

Original Articles

COMPARISON OF THE BRONCHODILATORY EFFECTS OF INHALED SALBUTAMOL AND COMBIVENT IN ASTHMATIC PATIENTS

G. DERAKHSHAN DEILAMI, A. GHOLAMHOSSEINI* AND M.H.
POURGHOLAMI*

*From the Division of Pulmonology, Imam Khomeini Hospital, Tehran University of Medical Sciences, and
the *Department of Pharmacology, Shaheed Beheshti University of Medical Sciences, Tehran, Islamic
Republic of Iran.*

ABSTRACT

A randomized, double-blind, crossover trial was designed to compare the acute effects of Combivent and salbutamol on spirometric parameters in patients with moderate to severe asthma. Nineteen patients with a mean baseline forced expiratory volume in 1 sec. (FEV_1) less than 65% predicted, were randomized on two separate days to receive two puffs of salbutamol (200 μ g) or two puffs of Combivent (200 μ g salbutamol plus 40 μ g of ipratropium bromide) by metered dose inhalers. On study days using spirometry, FEV_1 , forced vital capacity (FVC), maximal mid-expiratory flow rate (MMEF) and peak expiratory flow rates (PEFR) were measured at baseline and at 15, 60 and 180 minutes after drug administration. Blood pressure and pulse rate were also determined before and 3 hours post drug inhalation.

The results of this study show that Combivent produces significantly greater improvement compared to salbutamol in all four spirometric parameters at 15, 60, and 180 minutes after drug treatment. The greatest differences between the bronchodilating effects of the two regimens were observed at 180 minutes after drug inhalation. There were no clinically significant changes in heart rate or blood pressure.

It may therefore be concluded that in patients with moderate to severe asthma, Combivent provides better bronchodilation than salbutamol alone at clinically relevant doses without increasing side-effects.

Keywords: Asthma, bronchodilator, Combivent, ipratropium, salbutamol.

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INTRODUCTION

Combivent is a new metered-dose inhaler (MDI) formulation that contains both salbutamol and

ipratropium.^{1,2} Each puff contains 100 μ g of salbutamol sulphate and 20 μ g of ipratropium bromide.

In asthma, β_2 -agonists are used as firstline therapy for bronchodilation.^{3,4} There are considerable data suggesting

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that addition of ipratropium bromide to a β_2 -agonist provides additive benefit for the treatment of asthma.⁵⁻⁹ One rationale for using such a combination to treat asthma is that the two drugs cause bronchodilation via different pharmacological mechanisms.^{1,4,9-11} In addition, it has been reported that β -adrenergic receptors are more peripherally distributed while cholinergic receptors occur primarily in the larger airways.⁹⁻¹² As a result of this, salbutamol dilates distal airways while ipratropium preferentially dilates the proximal airways.¹³ However, there has been some discrepancy regarding the usefulness of combination therapy in patients with asthma. On the other hand, in recent studies concerning childhood asthma, the addition of ipratropium to salbutamol has been shown to be both efficacious and safe.^{9,14} Therefore, the objective of the present study was to study the acute bronchodilating effects of Combivent compared to that of salbutamol in adult patients suffering from moderate to severe asthma.

PATIENTS AND METHODS

Patient selection

Nineteen patients with moderate to severe asthma were selected from the Specialty Clinic of Pulmonary Diseases of Imam Khomeini Hospital, Tehran, between March 1996 and June 1996. They had an FEV₁ of less than 65% of the predicted normal value, and an FEV₁/FVC ratio of less than 70%. All patients met the Global Initiative Criteria for the diagnosis of asthma. Patients were excluded from the study if they had a history of bronchitis, cardiovascular disease, hypersensitivity to adrenergic or anticholinergic compounds, allergic rhinitis, or if they had a history of smoking. Before entry into the study, the purpose and the nature of the investigation was explained to each patient and informed written consent was obtained. Theophylline and other medications related to their pulmonary illness, and inhalational

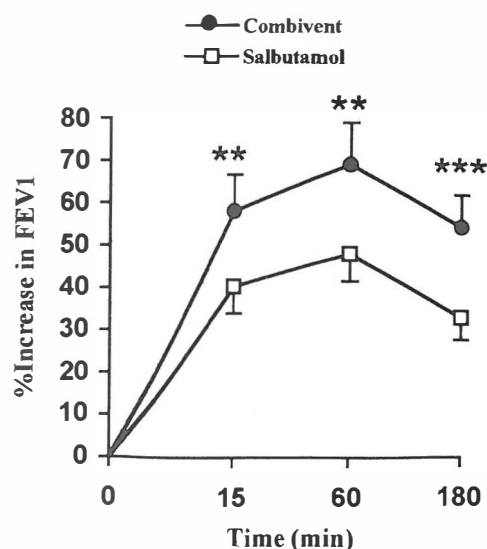


Fig. 1. Mean difference (\pm SEM) from baseline of percentage of predicted FEV₁ with time. Patients (n=19) received 2 puffs of either salbutamol or Combivent on two separate test days. ** p <0.01, *** p <0.001.

bronchodilators were withheld 12 hours prior to pulmonary function testing, but patients were not abstained from corticosteroids. Subjects were also asked to avoid caffeine-containing beverages for 12 hours before testing and during the experiments.

The characteristics of the patient population (10 men and 9 women) are presented in the following tabulation:

Characteristic	Mean \pm SEM
Age (years)	54.32 \pm 2.67
FEV ₁ , %predicted	47.08 \pm 2.76
FVC, %predicted	60.75 \pm 2.95
MMEF, %predicted	28.09 \pm 2.62
PEFR, %predicted	51.72 \pm 3.69

Table I. Effects of salbutamol and Combivent on PEFR and MMEF.

Time (min)	PEFR		MMEF	
	Salbutamol	Combivent	Salbutamol	Combivent
15	44.33 \pm 6.45	60.19 \pm 8.01*	58.25 \pm 9.45	8.57 \pm 13.38*
60	50.18 \pm 6.69	71.57 \pm 9.66*	68.98 \pm 9.33	112.51 \pm 16.50*
180	32.22 \pm 5.02	57.65 \pm 8.13**	48.86 \pm 8.36	82.83 \pm 12.23*

Mean difference (\pm SEM) from baseline of percentage of predicted PEFR and MMEF with time. Patients (19) received 2 puffs of either salbutamol or Combivent on two separate test days. * p <0.01, ** p <0.001

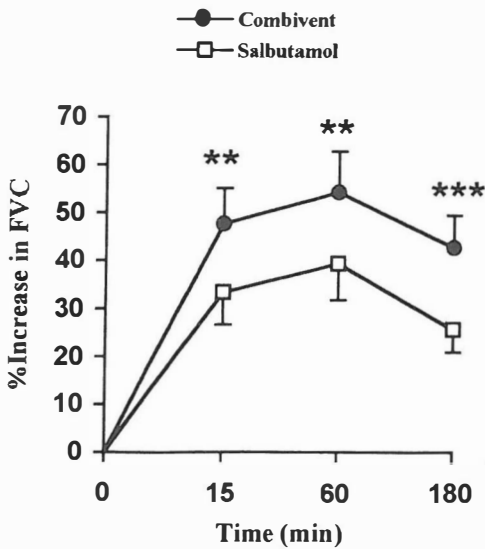


Fig. 2. Mean difference (±SEM) from baseline of percentage of predicted FVC with time. Patients (n= 19) received 2 puffs of either salbutamol or Combivent on two separate test days. ***p*<0.01, ****p*<0.001.

Table II. Summary of cumulative changes in spirometric parameters after drug inhalation.

Parameter	Salbutamol	Combivent
FEV ₁	121.91±17.06	182.44±25.66**
FVC	98.34±18.40	144.65±22.20**
PEFR	125.13±17.32	189.41±25.29**
MMEF	176.09±24.43	280.05±41.11*

Mean (±SEM) of cumulative changes (0-180 min) relative to baseline in spirometric parameters after 2 puffs of either salbutamol or Combivent inhalation. **p*<0.01, ***p*<0.001

Study design

After meeting the entry criteria, patients were studied on each of the two test days, that were separated by 24 hours. The entry FEV₁ on the second test day had to be within 15% of the value on the first study day. Spirometry (Phillips) was performed with the patients seated. After recording baseline parameters, subjects randomly received two puffs of either salbutamol (Norton, Ireland) or Combivent (Boehringer Ingelheim, Germany), delivered by identical metered dose inhalers. The patients and the investigators were blinded as to the medication used. After aerosol administration, spirometry was performed again after 15, 60 and 180 minutes. Blood pressure (systolic and diastolic) and pulse rate were determined before and after treatment just before each

spirometry. Drug administration and spirometric measurements were performed by an experienced nurse.

Data analysis

Results are expressed as percentage change from baseline. The cumulative change in spirometric parameters during the total test time (180 min) was also calculated for each treatment.

Statistical evaluation included an analysis of variance (ANOVA) between the three points. In addition, paired t-test (Newman Keuls) was used to compare the drug regimen for post treatment improvement in parameters as percent change above baseline. A p-value of less than 0.05 was considered to represent a significant change.

RESULTS

The mean baseline spirometric values in the two test days were not significantly different. The mean percentage increase (compared to baseline values) in FEV₁ and FVC at the three different time points of 15, 60 and 180 minutes after drug administration can be seen in Figs. 1 and 2, while those for MMEF and PEFR are presented in Table I. Both salbutamol and Combivent produced significant increases in pulmonary function test parameters. However, compared to salbutamol, Combivent produced significantly greater improvements in all four parameters. For both regimens, the peak bronchodilatory effect was obtained 60 min post drug inhalation, where again patient responsiveness to Combivent was greater than salbutamol, while the greatest difference between the two treatments was recorded at 180 min post drug inhalation (Figs. 1&2 and Table I).

The cumulative changes (0-180 min) in FEV₁, FVC, MMEF and PEFR obtained after salbutamol or Combivent inhalation are shown in Table II. It is evident from these results that the degree of improvement in spirometric parameters produced over 180 min post Combivent inhalation is significantly higher than those produced after salbutamol use.

The pattern of blood pressure and pulse rate response was not different between treatment regimens or between the two days of treatment.

DISCUSSION

Results of this study show that in patients with moderate to severe asthma, a combination of salbutamol plus ipratropium in the form of a single metered dose inhaler (Combivent), elicits statistically greater bronchodilatory responses compared to salbutamol alone. The differences in pulmonary function test parameters

after monotherapy with salbutamol alone or combination therapy with Combivent was evident throughout the time period of the study, i.e., at 15, 60 and 180 min post drug inhalation. This may suggest an additive effect between the β_2 -agonist and the anticholinergic agent. One rationale behind using a combination of salbutamol and ipratropium to treat asthma is that these two drugs belong to different classes of compounds and that they cause bronchodilation via different pharmacological mechanisms.⁹⁻¹¹ Salbutamol acts by stimulating β_2 adrenoceptors, leading to an increase in cAMP production and consequently smooth muscle relaxation, while ipratropium blocks muscarinic cholinergic receptors, leading to an attenuation of cGMP levels, thereby producing smooth muscle relaxation.¹⁶ In addition, it has been reported that β_2 -agonists dilate distal airways, while anticholinergics preferentially dilate proximal airways.¹³

Most of the reported studies where a combination of a β_2 -agonist and ipratropium bromide have been tested against the β_2 -agonist alone in adult patients with asthma have shown the combination to be superior,^{11,17,18} while other studies have not been able to show significant differences between the two treatments.¹⁹⁻²¹ This discrepancy may be attributable mainly to the dose of the β_2 -agonist used in these studies, where doses higher than the normal therapeutic doses were employed. It is a well known fact that β_2 -agonist use—especially at high doses—can lead to adverse cardiovascular effects,^{22,23} and that patients with cardiovascular disease are much more vulnerable to these side effects.²² In addition, recent studies by Schuh et al.⁹ and Qureshi & Zaritsky¹⁴ have shown that in the management of children with severe asthma, addition of ipratropium to salbutamol increases the bronchodilation achieved and prolongs the therapeutic response. Similarly, most of the studies in COPD patients have shown the combination to be superior to either agent alone.^{1,12,24} In this regard, recently in different studies, Levin et al.²⁵ and Tashkin et al.²⁶ have reported that the addition of ipratropium solution to salbutamol or metaproterenol respectively, leads to greater bronchodilation and longer duration of action. Moreover, ipratropium bromide can also produce additive bronchodilatory effects when added to a regimen of theophylline or theophylline plus β_2 -agonist, and this may even allow reduction of corticosteroid dosages. This supplemental bronchodilator benefit in moderate to severe asthma is sustained during chronic therapy with no evidence of tachyphylaxis.⁴ In the present study, the most significant difference in spirometric parameters observed after the two regimens was at 180 min post drug inhalation. This may be attributable to the presence of ipratropium in the Combivent inhaler. It has been reported that ipratropium has a longer duration of action than salbutamol.^{10,24,27}

There were no differences in heart rate or blood pressure responses between the two treatments. Ipratropium is of low lipid solubility and has poor systemic absorption and therefore has no clinically important side effects,^{9,12,18,22} while adverse effects—especially tremor and palpitations—that are caused by β_2 receptor agonists are fairly common, especially in the higher dose range.^{3,22} Furthermore, in patients with pre-existing coronary artery disease, other adverse effects like hypokalemia, tachyarrhythmias and angina pectoris may also be induced by β_2 -agonists.²² Some of these side effects are dose dependent and, therefore, a combination therapy with a relatively low dose of β_2 -agonist and an anticholinergic agent may offer a valuable alternative to higher doses of β_2 -agonists. It has also been reported that the number and sensitivity of β -adrenoceptors is reduced with age, thus making anticholinergics more important.²⁸

In conclusion, our results suggest that in patients with moderate to severe asthma, Combivent produces a significantly greater magnitude and duration of bronchodilation than salbutamol.

REFERENCES

1. Combivent Inhalation Aerosol Study Group: In chronic obstructive pulmonary disease, is a combination of ipratropium and albuterol more effective than either agent alone? *Chest* 105: 1411-19, 1994.
2. Tashkin DP: Multiple dose regimens. Impact on compliance. *Chest* 107(suppl): 176S-182S, 1995.
3. Abramowicz M, Rizack MA: Drugs for asthma. *Med Lett Drugs Ther* 34(939): 1-4, 1995.
4. Chapman KR: An international perspective on anticholinergic therapy. *Am J Med* 100(suppl 1A): 2s-4s, 1996.
5. Beck R, Robertson C, Glades-Sebalt SM, Levison H: Combined salbutamol and ipratropium bromide by inhalation in the treatment of severe acute asthma. *J Pediatr* 107: 605-8, 1985.
6. Rebeck AS, Chapman KR, Abboud R, et al: Nebulised anticholinergic and sympathomimetic treatment of asthma and chronic obstructive airways disease in the emergency room. *Am J Med* 82: 59-64, 1987.
7. Watson WTA, Becker AB, Simons FER: Comparison of ipratropium solution, fenoterol solution, and their combination administered by nebulizer and face mask to children with acute asthma. *J Allergy Clin Immunol* 82: 1012-8, 1988.
8. O'Driscoll BF, Taylor RJ, Horsley M, Chambers DK, Bernstein A: Nebulised salbutamol with and without ipratropium bromide in acute airflow obstruction. *Lancet* 1: 1418-20, 1989.

9. Schuh S, Johnson DW, Callahan S, Ganny G, Levison H: Efficacy of frequent nebulized ipratropium bromide added to frequent high-dose albuterol therapy in severe childhood asthma. *J Pediatr* 126: 639-45, 1995.
10. Haahtela T, Ahokas I, Ahonen A, et al: Inhaled bronchodilators in asthma: low or high dose? *Ann Allergy* 66: 175-180, 1991.
11. Petty TL: The combination of ipratropium and albuterol is more effective than either agent alone. *Chest* 107(Suppl): 183s-186s, 1995.
12. Martinati LC, Boner AL: Anticholinergic antimuscarinic agents in the treatment of airways bronchoconstriction in children. *Allergy* 51: 2-7, 1996.
13. Barnes PJ: Using anticholinergics to best advantage. *J Respir Dis* 8: 84-95, 1987.
14. Qureshi FA, Zaritsky A: Emergency department use of ipratropium in severe asthmatic children. *Pediatr Res* 39(4): 23A, 1996.
15. Woolcock AJ: Definitions and Clinical Classification, In: Barnes PJ, Grunstein MM, Leff AR, Woolcock AJ, (eds.), *Asthma*. Philadelphia: Lippincott-Raven, p. 27, 1996.
16. Rebeck AS, Gent M, Chapman KR: Anticholinergic and sympathomimetic combination therapy of asthma. *J Allergy Clin Immun* 71: 317-323, 1983.
17. Rubin BK, Albers GM: Use of anticholinergic bronchodilation in children. *Am J Med* 100(Suppl 1A): 49s-53s, 1996.
18. Chapman KR: Anticholinergic bronchodilators for adult obstructive airway disease. *Am J Med* 91(Suppl 4A): 13s-16s, 1991.
19. Higgins RM, Stradling JR, Lane DJ: Should ipratropium bromide be added to beta-agonists in treatment of acute severe asthma? *Chest* 94: 718-22, 1988.
20. Summers QA, Tarala RA: Nebulized ipratropium in the treatment of acute asthma. *Chest* 97: 425-9, 1990.
21. Filiz A, Ekinic E, Dikensoy O, Bulgur D, Oz M: Comparison of a single dose of aerosol salbutamol and fenoterol/ipratropium on bronchial asthmatic patients. *Del Med J* 66: 549-552, 1994.
22. Imhof E, Elsesser S, Karrer W, et al: Comparison of bronchodilator effects of fenoterol/ipratropium bromide and salbutamol in patients with chronic obstructive lung disease. *Respiration* 60: 84-8, 1993.
23. Lipworth BJ, Newnham DM, Clark DP, et al: Comparison of the relative airways and systemic potencies of inhaled fenoterol and salbutamol in asthmatic patients. *Thorax* 50: 54-61, 1995.
24. Wesseling G, Mostert R, Wouters EM: A comparison of the effects of anticholinergic and β_2 -agonist and combination therapy on respiratory impedance in COPD. *Chest* 101: 166-173, 1992.
25. Levin DC, Little KS, Laughlin KR, et al: Addition of anticholinergic solution prolongs bronchodilator effect of β_2 -agonists in patients with chronic obstructive pulmonary disease. *Am J Med* 100(Suppl 1A): 40s-48s, 1996.
26. Tashkin DP, Bleecker E, Braun S, et al: Results of a multicentre study of nebulized inhalant bronchodilator solutions. *Am J Med* 100(Suppl 1A): 62s-69s, 1996.
27. Braun SR, Levy SF, Grossman J: Comparison of ipratropium bromide and albuterol in chronic obstructive pulmonary disease: a three-centre study. *Am J Med* 91(Suppl 4A): 28s-32s, 1991.
28. Gayres J: Late onset asthma. *BMJ* 300: 1602, 1990.

