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A Comparison of the Bronchodilating Effects of Salmeterol, Salbutamol and Ipratropium Bromide in Patients with Chronic Obstructive Pulmonary Disease

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SUMMARY: Bronchodilator efficacy of salbutamol (200 μg), salmeterol (50 μg) and ipratropium bromide (40 μg) aerosols has been compared in 16 patients with stable chronic obstructive pulmonary disease (COPD) using a double-blind placebo controlled cross-over design. When absolute changes in FEV_1 were used as the response criterion, efficacy of the three drugs was significantly better than placebo ($P<0.05$). The onset of bronchodilatation after ipratropium bromide was slower than after salbutamol, but ipratropium induced more and longer-lasting bronchodilatation than the adrenergic drug. Salmeterol was slower but its duration was longer than salbutamol. The onset of the effect of salmeterol was slower than ipratropium bromide, but salmeterol showed, on average, superior bronchodilator efficacy compared with the anticholinergic agent, sustaining bronchodilation longer than ipratropium bromide (responses to salmeterol were significantly ($P<0.05$) greater than those to ipratropium bromide from 4–12 h time period, but from 15 min to 1 h time periods response to ipratropium bromide exceeded salmeterol). The mean FEV_1 area under the curve was significantly ($P<0.05$) larger after salmeterol when compared to ipratropium bromide and salbutamol. Moreover, the mean FEV_1 area under the curve after ipratropium bromide was significantly ($P<0.05$) higher than that after salbutamol. In any case, our data showed individual differences in patient response. We conclude that salmeterol compares favourably with ipratropium bromide in terms of effects on lung function at clinically recommended doses because it has a longer duration of action than ipratropium bromide. The longer dosing intervals, which may enhance compliance, encourage its administration in patients with COPD.

KEY WORDS: Salmeterol, Salbutamol, Ipratropium bromide, Chronic obstructive pulmonary disease.

INTRODUCTION

Anticholinergic agents have been proved to be more potent bronchodilators than adrenergic agents in patients with chronic obstructive pulmonary disease (COPD) and are now usually recommended as first-line drugs in stable chronic bronchitis.[1] The bronchodilator superiority of anticholinergic drugs appears to be a consequence of pathological cholinergic tone in chronic airflow obstruction.[2] In fact, cholinergically mediated airway smooth muscle tone may be increased in COPD, which might account in large part for the reversible component in airflow obstruction.[3] It has also been suggested that patients with COPD are less responsive to adrenergic agents because these agents inhibit the smooth muscle contraction induced by mediators such as histamine and the leukotrienes, which play only a minor role in COPD.[4]

However, the introduction of long acting β-agonist bronchodilators gives physicians additional therapeutic options for COPD. Clinical efficacy of these bronchodilators indicate that they might be a major step forward in the therapy of chronic stable bronchitis, exceeding the therapeutic efficacy of the β_2-agonists available to date.[5–9]

The purpose of this study was to compare the time course of inhaled salmeterol, a long acting β-agonist, and salbutamol, a short acting β-agonist, with that of ipratropium bromide, an anticholinergic agent, in a group of patients with stable COPD. Our study population was specifically chosen to include elderly

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Table 1 Anthropometric data and pulmonary function of patients.

Patient	Sex	Age (years)	FEV_1 (l)	FEV_1 (% predicted)	% Reversibility 15 min after 200 μg salbutamol
1	M	63	0.40	15	74
2	M	70	0.89	43	21
3	M	73	0.64	28	38
4	M	62	1.89	69	8
5	M	63	1.42	54	1
6	M	67	0.46	16	32
7	M	67	1.77	48	11
8	M	71	0.68	29	2
9	M	65	0.95	34	15
10	M	67	0.96	39	27
11	M	65	0.35	17	35
12	M	71	0.72	26	8
13	M	68	0.48	21	61
14	M	71	0.43	17	11
15	M	72	0.65	28	10
16	M	66	0.38	15	12

patients since ipratropium bromide has been shown to have particular relevance in such patients[10] and, moreover, it has been suggested that the ageing process is accompanied by decline in β_2 receptor function in the airways of patients with COPD.[11]

PATIENTS AND METHODS

Sixteen patients (all men) with moderate to severe COPD participated in the study after giving their informed consent. All fulfilled the American Thoracic Society criteria for chronic bronchitis:[12] i.e. they were current or former heavy smokers, 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 preceding 4 weeks, had shown no signs of respiratory tract infection in the month preceding or during the trial, were not taking oral corticosteroids and had a FEV_1 between 15 and 69% of predicted values after β_2-agonists had been withheld for 24 h. Patients with a history of asthma, allergic rhinitis, atopy, or with a total blood eosinophil count over 400/mm^3 were excluded. The typical patient was elderly with relatively severe airflow limitation. Table 1 describes the baseline characteristics of the population studied.

The study, which was performed according to the rules of the declaration of Helsinki and was approved by an independent Ethics Committee, was designed as a double-blind, multiple cross-over, randomized design. According to the randomization, patients were allocated to the various treatment sequences which included each of the following four inhaled treatments: 50 μg salmeterol hydroxynaphthoate (Glaxo, Verona, Italy), 200 μg salbutamol sulphate (Glaxo, Verona, Italy), 40 μg ipratropium bromide (Boehringer Ingelheim, Florence, Italy) and placebo, which were all inhaled from a metered dose inhaler and holding chamber (AeroChamber) with mouthpiece. The subjects had not taken any inhaled bronchodilator for at least 12 h and oral theophylline for at least 24 h before the investigation started, and consumption of cola drinks, coffee, tea, and smoking in the hours immediately before and during the investigation were also avoided. All experiments began at 8 a.m. to avoid well-known interference of the circadian rhythm on bronchomotor tone.

Spirometric testing was performed according to the procedures described in the American Thoracic Society's 1987 update.[12] Three acceptable forced expiratory manoeuvres were performed in order to obtain two reproducible results for FVC and FEV_1. The highest FVC, FEV_1 and instantaneous forced expiratory flow after 50% of the FVC is exhaled (FEF_{50}), 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.

The functional indices' increases from baseline after salmeterol, salbutamol, ipratropium bromide and placebo were assessed. Further determinations included maximum change in the post-treatment FEV_1, time of onset of 15% increase from baseline FEV_1 and time to occurrence of peak FEV_1 value. Comparisons of baseline characteristics among the four groups were performed by ANOVA analysis and Fisher's exact test. Analysis of spirometric data was performed using the Student's *t*-test for paired variables. The time-averaged changes in the 12 h after drug administration, between each treatment and placebo, and between drugs were compared by means of the distribution free cross-over analysis.[13] With respect to the multiple testing of three lung function parameters, the significance level of 0.05 was considered as relevant. The FEV_1 areas under the curve (AUC) from baseline to 12 h were determined using the trapezoidal rule.

RESULTS

All 16 patients completed the 5-day study. There were no significant differences between the baseline spirometric values of the four treatment groups ($P>0.05$).

Rate of onset of action

Eight out of 16 patients presented an increase in FEV_1 of at least 15% 15 min after inhalation of salbutamol, four patients presented this increase after salmeterol

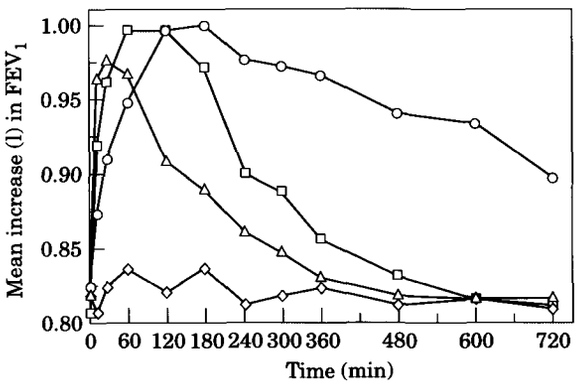

Fig. 1 Mean increases (l) in FEV_1 after the inhalation of salmeterol (SMT), salbutamol (SBT), ipratropium bromide (IP) or placebo (P). —○—: SMT; —△—: SBT; —□—: IP; —◇—: P.

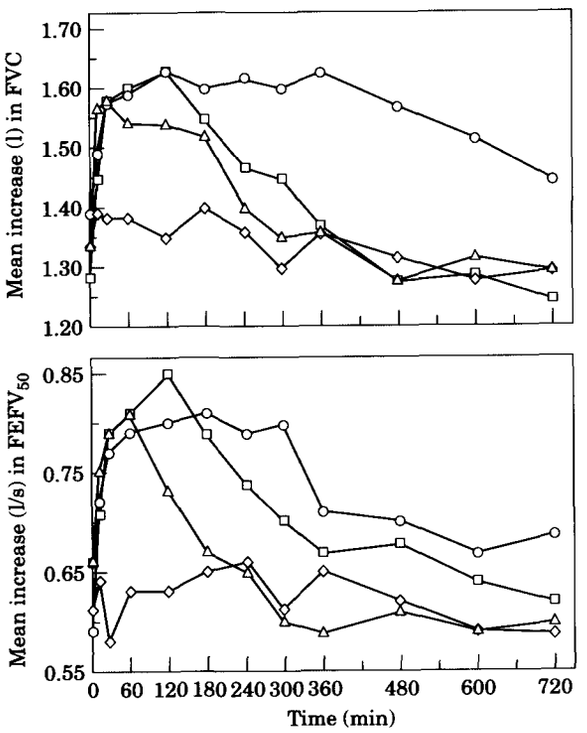

Fig. 2 Mean increases (l or l/s) in FVC and FEF_{50} after the inhalation of salmeterol, salbutamol, ipratropium bromide or placebo. Key as in Fig. 1.

and seven after ipratropium bromide. Using an increase in FEV_1 of 160 ml as cut-off, as suggested by Tweeddale et al,[14] seven out of 16 patients achieved such a response 15 min after inhalation of salbutamol, three patients after inhalation of salmeterol and four patients after ipratropium bromide.

Maximum response

The mean individual peak bronchodilation, expressed as the maximum increase in FEV_1 over baseline values, occurred 30 min after inhalation of salbutamol (range: 15–120 min), 3 h after inhalation of salmeterol (range: 30–360 min), and 2 h after inhalation of ipratropium (range: 15–300 min). However, patients varied in their maximum response to the different bronchodilator although those patients who were low responders to one of these agents showed little variation between drugs, whereas the between-drug variation seemed larger for the remainder of the patients. Subgroup analysis in our study population did not show any statistically significant difference between response to each bronchodilator and severity of airway obstruction before treatment.

Time course of bronchodilating effect

The mean absolute changes in FEV_1 from baseline after administration of salmeterol, salbutamol, ipratropium bromide or placebo are shown in Fig. 1, and the changes of FVC and FEF_{50} in Fig. 2. The change in FEV_1 was chosen as the primary outcome variable to demonstrate bronchodilation.[15] When the 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 action of ipratropium was somewhat shorter, lasting for 6 h, and salbutamol sustained the action over baseline for 3 h. Responses to salmeterol were significantly ($P<0.05$) greater than those to ipratropium bromide from 4 to 12 h time period, whereas from 15 min to 1 h time period ipratropium surpassed salmeterol but differences were not significant ($P>0.05$). Salmeterol was slower although its duration was longer than salbutamol. Ipratropium bromide exceed in response salbutamol from 30 min to 6 h time period. However, when individual subjects were considered, there was a heterogeneous response to the various bronchodilator regimens. The tendency of the response over 12 h course was similar for all the functional variables.

FEV_1 area under the curves

The mean FEV_1 area under the curve was significantly ($P<0.05$) larger after salmeterol when compared to ipratropium bromide and salbutamol (Fig. 3). Moreover, the mean FEV_1 area under the curve after ipratropium bromide was significantly ($P<0.05$) higher than that after salbutamol.

DISCUSSION

In the present study, the onset of bronchodilation after ipratropium bromide was slower than that after salbutamol, but ipratropium bromide induced more and longer-lasting bronchodilation than adrenergic drug. This is consistent with some previous

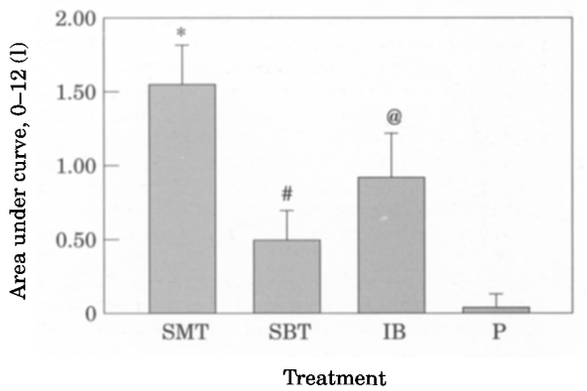

Fig. 3 Area under the time-response curve (mean ± SEM) after the inhalation of salmeterol (SMT), salbutamol (SBT), ipratropium bromide (IP) or placebo (P). *: versus salbutamol, ipratropium bromide and placebo, $P>0.05$; @: vs. salbutamol and placebo, $P>0.05$; #: vs. placebo, $P>0.05$.

studies,[16,17] although literature reports on the relative bronchodilator efficacy of ipratropium bromide and β_2-sympathomimetic bronchodilators are somewhat confusing.

Whether compared with relatively unselective β-agonists such as isoproterenol or highly selective β_2-agonists such as salbutamol, the anticholinergic agents consistently show greater and longer mean bronchodilation.[18–20] Chapman[21] has noted that, of 38 published studies which contrasted anticholinergic and adrenergic bronchodilators in COPD, all but two found the anticholinergic agents to be at least equal to and generally superior to the adrenergic agents in terms of spirometric responses. The long duration of bronchodilation with anticholinergic compared with β_2-agonists may be an advantage in patients with COPD.

However, results of other studies conflict with these conclusions. Tests in stable outpatients with COPD demonstrated that, with sufficient dosing and delivery, an inhaled bronchodilator (either an anticholinergic or a β_2-agonist) can result in complete bronchodilation (as measured by FEV_1);[22,23] these findings were independent of the class of agent utilized since, in the dose regimens studied, both types of bronchodilators were similarly effective. Moreover, Karpel[24] reported that the bronchial responsiveness to both anticholinergic and β-adrenergic agents is equivalent and suggested that the amount of smooth muscle relaxation that can be achieved in any specific patient is limited and independent of the mechanism that generates the bronchodilation.

It is worth noting that, while the anticholinergic agent may induce smooth muscle relaxation via vagal tone which is modulated by muscarinic receptors, the β-adrenergic agent may achieve the same effect by indirect modulation of vagal tone; in fact, there are prejunctional inhibitory β_2 receptors on cholinergic fibres which might conceivably result in attenuation of resting vagal tone, in addition to direct β_2 mediated smooth muscle relaxation.[25]

Earlier published reports from our laboratory[8] showed superior bronchodilator efficacy of salmeterol compared with salbutamol in patients suffering from COPD; salmeterol was slower but its duration was longer than salbutamol. The results of the current study have confirmed these findings.

In the present investigation we have also observed that the onset of the effect of salmeterol was slower than ipratropium bromide, but salmeterol showed, on average, greater bronchodilator power compared with the anticholinergic agent, sustaining bronchodilation longer than ipratropium bromide. However, because an average is a condensation of individual results, it inevitably loses some information inherent in the original data. In fact, in our study, salmeterol was the best drug (absolute improvement in FEV_1) for eight patients and ipratropium bromide for the other eight patients. This finding suggests that, despite the fact that average responses over many patients may be superior for a bronchodilator, individual patients may require a specific drug for the best effect.

We must also highlight that the dose of ipratropium bromide which we have used (40 μg) might be considered a possible bias since it has been demonstrated that FEV_1 reached a plateau in patients with COPD only after administration of a cumulative dose of 280 μg (14 puffs) of this drug,[26] whereas we have observed that the best dosage for salmeterol is 50 μg and a higher dose does not elicit additional improvement in these patients.[27] Since penetration of inhaled drugs into the airways is impaired in presence of severe bronchial obstruction, higher than usual dosages of bronchodilators may be needed for a maximal effect in patients with severe COPD.[28,29] However, salmeterol must be considered an exception since the consequence of an increased concentration of salmeterol is not a true relaxation–concentration response, owing to its plasmalemma diffusion microkinetics.[30] In any case, 50 μg salmeterol and 40 μg ipratropium bromide are dosages recommended for regular therapy[21,31] and, in clinical practice, when obstruction is severe, one would not wish to have to spend time trying to find the best bronchodilating dose for the individual patient. Moreover, it is somewhat unlikely that a patient suffering from COPD would inhale 14 cumulative puffs in rapid succession 3–4 times daily.

Lastly, our findings do not support the assumption that elderly patients suffering from COPD are less sensible to action of β_2 agonists; in fact, salmeterol was more potent than ipratropium bromide, although our study population was expressly chosen to include aged patients. We must emphasize that it has been suggested that, whilst the function of β_2 receptors may

become impaired with age,[11] their responsiveness is nonetheless well preserved;[32] this suggestion supports our data.

In summary, our results have shown that, on average, salmeterol compares conveniently with ipratropium bromide in terms of effects on lung function at clinically recommended doses because it has a longer duration of action than ipratropium bromide. The prolonged dosing intervals, which may enhance compliance, encourage its administration in patients with COPD. Whether or not salmeterol would induce greater benefit in the long term than ipratropium bromide has yet to be proved. Therefore, multi-dose and long-term studies are essential to compare more correctly the clinical efficacy of these two agents.

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