CONTROVERSIAS EN EL TRATAMIENTO FARMACOLÓGICO DE LA EPOC

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Introduction

Current treatment for chronic obstructive pulmonary disease (COPD) is aimed at increasing airflow, decreasing respiratory symptoms (particularly dyspnea), decreasing exacerbations, and improving the quality of life. Consequently, it is not surprising that both the Global Initiative for Obstructive Lung Disease (GOLD) guidelines1, and the recent American Thoracic Society (ATS)/European Respiratory Society (ERS) position paper recommend, for moderate-to-very severe COPD, use of regular treatment with long-acting bronchodilators (e.g., salbutamol, terbutaline, ipratropium or oxitropium) or long-acting (e.g., formoterol, salmeterol, or tiotropium). Both the GOLD Update and the ATS/ERS position paper recommend, for moderate-to-severe COPD, use of regular treatment with long-acting bronchodilators rather than short acting bronchodilators, with the choice depending on the availability of medication and the patient’s response.2-5

For patients whose conditions are not sufficiently controlled by monotherapy, these guidelines highlight that combining medications of different classes, in particular an inhaled anticholinergic with a β2-AR agonist, seems a convenient way of delivering treatment and obtaining better results.2-3 This includes better lung function and improved symptoms.

Rationale for combining β2-adenoreceptor agonists and anticholinergic agents

Postganglionic, parasympathetic-cholinergic nerves innervate the airways. When activated, these nerves are capable of obliterating the lumen of small bronchi and bronchioles, and markedly increasing airway resistance in larger, cartilaginous airways, by secretion of the bronchoconstricting mediator acetylcholine (ACH), which causes activation of muscarinic receptors at the level of the target cells, such as bronchial smooth muscle and goblet cells. Conversely, sympathetic nerves may control tracheobronchial blood vessels, but no innervation of human airway smooth muscle has been demonstrated. β2-ARs, however, are abundantly expressed on human airway smooth muscle and activation of these receptors causes its relaxation.6

Bronchodilatation may, therefore, be obtained either by stimulating the β2-ARs with β2-AR agonists, or by inhibiting the action of ACH at muscarinic receptors with anticholinergic agents. In any case, anticholinergics are more likely to decrease central airway resistance, although there are muscarinic receptors that are expressed in the smooth muscle of small airways which do not appear to be innervated by cholinergic nerves, and β2-AR agonists have a greater effect on peripheral airway resistance in patients with COPD. It is reasonable to postulate that attempts to reduce bronchoconstriction through two distinct mechanisms (anticholinergic and sympathomimetic) with a different prevalent site of action may maximize bronchodilator response. Interestingly, the presence of small dense-cored vesicles containing adrenergic nerve varicosities, occasionally in close proximity to morphologically characteristic cholinergic nerve-endings, has been identified in human airways,7 suggesting that cholinodilates might modulate cholinergic neurotransmission (fig. 1). However, different studies have led to dissimilar conclusions. Early research papers based on force measurement alone suggested that stimulation of β2-ARs inhibits cholinergic neurotransmission8, most probably by the release of inhibitory prostaglandins from the airway mucosa. However, interpretation of these data is seriously hampered by the large postfunctional effects of β2-AR agonists. Zhang et al3 were the first to report an excitatory β2-AR in airway parasympathetic nerves. After their report in studies on the horse, this receptor was subsequently reported in guinea pig3 and in human airway parasympathetic nerves.3 Activation of β2-ARs by isoproterenol, by the racemic mixture of specific β2-AR agonists such as salbutamol and formoterol or by R-
enantiomers of β₂-agonists can increase ACh release in a concentration-dependent manner. Consistent with the results of β₂-AR stimulation, direct activation of the β₂-AR coupled G protein by cholera toxin, which increases the activity of adenyl cyclase, caused an increase in ACh release in epithelium-denuded guinea pig tracheal muscle. In airway smooth muscle cells, however, stimulation of G protein directly opens large Ca²⁺-activated potassium (Kᵥ) channels, which has been found to decrease ACh release in guinea pig tracheal cells. Recently, Brichetto et al. have confirmed that β₂-AR agonists attenuate cholinergic neurotransmission in the isolated bovine tracheal model and this happens by a mechanism not involving cAMP but Kᵥ channels.

Whatever the type of interaction between the two systems may be, combining β₂-AR agonists and anticholinergic agents is pharmacologically useful. In fact, in the first case, the addition of a β₂-AR agonist decreases the release of ACh because of the modulation of cholinergic neurotransmission by prejunctional β₂-ARs and, consequently, amplifies the bronchial smooth muscle relaxation directly induced by the anticholinergic agent. On the contrary, in the second circumstance, the addition of an anticholinergic agent can reduce the peripheral bronchoconstrictor effects of ACh, whose release has been facilitated by the β₂-AR agonist, and in this manner can amplify the bronchodilation elicited by the β₂-AR agonist through the direct stimulation of smooth muscle β₂-ARs.

Combination therapy with ipratropium and a β₂-agonist

It has been documented that standard doses of short acting β₂-agonists do not give optimal results in patients with COPD and that an anticholinergic agent gives additional bronchodilation. In addition, the reproducibility of responsiveness to bronchodilators in patients with COPD is improved when the pulmonary function test is performed using a combination of ipratropium and salbutamol. In effect, although a few articles question the value of combination therapy with ipratropium bromide and a β₂-AR agonist, several large trials suggest that the two drugs, both at low doses and at high doses, have complementary, or additive, bronchodilator actions without any increase in the incidence of adverse reactions, which makes them an excellent combination for the treatment of COPD. The inclusion of a second agent of a different class in a pharmacologic treatment regimen is associated with a lower rate of exacerbations in COPD. The overall result is lower total treatment costs and improved cost-effectiveness.

The introduction of long acting β₂-AR agonist bronchodilators gives physicians additional therapeutic options for COPD. Both salmeterol and formoterol appear to be more effective than short acting β₂-AR agonists and in patients with stable COPD they are more effective than anticholinergic agents.

Two published studies that had evaluated small cohorts suggested that there is no substantial additive effect when a long-acting β₂-AR agonist is combined with ipratropium bromide given acutely at the clinically recommended dose (40 µg) in patients with COPD but it must be stressed that the dose of ipratropium bromide needed to produce near maximal bronchodilation is several times higher than the customary dosage. In fact, the results of some studies suggest that higher than normal doses of an anticholinergic drug must be used for further relief of bronchospasm in patients with COPD when a single conventional inhaled dose of formoterol or salmeterol is given first.

In any case, van Noord et al. demonstrated that a 12-week treatment with salmeterol 50 µg twice daily plus ipratropium bromide 40 µg four times daily was more effective than salmeterol 50 µg twice daily in improving forced expiratory volume in 1 second (FEV₁) and specific airway conductance. This study was the first to point out that the association of a long acting β₂-AR agonist and an anticholinergic agent is useful in the long term therapy of stable COPD.

Subsequently, D’Urzo et al. only confirmed this therapeutic possibility, but even documented that the addition of formoterol (12 µg twice daily) to ipratropium bromide (40 µg four times a day) is more effective than the addition of salbutamol (200 µg four times a day) in patients with COPD who required combined bronchodilator therapy. This finding clearly indicates that long-acting β₂-AR agonists may represent the most effective option for combination therapy with an antimuscarinic agent.

The functional impact of combining long-acting bronchodilators

Clinical studies show that tiotropium administered 18 µg once daily improves lung function over its 24-h dosing interval, as shown by FEV₁, forced vital capacity...
CAZZOLA M. ET AL. ASSOCIATION OF $\beta_2$ ADRENERGIC AGONISTS AND TIOSTOPUM: IS THE COMBINATION JUSTIFIED?1

(FVC), peak expiratory flow rate (PEFR) and measures of hyperinflation and provides superior spirometric improvements compared with ipratropium 40 µg four times daily.29 Considering this important finding, in an elegant review in which the pharmacological actions of the long-acting $\beta_2$-AR agonists and a long-acting muscarinic antagonist (tiotropium bromide) were summarized, Tennant et al.30 highlighted the need for investigating the role of tiotropium in an accompanying editorial comment.31 Using the traditional method of integrating research studies that, unfortunately, does not allow to determine if the differences between the study outcomes are due to chance, to inadequate study methods or to systematic differences in the characteristics of the studies, emphasized the advantage of tiotropium on long-acting $\beta_2$-agonists, and suggested adding salmeterol or formoterol to tiotropium bromide, at least in patients suffering from COPD with more severe symptoms (stage III or IV of the GOLD classification).31 However, Cazzola and Matera32 in an accompanying editorial comment highlighted that no published study has documented the superiority of tiotropium over formoterol, although two studies, specifically designed to explore the potential differences between tiotropium and salmeterol, seem to indicate a greater efficacy of tiotropium than long-acting $\beta_2$-AR agonists.33-35 The different pharmacodynamic profile of formoterol when compared to salmeterol36 might induce a different type of bronchodilatory effect, mainly if one considers onset of action or peak bronchodilatation. This may lead to a different conclusion when comparing formoterol with salmeterol. Moreover, it is not known if the combination of a long-acting $\beta_2$-AR agonist and a long-acting antimuscarinic agent provides further advantages in terms of bronchodilatation over either drug alone, nor if the choice of the specific long-acting $\beta_2$-agonist to be used is trivial.

Acute functional effect of combining formoterol or salmeterol and tiotropium

Some studies have tried to give an answer to these questions. A pilot investigational trial,37 which enrolled 20 outpatients clinically diagnosed with stable COPD and a mean baseline FEV$_1$ of 0.87 l (95% confidence interval [CI], 0.70-1.04) and FVC of 1.49 l (95% CI, 1.30-1.69), showed that 12 µg formoterol, either alone or in combination with 18 µg tiotropium, elicited a significantly faster onset of action (the change in FEV$_1$ 10 min after inhalation of formoterol alone [0.088 l; 95% CI, 0.049-0.127] was greater than that induced by tiotropium alone [0.039 l; 95% CI, 0.006-0.071], but not than that elicited by formoterol + tiotropium [0.085 l; 95% CI, 0.044-0.126]) (fig. 2 A). Moreover, this study also documented a trend for a greater maximum bronchodilation with combination than with formoterol or tiotropium alone (the mean maximum increases in FEV$_1$ from pre-dosing value on each of the dosing days were 0.192 l [95% CI, 0.125-0.259] for formoterol, 0.176 l [95% CI, 0.100-0.253] for tiotropium, and 0.210 l [95% CI, 0.158-0.261] for the combination and occurred two hours after formoterol and three hours after inhalation of tiotropium and the combination, but the difference between treatments was not significant [p = 0.475]) (fig. 2 B). At twenty four hours, mean FEV$_1$ continued to be significantly higher than pre-dosing value following tiotropium 0.084 l [95% CI, 0.003-0.134; p = 0.003] and formoterol + tiotropium 0.088 l; 95% CI, 0.002-0.173; p = 0.045), but did not achieve significance for formoterol alone (0.058 l; 95% CI, 0.000-0.117; p = 0.051) (fig. 2 B). However, at this time point, the differences between treatments were not significant (p = 0.731). The failure to show a statistically significant difference between treatments when we explored the maximum bronchodilatation and the duration of action was likely associated with an insufficient statistical power in the study. We believe that there was a possibility of a type II error, which supported the lack of significance that we have repeatedly observed. It is possible that a study with a larger sample would achieve statistical significance.

The results of this study indicate that formoterol and tiotropium have different profiles (formoterol has a faster onset of action and greater bronchodilating effect, tiotropium has a longer duration of action, which allows...
for once daily administration) that make both agents attractive alternatives in the treatment of stable COPD. Moreover, the two drugs appear complementary: tiotropium ensures prolonged bronchodilation, whereas formoterol provides fast onset and a greater peak effect. However, because formoterol is given twice daily, but tiotropium is required only once daily, and results of our study do not allow suggesting the once daily dosing of formoterol, the challenge is to develop a combined inhaler that can be employed on a daily basis. The pharmacodynamic characteristics of salmeterol might permit the once daily contemporaneous administration of the two drugs that could simplify the therapy.

In a further study that has enrolled 20 outpatients with stable COPD and a mean baseline FEV\textsubscript{1} of 1.10 l (95% CI, 0.91-1.29) and FVC of 1.85 l (95% CI, 1.62-2.07), single doses of 18 μg tiotropium, 50 μg salmeterol, and 18 μg tiotropium + 50-μg salmeterol were given. The change in FEV\textsubscript{1} 30 min after inhalation of salmeterol alone (0.058 l; 95% CI, 0.032-0.083) was greater than that induced by tiotropium alone (0.037 l; 95% CI, 0.013-0.062), but not than that elicited by tiotropium + salmeterol (0.121 l; 95% CI, 0.073-0.170) (fig. 3 A). The difference between the improvement after salmeterol and that after tiotropium was not statistically significant (p = 0.231), but the differences between the improvement after tiotropium + salmeterol and that after tiotropium alone and salmeterol alone were statistically significant (p = 0.014 and p = 0.026, respectively). The mean maximum increases in FEV\textsubscript{1} on each of the dosing days were 0.165 l (95% CI, 0.098-0.232) for tiotropium, 0.241 l (95% CI, 0.151-0.332) for salmeterol, and 0.290 l (95% CI, 0.013-0.062), but not than that elicited by tiotropium + salmeterol (0.121 l; 95% CI, 0.073-0.170) (fig. 3 A). The difference between the improvement after tiotropium + salmeterol and that after tiotropium alone and salmeterol alone were statistically significant (p = 0.014 and p = 0.026, respectively).

The mean maximum increases in FEV\textsubscript{1} from pre-dosing value on each of the dosing days were 0.165 l (95% CI, 0.098-0.232) for tiotropium, 0.241 l (95% CI, 0.151-0.332) for salmeterol, and 0.290 l (95% CI, 0.013-0.062) for tiotropium + salmeterol. The combination and occurred four hours after inhalation of tiotropium or salmeterol and three hours after that of the combination (fig. 3 B). At twenty four hours, the mean FEV\textsubscript{1} value was still higher than the mean pre-dosing value for tiotropium (0.042 l; 95% CI, 0.012-0.079; p = 0.119) and the tiotropium + salmeterol combination (0.051 l; 95% CI, 0.015-0.087; p = 0.008), but not salmeterol alone (0.013 l; 95% CI, 0.004 to 0.041; p = 0.324) (fig. 3 B). At this point, the differences between tiotropium and salmeterol and between tiotropium + salmeterol, but not between tiotropium and tiotropium + salmeterol, were statistically significant (p = 0.010, p = 0.006, and p = 0.752, respectively).

These findings support the possibility of combining tiotropium and salmeterol in patients suffering from stable COPD, but exclude the once-daily co-administration of the two drugs. The potential of salmeterol to increase its onset of action when combined with tiotropium is worthy of attention considering that both agents elicit a slow onset of action. Ethier et al. speculated that salmeterol has a low affinity binding interaction with the muscarinic receptor/G-protein complex itself or reversibly alters the plasma membrane environment surrounding the complex. In any case, these effects of salmeterol did not depend on stimulation of β\textsubscript{2}-ARs. If this finding were also true for human airways, we could speculate that salmeterol reduces the bronchospastic activity of endogenous AChs, without influencing the effect of tiotropium. Salmeterol has also high affinity for muscarinic receptors and this indicates a potential for amplifying the action of tiotropium. However, the question of whether high local concentrations after inhalation of salmeterol could contribute to its therapeutic effects by antagonism with ACh on muscarinic receptors remains to be answered.

**Functional effect of a regular treatment with formoterol or salmeterol and tiotropium**

Although these results indicate that a combination of tiotropium and a long-acting β\textsubscript{2}-AR agonist is more effective than single drugs alone in inducing bronchodilatation in patients suffering from COPD, there is a funda-
moterol was significantly reduced in patients receiving the combination of tiotropium + formoterol (p < 0.05 versus formoterol). The documentation that tiotropium was more active than formoterol in daytime but not in night-time was, in our opinion, in agreement with the fact that the activity in the sympathetic system appears to be prominent during the day as reflected by the peak located around noon of the urinary catecholamine excretion, whereas the vagal system appears to be prominent during the remainder of the day\(^5\). In any case, these results indicate that once daily combination therapy of tiotropium + formoterol is safe and provides significant additive effects in patients with moderate-to-severe COPD. Moreover, they suggest that once daily administration of the two drugs could be a possibility in the treatment of stable COPD. A bronchodilator-media
da symptom benefit of the once daily combination is also reflected in significant decrease in salbutamol use as rescue therapy.

However, another trial that explored tiotropium maintenance therapy in 91 patients with COPD and the twenty four hour spirometric benefit of adding once or twice daily formoterol during two-week treatment periods\(^5\), documented that add-on therapy of a second formoterol dose significantly (p < 0.05) improved FEV\(_1\) and PVC variables when compared with tiotropium + formoterol once daily, although most of the spirometric add-on benefit was found with the morning formoterol dose. The average FEV\(_1\), AUC\(_{0-24\ h}\) was 80 ml after tiotropium, 162 ml after tiotropium + formoterol once daily and 198 ml after tiotropium + formoterol twice daily, the average FEV\(_1\), AUC\(_{0-24\ h}\) was 125 ml after tiotropium, 238 ml after tiotropium + formoterol once daily and 241 ml after tiotropium + formoterol twice daily, whereas the average FEV\(_1\), AUC\(_{0-24\ h}\) of tiotropium + formoterol twice daily (fig. 5). FEV\(_1\), AUC\(_{12-24\ h}\), of tiotropium + formoterol tio-
The best strategy for adding long-acting \( \beta_2 \)-agonists and long-acting anticholinergics

These findings raise an important question. What is the best strategy for adding long-acting \( \beta_2 \)-AR agonists and long-acting anticholinergics in COPD? Some studies have examined various strategies for adding short-acting \( \beta_2 \)-AR agonists and anticholinergics in COPD. Unfortunately, they have provided conflicting results. Rennard\(^1\) has correctly stressed that this may depend on the nature of the circumstances of the patient at the time when the study was carried out and may depend on the design by which the studies were conducted and the drugs administered.

In one of our previous trials, which was the first to our knowledge that compared a long-acting \( \beta_2 \)-AR agonist and an anticholinergic agent given by sequential inhalation at the recommended dosages, we documented that the sequential administration of formoterol and oxitropium bromide induced an improvement in pulmonary function in a population of COPD patients similar to that examined in the present trial\(^1\). However, prior administration of the long-acting \( \beta_2 \)-AR agonist allowed a response to the anticholinergic drug, which was higher than that observed when inhalation of oxitropium was preceded by that of formoterol.

In order to explore whether this finding is true even when tiotropium is used instead of oxitropium, we have examined the potential of an additive effect of a recommended dose of second long-acting bronchodilator (tiotropium or formoterol) in COPD patients under regular treatment with a long-acting bronchodilator of a different class (formoterol or tiotropium, respectively). We conducted a randomized, crossover trial in 20 patients with 18 \( \mu g \) tiotropium once daily and 12 \( \mu g \) formoterol twice daily over a five-day period for each drug, with a ten-day washout period\(^1\). At the end of each period, patients inhaled both drugs separated by 180 min in alternate sequence. Thirty minutes after inhalation of the last dose of tiotropium, there was a statistically significant increase of 0.099 l (95% CI, 0.062-0.138) in FEV\(_1\), over baseline (\( p < 0.002 \)). The mean maximal change in FEV\(_1\) over baseline was 0.226 l (0.154-0.298) in group A (regular tiotropium and add-on formoterol) and 0.201 l (0.165-0.241) in group B (regular formoterol and add-on tiotropium). The mean maximal change in FEV\(_1\) over pre-inhalation of the second drug value was 0.081 l (95% CI, 0.029-0.133) after tiotropium → formoterol and 0.054 l (95% CI, 0.016-0.092) after formoterol → tiotropium. The mean maximal change in FVC, over baseline was 0.519 l (95% CI, 0.361-0.676) in group A and 0.495 l (95% CI, 0.307-0.683) in group B. The mean maximal change in FVC over pre-inhalation of the second drug value was 0.159 l (95% CI, 0.048-0.270) after tiotropium-formoterol and 0.175 l (95% CI, 0.083-0.266) after formoterol → tiotropium.

These results suggest that supplementing a second different long-acting bronchodilator to a regularly administered long-acting bronchodilator seems to be to the patient’s advantage in terms of bronchodilation. We cannot exclude that the greater bronchodilatory response that we observed when a second bronchodilator was given after the first one may be justified by a carry over effect, considering that both formoterol and tiotropium are long-lasting bronchodilators. Nonetheless, it is well known that the mean peak bronchodilation with both formoterol and tiotropium in COPD patients is reached after two to three hours\(^8\) and we have documented that the addition of a second bronchodilator three hours after the inhalation of the first agent, could amplify the maximum bronchodilation of the first agent. This result seems to be important because it indicates the possibility.
that a patient who is unable to perceive bronchodilation or must perform an exercise could use a second long-acting bronchodilator that will assure a long-lasting effect. In any case, it must be highlighted that significant improvement in pulmonary function has been achieved by adding tiotropium or formoterol at the recommended dosages in patients already in regular treatment with formoterol or tiotropium, respectively, with no statistically significant difference between the different sequences. This finding supports Remiard’s opinion that treatment can be initiated with an agent from any of the available classes. If symptomatic control is inadequate, an agent from another class can be added.

Conclusions
At present time, there is no clear documentation that tiotropium is superior to formoterol or the contrary. At the recommend doses for COPD therapy, formoterol twice daily and tiotropium once daily induce comparable night time bronchodilation after regular treatment.

A combination of tiotropium and a long-acting β2-AR agonist is more effective than single drugs alone in inducing bronchodilation and bronchodilator-mediated symptoms in patients suffering from COPD. Add-on therapy of formoterol in the morning to maintain therapy with tiotropium significantly improves FEV1, and IC for more than twelve hours in patients with moderate-severe COPD. Add-on therapy of a second formoterol dose administered in the evening produces a further increase in average FEV1, and IC, but not in trough IC. All these findings support, in our opinion, the possibility of combining tiotropium and formoterol, and likely salmeterol, in patients suffering from stable COPD, but exclude the once-daily administration of the two drugs in combination within a single inhaler. It must be noted that combining tiotropium is more effective when administered in the evening compared with morning dosing, in view of the circadian variation of bronchial tone.

Because long-acting β2-AR agonists are given twice daily but tiotropium bromide is required only once daily, the challenge is now to develop a combined inhaler that can be employed on a once daily basis. The incorporation of once daily dosing is an important strategy to improve compliance since it is a regime preferred by most patients.

REFERENCES

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