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Can asthma treatment in sports be doping? The effect of the rapid onset, long-acting inhaled β_2-agonist formoterol upon endurance performance in healthy well-trained athletes

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Inhaled β_2-agonists have been subject to restrictions in relationship to sports due to fear of possible improvement in endurance performance. According to the international doping regulations only inhaled salbutamol, terbutaline and salmeterol are allowed for use in sports. Formoterol is a recently introduced rapid onset-long-acting inhaled β_2-agonist.

The main aim of the present randomized, double-blind placebo-controlled study was to investigate possible improvement in endurance performance of inhaled formoterol in 24 healthy well-trained competitive male athletes, 21–29 years old.

Lung function (flow–volume loops) was measured before, 15 min after each inhaled study drug and before and repeatedly after exercise. On day 1, maximum oxygen uptake (VO_{2max}), peak ventilation (VE_{peak}) and running time till exhaustion were measured and used to determine the exercise load on days 2 and 3. On days 2 and 3 the subjects inhaled the study drugs, rested for 1 h, then exercised, and VO_{2max}, VE_{peak} and running time until exhaustion were determined.

Inhaled formoterol did not improve any parameter of endurance performance. On the other hand a statistically significant, although not clinically significant ($0{\cdot}05\,ml^{-1}min\,kg^{-1}$), change was found in estimated difference of VO_{2max} between formoterol and placebo in favour of placebo. Lung function increased significantly after inhaled formoterol, and after exercise also for placebo, but without differences between the β_2-agonist and placebo after exercise.

In conclusion, inhaled formoterol did not improve endurance performance compared to placebo.

Key words: formoterol; endurance performance; maximum oxygen uptake; peak ventilation; lung function; healthy athletes.

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Introduction

Bronchodilating drugs taken prior to physical activity, especially inhaled β_2-agonists, are recommended drugs for the prevention of exercise induced asthma (EIA) (1). Also, the long-acting β_2-agonists salmeterol and formoterol have been shown to be effective in this aspect (2,3). These drugs are particularly important for endurance sports due to their long-acting effect. Increasing concern has been raised due to the common use of inhaled β_2-agonists to prevent EIA among elite athletes, especially among skiers (4), with regard to an over-use and potential beneficial performance effects on non-asthmatic athletes. Over-use may put the β_2-agonist under suspicion of a possible doping effect. These drugs are very important for athletes with asthma to be able to perform their sports, and a possible ban of these drugs may render many athletes incapable of participating in sports. A possible ban of these drugs might also affect compliance rate in children and adolescents with asthma who use these drugs to be able to master their daily life and activity. Due to fear of possible doping effects of β_2-agonists, including both improved performance and possible anabolic effect upon muscle (5), the Medical Commission of the International Olympic Committee already in 1993 put certain restrictions upon the use of inhaled β_2-agonists, allowing only the two short-acting inhaled β_2-agonists salbutamol and terbutaline for use in sports. Hence, the long-acting inhaled β_2-agonists, salmeterol and formoterol, have not been permitted for use in sports in spite of reports of their excellent preventive effect of EIA (2,3,6). However, studies performed with salmeterol on healthy and asthmatic top-trained athletes (6–8) do not

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demonstrate any beneficial effect upon performance during exercise. In one study on healthy athletes the time for endurance running to exhaustion (6), was better after placebo than after both salmeterol and salbutamol. Thus, inhaled salmeterol was allowed by IOC to treat and prevent EIA in relationship to sports from 1 February 1996.

Formoterol is a long-acting β_2-agonist for inhalation. Formoterol combines a rapid onset of action with a long duration of 12 h. Thus, the drug represents a valuable addition in the treatment of asthmatic patients, especially those with ongoing symptoms. Due to its long duration of action and the rapid onset of action, this drug will benefit the asthmatic athlete performing in endurance sports both for prevention of EIA and as regular treatment of chronic asthma in athletes.

As formoterol was not allowed for use in sports, the present study was set up to study the effect of inhaled formoterol upon performance in healthy athletes in order to establish the role of the drug in relation to sports and doping regulations.

The main objective of the present study was to evaluate if formoterol improved endurance performance in healthy athletes compared to placebo. The secondary aim was to assess the effect of formoterol upon lung function in healthy well-trained athletes compared to placebo in relationship to heavy exercise.

Subjects and methods

SUBJECTS

Twenty-four well-trained male competitive athletes were included in the study. Inclusion criteria were: male subjects, 18–30 years of age, participating on a competitive level in endurance sports. They had to achieve maximum oxygen uptake (VO_{2max}) of at least $5 l/min^{-1}$ and peak ventilation (VE_{peak}) above $170 l/min^{-1}$, and to demonstrate their ability to use the Turbuhaler® as an inhalation device and to be able to perform the study procedures. The subject could not suffer from any respiratory disease or any other disease, which might influence the results, and they could not have had any respiratory tract infection during the last 3 weeks before inclusion in the study. Furthermore, they could not use tobacco in any form or any regular medication. Exclusion criteria also included recognised asthma or allergy during the last 2 years before the start of the study and a reduction in forced expiratory volume during 1 sec (FEV_1) of $\geq$10% during the first 10 min after running to exhaustion on visit one.

DESIGN

The study was a randomized, double-blind, placebo-controlled cross-over design with inhalation of either 9 μg formoterol or placebo. There were three study days in total (visits). On study day 1 all subjects performed an exercise test without any drug to establish a performance baseline for each subject and to verify that they satisfied the inclusion criteria. If satisfying the inclusion criteria the subjects were randomized to one of the two treatment sequences: Oxis Turbuhaler® (formoterol) on the second study day and placebo Turbuhaler® on the third or placebo Turbuhaler at the second study day followed by Oxis Turbuhaler® (formoterol) on the third day.

Lung function was measured before and 15 min after inhalation of the drugs. Exercise was started 60 min after inhalation of the drugs (on days 2 and 3). Lung function was measured immediately before and immediately after, and 3, 6, 10 and 15 min after exercise.

The subjects were randomized consecutively to one of the two treatment blocks according to random order generated by a computer programme to ensure that equal number of subjects received either formoterol or placebo as the first study drug.

On study days 2 and 3 the subjects performed according to identical protocols. Maximum oxygen uptake during running on a treadmill, running time untill exhaustion, maximum ventilation and lung function were determined.

The study was performed in accordance with the principles stated in the Declaration of Helsinki. The Regional Medical Ethics committee approved the study. The study subjects signed an informed consent form after given oral and written information about the study objectives and methods.

METHODS

Lung function

Lung function was measured by maximum expiratory flow volume loops (Pneumoscreen, Jaeger®, Germany). FEV_1 and maximum flow at 50% of remaining vital capacity (MEF_{50}) were the lung function parameters chosen for assessment of lung function.

Inhaled drugs

The drugs were inhaled as dry powder by use of the turbuhaler: formoterol (Oxis®) 9 μg delivered dose and placebo. Placebo consisted of lactose only. The drugs were inhaled by forced, rapid inspiration with breath-holding for 15 sec after inspiration.

Heart rate

Heart rate was measured electronically by Polar Vantage™ (Polar Electro, Finland) and recorded at 30 sec intervals during exercise testing.

Exercise, maximum oxygen uptake (VO_{2max}), peak ventilation (VE_{peak}) , running time until exhaustion and peak heart rate

Visit 1. After warming up for 10 min with a heart rate around 130 beats min^{-1} (Polar Vantage), the subjects ran

at four submaximal workloads on the treadmill (Woodway) with a range of approximately 60–85% of VO_{2max}. Each load lasted for 5 min (in order to reach a VO_2 plateau) and $'VO_2$ was measured the last minutes using a nose-clip and a mouthpiece (Hans Rudolph, one-way-valve) connected to an automated gas exchange analyser (Oxycon Champion, Jaeger®). Between each bout there was a 30 sec pause for fingertip sampling of capillary blood (50 μl) used for determination of blood lactate concentration (1500 Sport, YSI Lactate analyser®, U.S.A.).

The speed was increased in steps of 1 km h^{-1} and the inclination of the treadmill was 6° throughout the entire test. Lactate concentration was used as an indicator of the anaerobic contribution and should not exceed 3·0 mmol l^{-1}.

After the fourth submaximal workload, the speed was increased every 30 sec for 2 min reaching a level the subject felt he could keep for another 1·5–2 min. The test was then continued until exhaustion. VO_{2max} was defined as the highest average over a range of 1 min. VE_{peak} was defined as the highest average over a range of 30 sec.

Visits 2 and 3. Based on the fact that there is an almost linear relationship between energy demand and speed of running (9), a linear regression formula was calculated for each subject using their VO_2 from the four submaximal workloads as an approximation of the total energy expenditure. Anaerobic contribution was assumed negligible. Using the VO_{2max} in this equation, the theoretical running speed at 105% of VO_{2max} was calculated by extrapolation for each subject. After a 20 min warm-up at 60% of VO_{2max}, the subject rested for 2 min. The speed was then set to 105% of VO_{2max} and the subject was motivated to run until total exhaustion. Mouthpiece and nose-clip was kept on through the whole test and VO_2, ventilation, RQ and heart rate was measured every 15 sec.

Time from start untill the end of the run at 105% of VO_{2max} was set as the running time to exhaustion. VO_{2max} and VE_{peak} were determined as described under visit one, and peak heart rate was the highest single measurement.

Statistical methods

Sample size determination was based upon the assumption that the expected true value for difference between the two treatments of VO_{2max} was within the 90% confidence limits of 2 ml.kg^{-1} minute^{-1} $\pm$ 3·25 ml.kg^{-1}minute^{-1} with a standard deviation (SD) not exceeding 1·5 ml.kg^{-1}minute^{-1}. It was calculated that a total of 20 subjects were needed to obtain a statistical power of 80%.

Results are unless otherwise stated given as mean with 95% confidence intervals (95% CI). Demographic data are given as mean with SD.

Differences between the treatment groups were assessed by multivariate analysis of variance based upon the main variables VO_{2max}, VE_{peak}, running time untill exhaustion and lung function, FEV_1 and MEF_{50}. Direct medication effect, subject ID, period, carry-over and group (value 1 if formoterol in first period and 2 if placebo in first period) was included as factors in the analysis. The subject ID was considered to be random, the other ones fixed. If no carry-over was found, the term was removed from the model.

Differences between the groups were considered statistically significant with *P*-values less than or equal to 0·05. All tests were two-tailed.

Results

Twenty-four male subjects, 21–29 years of age, satisfying the inclusion criteria were included in the study. They were actively participating in competition sports: cross-country skiing ($n=11$), orienteering ($n=5$), basketball ($n=1$), soccer ($n=4$), skating ($n=1$) and paddling ($n=2$). Demographic data are shown in Table 1.

Formoterol was not found to improve endurance performance with regard to any of the main variables. No significant differences were found in the main variables VO_{2max}, VE_{peak} or running time until exhaustion between formoterol and placebo (Table 2). However, in the estimated difference between placebo and formoterol in VO_{2max} a small, although statistically significant difference was found for VO_{2max}, 0·05 ml min^{-1}kg in favour of placebo (Table 3). For the two other main variables no statistically significant differences between formoterol and placebo were found.

Lung function (FEV_1 and MEF_{50}) did not differ at baseline measurements on the two study days (Table 4). Fifteen and 60 min after inhaled drug lung function increased in the formoterol group, but not in the placebo group. The increase in FEV_1 after formoterol was not statistically significant 15 min after inhaled drug, but was so after 60 min ($P=0·0045$), immediately after running ($P=0·02$) (Table 4), and after 3 min ($P=0·02$), but not thereafter. Also MEF_{50} increased significantly 60 min after inhaled formoterol ($P=0·026$), immediately after running ($P=0·0001$) and after 3 min ($P=0·0022$) and 6 min ($P=0·016$) compared to baseline. The increase remained significantly higher also 10 and 15 min after running ($P=0·02$) (Table 4).

After inhalation of placebo no significant difference was found for FEV_1 compared to baseline until immediately after exercise ($P=0·0090$). The same was found for MEF_{50} ($P=0·0009$). Immediately after exercise no significant differences were found for either lung function parameter comparing placebo and formoterol as premedication (Table 4).

TABLE 1. Demographic variables of the 24 male study subjects

Variable	Mean value (SD)	Range
Age (years)	25·0 (2·8)	21–29
Height (cm)	183·6 (5·3)	174·0–194·0
Weight (kg)	80·1 (5·8)	68·0–90·0

TABLE 2. Results of testing procedures at maximum performance on two different days with placebo and formoterol 9 μg inhaled before exercise in 24 well-trained healthy young adults. Results are given as mean values with standard deviation in parentheses (SD) and 95% CI in square brackets

	Placebo	Formoterol	Significance
Peak ventilation ($l\,min^{-1}$)	183·0 (16·8) [175·9–190·1]	182·8 (18·6) [175·0–190·7]	NS
Maximum O_2 uptake (VO_2) ($ml.kg^{-1}min^{-1}$)	5·4 (0·4) [5·2–5·5]	5·4 (0·4) [5·3–5·6]	NS
Running time until exhaustion (sec)	300·0 (45·7) [280·7–319·3]	303·4 (42·3) [285·5–321·3]	NS

NS: not significant.

TABLE 3. Estimated differences between placebo and formoterol in maximum oxygen uptake (VO_{2max}), peak ventilation (VE_{peak}) and running time untill exhaustion

	Estimated difference mean value [95% CI]	Significance
Maximum oxygen uptake (VO_{2max}) ($ml\,min.kg^{-1}$)	−0·05 [−0·09–−0·02]	P = 0·008
Running time untill exhaustion (sec)	−0·25 [−9·0–+7·0]	NS
Peak ventilation (VE_{peak}) ($l\,min^{-1}$)	−0·50 [−3·15–+3·25]	NS

Discussion

After the many reports on increasing prevalence of asthma among top athletes within endurance sports (4,10–13) and the frequent use of inhaled β_2-agonists that led IOC medical commission to restrict the use of inhaled β_2-agonists in asthmatic athletes to salbutamol and terbutaline in 1993, the long-acting inhaled β_2-agonists salmeterol was allowed from 1996 after studies on the effect of salmeterol on endurance as well as anaerobic performance (7,14). However, inhaled formoterol with a rapid onset of action as well a long duration of action, has not been allowed for the use in sports. The present study demonstrates no improvement on endurance performance of inhaled formoterol in well-trained endurance athletes. Endurance was measured by VO_{2max}, VE_{peak} as well as running time untill exhaustion. After preliminary information about the results of the present study was given to IOC medical commission, the rules are presently under consideration.

It is of particular interest that a small though statistically significant difference was found for VO_{2max} with higher values after placebo than after the active drug. The difference was of no clinical significance, and also negligible in relationship to sports performance. However, this demonstrates that no benefit may be obtained by improper use of inhaled formoterol in relationship to sports. On the other hand, the difference in VO_{2max} was so small that this should not discourage asthmatic athletes from using inhaled long-acting β_2-agonists to control their asthmatic symptoms and their EIA. The same may be said for salmeterol, as a small difference in favour of placebo was found for running untill exhaustion in a previous study (6). These small effects on exercise performance by the long-acting inhaled β_2-agonists would not encourage the healthy athlete to use these drugs in the abscence of asthma, whereas the beneficial effect upon EIA and exercise tolerance in asthmatic subjects (2,3,15) far outweighs the negligible effects on exercise performance.

As was the case for salmeterol and salbutamol (14), a significant increase in lung function was found after inhalation of the active drug before exercise performance. Also this time the difference between placebo and the active drug in lung function disappeared during and immediately after exercise (Fig.1). Thus, one may conclude that during exercise, exercise itself has a bronchodilating effect that more than outweighs the change in baseline lung function caused by the inhaled β_2-agonist. As seen in Fig 1, when the effect of exercise diminished, the difference in baseline lung function brought about by formoterol became evident again.

Inhaled formoterol has a long-lasting effect in common with salmeterol. This may be of particular value for sport activities of long duration e.g. long distance running or long distances of cross-country skiing. On the other hand, inhaled formoterol has also a rapid onset of action, comparable to salbutamol (16). Rapid onset of action enables formoterol to be used as premedication before exercise in contrast to a regular twice-daily use of the drug, which has usually been recommended for long acting β_2-agonists. This may limit the regular use of the drug for EIA, and also reduce the tolerance development, which has been reported for long acting β_2-agonists (17,18). Thus, formoterol may be of benefit for the use of EIA in relationship to sports, and possibly reduce the need for regular or frequent medication. The present study demonstrates no benefit on endurance performance by the use of inhaled formoterol in healthy individuals. If any effect at all, it was a small reduction in VO_{2max} after formoterol. Thus, it

TABLE 4. Lung function (FEV_1) at baseline, 15 min after inhaled drug and after exercise on the two study days with inhaled placebo and inhaled formoterol (9 μg) in 24 male healthy well-trained young adults. Results are given as mean values with standard deviation (SD) in parentheses and 95% CI in square brackets

	Placebo		Formoterol	
	FEV_1 ($l\,sec^{-1}$)	MEF_{50} ($l\,sec^{-1}$)	FEV_1 ($l\,sec^{-1}$)	MEF_{50} ($l\,sec^{-1}$)
Before study drugs	5·08 (0·44)	5·46 (1·04)	5·06 (0·46)	5·45 (1·11)
	[4·90–5·27]	[5·02–5·90]	[4·86–5·25]	[4·98–5·92]
15 min after drug,	5·06 (0·48)	5·38 (0·91)	5·20 (0·49)	6·02 (1·19)
before exercise	[4·85–5·26]	[5·00–5·77]	4·99–5·41]	[5·52–6·52]
60 min after drug,	5·08 (0·40)	5·48 (1·06)	5·24 (0·51)	6·26 (1·32)
before exercise	[4·91–5·25]	[5·03–5·92]	[5·02–5·46]	[5·70–6·82]
Immediately (1 min)	5·40 (0·37)	6·81 (1·54)	5·44 (0·42)	6·97 (1·40)
after exercise	[5·24–5·56]	[6·16–7·46]	[5·26–5·62]	[6·38–7·55]
3 min after exercise	5·25 (0·34)	6·17 (1·29)	5·36 (0·41)	6·62 (1·38)
	[5·10–5·39]	[5·62–6·71]	[5·19–5·54]	[6·03–7·20]
6 min after exercise	5·16 (0·39)	5·78 (1·29)	5·29 (0·43)	6·39 (1·47)
	[5·00–5·33]	[5·24–6·32]	[5·10–5·47]	[5·77–7·01]
10 min after exercise	5·13 (0·42)	5·77 (1·42)	5·33 (0·48)	6·31 (1·28)
	[4·95–5·31]	[5·17–6·37]	[5·12–5·53]	[5·77–6·86]
15 min after exercise	5·14 (0·47)	5·59 (1·19)	5·32 (0·46)	6·25 (1·30)
	[4·94–5·34]	[5·09–6·10]	[5·13–5·52]	[5·71–6·80]

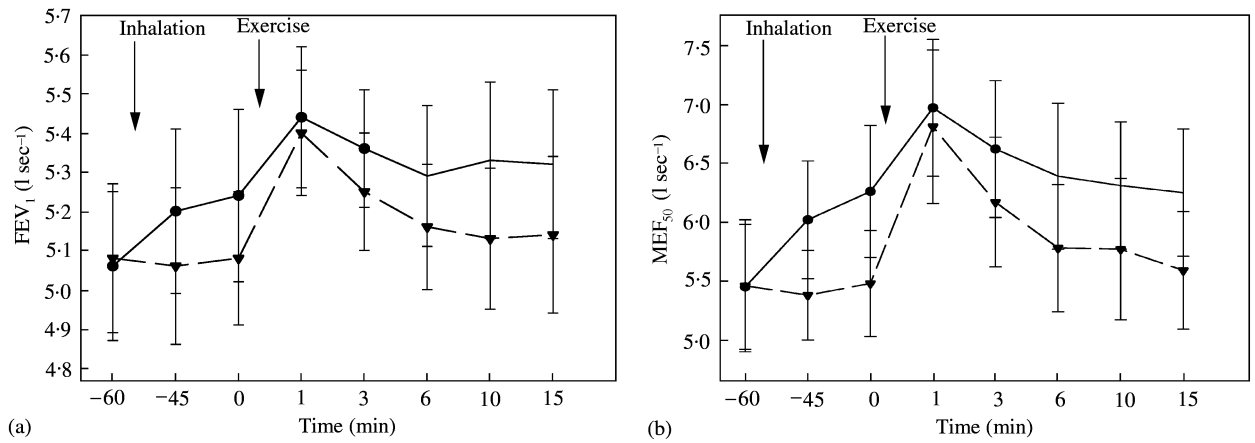

FIG. 1. (a) Forced expiratory volume in 1 sec (FEV_1) and (b) maximum expiratory flow at 50% of vital capacity (MEF_{50}) measured before, 15 and 60 min after inhaled formoterol (●)and placebo (▼), and immediately, 3, 6, 10 and 15 min after exercise. Values are shown as mean with 95% confidence intervals.

should not influence athletes to use this drug unless a proper diagnosis of EIA has been made. It is our hope that the present study may contribute to a decision to allow the use of inhaled formoterol by asthmatic athletes in sports. This drug is also of benefit to children and adolescents with persistent asthma and chronic asthma. In order to master asthma, compliance with prescribed treatment is important. By withdrawing formoterol from the list of forbidden drugs in sports, the drug may become more acceptable to adolescents and children with asthma.

Thus, both out of consideration for the asthmatic athlete, as well as for the asthmatic adolescent and child, it is important that formoterol should be allowed for use in asthmatic athletes.

Conclusion

The inhaled rapid-onset, long-acting inhaled β_2-agonist formoterol did not improve endurance performance in healthy, well-trained competitive athletes, measured by VO_{2max}, VE_{peak} and running time until exhaustion. As formoterol has the advantage of a rapid onset in addition to long duration of action, the drug may be used not only on a

regular basis, but also as pretreatment before exercise and on-demand. This may in asthmatic athletes lead to a reduction in the number of doses of inhaled β_2-aonists needed. Thus, we conclude that the drug taken correctly should be allowed for use in sports by asthmatic athletes.

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