

## Beta<sub>2</sub> adrenoceptor agonists and the Olympic Games in Beijing

### 1. INTRODUCTION

Article 4 of the World Anti-Doping Code refers to the Prohibited List as an International Standard. This List, which is revised annually and came into force on 1 January 2008, stipulates that:

All beta<sub>2</sub> agonists including their D- and L- isomers are prohibited. Their use requires a Therapeutic Use Exemption.

As an exception, formoterol, salbutamol, salmeterol and terbutaline, when administered by inhalation require an Abbreviated Therapeutic Use Exemption.

An ATUE stating that the athlete needs to use inhaled beta<sub>2</sub> agonist(s) to treat asthma and/or exercise-induced asthma (EIA) or exercise-induced bronchoconstriction (EIB) will be systematically reviewed by the IOC TUEC during the period of the 2008 Olympic Summer Games in Beijing, in accordance with section 8.5 of the International Standards for Therapeutic Use Exemptions of WADA.

Athletes who request permission to inhale a beta<sub>2</sub> agonist during the Olympic Summer Games in 2008 in Beijing will be required to submit test results to confirm that the athlete has objective evidence of asthma and/or EIA or EIB.

Applications must be addressed to the IOC Medical and Scientific Department using the **on-line Therapeutic Use Exemption request form** which will be available from the end of March 2008.

The doping control laboratory will report the presence in urine of any beta<sub>2</sub> agonist. For any athlete who has not received an authorisation from the IOC Medical Commission to inhale a beta<sub>2</sub> agonist(s), or who has not respected an approval granted to use any of these substances, the result of the doping control will be considered as an adverse analytical finding. The procedures in place for an adverse analytical finding will then be applied.

For any question related to the on-line form, please contact the IOC Medical and Scientific Department, preferably by e-mail at [beta2@olympic.org](mailto:beta2@olympic.org) or by telephone on +41 21 621 6111.

**BACKGROUND** to the decision to require documented evidence of asthma and/or EIA/EIB.

In May 2001, the IOC Medical Commission convened a workshop to examine asthma, beta<sub>2</sub> agonists and the Olympic Games. The workshop concluded that:

- At recent Olympic Games, there had been a large increase in the number of athletes notifying the need to inhale a beta<sub>2</sub> agonist
- Some athletes may have been misdiagnosed and did not have asthma and/or EIA/EIB
- There is no scientific evidence to confirm that inhaled beta<sub>2</sub> agonists enhance performance in doses required to inhibit EIA/EIB
- A skewed distribution of notifications of beta<sub>2</sub> agonists by sport was observed with a higher prevalence in endurance sports
- The geographic distribution of notifications of inhaled beta<sub>2</sub> agents was markedly skewed but correlated well to the reported prevalence of asthma symptoms in those countries
- There is evidence that daily use of an inhaled beta<sub>2</sub> agonist may result in tolerance to the medication, [1,2,3]
- Inhaled corticosteroids may be under-used in athletes notifying the use of beta<sub>2</sub> agonists
- Eucapnic voluntary hyperpnoea (EVH) was considered to be the optimal laboratory based challenge to confirm that an athlete has EIA/EIB
- Beta<sub>2</sub> agonists when administered systemically do have anabolic effects

In October 2001, the IOC Medical Commission appointed an Independent Panel of experts who established the necessary criteria for an athlete to be granted permission to inhale a beta<sub>2</sub> agonist at the Olympic Games in Salt Lake City. The outcome of applications processed by the Independent Panel have been published after Salt Lake City 2002 [4] and after Athens 2004 [5]. Due to the successful experience at these Games [6] and the Olympic Winter Games in Turin 2006 [7], the IOC decided to continue this system for Beijing 2008.

In January 2008, a follow up meeting was held in Lausanne to achieve consensus on the diagnosis and treatment of asthma in elite athletes.

- There was consensus that the diagnosis of asthma could not be made in elite athletes on the basis of respiratory symptoms alone and spirometric evidence of reversible airways obstruction or airway hyper responsiveness was needed to confirm the diagnosis.
- The use of national and international guidelines for treatment was recommended with a note that there are special issues for elite athletes. One of these issues relates to the tolerance that can develop with frequent use of inhaled beta<sub>2</sub> agonists and that those who use them daily may find them less effective against exercise-induced bronchoconstriction (EIB).
- The use of inhaled corticosteroids was encouraged for treatment of asthma and EIB. The use of long acting beta<sub>2</sub> agonists as monotherapy was discouraged.
- The importance of athletes receiving education with respect to asthma, EIB and correct use of their medications was stressed.

The full consensus statement on Asthma in the Elite Athlete is available on the IOC website: [http://multimedia.olympic.org/pdf/en\\_report\\_1301.pdf](http://multimedia.olympic.org/pdf/en_report_1301.pdf)

## 2. PROCEDURE

The on-line Therapeutic Use Exemption request form for inhaled beta<sub>2</sub> agonists for the Games in Beijing must reach the IOC Medical and Scientific Department as soon as possible and preferably before 26 July 2008.

Please note that the on-line form allows an athlete to request permission to inhale only one short acting beta<sub>2</sub> agonist (salbutamol or terbutaline) and/or one long acting beta<sub>2</sub> agonist (formoterol or salmeterol). If an athlete is inhaling a corticosteroid, this information is sought on the application form and will be accepted by the IOC Medical Commission as an Abbreviated Therapeutic Use Exemption (ATUE) for that corticosteroid whether the athlete's application for beta<sub>2</sub> agonist use is approved or not.

Applications will be examined by a group of independent experts. The Independent Panel's decision will be notified by e-mail to the doctor in charge of the request and it will be his/her responsibility to inform the athlete of the status of his/her application. The NOC's chief physician will also be informed in writing of the Panel's decision. The Panel recommends that bronchial provocation tests are performed as early as possible in 2008.

Any athlete whose application is refused will have the opportunity to be retested in Beijing. Please contact **Dr Lu Yong**, Department of Pulmonary and Critical Care Medicine, Beijing Chaoyang Hospital & Beijing Institute of Respiratory Medicine, 8 Baijiazhuang Road, Chaoyang District, Beijing, 100020, P.R.China. Tel:86-10-85231304, Fax: 86-10-65060167. Email: [luyong8764@sina.com](mailto:luyong8764@sina.com).

These tests may take up to 1 hour and 30 minutes.

The cost of the test in Beijing will be US\$250 and payable by the NOC.

The results of such investigation shall be final.

### Athletes having received an authorisation at past editions of the Olympic Games (Athens or Turin).

For athletes who received the IOC Medical Commission's authorisation to inhale beta<sub>2</sub> agonist(s) at the Games of the XXVIII Olympiad in Athens in 2004 or the XX Olympic Winter Games in Turin 2006, that authorisation will be valid for the XXIX Olympiad in Beijing in 2008. No additional tests are required. However, so that the IOC Medical Commission can clearly identify these athletes, the first part of the on-line application form must be completed and submitted.

## 3. METHODOLOGY

The measures of forced expiratory volume (FEV<sub>1</sub>) at rest, as well as changes in FEV<sub>1</sub> in response to either an inhaled bronchodilator or to a bronchial provocation test, are the essential criteria that must be completed on the on-line application form for beta<sub>2</sub> agonists (see below for further details on these tests).

### **Peak Expiratory Flow (PEF) measurements are unacceptable.**

In the application form, information must be provided for at least one of the tests below.

Only tests performed **after August 2004** will be taken into consideration by the Panel.

Spirometry recordings need not be forwarded but must be retained and the independent panel reserves the right to request to view them before issuing any approval.

### **Recommendation for withholding medications prior to bronchodilator test**

To provide the optimal test circumstances, short acting bronchodilators (e.g. salbutamol and terbutaline) and ipratropium bromide should be withheld for 8 hrs and long acting bronchodilators (salmeterol and formoterol) and tiotropium bromide for 24 hrs or longer. No corticosteroids should be inhaled for 24 hours.

### BRONCHODILATOR TEST:

After administering a "permitted" beta<sub>2</sub> agonist by inhalation, a bronchial reversibility test is considered positive if the increase in FEV<sub>1</sub> is 12% or more of the baseline FEV<sub>1</sub> or the predicted FEV<sub>1</sub> and exceeds 200 ml.

### BRONCHIAL PROVOCATION TESTS:

#### **Recommendation for withholding medications prior to tests**

To provide the optimal test circumstances, some medications must be withheld for 8 to 96 hours before the bronchial provocation test. No short-acting bronchodilators, sodium cromoglycate, nedocromil sodium, or ipratropium bromide for 8 hours. No long-acting bronchodilators or antihistamines for 48 hours. No leukotriene antagonists for four days. Steroids should not be inhaled on the day of the test. No caffeine should be taken on the morning of the test. Avoid vigorous exercise for at least four hours prior to the start of the test and avoid any exercise on the day of testing.

Various bronchial provocation tests may be used:

- a) eucapnic voluntary hyperpnea test
- b) exercise challenge in the laboratory or an exercise test in the field
- c) hyperosmolar aerosols i.e. 4.5gm% saline or dry powdered mannitol
- d) methacholine test

#### a) Eucapnic voluntary hyperpnea test

The eucapnic voluntary hyperpnea test is considered positive when a fall in FEV<sub>1</sub> of 10% or more from baseline is recorded after a 6 minutes period of hyperpnea in dry air. To overcome the problem of any post-test respiratory muscle fatigue, the FEV<sub>1</sub> should first be recorded at least 3 minutes after challenge. It is usual for the reduction to be sustained over the next five minutes to be consistent with hyperpnea-induced bronchoconstriction. [8,9]

#### b) Exercise challenge in the laboratory or an exercise test in the field

The response to the exercise challenge is considered positive when there is a fall in FEV<sub>1</sub> of 10% or more compared to baseline during the first 30 minutes post exercise.

To maximise the opportunity for a positive test, the exercise test should be performed breathing dry air for 8 minutes with the intensity of exercise close to maximal for the last 4 minutes. To overcome the problem of any post-test respiratory muscle fatigue, the FEV<sub>1</sub> should first be recorded at least 3 minutes after challenge. It is usual for the reduction to be sustained over the next 5 minutes to be consistent with exercise-induced bronchoconstriction (EIB) [8].

#### c) Hyperosmolar aerosols

A fall in FEV<sub>1</sub> of 15% or more from baseline after inhaling 22.5 ml of 4.5 gm% saline (e.g. 4.5 g NaCl /100 ml water) or a dose of 635 mg of dry powdered mannitol is a positive response and is consistent with a diagnosis of currently active asthma or EIA/EIB. The response to 4.5% saline and the response to mannitol is usually reported as the dose required to provoke a 15% fall in FEV<sub>1</sub> (PD<sub>15</sub>) but should also be reported as the maximum fall after the final dose of aerosol [10].

#### d) Methacholine test

A test is considered positive if there is a fall in FEV<sub>1</sub> of 20% or more from baseline at a dose (PD<sub>20</sub>) less than or equal to 400 microgram / 2 micromoles (cumulative dose) or 200 micrograms / 1 micromole (non cumulative dose) or a concentration (PC<sub>20</sub>) less than or equal to 4mg/ml (tidal breathing technique ATS guidelines 1999 [12]) **when the subject is not taking inhaled corticosteroids or has taken them for less than one month.**

**For applicants taking inhaled corticosteroids for at least one month**, the PD<sub>20</sub> should be less than or equal to 1600 micrograms /8.0 micromoles (cumulative dose) or 800 micrograms / 4.0 micromoles (non cumulative dose), or a PC<sub>20</sub> less than or equal to 16.0mg/ml (tidal breathing ATS guidelines 1999 [12]) to be accepted as proof of airway hyperresponsiveness (AHR) [11,12]

It should be noted that a negative response to methacholine does not exclude exercise-induced asthma/bronchoconstriction in an athlete and in the event of a negative response, an alternative bronchial provocation test is recommended. The method of delivery of methacholine may influence the outcome [13,14]. If the values for PC<sub>20</sub> or PD<sub>20</sub>, during methacholine challenge are in excess of the thresholds mentioned above, the athlete may undergo an EVH test or an exercise test on site in Beijing \* prior to the start of the Games

#### **IMPORTANT NOTE**

**The results of bronchial provocation tests using pharmacological agents other than methacholine (e.g. carbachol, histamine or adenosine monophosphate) WILL NOT BE ACCEPTED.**

\* Please contact **Dr Lu Yong**, Department of Pulmonary and Critical Care Medicine, Beijing Chaoyang Hospital & Beijing Institute of Respiratory Medicine, 8 Baijiazhuang Road, Chaoyang District, Beijing, 100020, P.R.China. Tel:86-10-85231304, Fax: 86-10-65060167, Email: [luyong8764@sina.com](mailto:luyong8764@sina.com)

#### **WELL-CONTROLLED ASTHMA with negative response to all the tests**

In the case of an athlete with known, but well-controlled, asthma recording a negative result to the bronchial provocation test(s), but still seeking approval for the use of inhaled beta<sub>2</sub> agonist(s), the following documentation must be included in the medical file: consultations with their physician for treatment of asthma, hospital emergency department attendance or admission for acute exacerbations of asthma or treatment with oral corticosteroids.

Additional information that may assist includes: the age of onset of asthma; detailed description of the athlete's asthma symptoms, both day and night; trigger factors; medication use; past history of atopic disorders and/or childhood asthma; and physical examination, together with results of skin prick test or RAST to document the presence of allergic hypersensitivity.

The results of negative bronchial provocation test(s) must be sent electronically to the IOC Medical and Scientific Department. Prior to this submission, please indicate clearly in the "Comments" section underneath the bronchial provocation test(s) with a negative response, that the athlete's asthma is well controlled and that his/her medical file is being forwarded. This is important so that the application will not be automatically refused.

The files must be sent **by registered delivery** to the following address: International Olympic Committee, Medical and Scientific Department, Château de Vidy, CH – 1007 Lausanne, Switzerland.

For any further information or assistance, please contact the IOC Medical and Scientific Department, preferably by e-mail at [beta2@olympic.org](mailto:beta2@olympic.org) or by telephone on +41 21 621 61 11 or Dr Ken Fitch, Moderator of the Independent Panel on [kfitch@cyllene.uwa.edu.au](mailto:kfitch@cyllene.uwa.edu.au)

#### 4. BIBLIOGRAPHY

1. Anderson SD, Caillaud C, Brannan JD.  $\beta_2$  agonists and exercise-induced asthma. *Clin Rev Allergy Immunol* 2006;31:163-180
2. Hany S, Hancox RJ. Recovery from bronchoconstriction and bronchodilator tolerance. *Clin Rev Allergy Immunol* 2006; 31(2-3): 181-196
3. Cockcroft DW. Clinical concerns with  $\beta_2$  agonists: adult asthma. *Clin Rev Allergy Immunol* 2006; 31(2-3): 197-208
4. Anderson SD, Fitch K, Perry CP, Sue-Chu M, Crapo R, McKenzie D, Magnussen H. Responses to bronchial challenge submitted for approval to use inhaled  $\beta_2$ -agonists before an event at the 2002 Winter Olympics. *J Allergy Clin Immunol* 2003: 111: 45-50.
5. Anderson SD, Sue-Chu M, Perry CP, Gratziau C, Kippelen P, McKenzie DC et al. Bronchial challenges on athletes applying to inhale a  $\beta_2$  agonist at the 2004 Summer Olympics. *J Allergy Clin Immunol* 2006; 117 767-73
6. Dickinson JW, Whyte GP, McConnell AK, Harries MG. Impact of changes in the IOC-MC asthma criteria: a British perspective. *Thorax* 2005; 60: 628-32
7. Fitch KD.  $\beta_2$  agonists at the Olympic Games *Clin Rev Allergy Immunol* 2006; 31 (2-3): 259-68
8. Anderson SD, Brannan JD. Methods for 'indirect' challenge tests including exercise, eucapnic voluntary hyperpnea and hypertonic aerosols. *Clin Rev Allergy Immunol* 2003; 24: 63-90
9. Hurwitz KM, Argyros GJ, Roach JM, Eliasson AH, Phillips YY. Interpretation of eucapnic voluntary hyperventilation in the diagnosis of asthma. *Chest*, 1995; 108: 1240-5
10. Brannan JD, Anderson SD, Perry CP, Freed-Martens R, Lassig AR, Charlton B. The safety and efficacy of inhaled dry powder mannitol as a bronchial provocation test for airway hyperresponsiveness: a phase 3 comparison study with hypertonic (4.5%) saline. *Respir Res* 2005;6: 144
11. Sterk PJ, Fabbri LM, Quanjer PH, Cockcroft DW, O'Byrne PM, Anderson SD, et al. Airway responsiveness: Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. *Eur Respir J* 1993; 6:53-83
12. Crapo RO, Casaburi R, Coates AL, Enright PL, Hankinson JL, Irvin CG, et al. Guidelines for methacholine and exercise challenge testing - 1999. *Am J Respir Crit Care Med* 2000; 161:309-29
13. Cockcroft DW, Davis BE. The bronchoprotective effect of inhaling methacholine by using total lung capacity inspirations has a marked effect on the interpretation of the test result. *J Allergy Clin Immunol* 2006; 117:1244-8
14. Cockcroft DW, Davis BE, Todd DC, Smycniuk AJ. Methacholine challenge: comparison of two methods. *Chest* 2005; 125:839-44
15. Johns DP, Pierce R. *Pocket Guide to Spirometry* (ISBN 0-07-471331-0).. McGraw-Hill Australia. 2003