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COMPARISON OF THE ACUTE BRONCHODILATING EFFECTS OF INHALED IPRATROPIUM BROMIDE AND SALBUTAMOL IN PATIENTS WITH CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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ABSTRACT

Forty-five patients with chronic obstructive pulmonary disease were studied to compare the acute effects of ipratropium bromide (60 μg), salbutamol (300 μg) and placebo (3 puffs) on the forced expiratory volume in 1 sec (FEV_1) and forced vital capacity (FVC). Ipratropium bromide produced a significantly greater improvement than salbutamol in both FEV_1 and FVC at 15, 60 and 180 minutes after drug administration. It may therefore be concluded that in patients with chronic obstructive pulmonary disease, ipratropium bromide has greater potency and a longer duration of action than salbutamol.

Key words: Ipratropium bromide, salbutamol, anticholinergic, chronic obstructive pulmonary disease.

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INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is one of the leading causes of death[12] and one of the few diseases with an increasing prevalence. [7,13,14] Treatment of patients with COPD is often frustrating as it was previously thought to be an irreversible disease.[3,14] However, in the intricate system of control of airway caliber, the cholinergic nervous system has an important role,[16] and parasympathetic activity has been shown to be a dominant reversible component of airway obstruction in COPD.[8,10,11] This may explain why patients with respiratory complaints benefitted from smoking atropine-containing botanicals such as *Datura stramonium*.[4] Today, interest in anticholinergic bronchodilator therapy has been rekindled by the development of safe yet effective quarternary anticholinergic compounds like ipratropium which have modified treatment strategies for COPD.[4,11,13] Although to date several studies have confirmed the place of ipratropium bromide in the management of COPD patients,[1,2,6,9,15] the relative potency and efficacy of this agent compared to the beta-adrenergic agent salbutamol is still an interesting issue which may provide further insight into better management of these patients. Therefore, the present study was performed to compare the effects of ipratropium bromide with salbutamol on respiratory function tests (FVC, FEV_1) in patients with COPD.

MATERIALS AND METHODS

Forty-five newly diagnosed patients with COPD with forced expiratory volumes in 1 second (FEV_1) of less than 70% of the predicted normal value were selected from the pulmonary clinic at Imam Khomeini Hospital of the University of Tehran. The characteristics of the patient population (25 male and 20 female) can be seen in the following tabulation:

Table I. Percentage increase in FVC.

Drug treatment	Time (min)		
	15	60	180
Placebo	-0.80±1.04	3.0.3±0.87	0.57±1.80
Salbutamol	17.14±2.15**	15.26±2.57**	10.05±2.12*
Ipratropium bromide	19.43±1.45**	27.15±1.94++	23.92±2.22++

FVC values were determined at 15, 60 and 180 min. after drug or placebo treatment (3 puffs in each case).
Each value represents the mean±S.E.M. of percentage increase from test day baselines for a group of 15 patients.

*$p<0.01$, **$p<0.001$: significantly different from control (placebo).

+$p<0.05$, ++$p<0.001$: significantly different from salbutamol.

Age	65.13±7.08 years
FEV_1	1.19±2.06 liters
FVC	2.03± 0.35 liters

All subjects gave a history that met the definition of chronic bronchitis (wheezing, shortness of breath, coughing, and tightness of chest). They all had an FEV_1/FVC ratio of less than 65%.

Subjects were excluded if they had significant cardiovascular, renal, hepatic, endocrine, metabolic, or asthmatic disorders or any other major systemic disease, or had a contraindication for using adrenergic or anticholinergic medications. All patients were fully informed of the nature of the study and gave their written consent to participate. All tests were performed between 8:00 to 12:00 AM. On the test days, spirometry (Fudac 50-Fukuda Sangyo) was performed at baseline and at 15, 60 and 180 minutes after administration of the study drug or placebo. Patients were randomly assigned into 3 groups (n=15) as follows:

Group 1	Salbutamol (3 puffs=300 μg)
Group 2	Ipratropium bromide (3 puffs=60 μg)
Group 3	Placebo (3 puffs)

Both the drugs and the placebo were delivered by metered dose inhalers by the same technician throughout the study. The study was designed as double blind to the patients and the operator.

Data analysis

FEV_1 and FVC of all 45 patients at each time point and for each treatment were compared to baseline values and the percentage of change measured.

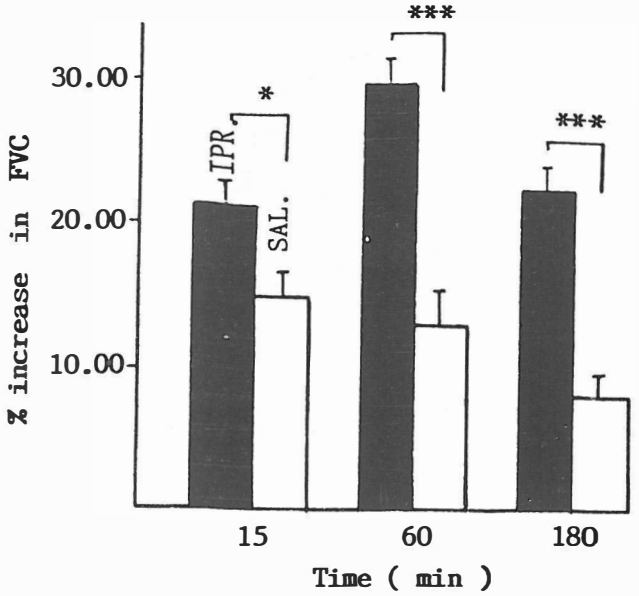

Fig. 1. Comparative effects of ipratropium bromide (IPR) and salbutamol (SAL) on percentage increase in FVC 15, 60 and 180 minutes after drug administration. (*$p<0.05$, **$p<0.001$)

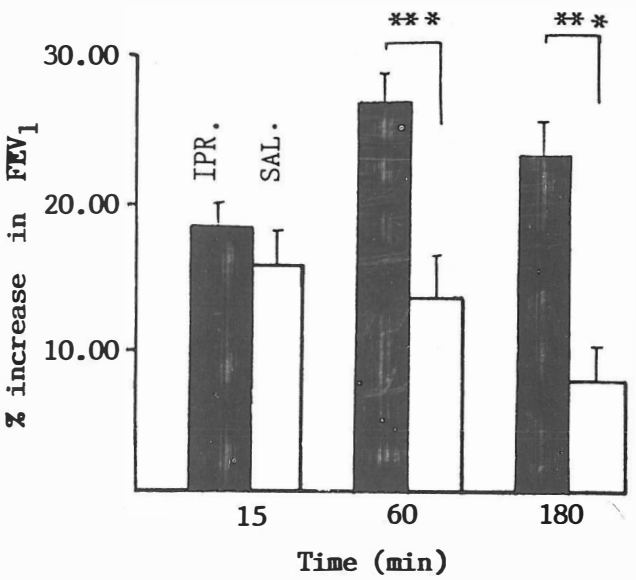

Fig. 2. Comparative effects of ipratropium bromide (IPR) and salbutamol (SAL) on percentage increase in FEV_1 15, 60 and 180 minutes after drug administration. (**$p<0.001$)

Newman-Keuls, analysis of variance (ANOVA) and paired t-test were used to compare the values before treatment and to compare the values for the different treatment groups.

Table II. Percentage change in FEV_1

Drug treatment	Time (min)		
	15	60	180
Placebo	2.11±1.03	3.70±1.05	3.50±1.47
Salbutamol	16.30±1.60**	14.78±84**	10.37±1.55*
Ipratropium bromide	22.11±1.48+	29.50±1.51++	23.17±1.43++

FEV_1 values were determined at 15, 60 and 180 min. after drug or placebo treatment (3 puffs in each case).
Each value represents the mean±S.E.M. of percentage change from test day baselines for a group of 15 patients.

*$p<0.01$, **$p<0.001$: significantly different from control (placebo).
++$p<0.001$: significantly different from salbutamol.

RESULTS

The mean FVC and FEV_1 response throughout the three hours of study after the different treatments are presented in Tables I and II. Both ipratropium and salbutamol produced significant improvements in the FVC over placebo at all indicated times. However, there were significantly better responses to ipratropium at the three different time points (Fig. 1). At the 60 and 180 minute time points, the increases in FVC values obtained after ipratropium administration were almost twice that obtained for salbutamol ($p<0.001$). The changes in FEV_1 also reflect an exactly similar pattern where again at both 60 and 180 minutes after drug administration, the responses to ipratropium were significantly ($p<0.001$) better than salbutamol (Fig. 2).

DISCUSSION

In this study, ipratropium bromide delivered at the usual clinical dose of 3 puffs was significantly more effective than salbutamol in improving spirometry values in patients with COPD. Furthermore, the bronchodilation produced after ipratropium administration was of longer duration. This is evident from comparison of the FVC and FEV_1 values obtained at 180 minutes. Several studies have reported the efficacy of ipratropium in improving spirometric parameters,[1,2,15] and in having a long duration of action.[1,2,6,9] On the other hand, by virtue of having low lipid solubility, ipratropium has been reported to be poorly absorbed into the circulation and therefore virtually free of adverse systemic effects.[4,6,9,12,14]

The advent of inhalatory anticholinergic bronchodilators has prompted studies like the present one, which not only demonstrate the potential for bronchodilation in patients with COPD, but also provide some insight into the autonomic mechanisms which control airway caliber in disease. It has been suggested by way of explanation that cholinergically-mediated airway smooth muscle tone may be increased in COPD, and/or accounts in large part for the reversible component of airway obstruction in COPD, or 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 a minor role in COPD.[5] Putting together the results obtained in the present study and those previously reported in the literature regarding the efficacy, duration of action and the safety of these drugs, it may be concluded that in patients with COPD, ipratropium bromide could well be considered as the first line of therapy.

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