A comparison of bronchodilating effects of salmeterol and oxitropium bromide in stable chronic obstructive pulmonary disease

M. CAZZOLA*, M. G. MATERA+, F. DI PERNAC, F. CALDERAROD, C. CALIFANO* AND A. VINCIGUERRA*

*Division of Pneumology and Allergology and Respiratory Clinical Pharmacology Unit, A. Cardarelli Hospital, Naples, Italy

†Institute of Pharmacology and Toxicology, Medical School, Second Neapolitan University, Naples, Italy

Anti-cholinergic agents are generally regarded as the bronchodilator therapy of first choice in the treatment of stable chronic obstructive pulmonary disease (COPD), considering that they may be more effective than inhaled β₂-agonists. However, results of the authors' recent studies conflict to some extent with this suggestion because they demonstrate that this is true only for short-acting β₂-agonists but not for long-acting β₂-agonists. Oxitropium bromide is an anti-cholinergic drug that has been shown to produce a similar degree of bronchodilation to that obtained with ipratropium bromide, but with a longer-lasting effect. In the present study, the time course of inhaled oxitropium bromide bronchodilation in comparison to that of inhaled salmeterol in a group of patients with partially reversible COPD was evaluated. Twelve male patients with moderate to severe COPD participated in the study. The study had a single-blind, cross-over, randomized design. The bronchodilator activity of 50 µg salmeterol hydroxynaphthoate, 200 and 400 µg oxitropium bromide and placebo, which were all inhaled from a metered-dose inhaler, was investigated on several non-consecutive days. The highest FVC and FEV₁, obtained from one or the other of the reproducible curves, were kept for analysis. Measurements were performed at the following times: immediately before inhalation of treatment, and at 15, 30, 60, 120, 180, 240, 300, 360, 480, 600 and 720 min after inhalation of the individual treatment. Salmeterol tended to have a delayed time to peak effect, but had a longer duration of effect than oxitropium. The response to salmeterol exceeded the response to 200 µg oxitropium for 12 h, but its responses were significantly (P<0.05) greater than those to 200 µg oxitropium from 10 to 12 h. From 3 to 12 h, salmeterol also surpassed 400 µg oxitropium but differences were not significant (P>0.05). The mean FEV₁ area under the curve was significantly (P<0.05) larger after salmeterol when compared to 200 µg oxitropium bromide, but there was no significant difference (P>0.05) between salmeterol and 400 µg oxitropium bromide. No significant changes in pulse rate, blood pressure or electrocardiograms were found among the four groups as compared with placebo group. These findings confirm and extend what has been demonstrated by the authors' previous studies, and show that salmeterol compares conveniently with anti-cholinergic drugs in terms of effects on lung function at clinically recommended doses.

Introduction

Recent guidelines from the American Thoracic Society (1) suggest the inhaled administration of an anti-cholinergic agent as first-line therapy in stable chronic obstructive pulmonary disease (COPD), considering that in most patients who have COPD, inhaled quaternary anti-cholinergic drugs offer greater bronchodilation than that seen with an inhaled β₂-agonist (2). However, results of the present authors' study (3) conflict with this suggestion to some extent because they demonstrate that this is true only for short-acting β₂-agonists, and not for long-acting β₂-agonists. The authors have recently shown that the onset of bronchodilation after 40 µg ipratropium bromide is slower than that after 200 µg salbutamol. Moreover, ipratropium bromide produces a longer-lasting bronchodilation than salbutamol. In contrast, 50 µg salmeterol, a long-acting β₂-agonist, is as effective as ipratropium bromide in terms of the degree of bronchodilation, and has a longer duration of action (12 h) than anti-cholinergic agents (6 h).
Oxitropium bromide is another anti-cholinergic drug. It has been shown to produce a similar degree of bronchodilation to that obtained with ipratropium bromide, but with a longer-lasting effect (4). The duration of action would suggest that a twice daily regimen might be suitable for some individuals. However, a direct comparison of the profile of the bronchodilatory effects of oxitropium bromide and salmeterol over a 12-h study period in a controlled laboratory environment in patients with COPD is still lacking.

Therefore, the time course of inhaled oxitropium bromide bronchodilation in comparison to that of inhaled salmeterol in a group of patients with stable COPD was evaluated in the present study.

Patients and Methods

Twelve male patients with moderate to severe COPD, but in a stable phase of disease, participated in the study after giving their informed consent. All fulfilled the criteria proposed by the American Thoracic Society (5): i.e. >40 years of age; current or former smokers (>10 pack-years) without a history of asthmatic attacks; reporting either chronic cough with or without sputum production or dyspnoea when walking quietly on level ground, or both; had had no change in symptom severity or treatment in the preceding 4 weeks; had shown no signs of a respiratory tract infection in the month preceding or during the trial; were not taking oral or inhaled corticosteroids for at least 3 months; and had a FEV₁ < 70% after bronchodilators had been withheld for 24 h. Patients with a history of asthma, allergic rhinitis or atopy, or with a total blood eosinophil count over 400 mm⁻³ were excluded. Table 1 outlines the baseline characteristics of the population studied.

The study, which was carried out according to the rules of the declaration of Helsinki, was performed using a single-blind, balanced, cross-over, randomized design. The bronchodilator activity of 200 and 400 μg oxitropium bromide (Boehringer Ingelheim, Florence, Italy), 50 μg salmeterol hydroxynaphthoate (Glaxo, Verona, Italy) and placebo, which were all inhaled from a metered-dose inhaler and holding chamber (AeroChamber) with mouthpiece, was investigated on several non-consecutive days. The four treatments were: (i) oxitropium bromide (200 μg, 100 μg per inhalation) plus placebo (two inhalations); (ii) oxitropium bromide (200 μg) plus oxitropium bromide (200 μg); (iii) salmeterol (50 μg, 25 μg per inhalation) plus placebo; and (iv) placebo plus placebo. No oral bronchodilators were permitted for 1 week before or during the study, whereas inhaled short-acting bronchodilator drug and inhaled long-acting bronchodilator agent were not permitted for at least 12 or 24 h prior to each test, respectively. Consumption of cola drinks, coffee or tea, and smoking in the hours before and during the investigation were also avoided.

Spirometric testing was performed according to the procedures described in the American Thoracic Society’s 1987 update (5). Three acceptable forced expiratory manoeuvres were performed in order to obtain two reproducible results for FVC and FEV₁. The highest FVC and FEV₁, obtained from one of the other of the reproducible curves, were kept for analysis. Measurements were performed at the following times: immediately before inhalation of treatment, and at 15, 30, 60, 120, 180, 240, 300, 360, 480, 600 and 720 min after inhalation of the individual treatment. The pulse rate and blood pressure were also measured after at least 5 min of rest prior to each spirometric measurement, and 12-lead electrocardiogram was taken prior to the inhalation of every treatment and after 3, 6 and 12 h. Patients were asked to note any side-effects at each time period.

The functional indices’ increases from baseline after salmeterol, oxitropium bromide and placebo were assessed. The change in FEV₁ was chosen as the primary outcome variable to demonstrate bronchodilation (6). As an expression of the total effect of each treatment, the areas under the FEV₁ response-time curves (AUC) from baseline to 12 h were determined for each patient using the trapezoidal rule. Comparisons of baseline characteristics among the four groups were performed by ANOVA analysis and Fisher’s exact test. Analysis of spirometric data and those of pulse rate and blood pressure were performed using the Student’s t-test for paired variables. The time-averaged changes in the

<table>
<thead>
<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Height (cm)</th>
<th>Weight (kg)</th>
<th>FEV₁ (l)</th>
<th>FEV₁ (% predicted)</th>
<th>FVC (l)</th>
<th>FVC (% predicted)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>53</td>
<td>173</td>
<td>75</td>
<td>1.21</td>
<td>35</td>
<td>1.80</td>
<td>42</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>57</td>
<td>165</td>
<td>71</td>
<td>1.58</td>
<td>54</td>
<td>2.18</td>
<td>59</td>
</tr>
<tr>
<td>3</td>
<td>M</td>
<td>69</td>
<td>156</td>
<td>54</td>
<td>0.43</td>
<td>19</td>
<td>1.03</td>
<td>55</td>
</tr>
<tr>
<td>4</td>
<td>M</td>
<td>50</td>
<td>163</td>
<td>92</td>
<td>0.98</td>
<td>32</td>
<td>1.42</td>
<td>38</td>
</tr>
<tr>
<td>5</td>
<td>M</td>
<td>54</td>
<td>161</td>
<td>65</td>
<td>0.49</td>
<td>21</td>
<td>0.81</td>
<td>77</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>58</td>
<td>167</td>
<td>71</td>
<td>0.45</td>
<td>15</td>
<td>0.78</td>
<td>21</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>59</td>
<td>167</td>
<td>83</td>
<td>0.59</td>
<td>20</td>
<td>0.86</td>
<td>23</td>
</tr>
<tr>
<td>8</td>
<td>M</td>
<td>57</td>
<td>157</td>
<td>65</td>
<td>0.35</td>
<td>13</td>
<td>0.58</td>
<td>18</td>
</tr>
<tr>
<td>9</td>
<td>M</td>
<td>49</td>
<td>161</td>
<td>53</td>
<td>0.78</td>
<td>26</td>
<td>1.41</td>
<td>39</td>
</tr>
<tr>
<td>10</td>
<td>M</td>
<td>69</td>
<td>164</td>
<td>63</td>
<td>1.18</td>
<td>46</td>
<td>1.64</td>
<td>50</td>
</tr>
</tbody>
</table>

Table 1. Anthropometric data and pulmonary function of patients
Results

All 12 patients completed the 4-day study. There were no significant differences between the baseline spirometric values of the four treatment groups \((P>0.05)\).

The mean absolute changes in FEV\(_1\) and FVC following the four treatment regimens are shown in Fig. 1. The mean individual peak bronchodilation, expressed as the maximum increase in FEV\(_1\) over baseline values, occurred 3 h after inhalation of salmeterol (range: 30-360 min), 2 h after inhalation of 200 \(\mu\)g oxitropium (range: 15-480 min) and 2 h after inhalation of 400 \(\mu\)g oxitropium (range: 15-480 min). It must be highlighted that when individual subjects were considered, there was a heterogeneous response to the various bronchodilator regimens. However, when the mean duration of drug action was evaluated by comparing the response to placebo with those of the test drug, salmeterol produced a significant \((P>0.05)\) increase over placebo for 12 h, whereas the duration of bronchodilation after 200 \(\mu\)g oxitropium was somewhat shorter, lasting for 5 and 8 h, respectively, and 400 \(\mu\)g oxitropium sustained the action over baseline for 10 h. Salmeterol tended to have a delayed time to peak effect, but a longer duration of effect than oxitropium. The response of salmeterol exceeded that of 200 \(\mu\)g oxitropium for 12 h but its response was significantly \((P>0.05)\) greater than those of 200 \(\mu\)g oxitropium from 10 to 12 h. From 3 to 12 h, salmeterol also surpassed 400 \(\mu\)g oxitropium but differences were not significant \((P>0.05)\). Of the salmeterol group, nine patients had at least 8 h 15% improvement of FEV\(_1\) over baseline, and six patients had at least 12 h; only three patients of the 200 \(\mu\)g oxitropium group had at least 8 h of FEV\(_1\) increase >15% over baseline and two had at least 12 h; six patients showed at least a 15% improvement for 8 h and three for 12 h following inhalation of 400 \(\mu\)g oxitropium. Analysis of the FVC responses showed similar effects to FEV\(_1\) by the four study treatments.

Discussion

The growing realization in recent years that airways obstruction in patients with COPD can be relieved significantly with the use of bronchodilators has changed the clinical approach to treating this disease. In light of the morbidity and mortality associated with COPD, there is adequate justification for physicians to use bronchodilators, individualized to the patient and clinical situation.

In patients with stable COPD, the conventional dose of anti-cholinergic drug, two puffs, usually produces more bronchodilation than two puffs of \(\beta\)-agonist. The result is probably a dose effect, i.e. two puffs of anti-cholinergic agent support a greater fraction of the maximum effect than the conventional doses of \(\beta\)-agonists (8,9). Unfortunately, very few studies have compared equi-effective doses of anti-cholinergic agents and \(\beta\)-adrenoceptor agonists, which questions the validity of many of the studies published previously in the literature. Skorodin et al. (10) found doses of 100-400 \(\mu\)g oxitropium bromide were better than 150 \(\mu\)g of isoproterenol. Firth et al. (11) showed that the effect of 200 \(\mu\)g oxitropium bromide was less rapid than that of 400 \(\mu\)g fenoterol, but its duration of action was greater than that of fenoterol. Moreover, it has been demonstrated that when larger than usual doses of each agent are given to COPD patients, anti-cholinergics induce a similar or a greater degree of bronchodilation than an adrenergic agent (17). All these studies concluded that an anti-cholinergic
drug produces better bronchodilation than an adrenergic agent. Thus, an anti-cholinergic bronchodilator would seem to be the first-line agent for the therapy of stable COPD.

In the present investigation, two puffs (200 µg) and four puffs (400 µg) of oxitropium bromide were compared to two puffs of salmeterol (50 µg). Salmeterol elicited a greater peak bronchodilation and longer duration of action than 200 µg oxitropium bromide, but four puffs of oxitropium bromide approximated two puffs of salmeterol in terms of mean peak response and duration of action. The failure to show a difference could be due to type II statistical error, i.e. insufficient statistical power in the study and, possibly, a study with greater power would have detected a difference.

The authors emphasize that 200 µg oxitropium bromide might be considered an insufficient dose since it has been demonstrated that FEV₁ reached a plateau only after administration of a cumulative dose of six puffs of oxitropium bromide (600 µg) in patients with COPD (12), whereas the authors have demonstrated previously that 50 µg salmeterol induces a good and long-lasting bronchodilation, but a higher dose does not elicit additional improvements in partially reversible severe COPD (13). In any case, 200 µg oxitropium bromide and 50 µg salmeterol are dosages recommended for regular therapy (14,15).

It is well known that minimization of the number of doses per day may improve compliance. Since fewer puffs of salmeterol are required to cause the bronchodilation which can be produced with oxitropium bromide, better patient adherence to treatment might be expected with this long-acting β₂-agonist. The authors highlight that compliance to medication regimens is of crucial importance for management of COPD (16). Obviously, to confirm this, long-term studies will have to be performed.

In conclusion, the present findings confirm and extend what has been demonstrated by previous studies (3,17), and show that salmeterol compares conveniently with anti-cholinergic drugs in terms of effects on lung function at clinically recommended doses. The use of salmeterol is expected to be associated with higher compliance by reducing the number of inhalations utilized and thereby simplifying the regimen. In addition, this long-acting β₂-agonist would appear to be the appropriate first-line bronchodilator in patients with stable COPD because, at this conventional dosage, it does not induce significant cardiovascular adverse effects. However, the differences between salmeterol and oxitropium bromide during regular treatment of this pathological condition need to be addressed, since long-term comparisons between long-acting β₂-agonists and anti-muscarinic drugs in the treatment of COPD are absent from the literature. Regular assessment of the patient’s physiological status will determine the clinical usefulness of these drugs. Therefore, carefully designed studies using valid and reliable adherence measures are required to define their role.

References


2. Chapman KR. Therapeutic approaches to chronic obstructive pulmonary disease; an emerging consensus. Am J Med 1996; 100 (Suppl. 1A): SS-10S.


