Bronchodilator Efficacy of Combined Salmeterol and Tiotropium in Patients With Chronic Obstructive Pulmonary Disease

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OBJECTIVE: Bronchodilators are still the most effective drugs for controlling the symptoms of chronic obstructive pulmonary disease (COPD). Tiotropium bromide, a long-acting anticholinergic drug, has recently been added to the therapeutic arsenal for the disease. To date, there have been no studies combining 2 long-acting bronchodilators. The aim of the present trial was to determine whether the combination of salmeterol and tiotropium improved lung function in COPD patients more than either of them alone.

PATIENTS AND METHODS: Twenty-two patients (20 men) diagnosed with COPD, with a mean age of 64 years, were enrolled in this cross-over trial. Active smokers were excluded. Mean (SD) forced expiratory volume in 1 second (FEV_1) was 43% (14%) of predicted. All patients were experienced in the use of inhalers. The following 3 therapeutic combinations were randomly assigned to be administered for a 1-week period: *a)* fluticasone (500 μg/12 h), salmeterol (50 μg/12 h) and placebo; *b)* fluticasone, tiotropium (18 μg/24 h), and placebo; and *c)* fluticasone, salmeterol, and tiotropium. At the end of each period, forced spirometry was performed before inhalation of the therapeutic combination (between 8:30 AM and 9:30 AM) and 2 hours after inhalation. Throughout the week, morning peak flow rates measured immediately before inhalation were recorded, and there was a 48-hour wash-out period between each therapeutic combination.

RESULTS: All the patients completed the protocol. There were no significant differences in preinhalation or postinhalation FEV_1 with salmeterol compared to tiotropium (preinhalation FEV_1, 1.17 [0.55] L compared to 1.19 [0.49] L; postinhalation FEV_1, 1.32 [0.65] L compared to 1.29 [0.61] L). In all cases postinhalation FEV_1 was significantly higher than preinhalation FEV_1. The combination of fluticasone, salmeterol, and tiotropium proved superior to the other 2 combinations with respect to both preinhalation FEV_1 and postinhalation FEV_1 (preinhalation FEV_1, 1.32 [0.56] L, [P<.03 in both comparisons]; postinhalation FEV_1, 1.49 [0.68] L [P<.001 in both comparisons]). Peak flow rate was also significantly higher with the combination of the 2 bronchodilators (345 L/min compared to 291 L/min and 311 mL, respectively [P <.04 in both cases]). There were no notable side effects.

CONCLUSIONS: In terms of improvement in lung function, the combination of salmeterol and tiotropium together with fluticasone is more effective in patients with moderate-to-severe COPD than either of the 2 bronchodilators administered alone.

Key words: *Chronic obstructive pulmonary disease (COPD). Salmeterol. Tiotropium. Spirometry.*

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Eficacia broncodilatadora de la asociación de salmeterol y tiotropio en pacientes con EPOC

OBJETIVO: Los broncodilatadores continúan siendo los fármacos más eficaces para el control de los síntomas de la enfermedad pulmonar obstructiva crónica (EPOC). Recientemente se ha añadido un anticolinérgico de acción larga, el bromuro de tiotropio, al arsenal terapéutico de esta enfermedad. No existen estudios que hayan asociado 2 broncodilatadores de acción sostenida. El objetivo de este estudio ha sido comprobar si la asociación de salmeterol y tiotropio a pacientes con EPOC mejora la función pulmonar respecto a cuando se administran aislados.

PACIENTES Y MÉTODOS: Se incluyó en el estudio a 22 pacientes diagnosticados de EPOC (20 varones), con una edad media de 64 años. Se excluyó a los fumadores activos. El volumen espiratorio forzado en el primer segundo (FEV_1) medio (± desviación estándar) fue un 43 ± 14% del teórico. Todos los pacientes tenían amplia experiencia en el uso de los dispositivos de inhalación. Se realizaron 3 combinaciones terapéuticas de forma aleatoria durante una semana: *a)* fluticasona (500 μg/12 h), salmeterol (50 μg/12 h) y placebo; *b)* fluticasona, tiotropio (18 μg/24 h) y placebo, y *c)* fluticasona, salmeterol y tiotropio. Al final de cada período se realizó una espirometría forzada entre las 8.30 y las 9.00 h, antes de la inhalación de la combinación y 2 h después de ésta. Durante toda la semana se recogió el pico de flujo matutino inmediatamente antes de la inhalación de los fármacos, dejando 48 h de lavado entre cada asociación.

RESULTADOS: Todos los pacientes finalizaron el protocolo. No hubo diferencias significativas en el FEV_1 tanto valle como postinhalación con salmeterol y tiotropio (FEV_1 valle: 1,17 ± 0,55 frente a 1,19 ± 0,49 l; FEV_1 postinhalación: 1,32 ± 0,65 frente a 1,29 ± 0,61 l). En todos los casos el FEV_1 postinhalación fue significativamente superior al FEV_1 valle. La combinación de fluticasona, salmeterol y tiotropio se mostró superior a las otras 2 tanto en el FEV_1 valle como postinhalación (FEV_1 valle: 1,32 ± 0,56 l, p < 0,03 en ambos casos; FEV_1 postinhalación: 1,49 ± 0,68 l, p < 0,001 en los 2 casos). El pico de flujo también fue significativamente mayor con la combinación de los 2 broncodilatadores (345 frente a 291 l/m y 311 l/m, respectivamente; p < 0,04 en ambos casos). No hubo efectos secundarios reseñables.

CONCLUSIONES: La asociación de salmeterol y tiotropio unidos a fluticasona en pacientes con EPOC de grado moderado-grave es más eficaz en términos de mejoría funcional respiratoria que cualquiera de los 2 broncodilatadores dados de forma aislada.

Palabras clave: *Enfermedad pulmonar obstructiva crónica (EPOC). Salmeterol. Tiotropio. Espirometría.*

Introduction

Chronic obstructive pulmonary disease (COPD) affects 9% of the adult population[1] and the incidence is expected to continue to increase, possibly making it the third cause of death in the western world by 2020.[2] The principal aim of treatment is to relieve symptoms and reduce the number of exacerbations. The use of bronchodilators is the most effective way to achieve symptomatic improvement.[3] The role of inhaled corticosteroids is still controversial.[4-6] While a promising study of the phosphodiesterase-4 inhibitor cilomilast[7] has recently been published, its clinical use seems improbable in the short term and bronchodilators, chiefly anticholinergics and β_2-agonists, remain the treatments of choice. To evaluate the efficacy of treatment, new parameters, such as the results of quality of life questionnaires, dyspnea scales, and stress tests, have been introduced. However, forced spirometry is still one of the most important tests in the monitoring of COPD patients. The first sustained-action bronchodilators were long-acting β_2-agonists, which have now been on the market for several years. Several clinical trials have shown these drugs to be more effective than placebo[8,9] or ipratropium[10] in improving lung function, quality of life, and stress tolerance. Recently a new bronchodilator was introduced: tiotropium, an anticholinergic whose characteristics make it a first-line drug in the therapeutic arsenal. Several trials have demonstrated its efficacy compared to both placebo and ipratropium,[11,12] and it has even been shown to be superior to salmeterol.[13] A trial that showed the superiority of the combination of fluticasone and salmeterol over either drug administered separately[14] was recently published, as was another that showed budesonide and formoterol to be superior to budesonide alone.[15] However, we know of no other study combining a long-acting β_2-agonist and tiotropium, which would appear *a priori* to be the most reasonable combination in patients with severe COPD.

In order to determine the bronchodilating efficacy of this combination we designed a preliminary trial in which we compared the combined use of salmeterol and tiotropium with each drug administered separately in patients with moderate-to-severe COPD.

Patients and Methods

Patients

Twenty-two patients diagnosed with COPD—forced expiratory volume in 1 second (FEV_1) less than 70% and the ratio of FEV_1 to forced vital capacity (FVC) less than 0.70—and followed in our department were invited to participate in the trial. All patients had been using an inhaled corticosteroid and a long-acting β_2-agonist as controller medication and ipratropium as rescue medication. This treatment had remained stable for at least 3 months prior to the trial. A minimum of 3 months without exacerbation was required for inclusion. None of the patients were active smokers and all received training in the use of the new inhalers in our department. In all cases the improvement in FEV_1 after 1000 µg of terbutaline was less than 15%. Table 1 shows patient characteristics. Patients with lung disease other than COPD were excluded, as were those with cardiovascular disease, major neurological diseases, prostate hyperplasia, known intolerance to any of the drugs, or inability to perform the lung function test maneuvers correctly. The trial was approved by the hospital ethics committee, and informed written consent was obtained from all patients.

Trial Protocol

A randomized, placebo-controlled, double-blind, cross-over design was used. After checking that inhalation technique was correct, a 2-week wash-out period was established, during which the only treatment was 500 µg of fluticasone and terbutaline on an as-needed basis. Three therapeutic combinations were established: *a)* fluticasone delivered via Accuhaler (500 µg/12 h), salmeterol delivered via Accuhaler (50 µg/12 h), and placebo (similar to tiotropium); *b)* fluticasone, tiotropium (18 µg/24 h), and placebo (similar to salmeterol); and *c)* fluticasone, salmeterol, and tiotropium. In order to distinguish the drug from the placebo, each inhaler had an identification number, but there was no difference in the appearance or the weight of the inhalers. Each of the combinations of inhalers was given to the patient in a closed previously-coded envelope. All the patients were randomly treated for 1 week with each of the combinations, with a 48-hour wash-out period between the different combinations, during which patients used fluticasone and terbutaline on an as-needed basis. On each visit the previous treatment was collected, the doses used checked, and the next treatment distributed.

Peak Flow Rate

Patients were instructed to record peak flow rates in a diary at around 9:00 AM every day, before inhalation of the drugs. The best of 3 measurements on a Personal Best peak flow meter (Respironics, Cedar Grove, New Jersey, USA) was used.

Spirometry

Spirometry was performed by an experienced nurse from the lung function testing laboratory who was unaware of the medication the patient had received the previous week. A Collins GS/Plus spirometer (Warren E. Collins, Inc, Braintree, Massachusetts, USA) was used and 3 maneuvers were performed in accordance with the guidelines of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR).[16] Preinhalation spirometry was performed between 8:30 and 9:00 AM, before the morning dose of medication; spirometry was repeated 120 minutes after inhalation of the therapeutic combinations.

Data Analysis

The principal objective of the study was to determine the difference between FEV_1 values obtained with the combination of salmeterol and tiotropium and those obtained with each of the drugs administered separately, both before and 2 hours after inhalation. Our secondary objective was to determine the difference in peak flow over a period of a week.

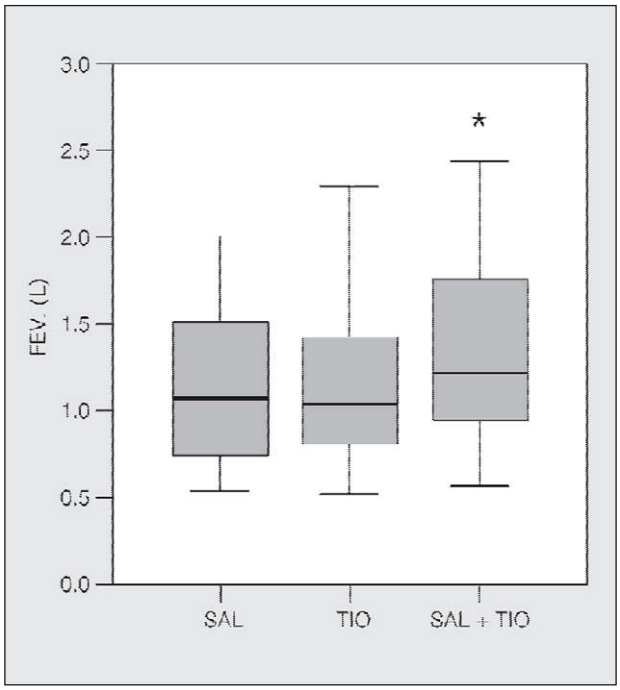

Figure 1. Preinhalation forced expiratory volume in 1 second (FEV_1). There were no significant differences between values obtained with salmeterol (SAL) and those obtained with tiotropium (TIO). *P<.03.

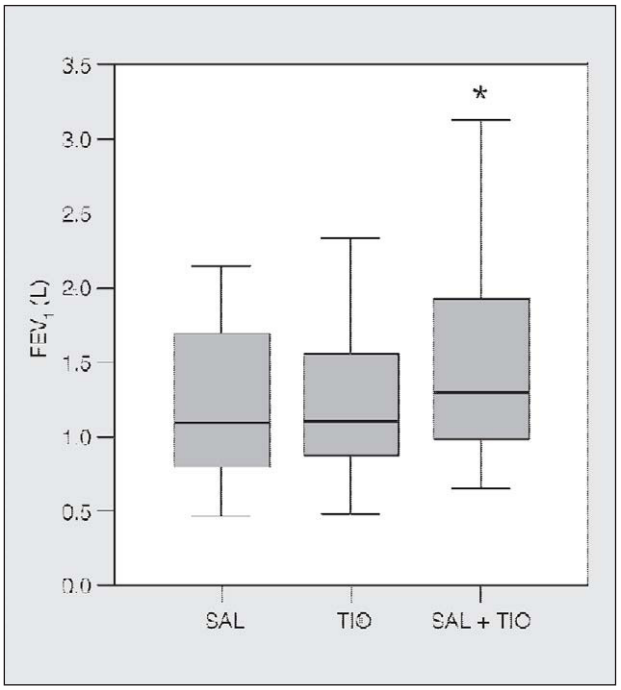

Figure 2. As in the case of preinhalation forced expiratory volume in 1 second (FEV_1), there were no significant differences between postinhalation FEV_1 obtained with salmeterol (SAL) and that obtained with tiotropium (TIO), and the combination of the 2 was statistically superior. *P<.001.

The highest and lowest values were excluded from the analysis, and the 5 central values were chosen. All values were expressed as means (SD). For comparisons of FEV_1, both absolute and percent of predicted values were used. The latter appear to be more significant in patients with moderate-to-severe COPD. For samples with normal distributions, analysis of variance was carried out and then the Bonferroni multiple comparison test applied; for non-normal distributions, the Wilcoxon test was used. A P value less than .05 was considered significant.

TABLE 1
Patient Characteristics*

Number of patients	22
Age, years	64 (range: 49-77)
Sex, M/W	20/2
FVC, L	2.69 (1.03)
FEV_1, L	1.16 (0.56)
FEV_1, % of predicted	43 (14)
FEV_1/FVC	43% (11%)
Peak flow rate, L/m	274 (108)

*Data are expressed as means (SD) or range. M indicates men; W, women; FVC, forced vital capacity; FEV_1, forced expiratory volume in 1 second.

TABLE 2
Forced Expiratory Volume in 1 Second Preinhalation and 2 Hours Following Inhalation of the Various Combinations*

Combination	Preinhalation FEV_1, L	Postinhalation FEV_1, L
FLU+SAL	1.17 (0.55)	1.32 (0.65)
FLU+TIO	1.19 (0.49)	1.29 (0.61)
FLU+SAL+TIO	1.32 (0.56)	1.49 (0.68)

*Data are expressed as means (SD). FEV_1 indicates forced expiratory volume in 1 second; FLU, fluticasone; SAL, salmeterol; TIO, tiotropium.
In all cases, postinhalation FEV_1 was significantly higher than preinhalation FEV_1.

Results

All 22 patients completed the protocol and all treatments were well tolerated. Only 2 of the patients, whose characteristics are shown in Table 1, were women. Active smokers were excluded from the study. The mean (SD) basal FEV_1 was 1.16 (0.56) L (43% [14%] of predicted) and mean peak flow rate was 274 L/m. Postinhalation FEV_1 was significantly higher than preinhalation FEV_1 in all cases. An improvement greater than 10% was achieved in approximately half the patients, with no notable differences between the 3 treatments (Table 2). There were no significant differences from basal FEV_1 or in the peak flow rate after treatment with either the fluticasone plus salmeterol or the fluticasone plus tiotropium combination. The combination of salmeterol plus tiotropium (Table 3) was superior to either of the 2 bronchodilators administered alone for both preinhalation and postinhalation FEV_1, as can be seen in Figure 1 and Figure 2 (P<.03 in all cases). The peak flow rate was also significantly better with the combination of the 2 bronchodilators (345 [179] compared to 291 [126] L/m with salmeterol and 311 [151] L/m with tiotropium; in both cases, P<.04). There were no differences in the results achieved with salmeterol and those achieved with tiotropium (Figure

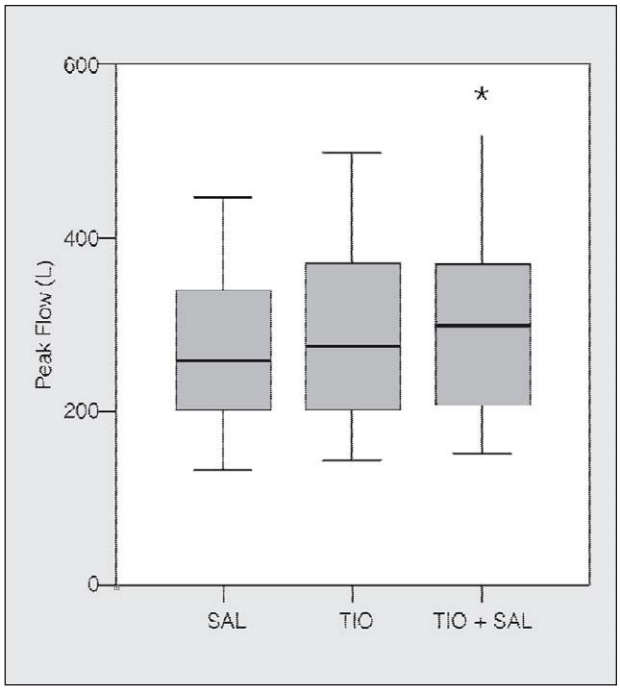

Figure 3. Peak flow rate values are expressed as the mean of the 5 central values (see text). In this case as well, the combination of bronchodilators was shown to be superior, although not as significantly as in the case of FEV_1. SAL indicates salmeterol; TIO, tiotropium. *P<.04.

3). No patients were intolerant to any of the various combinations, nor were there notable side effects.

Discussion

This preliminary trial appears to show the superior bronchodilator efficacy of the combination of tiotropium and salmeterol compared to either of them administered separately. COPD still poses considerable therapeutic challenges. The role of inhaled corticosteroids in the treatment of COPD is controversial, and their use has produced only modest benefits. Long-acting β_2-agonists seem to improve quality of life, but to date they have not been shown to have a long-term positive effect on lung-function loss.[17] Tiotropium, an anticholinergic drug with long-acting bronchodilator effects and kinetic selectivity for M_3 receptors, has recently joined the therapeutic arsenal for COPD. Several comparative studies have shown tiotropium to be superior to ipratropium and to have some advantages compared to salmeterol.[11-13] A large study is now being carried out to determine tiotropium's long-term effect on lung function loss in COPD patients. To date, we know of no study combining a long-acting β_2-agonist and tiotropium. The available evidence suggests that such a combination would be the treatment of choice in cases of severe disease, given that β_2-agonists and anticholinergics have different mechanisms of action and that both exhibit prolonged binding to their respective receptors, thus allowing sustained bronchodilation.

In evaluating the efficacy of a drug for the treatment of COPD, there are several possible objects of study: global improvement in quality of life, decrease in the number of exacerbations, increase in life expectancy, and functional improvement. Quality of life is not directly proportional to lung function variables, especially FEV_1, but in general patients shown by spirometry to have greater airway obstruction have a worse score on quality of life questionnaires, more exacerbations, and, especially in severe COPD, shorter life expectancy. It has long been established that the reversibility of airway obstruction has implications for prognosis.[18] The St. George's Respiratory Questionnaire, one of the most widely-used instruments for assessing health-related quality of life, shows good correlation with FEV_1.[19] Achieving significant improvements in FEV_1 would seem, therefore, to be a reasonable therapeutic objective. The present study clearly supports the use of salmeterol and tiotropium in moderate-to-severe COPD patients. Some of our data are particularly significant and worthy of special note. In all cases postinhalation FEV_1 was significantly higher than preinhalation values, although in the case of tiotropium, the mean improvement (approximately 8%) did not reach clinical significance. Although there was considerable variation among patients, the number of those who achieved clinically significant bronchodilation with each treatment was quite similar (11 patients with salmeterol, 9 with tiotropium, and 12 with the combination), and in a larger sample the similarity might be even greater. Another noteworthy finding was that there were no differences between salmeterol and tiotropium with respect to preinhalation and postinhalation FEV_1. This somewhat contradicts the results obtained by Donohue et al,[13] who found all spirometric variables to be consistently superior with tiotropium treatment, which was also associated with improved quality of life. Such differences cannot be attributed to the severity of functional impairment, as this was similar in the 2 studies (FEV_1 of 40% [12%] of predicted compared to 43% [14%]).

TABLE 3
Differences in Preinhalation and Postinhalation Forced Expiratory Volume in 1 Second With the Various Combinations*

Combinations	Preinhalation FEV_1, L	Postinhalation FEV_1, L
FLU+SAL compared to FLU+TIO	1.17 (0.55) compared to 1.19 (0.49) (NS)	1.32 (0.65) compared to 1.29 (0.61) (NS)
FLU+SAL+TIO compared to FLU+SAL	1.32 (0.56) compared to 1.17 (0.55) (P=.023)	1.49 (0.68) compared to 1.32 (0.65) (P<.001)
FLU+SAL+TIO compared to FLU+TIO	1.32 (0.56) compared to 1.19 (0.49) (P=.014)	1.49 (0.68) compared to 1.29 (0.61) (P<.001)

*Data are expressed as means (SD). FEV_1 indicates forced expiratory volume in 1 second; FLU, fluticasone; SAL, salmeterol; TIO: tiotropium; NS, not significant. There were no significant differences in preinhalation or postinhalation FEV_1 with the combinations of FLU+SAL or FLU+TIO. The combination of FLU+SAL+TIO was significantly superior in both cases.

Morning peak flow measurements are of limited value in monitoring COPD. Nevertheless, we believed the inclusion of such information in a functional study such as ours to be of interest. Morning peak flow behaved similarly to FEV_1: no significant differences were found between salmeterol and tiotropium, but peak flow was clearly superior when the 2 drugs were combined, although the statistical significance of the difference was less than that observed for FEV_1.

It is unusual nowadays for the treatment of patients with severe COPD not to include inhaled corticosteroids. These drugs partially compensate for the loss of efficacy of prolonged β_2-agonist use. Thus, we decided to include fluticasone in all the combinations in order to bring the treatments closer to real clinical practice.

The present preliminary trial has several limitations. First, obviously, is the size of the sample. While the inclusion of a greater number of patients might have altered the results, substantial variation in the data is unlikely, and even smaller numbers of patients have been used in other studies of bronchodilation.[20,21] In order to minimize the problem, we chose patients who were familiar with correct spirometry technique and with the objectives of the study. All the tests were performed by the same nurse, who had considerable experience in lung-function testing. We consider the present study to be a preliminary one because it dealt only with lung function variables, but we believe the results support the design of another more ambitious project that would allow us to determine the long-term impact of a combination of a long-acting β_2-agonist and tiotropium on quality of life, exacerbations, and lung function loss.

In conclusion, the present study showed combined salmeterol and tiotropium to have a greater bronchodilating effect in patients with moderate-to-severe COPD than either drug administered separately. This opens the door to the use of such a combination in clinical practice for such patients.

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