the responsibilities of the IOC's Asthma Panel in the 2002 Games in Salt Lake City and in the 2004 Games in Athens have been published (8,9). Since the introduction of this policy in 2001, evidence has accumulated to support the IOC's decision. Daily use of short-acting β_2 -agonists (SABAs) may increase the severity of EIA (10), and daily administration of long-acting β_2 -agonists (LABAs) decreases the duration of their protection (11) against EIA, and the recovery from EIA following a bronchodilator is slower (12). Tolerance to β_2 -agonists resulting from down-regulation of the β_2 -receptors may develop

following daily exposure (13) but is rapidly reversible with cessation of the medication (14). An article by Anderson and Brannan in this issue provides a detailed examination of the negative consequences on EIA of daily therapy with inhaled β_2 -agonists.

Outcomes of the IOC's Policy on Asthma

These outcomes were reviewed by the Panel (8,9) and in a recent European Respiratory Monograph (15). Table 2 compares the introduction of this policy for 2002 Salt Lake City, 2004 Athens, and 2006 Turin Games with the necessity of notifying the use of permitted inhaled β_2 -agonists in the 1998 Nagano and 2000 Sydney Games.

It is predicted that an additional 100 to 150 athletes may have inhaled a β_2 -agonist in the Athens Games if the notification process had been continued from Sydney. A similar proportion of athletes were denied permission in Salt Lake City. However, the high prevalence of athletes who met the IOC criteria in Turin was unexpected (Table 2). The IOC is conscious of the considerable time, effort, and cost involved in performing bronchial provocation tests, especially in national teams with 50 to 60 athletes with asthma. Nevertheless, team physicians, who were initially reluctant to subject their athletes to such testing, have acknowledged that this IOC requirement has assisted them to better manage their asthmatic athletes, and some athletes whose asthma had been undetected have been identified (16). In 2003, the International Amateur Athletic Federation followed the IOC's lead and introduced identical regulations for their athletes.

As previously reported (8,9,15), the prevalence of use of β_2 -agonists by Olympic athletes has been consistent but markedly different across sports and countries. High levels of use of β_2 -agonists by athletes in endurance events contrast with the low levels of use in nonendurance competitions. More than 11% of cyclists,

swimmers, and triathletes inhaled a β_2 -agonist in both the Sydney and Athens Olympics compared to less than 2% of weightlifters, wrestlers, and boxers at the same Games. Similar outcomes were observed in winter sports, where athletes in cross country skiing and speed skating events had a prevalence of β_2 -agonist use in excess of 10.5% in Salt Lake City, but less than 3% of competitors in luge, bobsleigh/skeleton, and alpine skiing were approved to inhale β_2 -agonists. More than 70% of the approvals for Salt Lake City were for those whose events involved skating or skiing, and a similar trend was observed in 2006. Perhaps the most striking example of the different prevalence of use between endurance and nonendurance events is the Nordic combined competition, where a ski jump is followed the next day by 15-km cross country skiing. In Salt Lake City, 10.6% athletes in the Nordic combined event were approved for β_2 -agonist use compared with only 2.6% of ski jumpers. A similar trend was observed in Turin.

Numerous theories have been proposed regarding why endurance athletes are more prone to bronchial hyperreactivity (17). For many years, children with asthma were recommended to swim with favorable outcomes (18), and this appears to be a factor in the high prevalence of asthma in elite swimmers. However, the high prevalence of asthma and EIA in sports such as cycling, triathlon, and cross country skiing has no such association, and the possibility that it results from years of endurance training in the prevailing climatic conditions cannot be excluded (19). Of 193 athletes approved for β_2 -agonist use in Turin, only 32.1% had childhood asthma and as many as 48.7% had the onset of asthma and/or EIA at age 20 yr or older. An examination of the use of β_2 -agonists by countries is even more divergent. More than 11% of athletes from Great Britain, Australia, Finland, and New Zealand were inhaling a β_2 -agonist in Sydney and Athens. Conversely, Russia, China, Korea, and Ukraine had less than 1% of athletes inhaling a

Table 2
Proportion of Athletes Using of β_2 -Agonists in the Olympic Games Since 1998

	Winter			Summer	
	Nagano (1998)	Salt Lake City (2002)	Turin (2006)	Sydney (2000)	Athens (2004)
Total no. of athletes	2296	2517	2478	10,739	10,563
Notifications (pre-2002)	128			607	
Applications (approvals)		159 (130)	208 (193)		490 (445)
Percentage of athletes	5.8%	6.3% (5.2%)	8.4% (7.8%) ^a	5.7%	4.6% (4.2%)

^a52 (26.9%) were athletes who had been approved for Salt Lake City and were not required to undergo additional testing. The validity of an approval includes the next Games of the same type (i.e., 4 yr).

β_2 -agonist in the same two Games. Close examination of the use of β_2 -agonists by country revealed that the proportion of athletes notifying or approved for β_2 -agonist use closely reflected the prevalence of symptoms compatible with asthma as identified by their country's ISAAC ranking (20) or in the European Community Respiratory Health Survey (21).

Asthma Medication Used by Olympic Athletes

Short-Acting β_2 -Agonists

Of the 420 athletes who applied to inhale a β_2 -agonist in Athens and who stated the SABA used, 94.5% were inhaling salbutamol. In Salt Lake City, the percentage inhaling salbutamol was 92.1% of 124 approvals.

Long-Acting β_2 -Agonists

In Sydney, 93 (15.3%) of the 607 athletes reported inhaling salmeterol (the only LABA permitted), and 20 (3.3%) of these athletes did not report use of a SABA. In Salt Lake City, 40 (30.8%) of 130 athletes who received approval by the IOC inhaled both a SABA and a LABA. A further 12 (9.2%) inhaled solely an LABA (8 formoterol, 4 salmeterol). In both these Games, GCS were unrestricted; it is unknown how many athletes inhaled a LABA without a GCS. In 2004, WADA required GCS use to be reported by a process known as an abbreviated

therapeutic use exemption. In Athens, 62 (12.7%) athletes applied to inhale a LABA without a SABA. Of these, 13 (2.7%) did not inhale a GCS. Therefore, only a small percentage attempted to control their asthma with a LABA only, with no SABA or inhaled GCS.

Glucocorticosteroids

Of the 490 athletes who applied to the IOC-MC for permission to inhale a β_2 -agonist in 2004, 325 (66.3%) advised on their application that they were inhaling a GCS. An additional 37 athletes notified that they were inhaling a GCS but not a β_2 -agonist. All but three of these stated asthma as the reason. Therefore, 34 athletes managed their asthma solely with an inhaled GCS, either because they were unable to meet the criteria necessary to obtain approval to inhale a β_2 -agonist or this was their customary method of managing their asthma and/or EIA. There were 45 athletes who were refused permission to inhale a β_2 -agonist. Of these, 14 (31%) inhaled a GCS. It is logical to assume that they continued this treatment. Therefore, 48 (9.1%) athletes of a total of 524 managed their asthma solely by inhaled GCS. Somewhat unexpectedly, of the other 31 athletes who were refused permission to inhale a β_2 -agonist in Athens and who were not previously inhaling a GCS, not one advised the IOC that they had commenced inhaled GCS because of this refusal.

Has the Performance of Olympic Athletes Denied Permission to Inhale a β_2 -Agonists Been Affected?

For many years, athletes with asthma experienced success at the Olympic Games. Over a period of 24 yr (between 1956 and 1980), asthmatics won medals in swimming events at every Olympic Summer Games (22). This trend was continued by Australian Olympic swimmers with asthma in Los Angeles (1984), Seoul (1988), and Barcelona (1992). Numerous medal-winning successes by asthmatics from the United States and Australia occurred in the pool at Atlanta. In Sydney, 115 (19.0%) of the 607 athletes who notified using a β_2 -agonist won one or more medals. Forty-seven of the 115 athletes won 57 individual medals, and as a group, the 115 athletes won 85 team medals. (The definition of a team was two or more members.)

There is little or no evidence that denying athletes permission to inhale a β_2 -agonist has resulted in unfavorable outcomes on their performance. In Salt Lake City, 30 (23.1%) of the 130 athletes who were approved to inhale a β_2 -agonist won 46 medals (30 individual and 16 team medals). Seven (24.1%) of the 29 athletes who were denied permission to inhale a β_2 -agonist won a total of eight medals (two individual and six team medals). In Athens, 6 (8.5%) of the 45 athletes who were refused permission to inhale a β_2 -agonist won six medals (three gold, two silver, and one bronze medal).

β_2 -Agonists and Athletic Performance

In 1972, the IOC prohibited β_2 -agonist use in athletics because of concerns that they possessed stimulant properties. At that time, stimulants and narcotics were the only two classes of drugs prohibited in sport. Anabolic agents were prohibited in 1975. During the 1980s, body builders and power athletes began to take the β_2 -agonist clenbuterol as an anabolic agent (3,23). Predominately used in veterinary science as a repartitioning agent for cattle prior

to sale and to treat asthma in large animals (24), clenbuterol was marketed for human use in southern Europe and South America. In 1992, the IOC prohibited clenbuterol use both by inhalation and orally.

Prior to this decision, a series of studies began to be published regarding the effect of inhaled salbutamol on performance. The majority demonstrated by double-blind studies that therapeutic doses of inhaled salbutamol (25–28), salmeterol (29,30), formoterol (31,32), and terbutaline (33) did not enhance physical performance. However, the article by Martineau (5), which confirmed that oral salbutamol can improve performance, provoked further studies demonstrating that oral salbutamol improved endurance during intense submaximal exercise (34), increase strength following resistance exercise (35,36), and increase strength and endurance (37) and power (38), although side effects could be unpleasant (37). Consequently, the IOC considered it important to be able to distinguish oral from inhaled administration of salbutamol. A study was funded to focus on estimating the concentration of nonconjugated S(+) and R(–) enantiomers of salbutamol excreted in the urine and their ratio (39). Because of higher rates of conjugation of the S(+) compared with the R(–) enantiomer after oral rather than inhaled administration of salbutamol, the ratio of S(+) to R(–) enantiomers proved a valuable aid in identifying the method of administration.

Sixteen healthy nonasthmatic subjects were administered 1600 μg of inhaled salbutamol over 24 h, with 800 μg in the last 4 h. This dosage was selected because the IOC-MC considered it to be the maximum advisable dosage for asthmatic subjects prior to competition (40) and it was within the manufacturer's recommendations. Urine samples were collected 60 min after the last dose. With an interval of at least 7 d between treatments, these 16 subjects took five 4-mg tablets orally six times per hour, and urine was collected 2 h after the last dose. The ratio of S(+) to R(–) after oral salbutamol exceeded 2.5 conversely to the ratio after the

inhaled drug, when the majority had a ratio less than 2.5. This is because salbutamol is metabolized in the intestine and the liver, whereas little metabolism occurs in the lungs. However, because a variable proportion of the inhaled drug is swallowed, this distinction was not absolute. Urinary concentrations of total free salbutamol were greater than 500 $\mu\text{g}/\text{L}$ after oral administration, and in almost all subjects, the urinary concentration was less than 500 $\mu\text{g}/\text{L}$ after the inhaled drug and all had a concentration less than 1000 $\mu\text{g}/\text{L}$. Therefore, both the concentration of total free salbutamol and the ratio of S(+) to R(-) were considered valuable indices to distinguish oral from inhaled administration. A discriminant function was developed from the data:

$$D = -3.776 + 1.46 \times 10^{-3} ([S(+)] + R(-)) + 1.012 \times ([S(+)]/[R(-)]) \text{ where } D = 1.06 \text{ or greater indicates oral consumption (41).}$$

In 2000, the IOC introduced a cutoff at no more than 500 ng/mL of salbutamol to distinguish between inhaled (permitted) and oral (prohibited) administration; however, a year later, this was increased to no more than 1000 ng/mL. This was considered a conservative level. The same year, the IOC permitted laboratories to screen and not confirm concentrations of less than 100 ng/mL urinary salbutamol. Subsequently, WADA continued the IOC's policy and stated that a urinary concentration of salbutamol (free and conjugated) greater than 1000 ng/mL would be considered an adverse analytical finding, unless the athlete proved that the abnormal result was the consequence of the therapeutic use of inhaled salbutamol (42). At the Olympic Games in Sydney and Salt Lake City, a total of 26 urine samples were identified by the laboratory as having a urinary concentration of salbutamol greater than 100 ng/mL. All athletes had notified their intention (Sydney) or received approval (Salt Lake City) to inhale a β_2 -agonist. The highest concentrations were 264 ng/mL in Sydney and 280 ng/mL in

Salt Lake City. In Athens, 39 urine samples had a concentration of salbutamol greater than 100 ng/mL, but no concentration levels were provided by the laboratory. However, at least six athletes are known to have had a urinary concentration greater than 1000 ng/mL, and three of these cases warrant a closer examination.

Case 1

A 15-yr-old fencer with documented asthma from age 6 yr was stabilized on fluticasone and salmeterol twice daily plus "rescue salbutamol." During an international junior competition, when she experienced increased problems with asthma because of the cold weather and cigarette smoke in a poorly ventilated stadium, she was selected for a doping control. The athlete and her coach considered that she had taken two inhalations of salbutamol via a spacer four to five times (800–1000 μg) during a 3-h period prior to her urine sample collection. The pH of the urine was 6.0, the SG was 1015, and the salbutamol concentration was reported as 1270 ng/mL. The Barcelona laboratory reported the S(+)/R(-) ratio as 2.49 and the D value as -0.19, compatible with inhaled salbutamol. The athlete was exonerated.

Comment

High doses of inhaled salbutamol during a brief period had resulted in this athlete exceeding the threshold of 1000 ng/mL in urine of normal density. The use of a spacer is unlikely to be a factor because no difference in either urinary concentrations or the S(+)/R(-) enantiomer ratio was noted after administration by a metered-dose inhaler (8).

Case 2

After playing a full game in a semifinal of an international club competition, a 26-yr-old 100-kg rugby hooker (who had asthma treated with salbutamol since prior to his second birthday) was selected for a doping control test. He was dehydrated, had widespread postgame

cramps, and needed to drink copious fluids before producing initially an inadequate urinary volume (partial sample). It was 100 min after the game before he could produce the necessary 80 mL of urine that was recorded on site as having a pH of 5.0 and a SG 1030. In the laboratory, these were reported as being 5.5 and 1024, respectively. The athlete stated that he had used his salbutamol metered-dose inhaler, as was customary prior to this and other matches. He took two inhalations on arrival at the stadium, two at the start of warm-up, two immediately prior to the game, and two at half time (800 µg). The urinary salbutamol was reported as 1644 ng/mL. Analysis of enantiomers in Barcelona revealed 1036 ng/mL S(+) and 538 ng/mL R(-). The S(+)/R(-) ratio was estimated to be 1.9 and the D-value was 0.47 and considered compatible with inhaled therapy. Two weeks earlier, the athlete had played a full game in a quarterfinal match and had also been a random selection for a doping test. He had declared an identical use of his metered-dose inhaler and the urine (pH 5.7 and SG 1012) was analyzed in a different laboratory and was reported to have a concentration of salbutamol of approx 80 ng/mL. This was on screening and was unconfirmed because the concentration was less than 100 ng/mL. The athlete was charged with a doping offense, was convicted of using an anabolic agent by a tribunal arranged by his sport, and was sanctioned for 2 yr. On appeal, the conviction was overturned.

Comment

Although dehydration can be anticipated to raise the urinary concentration significantly, a threefold (but not a 20-fold) increase in concentration may be expected between urines with specific densities of 1012 and 1024. The initial tribunal decision was in error, partly because of their rejection of the enantiomeric analysis.

Case 3

A 22-yr-old track athlete who had allergic asthma from age 4 yr inhaled 800 µg of salbutamol in the 4 h prior to his race and a "further dose" immediately after the race. He provided a urine sample 2 h later that was reported as having a concentration of salbutamol of about 8000 ng/mL. He was investigated by the Swiss Anti-Doping Commission. This included administering 900 µg (3 × 3 × 100 µg) of salbutamol over a 5-h period on each of 2 d, and a total of 22 urine samples were obtained and analyzed. On both days, 2 to 3 h after the last dose, the concentration of salbutamol rose rapidly to a maximum. These were assessed as peaking at 3000 to 4000 ng/mL on both days. No analysis of enantiomers was performed. The athlete received a warning (43).

Comment

This case confirms that the excretion of salbutamol after inhalation can result in unpredictably high urinary concentrations. Jacobson et al. (44) demonstrated "enormous inter-patient variability" in urinary salbutamol concentrations when studying inpatients with asthma on inhalation therapy. In a study by Glaxo (45), 15 healthy volunteers were administered a single dose of 1200 µg of inhaled salbutamol, and 7 of the 15 subjects had total salbutamol levels exceeded 1000 ng/mL, with one subject exceeding 3000 ng/mL.

It must be stressed that athletes with asthma who are subjected to doping controls should be advised by their physicians against excessive use of their metered-dose inhalers at the time of competition because they may exceed the urinary threshold for salbutamol. This likelihood increases if the competition results in significant dehydration. Doping authorities must acknowledge that when a laboratory reports a urinary concentration greater than 1000 ng/mL of salbutamol, enantiomeric analysis must be undertaken to assist discrimination between inhaled (permitted) and oral (prohibited) administration.

Conclusion

The IOC has had many changes to its policy on β_2 -agonists. The current approach that requires athletes to provide evidence of current asthma and/or EIA is a health measure and has been successful. Athletes without documented evidence of asthma who have been denied use inhaled β_2 -agonists do not appear to have experienced unfavorable outcomes in their Olympic performances. Recent evidence of undesirable effects of daily use of SABAs and LABAs and advice from team doctors that testing of their asthmatic athletes has resulted in improvements in their medical management provide support for this policy. Athletes from countries with known high or low prevalences of asthma apply to the IOC to inhale a β_2 -agonist with a similar high or low frequency. The reasons that competitors in endurance events have the highest use of β_2 -agonists remains a topic for further research. Although there have been no reports of athletes using oral salbutamol as an anabolic agent, athletes must be warned that multiple doses of inhaled salbutamol at the time of competition can result in the urinary salbutamol concentrations exceeding the threshold permitted by WADA.

References

1. Crane, J., Pearce, N., Flatt, A., et al. (1989), Prescribed fenoterol and death from asthma in New Zealand, 1981-83: case-control study. *Lancet* **1**, 917-922.
2. Clausnitzer, C. (1985), Communication to IOC Medical Commission 18 March.
3. Fitch, K. D. (1986), The use of anti-asthmatic drugs. Do they affect sports performance? *Sports Med.* **3**, 136-150.
4. Phillips, W. N. (1992). The secret of clenbuterol. Special Report #1, Golden, CO: Mile High Publishing.
5. Martineau, L., Horan, M. A., Rothwell, N. J., and Little, R. A. (1992), Salbutamol, a beta 2-adrenoceptor agonist, increases skeletal muscle strength in young men. *Clin. Sci. (Lond.)*, **83**, 615-621.
6. Larsson, K., Ohlsen, P., Larsson, L., Malmberg, P., Rydstrom, P. O., and Ulriksen, H. (1993), High prevalence of asthma in cross country skiers. *BMJ* **307**, 1326-1329.
7. http://www.olympic.org/uk/games/torino/atue/index_uk.asp, Accessed January 14, 2006.
8. Anderson, S. D., Fitch, K., Perry, C. P., et al. (2003), Responses to bronchial challenge submitted for approval to use inhaled beta2-agonists before an event at the 2002 Winter Olympics. *J. Allergy Clin. Immunol.* **111**, 45-50.
9. Anderson, S. D., Sue-Chu, M., Perry, C. P., et al. (2006), Bronchial challenges in athletes applying to inhale a β_2 -agonist at the 2004 summer Olympics. *J. Allergy Clin. Immunol.* **117**, 767-773.
10. Hancox, R. J., Subbarao, P., Kamada, D., Watson, R. M., Hargreave, F. E., and Inman, M. D. (2002), Beta2-agonist tolerance and exercise-induced bronchospasm. *Am. J. Respir. Crit. Care Med.* **165**, 1068-1070.
11. Ramage, L., Lipworth, B. J., Ingram, C. G., Cree, I. A., and Dhillon, D. P. (1994), Reduced protection against exercise induced bronchoconstriction after chronic dosing with salmeterol. *Respir. Med.* **88**, 363-368.
12. Storms, W., Chervinsky, P., Ghannam, A. F., Bird, S., Hustad, C. M., and Edelman, J. M. (2004), A comparison of the effects of oral montelukast and inhaled salmeterol on response to rescue bronchodilation after challenge. *Respir. Med.* **98**, 1051-1062.
13. Anderson, S. D. and Brannan, J. D. (2004), Long-acting beta 2-adrenoceptor agonists and exercise-induced asthma: lessons to guide us in the future. *Paediatr. Drugs* **6**, 161-175.
14. Haney, S. and Hancox, R. J. (2005), Rapid onset of tolerance to beta-agonist bronchodilation. *Respir. Med.* **99**, 566-571.
15. Anderson, S. D., Brusasco, V., Haahtela, T., and Popov, T. (2005), Criteria for diagnosis of asthma, exercise-induced bronchoconstriction and airway hyperresponsiveness for athlete: Lessons from the Olympic Games. In *Diagnosis, Prevention and Treatment of Exercise Related Asthma, Respiratory and Allergic Disorders in Sports*, Carlsen, K. -H., Delgado, L., and Del Giacco, S., eds., Eur Respir Mon. Wakefield, UK: European Respiratory Society, pp. 48-66.
16. Dickinson, J. W., Whyte, G. P., McConnell, A. K., and Harries, M. G. (2005), Impact of changes in the IOC-MC asthma criteria: a British perspective. *Thorax* **60**, 629-632.
17. Bjermer, J. and Anderson, S. D. (2005), Bronchial hyperresponsiveness in athletes; mechanisms for development. In *Diagnosis, Prevention and Treatment of Exercise Related Asthma, Respiratory and Allergic Disorders in Sports*, Carlsen, K.-H., Delgado, L., and Del Giacco, S., eds., Eur Respir Mon. Wakefield, UK: European Respiratory Society, pp. 19-34.
18. Fitch, K. D., Morton, A. R., and Blanksby, B. A. (1976), Effects of swimming training on children with asthma. *Arch. Dis. Child.* **51**, 190-194.

19. Drobic, F. and Haahtela, T. (2005), The role of the environment and climate in relation to outdoor and indoor sports. In *Diagnosis, Prevention and Treatment of Exercise Related Asthma, Respiratory and Allergic Disorders in Sports*, Carlsen, K. - H., Delgado, L., and Del Giacco, S., eds., Eur Respir Mon. Wakefield, UK: European Respiratory Society, pp. 35–47.
20. (1998), Worldwide variation in prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and atopic eczema: ISAAC. The International Study of Asthma and Allergies in Childhood (ISAAC) Steering Committee. *Lancet* **351**, 1225–1232.
21. Chinn, S., Burney, P., Jarvis, D., and Luczynska, C. (1997), Variation in bronchial responsiveness in the European Community Respiratory Health Survey (ECRHS). *Eur. Respir. J.* **10**, 2495–2501.
22. Fitch, K. D. (1984), Management of allergic Olympic athletes. *J. Allergy Clin. Immunol.* **73**, 722–727.
23. Delbeke, F. T., Desmet, N., and Debackere, M. (1995), The abuse of doping agents in competing body builders in Flanders (1988–1993). *Int. J. Sports Med.* **16**, 66–70.
24. Yang, Y. T. and McElligott, M. A. (1989), Multiple actions of beta-adrenergic agonists on skeletal muscle and adipose tissue. *Biochem. J.* **261**, 1–10.
25. McKenzie, D. C., Rhodes, E. C., Stirling, D. R., et al. (1983), Salbutamol and treadmill performance in non-atopic athletes. *Med. Sci. Sports Exerc.* **15**, 520–522.
26. Meeuwisse, W. H., McKenzie, D. C., Hopkins, S. R., and Road, J. D. (1992), The effect of salbutamol on performance in elite nonasthmatic athletes. *Med. Sci. Sports Exerc.* **24**, 1161–1166.
27. Morton, A. R., Papalia, S. M., and Fitch, K. D. (1992), Is salbutamol ergogenic? The effects of salbutamol on physical performance in high performance nonasthmatic athletes. *Clin. J. Sport Med.* **2**, 93–97.
28. Heir, T. and Stemshaug, H. (1995), Salbutamol and high-intensity treadmill running in nonasthmatic highly conditioned athletes. *Scand. J. Med. Sci. Sports* **5**, 231–236.
29. Morton, A. R., Joyce, K., Papalia, S. M., Carroll, N. G., and Fitch, K. D. (1996), Is salmeterol ergogenic? *Clin. J. Sport Med.* **6**, 220–225.
30. Sue-Chu, M., Sandsund, M., Helgerud, J., Reinertsen, R. E., and Bjermer, L. (1999), Salmeterol and physical performance at -15 degrees C in highly trained nonasthmatic cross-country skiers. *Scand. J. Med. Sci. Sports* **9**, 48–52.
31. Carlsen, K. H., Hem, E., Stensrud, T., Held, T., Herland, K., and Mowinckel, P. (2001), Can asthma treatment in sports be doping? The effect of the rapid onset, long-acting inhaled beta2-agonist formoterol upon endurance performance in healthy well-trained athletes. *Respir. Med.* **95**, 571–576.
32. Stewart, I. B., Labreche, J. M., and McKenzie, D. C. (2002), Acute formoterol administration has no ergogenic effect in nonasthmatic athletes. *Med. Sci. Sports Exerc.* **34**, 213–217.
33. Larsson, K., Gavhed, D., Larsson, L., Holmer, I., Jorfelt, L., and Ohlsen, P. (1997), Influence of a beta2-agonist on physical performance at low temperature in elite athletes. *Med. Sci. Sports Exerc.* **29**, 1631–1636.
34. Collomp, K., Candau, R., Lasne, F., Labsy, Z., Prefaut, C., and De Ceaurriz, J. (2000), Effects of short-term oral salbutamol administration on exercise endurance and metabolism. *J. Appl. Physiol.* **89**, 430–436.
35. Caruso, J. F., Signorile, J. F., Perry, A. C., et al. (1995), The effects of albuterol and isokinetic exercise on the quadriceps muscle group. *Med. Sci. Sports Exerc.* **27**, 1471–1476.
36. Caruso, J. F., Hamill, J. L., and De Garmo, N. (2005), Oral albuterol dosing during the latter stages of a resistance exercise program. *J. Strength Cond. Res.* **19**, 102–107.
37. van Baak, M. A., Mayer, L. H., Kempinski, R. E., and Hartgens, F. (2000), Effect of salbutamol on muscle strength and endurance performance in nonasthmatic men. *Med. Sci. Sports Exerc.* **32**, 1300–1306.
38. Collomp, K., Le Panse, B., Portier, H., et al. (2005), Effects of acute salbutamol intake during a Wingate test. *Int. J. Sports Med.* **26**, 513–517.
39. Ventura, R., Segura, J., Berges, R., et al. (2000), Distinction of inhaled and oral salbutamol by urine analysis using conventional screening procedures for doping control. *Ther. Drug Monit.* **22**, 277–282.
40. IOC Medical Commission. (1998), Minutes of meeting Nagano February 1998. Lausanne, Switzerland.
41. Berges, R., Segura, J., Ventura, R., et al. (2000), Discrimination of prohibited oral use of salbutamol from authorized inhaled asthma treatment. *Clin. Chem.* **46**, 1365–1375.
42. http://www.wada-ama.org/rtecontent/document/2006_LIST.pdf, Accessed January 15, 2006.
43. Schweizer, C., Saugy, M., and Kamber, M. (2004), Doping test reveals high concentrations of salbutamol in a Swiss track and field athlete. *Clin. J. Sport Med.* **14**, 312–315.
44. Jacobson, G. A., Peterson, G. M., and McLean, S. (1997), Investigation of urinary levels of salbutamol in asthmatic patients receiving inhaled therapy. *J. Clin. Pharm. Ther.* **22**, 119–126.
45. Glaxo Smith Kline. (1988), GSK Study GM198/00055/00.