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Tiotropium and salmeterol/fluticasone combination do not cause oxygen desaturation in COPD

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Summary
It has been documented that tiotropium is less likely to induce oxygen desaturation in stable COPD patients compared to long-acting β_2-agonists (LABAs) and combined administration of a LABA and an inhaled corticosteroid (ICS) reduces the potential for acute effects of LABA on blood-gas tensions. In this study, we have compared the acute effects of tiotropium 18 μg and salmeterol/fluticasone combination (SFC) 50/250 μg on arterial blood gases in 20 patients with stable COPD. Each subject was studied on 2 days, separated from one another by at least 4 days. Blood specimens were taken just before the inhalation and at 15, 30, 60, 180 and 360 min after inhalation of each treatment, and spirometry was performed at the same time points. As expected, both treatments significantly improved FEV_1 (greatest changes were 0.20 L, 95% CI: 0.13–0.27 at 360 min after tiotropium; and 0.13 L, 95% CI: 0.06–0.19 at 180 min after SFC). The greatest mean changes from baseline in PaO_2 were −1.7 (95% CI: −4.0 to 0.6) mmHg, $p = 0.134$, after tiotropium; −0.8 (95% CI: −2.2 to 0.6) mmHg, after SFC. Both changes were observed after 15 min. Both drugs caused a small decrease in $PaCO_2$ (greater changes: −1.9 (95% CI −3.2 to −0.6) mmHg, $p = 0.005$ at 60 min after tiotropium; and −2.4 (95% CI: −3.5 to −1.3) mmHg, $p = 0.0002$ at 180 min after SFC). These results indicate that both tiotropium and SFC are able to induce a significant long-last bronchodilation without affecting arterial blood gases. Moreover, they confirm that the impact of tiotropium on PaO_2 is small and without clinical significance and the addition of a LABA to an ICS can reduce the potentially dangerous acute effect of the LABA on blood gases.

Introduction

Long-acting bronchodilators, both in monotherapy or combined with an inhaled corticosteroid (ICS), are cardinal in the treatment of stable COPD.[1] However, in patients with a

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baseline $FEV_1 \leqslant 60\%$ predicted, we must still define if it is better to start with combined administration of a long-acting β_2-agonist (LABA) and an ICS, as suggested by the results of the TORCH study,[2] or the long-acting bronchodilator tiotropium, according the algorithm proposed by Taskhin and Cooper.[3] A recent study, which has compared the relative efficacy of the LABA/ICS combination (salmeterol/fluticasone propionate or SFC) 50/500 μg bd and tiotropium 18 μg od in preventing exacerbations and related outcomes in moderate-severe COPD, found no difference in exacerbation rate between SFC and tiotropium.[4] More patients failed to complete the study receiving tiotropium. A small statistically significant beneficial effect was found on health status, with an unexpected finding of lower deaths in SFC treated patients.

It is our opinion that, looking at the available data, the choice between a long-acting anticholinergic drug and a LABA/ICS combination as a first-line therapy for such a type of patients with COPD depends on the availability of medication and the patient's response. There are, in any case, other issues that that could influence this choice. For example, when we must treat a patient with hypoxemia caused by stable severe to very-severe COPD, the potential difference in the impact of LABA/ICS combination and tiotropium on blood gases could be crucial.

It has been documented that tiotropium is less likely to induce oxygen desaturation in stable COPD patients compared to LABAs,[5] but also, intriguingly, that combined administration of a LABA and an ICS reduces the potential for acute effects of LABA on blood-gas tensions.[6]

Since, to our best knowledge, no study has investigated the impact of SFC on blood gases, we have explored the acute effects SFC on the arterial blood-gas tensions in patients with stable COPD and compared them with those elicited by tiotropium.

Patients and methods

Twenty outpatients with moderate to severe stable COPD and a baseline $FEV_1 \leqslant 60\%$ predicted were enrolled. Exclusion criteria included: unstable respiratory status with a change in medication for COPD within the 4 weeks prior to the screening visit, a known history of asthma or chronic respiratory disease other than COPD, any clinically significant concurrent disease, a resting $PaO_2 \leqslant 55$ mmHg, or use of long-term oxygen therapy. All trial procedures were conducted according to the Declaration of Helsinki at the Unit of Respiratory Medicine, Department of Clinical and Experimental Medicine and Pharmacology, University of Messina, Italy.

This was a two-way crossover study. After a 2-week run-in period of during which fixed-combination LABAs and ICS were discontinued, whereas long-acting bronchodilator were permitted, all patients received tiotropium 18 μg, or SFC 50/250 μg from dry powder inhalers (DPIs) under randomized, crossover conditions. Each subject was studied for 2 days, separated from one another by at least 4 days. On each study day, subjects were required to withhold conventional inhaled bronchodilators for at least 12 h, salmeterol and formoterol or long-acting theophyllines for at least 24 h, and tiotropium for at least 48 h before study to avoid or, at least, minimize any carryover effect of drugs. Short-acting inhaled β_2-agonists were permitted soon after each test when required. Patients were asked not to consume cola drinks, coffee or tea and not to smoke in the hours before and during the investigation.

The study included spirometry and blood gases. The blood-gas analyzer output was checked daily with a standard test sample. On each study day, after a rest of 15 min while the patient was breathing room air, an arterial catheter was placed in the brachial artery. Samples of arterial blood (5 mL) were removed for measurement of PaO_2, $PaCO_2$, and pH with a blood-gas analyzer. Then, each patient received one of the two study treatments under supervision. Blood-gas analysis was repeated at 15, 30, 60, 180, and 360 min, always on room air. Spirometric tests were performed at the same time intervals.

The changes in PaO_2 and in FEV_1 after each treatment, from the baseline obtained on that day, were the primary outcome variables. The magnitude of changes in blood-gas tensions and functional values at each analysis time were compared among treatments. The paired *t*-test and analysis of variance (ANOVA) were used to determine the significance of differences among agents. Statistical significance was accepted at $p < 0.05$.

Results

As expected, both treatments significantly improved FEV_1 from baseline (greatest changes were: 0.20 L, 95% CI: 0.13 to −0.27, $p < 0.05$, at 360 min after tiotropium; and 0.13 L, 95% CI: 0.06 to −0.19, $p < 0.05$, at 180 min after SFC) (Figure 1). Also FVC changed in significant manner (greatest changes were 0.19 L, 95% CI: 0.10 to −0.28, $p < 0.05$, at 180 min after tiotropium; and 0.12 L, 95% CI: 0.06 to −0.18, $p < 0.05$, at 180 min after SFC. The difference between the two treatments was always not significant ($p > 0.05$) (Figure 2).

The impact of both treatments on arterial blood-gas tensions was really small. The greatest mean changes from baseline in PaO_2 were −1.7 (95% CI: −4.0 to −0.6) mmHg,

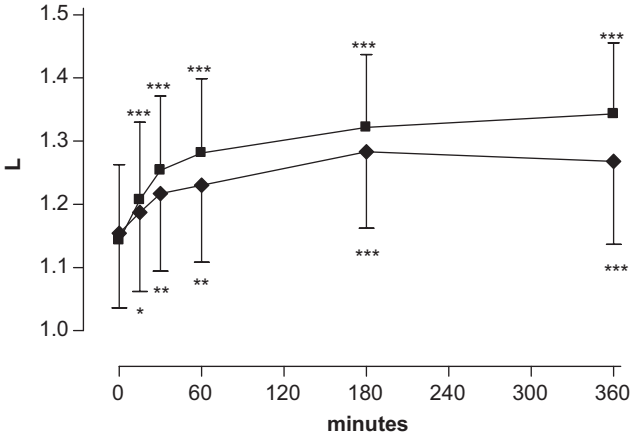

Figure 1 Mean changes (±S.E.) in FEV_1 with time after administration of tiotropium 18 μg (squares) and salmeterol/fluticasone combination 50/250 μg (rhombi). *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ vs. baseline.

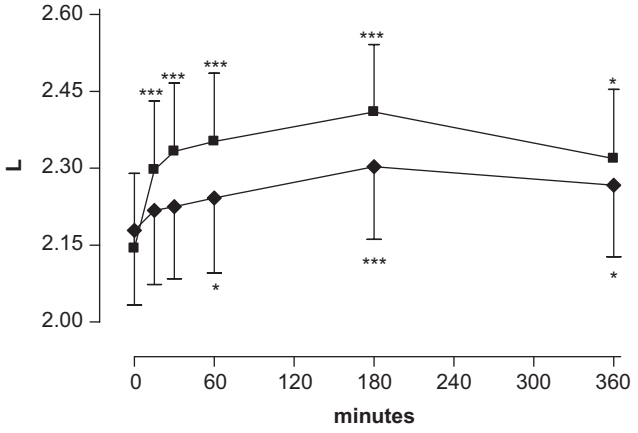

Figure 2 Mean changes (±S.E.) in FVC with time after administration of tiotropium 18 μg (squares) and salmeterol/fluticasone combination 50/250 μg (rhombi). *$p<0.05$, ***$p<0.001$ vs. baseline.

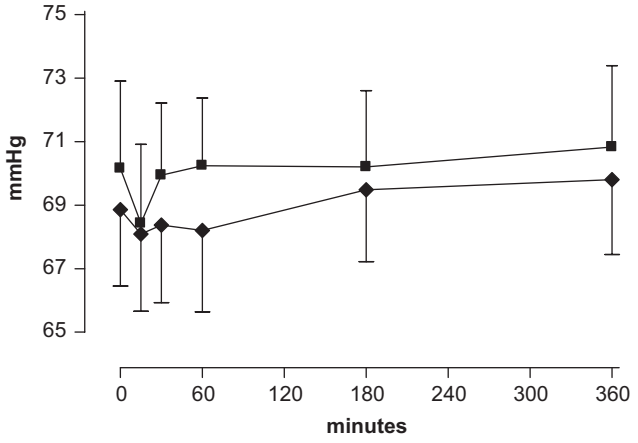

Figure 3 Mean changes (±S.E.) in PaO_2 with time after administration of tiotropium 18 μg (squares) and salmeterol/fluticasone combination 50/250 μg (rhombi). p was always >0.05 vs. baseline.

$p = 0.134$, $p>0.05$, after tiotropium; −0.8 (95% CI: −2.2 to −0.6) mmHg, $p>0.05$, after SFC (Figure 3). Both changes were observed after 15 min. Both drugs also caused a small decrease in $PaCO_2$ (greater changes: −1.9 (95% CI: −3.2 to −0.6) mmHg, $p = 0.005$ at 60 min after tiotropium; and −2.4 (95% CI: −3.5 to −1.3) mmHg, $p = 0.0002$ at 180 min after SFC) (Figure 4). The difference between the two treatments were always not significant ($p>0.05$) also considering their impact on arterial blood gases.

Discussion

These results indicate that both tiotropium and SFC are able to induce a significant long-last bronchodilation without affecting arterial blood gases. Moreover, they confirm that the impact of tiotropium on PaO_2 is small and without clinical significance and the addition of a LABA to an ICS can

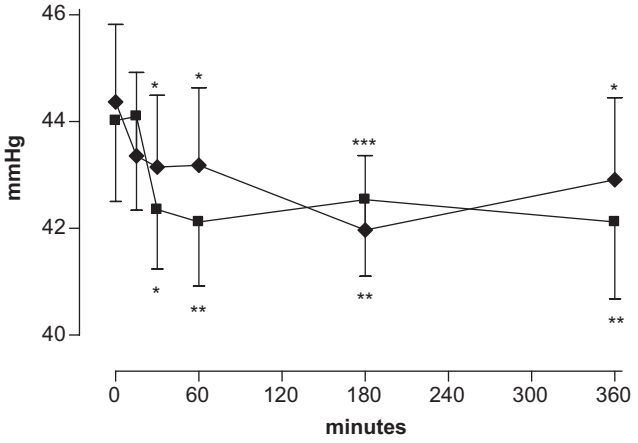

Figure 4 Mean changes (±S.E.) in $PaCO_2$ with time after administration of tiotropium 18 μg (squares) and salmeterol/fluticasone combination 50/250 μg (rhombi). *$p<0.05$, **$p<0.01$, ***$p<0.001$ vs. baseline.

reduce the potentially dangerous acute effect of the LABA on blood gases.

In a previous study, it has been documented that salmeterol is able to induce a significant although transient decrease in PaO_2.[5] The transient decrease in PaO_2 with β-adrenergic agents has been attributed to the pulmonary vasodilator action of these agents[7] due to the activation of β-adrenoceptors that are present in pulmonary vessels.[8] A possible explanation of the interference of fluticasone on the acute effect of salmeterol on blood gases is linked to the documented potential of ICSs to exert an acute reduction of bronchial blood flow.[9] This effect might be explained by the capacity of corticosteroids to interfere with noradrenaline uptake by smooth-muscle cells of human bronchial arteries (extraneural uptake: $uptake_2$). It could consequently increase noradrenaline concentration at α-adrenergic receptor sites of the bronchial vascular smooth muscle and explain the corticosteroid-induced vasoconstriction.[10] The pulmonary vasculature expresses α-adrenoceptors. The stimulation of these receptors induces produces vasoconstriction.[11] This effect might divert blood flow away from poorly ventilated alveoli to the regions that are better ventilated, thereby optimizing ventilation/perfusion ratio matching, and maintaining an adequate systemic PaO_2.[11] Intriguingly, it has been demonstrated *in vitro* that, $uptake_2$ is inhibited by steroid hormones through a nongenomic action.[12] This nongenomic action occurs within seconds to a few minutes.[13] Therefore, it could justify why the protective action of fluticasone on the vascular effect of salmeterol is immediate, as documented by our datas.

These results suggest that the impact of LABA/ICS combination and tiotropium on blood gases is not crucial in the choice between a long-acting anticholinergic drug and a LABA/ICS combination for treating a patient with hypoxemia caused by stable severe to very-severe COPD. They also confirm our opinion that tiotropium might be preferable in all patients with hypoxemia caused by stable COPD that do not need ICSs because it does not seem to carry a risk of worsening systemic hypoxemia.

Conflict of interest statement

We have no conflict of interest with this study that has not been sponsored by any Drug Company.

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