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Effect of three different bronchodilators during an exacerbation of chronic obstructive pulmonary disease

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ABSTRACT: This study evaluates the effect of three different bronchodilators (beta$_2$-adrenergic, anticholinergic and methylxanthine) alone and in randomized sequence, during an exacerbation in thirteen patients with chronic obstructive pulmonary disease. Dose-response curves were obtained for inhaled salbutamol and inhaled ipratropium bromide. The bronchodilator effect of a perfusion of aminophylline was also assessed. When a plateau of bronchodilatation was achieved with one agent, one dose of a second bronchodilator was administered to see whether additional bronchodilatation could be achieved. The increments in FEV_1 and FVC were similar with the three agents. The addition of a second bronchodilator did not result in significant increments in most of the patients. In at least half of the patients the doses of salbutamol and ipratropium that produced the maximal bronchodilatation were twice that currently employed.

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Whilst the role of bronchodilator drugs is well established in the treatment of asthmatics [1], the effect of these drugs in stable chronic obstructive pulmonary disease (COPD) patients is far from clear [1]. Even less is known about bronchodilator treatment during COPD exacerbations. To our knowledge there are no studies on the combined effect of different bronchodilators in COPD patients suffering from an acute exacerbation.

The purpose of this study is to assess the bronchodilator effect of three different bronchodilators (salbutamol, ipratropium bromide and aminophylline) during an exacerbation in COPD patients.

Patients and methods

Thirteen known COPD patients from our outpatient clinic, who were on regular bronchodilator treatment (including inhaled beta$_2$-adrenergics and oral theophylline), were included in the trial when they had been admitted to hospital due to acute exacerbation. Selection criteria included a clinical diagnosis of chronic bronchitis, emphysema or both, and evidence of severe airflow obstruction, with a forced expiratory volume in one second (FEV_1) of less than 1*l*. Patients with episodic attacks of wheezing indicative of bronchial asthma, and those with a reversibility of more than 15% after inhalation of two puffs of salbutamol whilst clinically stable were excluded. An informed consent was obtained.

Study design

Patients were studied in the course of an exacerbation of their disease, defined by an increase of their symptoms (breathlessness and mucus secretion) and gasometric deterioration, attributed to a bronchial infection. When signs and symptoms suggested that patients had overcome their initial critical condition, bronchodilators were withheld 24 h prior to the study. Corticosteroids and antibiotics were allowed. A single-blind design was used; patients were unaware of the nature and sequence of the tested drugs. The effects of intravenous aminophylline, inhaled salbutamol, and inhaled ipratropium bromide (using a metered-dose inhaler) were assessed using three protocols. The aerosol dosages and timing for assessment of response for each of the three protocols are shown in figure 1. Each day, before administration of the drugs, a blood sample was obtained for aminophylline measurements, and a forced spirometry (Vitalograph) was performed.

Protocol A consisted of 200 μg of inhaled salbutamol (two puffs), administered every 30 min until a plateau of bronchodilatation was reached. Then, a second agent (40 μg of ipratropium bromide or a loading dose of aminophylline, 5.6 $mg \cdot kg^{-1}$ in 30 min followed by a continuous infusion of 0.9 $mg \cdot kg^{-1} \cdot h^{-1}$) was given at random. All thirteen patients were tested for salbutamol and five received ipratropium as the second agent, whilst eight received aminophylline. If aminophylline was not used,

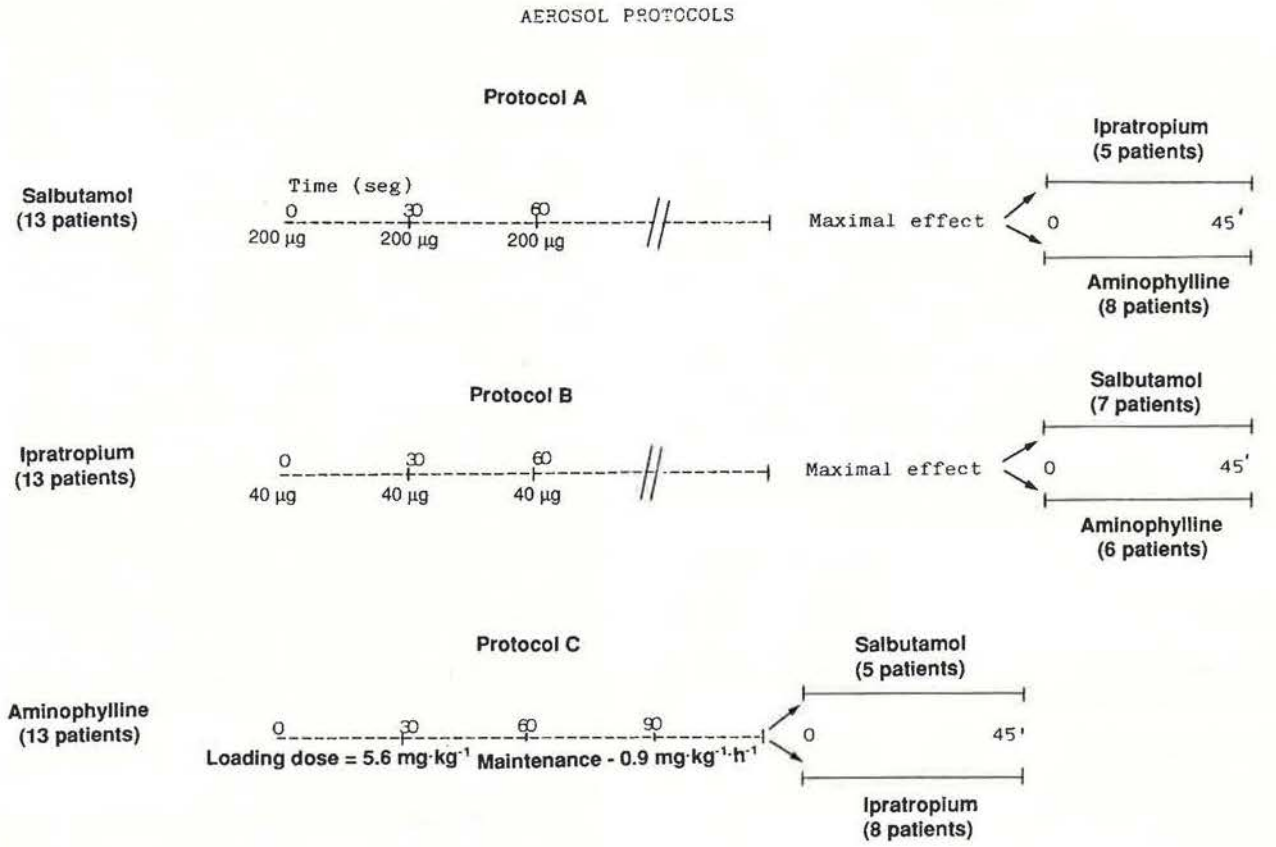

Fig. 1. In protocol A, 200 µg of inhaled salbutamol were administered every 30 min until reaching a plateau of bronchodilatation (maximal effect). Then an additional 40 µg of ipratropium or an infusion of aminophylline was administered and its additional effect was assessed at 45 min. In protocol B, 40 µg of inhaled ipratropium were administered every 30 min until reaching a plateau of bronchodilatation. An additional 200 µg of salbutamol or an infusion of aminophylline was then given and its effect assessed at 45 min. In protocol C, a loading dose of aminophylline was administered over a period of 30 min. The effect of a continuous infusion of the drug was then assessed every 30 min until reaching a plateau. Then 200 µg of salbutamol or 40 µg of ipratropium were given and the effect assessed at 45 min.

patients received a glucose infusion through the same intravenous line.

Protocol B consisted of 40 µg of inhaled ipratropium bromide administered every 30 min until a plateau of bronchodilatation was reached. Then a single dose of a second agent (200 µg of salbutamol or aminophylline as specified above) was administered at random. As before, when aminophylline was not used patients received a glucose infusion. Of the thirteen patients that were tested for ipratropium, six received aminophylline and seven received salbutamol as the second agent.

Protocol C consisted of the administration of aminophylline using a loading dose of 5.6 $mg \cdot kg^{-1}$ in 30 min, followed by a continuous infusion of 0.9 $mg \cdot kg^{-1} \cdot h^{-1}$. Its effect was assessed every 30 min and a blood sample was obtained for aminophylline measurements. After obtaining a plateau of bronchodilatation, a single dose of a second agent was administered in a randomized order. In five cases salbutamol was used as the second drug whilst ipratropium was used in eight.

For all protocols the effect of the second drug was assessed 45 min after its administration.

Assessment of the therapeutic effect

The effect of the drugs was evaluated by forced spirometry from the best of three attempts. We recorded absolute and relative increases of FEV_1 and forced vital capacity (FVC) with respect to the baseline values obtained each day before the administration of the drug tested. The effect produced by the addition of the second drug was assessed by comparing the absolute and relative changes of the spirometric values with respect to the maximal bronchodilatation obtained with the first agent.

Statistical analysis

Results were expressed as mean ± SEM of absolute and percentage changes with respect to the baseline pre-aerosol values. Two way analysis of variance was used to compare the increase of spirometric values in the three treatments, and to compare the baseline pre-aerosol FEV_1 of the three protocols. Paired t-tests were used to compare the increment of the spirometric values after the first and the second drug.

Results

The mean age of subjects was 65 ± 5.1 yrs. The lung function data of patients, before and after an inhaled beta$_2$-adrenergic agent, whilst clinically stable (on regular bronchodilator treatment) and during the exacerbation, are shown in table 1. Mean FEV_1 and FVC values in the clinically stable state were 0.82 ± 0.19 *l* and 2.45 ± 0.61 *l*, respectively, with a mean percentage increase after the inhalation of two puffs of salbutamol of 10.5 ± 4.9 and 8.6 ± 4.8%, respectively. Mean FEV_1 and FVC during the exacerbation were 0.64 ± 0.11 *l* and 1.87 ± 0.39 *l*, respectively. Mean baseline FEV_1 values pre-aerosol administration were 0.66, 0.66 and 0.64 *l* for protocols A, B and C, respectively. No significant differences were found between these values. Bronchodilator effects on airway function manifested by changes in FEV_1 during the study are shown in figure 2. The figure shows the maximal bronchodilatation reached with each drug when given alone, and after the addition of a single dose of a second agent expressed through percentage changes in FEV_1 with respect to baseline values.

Table 1. – Characteristics of 13 patients with severe chronic obstructive pulmonary disease

		Mean±SD	Range
Age yr		65±5.1	50–75
Pulmonary function between exacerbations *l*	FEV_1	0.82±0.19	0.54–1.1
	FVC	2.45±0.61	1.34–3.55
Broncho-reversibility between exacerbations (% increase after 2 puffs of salbutamol)	FEV_1	10.5±4.9	
	FVC	8.6±4.8	
Pulmonary function during exacerbation *l*	FEV_1	0.64±0.11	0.35–1.01
	FVC	1.87±0.39	1.40–2.58

FEV_1 and FVC denote forced expiratory volume in one second and forced vital capacity, respectively.

The three agents obtained a significant improvement with respect to baseline FEV_1 values, but there were no significant differences between ipratropium (absolute increase 0.167 ± 0.72 *l*, percentage increase 25 ± 4.43%), salbutamol (absolute increase 0.146 ± 0.102 *l*, percentage increase 22 ± 5%) and aminophylline (absolute increase 0.105 ± 0.97 *l*, percentage increase 16 ± 3.32%).

When ipratropium and aminophylline were given after salbutamol there was a 0% (0 *l*) and 3 ± 1.4% (0.065 ± 0.11 *l*) improvement, respectively, in relation to the plateau reached with salbutamol. The administration of salbutamol and aminophylline after ipratropium improved airflow by 6.3 ± 2.6% (0.053 ± 0.066 *l*) and 3.4 ± 2.6% (0.029 ± 0.065 *l*), respectively. The addition of salbutamol and ipratropium resulted in an improvement of 8.63 ± 1.78% (0.06 ± 0.03 *l*) and 6.1 ± 2.82% (0.046 ± 0.06 *l*), respectively, compared to the plateau reached with aminophylline. None of these increments were statistically significant.

The improvements in FVC with the three drugs were similar to those seen in FEV_1.

After the administration of aminophylline, mean serum level was 79.75 ± 19.8 $\mu mol \cdot l^{-1}$ (14.3 ± 3.6 $mg \cdot l^{-1}$).

The cumulative doses that produced the maximal increase in FEV_1 were the following: for salbutamol, 600 μg in two patients, 400 μg in seven patients, and 200 μg in four patients; and for ipratropium, 120 μg in

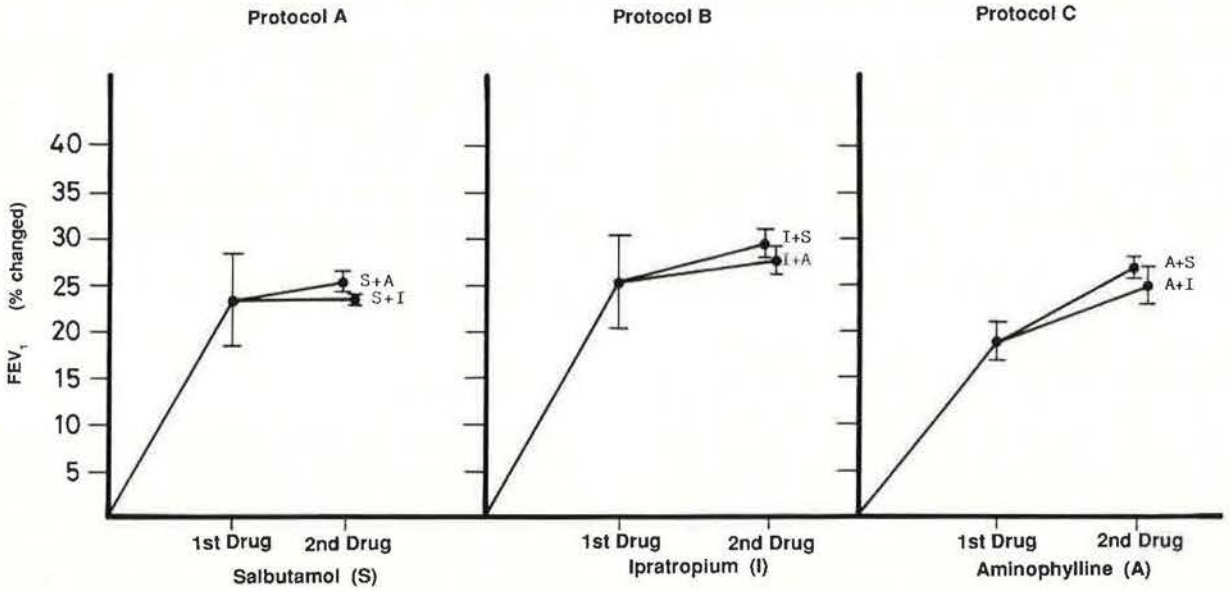

Fig. 2. This figure shows the percentage changes in FEV_1 (expressed as mean ± SEM) with the first drug and after the addition of a second agent in the three protocols. The effects of salbutamol, ipratropium and aminophylline were not significantly different. The additional effect of the three drugs when given as second agents was not significantly different with respect to that obtained with the first drug.

two patients, 80 μg in five patients and 40 μg in six patients. The cumulative plateau doses for FVC were similar.

Discussion

Our results show that in 50% of the COPD patients during an acute exacerbation the doses needed to reach the maximal bronchodilatation, expressed by the plateau in the dose-response curve, were at least 400 μg for salbutamol and 80 μg for ipratropium. The addition of a second bronchodilator, after the plateau with the first agent had been reached, did not produce significant increments. We also observed that there were no significant differences between the bronchodilatation achieved with salbutamol, ipratropium or aminophylline when given as first agents.

Studies examining the effects of combined bronchodilator therapy on COPD patients have led to contradictory and unclear results. Our main criticism against most of these studies [2–6] is that each drug has been given in doses which are not large enough to induce maximal bronchodilatation. The disparity with our results could also be partly attributed to differences in patient material. Our patients were selected on the basis of an irreversible bronchial obstruction defined as a failure to show an acute improvement in FEV_1 after the administration of an inhaled bronchodilator [1]. Moreover, research in this area has usually been limited to the study of patients in the clinically stable state, and therefore bronchodilator therapy during COPD exacerbations remains largely under-investigated. Two recent studies have been performed using high doses of inhaled bronchodilators, but again the different doses and agents used seem to be the cause of disparity in the results. EASTON *et al.* [7] showed no significant differences between the effect of albuterol and ipratropium, while GROSS and SKORODIN [8] found an additional improvement when ipratropium was administered after salbutamol. Our findings are comparable to those of EASTON *et al.*, on a similar population. However, our study was carried out during an exacerbation, whilst that of EASTON *et al.* was performed on patients in a stable clinical situation.

In our study the lowest bronchodilator effect was obtained with aminophylline, although the difference with respect to salbutamol and ipratropium was not significant. As we did not carry out a dose-response curve with this drug, the possibility that theophylline in higher serum concentrations could have induced a significantly higher bronchodilatation cannot be excluded. VOZEH *et al.* [9] found a significant improvement in lung function with the use of high concentrations of theophylline in COPD during an exacerbation. However, their patients were found to show a reversibility greater than 15% after recovery from the acute illness. EATON *et al.* [10] also showed a significant dose-related difference between low and high serum theophylline concentrations in pulmonary function of irreversible chronic airflow obstruction without other bronchodilator treatment. These results support the use of higher doses of theophylline in COPD patients. In these patients, the use of higher than recommended doses of theophylline, given alone or in combination with other drugs, must be evaluated and balanced against the potential adverse effects that it could produce, in the setting of an acute exacerbation.

Our results encourage the administration of high doses of a single agent during exacerbations in the subgroup of COPD patients with a severe and long-standing bronchial obstruction and little bronchoreversibility. The beneficial effect derived from the administration of a second drug seems negligible.

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RÉSUMÉ: Il s'agit d'une évaluation de l'effet de trois bronchodilatateurs différents (bêta-2 adrénergique, anticholinergique et méthylxantine) seuls et en succession, au cours d'une exacerbation chez 13 patients avec une maladie pulmonaire obstructive chronique. L'on a obtenu des courbes dose-réponse après l'inhalation de Salbutamol et de bromide d'Ipratropium. L'effet bronchodilatateur d'une perfusion d'Aminophylline a également été apprécié. Lorsqu'un plateau de bronchodilatation était obtenu avec un agent, une dose d'un second bronchodilatateur était administrée pour préciser si une bronchodilatation additionnelle pouvait être obtenue. Les augmentations de VEMS et de CVF farent similaires avec les trois médicaments. L'addition d'un second bronchodilatateur n'entraînait pas d'augmentation significative chez la plupart des patients. Les doses de Salbutamol et d'Ipratropium produisant une bronchodilatation maximale étaient doubles de celles couramment utilisées chez au moins la moitié des patients.