The cardiorespiratory response to submaximal exercise in subjects with asthma following pretreatment with controlled release oral salbutamol and high-dose inhaled salmeterol

S. M. Revill and M. D. L. Morgan

Department of Respiratory Medicine, Glenfield Hospital, Leicester LE3 9QP, U.K.

Treatment for exercise induced asthma (EIA) in sporting competition is controlled to prevent the use of agents which might enhance physical performance. There is little information concerning the effects of the long-acting inhaled, and oral, sustained release type bronchodilators on the cardiorespiratory effects of submaximal exercise. The aim of this study was to compare the cardiorespiratory effects of submaximal exercise in patients with EIA before and after pretreatment with high-dose inhaled salmeterol xinafoate (SX) and controlled release oral salbutamol (CR).

Patients were treated with SX (100 µg b.d.) and CR (8 mg b.d.) for 3 days in a double-blind randomized cross-over design, with a 5-14 day washout period between treatments. A submaximal exercise test (total exercise time 6 min, final 3 min at 60% of Speak) was performed prior to each treatment period, and repeated at 1, 6, and 12 h postdose at the end of the treatment period.

Two subjects were withdrawn from the study. Three subjects required relief medication after 1 h (CR) and one subject after 6 h (SX) and they did not perform further exercise tests. Both treatments increased baseline FEV₁, with SX producing significantly greater pre-exercise bronchodilation than CR (P=0.04). Following CR, there were no significant differences from the pretreatment values for VO₂, V̇, respiratory exchange ratio, heart rate, ventilatory equivalents for VO₂, and oxygen pulse during the submaximal exercise challenge. Following SX, there were no significant differences for any of the exercise variables except for V̇ at 6 and 12 h (mean increase 4.27 l min⁻¹ at 6 h, P<0.01 and 4.69 l min⁻¹ at 12 h, P=0.05).

The changes in ventilation following SX did not have an effect on oxygen consumption, and the ventilatory efficiency (V̇/VO₂) remained unchanged. The findings from this study demonstrate that, despite exercising from a higher baseline FEV₁, short pretreatment periods with controlled release oral salbutamol and with inhaled salmeterol do not confer any cardiorespiratory advantage during submaximal exercise in subjects with EIA.

Introduction

There are many sportspeople who are disadvantaged as a result of asthma. The treatment of EIA in such individuals may require individualized treatment, and therefore the opportunity to choose from a wide variety of agents is important. Prolonged control of EIA is particularly desirable for submaximal, endurance training schedules, and competition events which occur over 2-6 h. The short acting inhaled β₂-agonists have been permitted in sporting competitions for some time, and the long-acting, inhaled agents have recently gained approval (1). The oral β₂-agonists remain prohibited. Concern centres around any enhancing effects the agents might confer on the exercise response leading to competitive advantage.

We have recently demonstrated EIA inhibition over 12 h with the maximum dose of salmeterol (100 µg b.d.) and, surprisingly, protection for some patients using controlled release oral salbutamol (8 mg b.d.) (2). However, there is little information concerning the effects on exercise following short, pretreatment periods of either agent. The aim of this study was to examine the cardiorespiratory response to submaximal exercise following a short, pretreatment period with high dose salmeterol and controlled release oral salbutamol in subjects with EIA.

Methods

STUDY DESIGN

The design was double-blind, randomized cross-over with treatment periods of 3-5 days, and a washout period of
5–14 days between treatments. During an initial screening visit patients performed a maximal, incremental exercise test on the treadmill to measure peak ventilation ($V_{\text{peak}}$), and to assess the fall in FEV$_1$ postexercise. A value of 60% $V_{\text{peak}}$ was determined from the maximal test and used as a target value for all subsequent submaximal exercise challenges. At the second visit patients performed a submaximal exercise test lasting 6 min, with the final 3 min at a work rate which related to the target value of 60% $V_{\text{peak}}$. Ventilation, gas exchange and heart rate were measured throughout.

SUBJECTS

Fourteen patients (seven men), mean (sd) age 32 (12) years were recruited. Only patients with a history of asthma, and a baseline FEV$_1$ >60% of the predicted value were included in the study. All the patients demonstrated >20% fall in FEV$_1$ postexercise during an initial screening test. All of the patients used inhaled, short acting β$_2$-agonists as required, and eight patients were using regular inhaled steroids (<400 μg). No patients were on oral, or long acting, β$_2$-agonists. The group had been free from respiratory tract infections for more than 4 weeks prior to the study, and from exacerbations of asthma for a similar length of time. Informed consent was obtained, and the protocol was approved by the District Ethics Committee.

At the end of the second visit patients were issued with the randomized treatment and instructed to commence the regimen the following morning. After a treatment period of ≥3 days patients returned to the exercise laboratory (visit 3) and performed three submaximal exercise tests over a 12-h period following the administration of a dose of the randomized treatment. The tests were performed at 1, 6 and 12 h postdose, and the cardiorespiratory measurements were recorded during each test. At the end of visit 3 a treatment washout phase of 5–14 days commenced. At visit 4, patients repeated the submaximal exercise challenge, and were issued with their second treatment regimen. Again, following a treatment period of ≥3 days, patients performed three exercise challenges over a period of 12 h (visit 5), in the same manner as described for visit 3.

MEASUREMENTS

FEV$_1$ was measured using a wedge bellows spirometer (Vitalograph, model R, Bucks, U.K.) before and for 30 min postexercise at all visits. Three technically acceptable measurements were made according to the BTS/ARTP Guidelines (3) and the highest value was recorded for analysis. Predicted values were calculated from the European Guidelines (4).

The ventilation and gas exchange were measured using a computerized, breath-by-breath exercise system (Oxycon Beta, Erich, Jaeger, U.K. Ltd). Briefly, a small accelerometer (model 4367, Brulé and Kjaer, Denmark) was secured to the middle finger of the dominant hand, and measurements of acceleration recorded onto magnetic tape for 1 min. The forearm was supported and the hand extended. Digital spectral analysis of the tapes was performed by a dedicated computer programme in the Department of Physiology and Pharmacology, Queens Medical Centre, Nottingham.

DOSAGE REGIMEN AND SAFETY

The dosing regimen was salbutamol controlled release capsules (CR) 8 mg b.d. and salmeterol xinafoate (SX) 100 μg b.d. via MDI. Correct inhaler technique was ensured prior to the start of treatment. Relief medication during the treatment periods was salbutamol MDI (100 μg). All other asthma medications remained the same.

Resting blood pressure and a 12-lead ECG were performed during the screening visit to ensure there were no cardiovascular contra-indications to exercise. A single lead ECG was also monitored throughout the exercise tests. If there was a persistent fall in the FEV$_1$ of >30% postexercise, relief medication was administered for safety reasons and for patient comfort, and also at any other time if requested by the patient. Patients were not allowed to leave the laboratory until the FEV$_1$ had returned to 90% of the baseline value. All adverse events throughout the study period were documented.

STATISTICAL ANALYSIS

The end exercise values for $V_{\text{es}}$, $V_{\text{O}_2}$, RER, HR, $O_2$ pulse and $V_{\text{e}}$/$V_{\text{O}_2}$ from each of the exercise tests during the treatment phases (at 1, 6, and 12 h) were compared to the corresponding pretreatment measurements using analysis of variance (ANOVA). Within- and between-treatment differences at each of the time points were also compared using ANOVA. Changes in the pre-exercise FEV$_1$ were compared using repeated measures analysis to investigate differences in the profile of the FEV$_1$ measurement. The % fall in FEV$_1$ at each of the time points were compared between treatments using the Wilcoxon rank sum test. The change in finger tremor from pretreatment levels, for both dominant frequency and peak frequency band root mean square of tremor amplitude (PFB RMS), was compared between treatments using an ANOVA. Carry-over and treatment-by-period interaction were judged at the 10% level of significance, whilst all other effects were judged at the 5% level.
TABLE 1. Pre-exercise FEV\textsubscript{1} and % fall post exercise

<table>
<thead>
<tr>
<th>Time</th>
<th>SX</th>
<th>CR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pre-ex</td>
<td>Post-ex</td>
</tr>
<tr>
<td></td>
<td>FEV\textsubscript{1}</td>
<td>% fall</td>
</tr>
<tr>
<td>Pretreatment (i.e. visit 2 or 4)</td>
<td>3.17</td>
<td>33</td>
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<tr>
<td>Treatment phase</td>
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<td></td>
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<tr>
<td>1 h postdose</td>
<td>3.69</td>
<td>7</td>
</tr>
<tr>
<td>6 h postdose</td>
<td>3.75</td>
<td>9</td>
</tr>
<tr>
<td>12 h postdose</td>
<td>3.57</td>
<td>17</td>
</tr>
</tbody>
</table>

Adjusted mean FEV\textsubscript{1} (l) pre- and post-treatment prior to each exercise challenge, and median % fall in FEV\textsubscript{1} postexercise.

TABLE 2. Cardiorespiratory response to submaximal exercise

<table>
<thead>
<tr>
<th>Treatment</th>
<th>$\dot{V}_O_2$ (ml kg\textsuperscript{-1} min\textsuperscript{-1})</th>
<th>$\dot{V}_E$ (l min\textsuperscript{-1})</th>
<th>RER</th>
<th>HR (beat min\textsuperscript{-1})</th>
<th>$O_2$ pulse (ml beat\textsuperscript{-1})</th>
<th>$V_E/\dot{V}_O_2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>SX</td>
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<td></td>
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</tr>
<tr>
<td>Pre-R\textsubscript{a} (visit 2 or 4)</td>
<td>31.3 (1.3)</td>
<td>74.2 (2.5)</td>
<td>1.09 (0.05)</td>
<td>157 (7)</td>
<td>14.8 (0.4)</td>
<td>31.3 (0.8)</td>
</tr>
<tr>
<td>Postdose 1</td>
<td>31.6 (1.0)</td>
<td>77.8 (2.2)</td>
<td>1.11 (0.05)</td>
<td>158 (1)</td>
<td>14.9 (0.5)</td>
<td>31.7 (1.2)</td>
</tr>
<tr>
<td>time (h) 6</td>
<td>31.4 (0.4)</td>
<td>78.4 (1.2)**</td>
<td>1.13 (0.05)</td>
<td>159 (1)</td>
<td>14.9 (0.2)</td>
<td>32.5 (0.7)</td>
</tr>
<tr>
<td>12</td>
<td>30.6 (0.8)</td>
<td>78.8 (2.3)*</td>
<td>1.12 (0.06)</td>
<td>159 (1)</td>
<td>14.3 (0.2)</td>
<td>32.7 (0.9)</td>
</tr>
<tr>
<td>CR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-R\textsubscript{a} (visit 2 or 4)</td>
<td>32.3 (1.3)</td>
<td>77.3 (2.5)</td>
<td>1.07 (0.06)</td>
<td>150 (7)</td>
<td>15.4 (0.4)</td>
<td>30.5 (0.8)</td>
</tr>
<tr>
<td>Postdose 1</td>
<td>30.9 (1.1)</td>
<td>73.9 (2.2)</td>
<td>1.06 (0.04)</td>
<td>156 (1)</td>
<td>15.1 (0.5)</td>
<td>30.6 (1.2)</td>
</tr>
<tr>
<td>time (h) 6</td>
<td>30.6 (0.5)</td>
<td>75.6 (1.6)</td>
<td>1.05 (0.05)</td>
<td>160 (2)</td>
<td>14.6 (0.3)</td>
<td>31.2 (0.8)</td>
</tr>
<tr>
<td>12</td>
<td>29.8 (0.8)</td>
<td>74.3 (2.6)</td>
<td>1.05 (0.06)</td>
<td>159 (2)</td>
<td>14.2 (0.2)</td>
<td>31.4 (1.0)</td>
</tr>
</tbody>
</table>

*P=0.05, **P<0.01.
Pre- (visit 2 or 4) and post-treatment mean (SE) values of oxygen consumption ($\dot{V}_O_2$), ventilation ($\dot{V}_E$), respiratory exchange ratio (RER), heart rate (HR), oxygen pulse ($O_2$ pulse) and ventilatory equivalents for oxygen ($V_E/\dot{V}_O_2$) during repeated submaximal exercise challenge.

Results

Two patients were withdrawn from the study. One patient had severe tremor during the first treatment period (group 1, active treatment CR), and one patient was withdrawn due to an unstable baseline FEV\textsubscript{1} during the washout phase between treatments (>10% difference from the baseline measurement at visit 2). The results are presented for the remaining 12 patients.

One patient requested relief medication for wheeze and a tight chest after falling asleep between the 6 and 12 h exercise challenges on the SX challenge day. During the CR challenge day relief medication was administered to three patients for a persistent fall in FEV\textsubscript{1} (>30%) at 1 h. No further exercise tests were carried out following the administration of relief medication.

The mean % predicted FEV\textsubscript{1} was 93 (20) % at the baseline (screening) visit. The mean FEV\textsubscript{1} values prior to each treatment phase (visits 2 and 4), and prior to each exercise challenge are shown in Table 1. The median % falls postexercise are also given. SX produced significantly greater pre-exercise bronchodilation than CR (P=0.04).

There were no significant differences between treatments for the % fall in FEV\textsubscript{1}, however, the median % fall following CR was larger and just failed to reach significance at 6 h (P=0.07). Following SX, the fall in postexercise FEV\textsubscript{1} was attenuated (>20%) in eight patients for 6 h, and in six patients the inhibition persisted for 12 h. Following CR, the fall in FEV\textsubscript{1} was attenuated for 12 h in five patients (42% of the group). The postexercise fall in FEV\textsubscript{1} was inhibited by SX and not CR for three patients at all time points, whilst for two patients the fall in FEV\textsubscript{1} was inhibited by CR and not SX at all time points.

CARDIORESPIRATORY RESPONSE TO SUBMAXIMAL EXERCISE

A summary of the cardiorespiratory data from each of the treatment phases is shown in Table 2. During the SX treatment phase the $\dot{V}_E$ during the exercise test at 6 h was significantly higher than the pretreatment value [mean (SE) increase 4.27 (1.22) l min\textsuperscript{-1}, P<0.01] and at 12 h it was of
borderline significance [4.69 (1.93) 1 min⁻¹, P=0.05]. With the exception of these two values there were no other significant differences between the pre- and posttreatment values for VO₂, V̇ₐ, RER, HR, O₂ pulse and V̇ₐ/VO₂ for either treatment. In addition there were no significant differences between each time point within the same treatment phase. There was a tendency for a more variable heart rate response to exercise during the CR treatment phase. There were no significant carry-over or treatment-by-period interactions detected. The mean differences and 95% confidence intervals, between pretreatment and each of the exercise time points for V̇ₐ, VO₂ and HR are illustrated in Fig. 1.

FINGER TREMOR AND OTHER SIDE-EFFECTS

There was no significant change in the dominant frequency of the finger tremor with either treatment. However, both treatments increased the amplitude of finger tremor above the pretreatment values, with CR having the greater effect (Fig. 2). The greatest differences between treatments were at 15 min, 1 and 12 h postdosing (P values 0.09, 0.09 and 0.01, respectively). After the ‘chronic’ dosing period a single dose of either drug did not have an additional ‘acute’ effect.

Finger and general tremor were reported symptoms during both treatments, with slightly fewer patients noticing the symptom with SX (six reports with SX, and eight reports with CR). However, more patients reported palpitations, during the SX treatment period (n=3) compared to the CR treatment (n=1). Equal numbers of patients reported at least one incidence of headache (n=4 for both SX and CR).

Discussion

Individuals with EIA are at a disadvantage in performing exercise, and selected inhaled β₂-agonists are allowed for use in sports to enable asthmatics to compete on equal levels with healthy individuals. However, treatment should act to minimize the EIA and not augment athletic performance and therefore is permitted where there is evidence that asthmatics do not derive additional ergogenic benefit (6). In this study we examined the cardiorespiratory response to submaximal exercise following a short period of premedication with high-dose salmeterol and controlled release oral salbutamol, and, to our knowledge, these conditions have not been examined previously. Although the study was limited, it was tightly controlled in terms of patient
selection, stability of disease and repetition of exercise challenge. There was repeated performance of the submaximal exercise challenge over the time course of the study (mean duration 24 days, range 18–37 days) with no evidence of a treatment effect on the oxygen cost, or the heart rate response to the exertion. These results suggest any systemic effects did not interfere with the cardiorespiratory response to exercise.

There was an increase in the ventilatory response following the high-dose SX at the 6 and 12 h time points. Studies with short duration β-agonists have demonstrated changes in ventilation–perfusion relationships, effects on the respiratory drive (7), on cardiac output and tissue perfusion leading to cardiodynamic hyperpnoea (8), and increased lactate accumulation during exercise (9). In a study which compared salmeterol and inhaled salbutamol, blood lactate levels were significantly higher with salbutamol after 15 min of exercise, which the authors suggested may be related to alterations in the balance between carbohydrate and lipid metabolism induced by salbutamol (9). Although the blood lactate concentration was not measured in the present study, the respiratory exchange ratio, which reflects tissue metabolic activity and body stores of respiratory gases, was not significantly different between pre- and posttreatment periods. There was an upward trend in the RER following high-dose SX at the 6 and 12 h time points. Studies reflecting the high inhaled dose of SX employed.

Our main aim was to investigate the cardiorespiratory response to submaximal exercise. A number of studies have examined the effects of long-acting inhaled β2-agonists on maximal performance and oxygen consumption (VO2max) and demonstrated no significant effects (9–12). In a study of eight asthmatic men a single 50 μg dose of salmeterol was found not to alter the cardiorespiratory, haemodynamic or subjective responses to progressive, maximal exercise, or affect endurance capacity (9). Studies on non-asthmatic athletes using short-term (single-dose) salmeterol treatment have demonstrated no significant effects on short-term power output (10,11), or on a range of cardiorespiratory measurements including VO2, V̇E and HR during submaximal treadmill running (at 50–90% of VO2max) or on running time to exhaustion (12). Many sporting activities, team games and competitions involve exertion at submaximal levels over prolonged periods of time and are more akin to tests of endurance capacity. Treatments which offer prolonged control of symptoms are preferable in such circumstances. In this study we have examined the treatment effects on submaximal exercise and found no significant changes in the O2 cost, or the heart rate response, compared to the pretreatment values.

There is some evidence that controlled release oral salbutamol increases muscle strength with prolonged use (13). Systemic β2-agonists are classed as anabolic agents and remain prohibited by the International Olympic Committee (1). We did not measure muscle strength, however, any anabolic effects of systemic salbutamol are unlikely to be manifest after the short pretreatment period employed in this study. The use of the short pretreatment period (≥48 h) may have accounted for the attenuation in the postexercise fall in FEV1 in 42% of the group. Additionally, CR inhibited the postexercise fall in FEV1 for two patients where SX had failed to show an effect. It is well-recognized that side-effects tend to be greater with oral therapy and in this study CR produced more finger tremor than SX (Fig. 2). However, side-effects were similar for both treatments reflecting the high inhaled dose of SX employed. Most patients reported reducing tremor and 'shakiness' after the first 36 h of either treatment. For patients with problematic EIA, and where other inhaled treatments have failed to provide sufficient control, intermittent, short-term use of CR may be useful for attenuation of EIA, without significant effect on the cardiorespiratory response to submaximal exercise.

In conclusion, although subjects exercised from a higher baseline FEV1 following treatment, there was no evidence that short, pretreatment with either high-dose salmeterol or controlled release oral salbutamol modified the cardiorespiratory response to submaximal exercise.

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References

1. Information for athletes, coaches and medical practitioners on the permissible use of drugs in amateur


