

Beta₂ adrenoceptor agonists and the Olympic Games in Turin

1. INTRODUCTION

Article 4 of the World Anti-Doping Code refers to the Prohibited List as the international standard. This List, which came into force on 1 January 2005, stipulates that:

All beta-2 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 to prevent and/or treat asthma and exercise-induced asthma/broncho-constriction require an abbreviated Therapeutic Use exemption.

A simple notification from a respiratory or team physician stating that the athlete has asthma and/or exercise-induced asthma (or exercise-induced bronchoconstriction) **WILL NO LONGER BE ACCEPTABLE** as evidence for that athlete to inhale a permitted beta₂ agonist at the 2006 Olympic Winter Games in Turin.

Athletes who request permission to inhale a permitted beta₂ agonist during the Olympic Winter Games in 2006 in Turin will be required to submit test results in support of that athlete having objective evidence of asthma and/or exercise-induced asthma (EIA) or exercise-induced bronchoconstriction (EIB).

Requests must be addressed to the IOC Medical and Scientific Department using the on-line Therapeutic Use Exemption request form.

As for every edition of the Games since 2000, the doping control laboratory will report the presence in urine of any beta₂ agonist. For any athlete who has not received an authorisation from the IOC Medical Commission to inhale beta₂ agonists, or who has not respected the notifications related to the use of these products, the result of the doping control will be considered positive. The procedures in place for positive doping control cases 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 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 IOC-MC) convened a workshop to examine asthma, beta 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 beta₂ agonist
- Some athletes may have been misdiagnosed and did not have asthma and/or exercise induced asthma (EIA) or bronchoconstriction (EIB)
- There is no scientific evidence to confirm that inhaled beta₂ agonists enhance performance in doses required to inhibit EIA/EIB
- A skewed distribution of notifications of beta₂ agonists by sport was observed with a higher prevalence in endurance sports
- The geographic distribution of notifications of inhaled beta₂ agents was markedly skewed but correlated well to the reported prevalence of asthma symptoms in those countries
- There is some evidence that daily use of an inhaled beta₂ agonist may result in tolerance to the medication
- Inhaled corticosteroids may be under-used in athletes notifying the use of beta₂ agonists
- Eucapnic voluntary hyperpnoea (EVH) was considered to be the optimal laboratory based challenge to confirm that an athlete has EIA/EIB
- Beta₂ agonists when administered systemically do have anabolic effects

In October 2001, the IOC-MC appointed an Independent Panel of experts who established the necessary criteria for an athlete to be granted permission to inhale a permitted beta₂ agonist at the Olympic Games in Salt Lake City. The results obtained further to the application of these criteria at the Salt Lake City Games have been published, c.f. J Allergy & Clinical Immunology 2003;111:45-50. Due to the success of the application of these criteria, the IOC has decided to use this rule again at the next edition of the Winter Games in Turin.

2. PROCEDURE

The on-line Therapeutic Use Exemption request form for inhaled beta₂ agonists for the Games in Turin must reach the IOC Medical and Scientific Department as soon as possible before 31 January 2006.

Requests 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. It will be his/her responsibility to inform the athlete of the status of his/her request. The NOC's chief physician will also be informed in writing of the independent panel's decision.

Any athlete whose request is refused will have the chance to be retested in Turin.

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

The cost of the test in Turin will be €300 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 (Salt Lake City or Athens).

For athletes who received the IOC Medical Commission's authorisation to inhale beta₂ agonists at the XIX Olympic Winter Games in Salt Lake City in 2002 (or the Games of the XXVIII Olympiad in Athens in 2004), the authorisation will be carried over for the XX Olympic Winter Games in Turin in 2006, with no additional tests needed. However, so that the IOC Medical Commission can clearly identify these athletes, the on-line Therapeutic Use Exemption request form must imperatively be completed.

3. METHODOLOGY

A measure of forced expiratory volume (FEV₁) at rest, as well as changes in FEV₁ in response to an inhaled bronchodilator or further to a bronchial provocation test, are the indispensable elements that must appear on the on-line Therapeutic Use Exemption request form for beta₂ agonists (see below for further details on these tests).

Peak Expiratory Flow (PEF) measurements are unacceptable.

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

Only tests performed **after February 2002** will be taken into consideration by the independent 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.

BRONCHODILATOR TEST:

A bronchial reversibility test is considered positive if there is an increase in FEV₁ of 12% or more of the baseline FEV₁ and exceeds 200 ml after administering an inhaled permitted beta₂ agonist by inhalation.

Recommendation for withholding medications prior to bronchodilator test

To provide the optimal test circumstances, short acting bronchodilators (e.g. salbutamol, terbutaline, ipratropium bromide) should be withheld for 8 and long acting bronchodilators (salmeterol, formoterol, tiotropium bromide) for 24 hrs or longer.

BRONCHIAL PROVOCATION TESTS:

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) Hypertonic aerosol
- d) Methacholine test

a) Eucapnic voluntary hyperpnea test

The eucapnic voluntary hyperpnea test is considered positive when a fall in FEV₁ 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 FEV₁ should be recorded three minutes at least after challenge. It would be usual for the reduction sustained over the next five minutes to be consistent with hyperpnea-induced bronchoconstriction.

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.

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 FEV₁ 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.

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. Inhaled corticosteroids should not be administered on the day of the test. No caffeine should be taken on the morning of the study. Avoid vigorous exercise for at least four hours prior to the start of the test, and avoid all exercise on the day of testing.

c) Hypertonic aerosol

Hypertonic solution: a test is considered positive when there is a fall in FEV₁ of 15% or more from baseline after a dose of 22.5 ml of 4.5 gm% saline (e.g. 4.5 g NaCl /100 ml water) has been inhaled. The response is usually reported as the dose required to provoke a 15% fall in FEV₁ (PD₁₅) but can also be reported as the maximum fall after the final dose administered.

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 hour. No leukotriene antagonists for 4 days. Inhaled corticosteroids should not be administered on the day of the test. No caffeine should be taken on the morning of the study. Avoid vigorous exercise for at least four hours prior to the beginning of the test, and avoid all exercise on the day of testing.

d) Methacholine test

A test is considered positive if there is a fall in FEV₁ of 20% or more from baseline at a dose less than or equal to 2 micromoles, 400 micrograms (PD₂₀), after inhalation of a solution with a concentration less, or equal to, 4 mg/ml (PC₂₀), or after inhalation of a maximum of 40 breath units **when the subject is not taking inhaled corticosteroids**.

For applicants taking inhaled steroids for at least three months, the PD₂₀ should be equal to or less than 6.6 micromoles, 1320 micrograms or PC₂₀ equal to or less than 13.2 mg/ml, or inhalation of a maximum of 130 breath units, to be accepted as proof of airway hyperresponsiveness (AHR) (2,7).

It should be noted that a negative response to methacholine does not exclude exercise-induced asthma in an athlete, and in the event of a negative response, an alternative bronchial provocation test is recommended.

If values for PC₂₀ or PD₂₀, or breath units during the Methacholine challenge are in excess of the thresholds mentioned above, the athlete may undergo an EVH test or an exercise test on site in Turin * prior to the start of the Games.

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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.

Recommendation for withholding medications prior to tests

To provide the optimal test circumstances, it is recommended that some medications 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 4 days. Inhaled corticosteroids should not be administered on the day of the test. No caffeine should be taken on the morning of the study. Avoid vigorous exercise for at least four hours prior to the start of the test, and avoid all exercise on the day of testing.

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, but still seeking approval for the use of inhaled beta2-agonists, the following documentation must be included in the file₁ (in addition to negative results obtained in the bronchial provocation test(s) sent electronically): 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.

At the time of the submission of this type of request, 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. Please also inform us that you are sending a file, in order to avoid your request being automatically refused.

Should the athlete wish to submit a second bronchial provocation test result, the opportunity for further testing will be available in Turin. Please contact: **Dr Carlo GULOTTA**, Pneumologia II - Fisiopatologia Respiratoria, ASO San Luigi, Regione Gonzole, 10, 10043 Orbassano, Torino, Italie, tél. +39 011 9026 332, 372, 733, tél./fax + 39 011 9026 371, portable +39 335 7609 007, c.gulotta@sanluigi.piemonte.it, fpr@sanluigi.piemonte.it.

₁The files must imperatively be sent **by recorded 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 or by telephone on +41 21 621 61 11.

4. BIBLIOGRAPHY

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 β 2-agonists before an event at the 2002 Winter Olympics, *J Allergy & Clinical Immunology* 2003; 111: 45-50.

Eucapnic voluntary hyperpnea test

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.

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

Rundell KW, Anderson SD, Spiering BA, Judelson DA. Field exercise vs laboratory eucapnic voluntary hyperventilation to identify airway hyperresponsiveness in elite cold weather athletes. *Chest* 2004; 125:909-15.

Exercise challenge in the laboratory or an exercise test in the field

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.

Crapo RO, Casaburi R, Coates AL, et al. Guidelines for methacholine and exercise challenge testing - 1999. Am J Respir Crit Care Med, 2000; 161: 309-29.

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.

Hypertonic aerosol

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.

Smith CM, Anderson SD. Inhalational challenge using hypertonic saline in asthmatic subjects: a comparison with responses to hyperpnoea, methacholine and water. Eur Respir J 1990; 3: 144-51.

Sterk PJ, Fabbri LM, Quanjer PH, et al. Airway responsiveness: Standardized challenge testing with pharmacological, physical and sensitizing stimuli in adults. Eur Respir J, 1993; 6(Suppl 16): 53-83

Methacholine test

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.

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.

Cockcroft DW, Davis BE, Todd DC, Smycniuk AJ. Methacholine challenge: >comparison of two methods. Chest 2005; 125:839-844