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Tiotropium is less likely to induce oxygen desaturation in stable COPD patients compared to long-acting β_2-agonists

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Summary
In a three-way crossover pilot study, the acute effects of tiotropium 18 μg inhalation on the respiratory function and arterial blood gas tensions of 30 patients with stable chronic obstructive pulmonary disease (COPD) were compared with those of salmeterol 50 μg and formoterol 12 μg. In each study day, lung function and arterial blood gas analyses were performed before and up to 180 min after inhalation. All treatments significantly improved lung function, increased DLco, decreased PaO_2, and increased $P(A\text{-}a)O_2$, with no change in $PaCO_2$. The effects of salmeterol and tiotropium on PaO_2 were slower in onset and more prolonged than those of formoterol but $PaO_2AUC_{0-180\,min}$ was significantly greater for formoterol and salmeterol than for tiotropium. It is likely that the significant but small decreases in PaO_2 and increases in $P(A\text{-}a)O_2$ have been caused by pulmonary vasodilator effects. Since the three agents were similar in inducing bronchodilation, we believe that tiotropium is preferable in patients with hypoxemia caused by stable COPD because it seems to carry a smaller risk of worsening systemic hypoxemia.

Introduction

Both the Global Initiative for Obstructive Lung Disease (GOLD) guidelines[1] and American Thoracic Society (ATS)/European Respiratory Society (ERS) position paper[2] emphasize the role of bronchodilators in symptomatic management of all stages of chronic obstructive pulmonary disease (COPD) and recommend, for moderate-to-very severe COPD, use of regular treatment with long-acting bronchodilators, including tiotropium, rather than short-acting bronchodilators, with the choice depending on the availability of medication and the patient's response. The choice between anticholinergic drugs and β-agonists as a first-line therapy for patients with COPD is still a matter of debate. The choice

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of the specific agent depends on the availability of medication and the patient's response. However, Tashkin and Cooper[3] have emphasized the advantage of tiotropium, a new long-acting anticholinergic bronchodilator, over long-acting β_2-agonists, although only few studies have compared inhaled long-acting β-agonists and tiotropium in patients with COPD and most of them have focused on the improvement of spirometric data (usually as forced expiratory volume in 1s [FEV_1]).[4–12] Unfortunately, it is not clear whether pulmonary function tests parallel symptomatic improvement and/or exercise performance because studies that examined the effects of two classes of inhaled bronchodilators on dyspnea and exercise ability are scant.

Another issue that has not been examined yet is the possible difference in the impact of long-acting β_2-agonists and tiotropium on blood gases. It is known that the administration of β-adrenergic agents to patients with airways obstruction often results in a transient decrease in partial pressure of oxygen in arterial blood (PaO_2) despite concomitant bronchodilation,[13] whereas anticholinergic bronchodilators have been shown to have relatively small effects on arterial blood gases.[14] This finding is potentially important because it indicates that anticholinergic bronchodilators should be considered a safer choice. In fact, the clinical relevance of changes in oxygenation may be considerable for patients with COPD because findings reflecting bronchodilation do not necessarily correlate with the perception of breathlessness. Nevertheless, to date and to our best knowledge no published study has compared the effects of the three long-acting bronchodilators on the arterial blood gas tensions of patients with stable COPD.

Patients and methods

Study population

Thirty outpatients with stable COPD were enrolled. Inclusion criteria were: >45 years of age, current or former smoker (>10 pack-years), and a diagnosis of COPD as defined by the ATS/ERS position paper.[2] The diagnosis was substantiated by spirometry. The presence of a postbronchodilator $FEV_1 < 80\%$ of the predicted value in combination with an FEV_1/forced vital capacity (FVC) $<70\%$ confirmed the presence of airflow limitation that was not fully reversible. Exclusion criteria included: unstable respiratory status within the previous 4 weeks, a known history of asthma or chronic respiratory disease other than COPD, any clinically significant concurrent disease, a resting PaO_2 of less than 55 mmHg, or use of long-term oxygen therapy, and a change in medication for COPD within the 4 weeks prior to the screening visit. Each patient gave informed consent and the study protocol was approved by an independent ethics committee. Basal characteristics of patients are illustrated in Table 1.

Study protocol

This was a three-way crossover pilot study. All patients received tiotropium 18 μg, salmeterol 50 μg or formoterol 12 μg from dry powder inhalers (DPIs) under randomized, crossover conditions. Each subject was studied for 3 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. Subjects receiving an inhaled corticosteroid were instructed to take this as usual, together with all their usual nonpulmonary medications. 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, body plethysmography, diffusing capacity for carbon monoxide (DLco), and blood gases. The blood gas analyzer output was checked daily with a standard test sample. During the study period, the SD values were ± 0.5 mmHg for PaO_2, ± 0.4 mmHg for partial pressure of carbon dioxide in arterial blood ($PaCO_2$), and ± 0.008 for potential of hydrogen (pH). 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 three study treatments under supervision, with the order of treatment being randomized. Blood gas analysis was repeated at 15, 30, 60, 120, and 180 min, always in room air. All other 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. In addition, the area between the PaO_2 curve and the baseline value (area under the curve [AUC]) was calculated with the trapezoidal method. The paired t-test and analysis of variance (ANOVA) were used to determine the significance of differences among agents. Statistical significance was accepted at $p<0.05$.

We must highlight that the sample size of our study was not calculated because this was a pilot investigation, at least considering the impact of tiotropium and formoterol on blood gases, but the confidence intervals around the means that represent the plausible range in which the true treatment effect may lie were always reported.[15]

Results

All patients completed the 3-day study. Their baseline values of FEV_1 and PaO_2 were not significantly ($p>0.05$) different among the three treatments both as absolute value and, for FEV_1, also as percent of predicted value.

As expected, all treatments significantly improved FEV_1, FVC, and inspiratory capacity (IC) and decreased specific airway resistance (sRaw) at all time points when compared to the baseline without major differences among the three drugs (Fig. 1). Maximal changes from baseline were always recorded at 120 or at 180 min. FEV_1 improved (%) by 14, 12, and 17; FVC by 12, 12, and 13; IC by 21, 17, and 27; and

Table 1 Demographic data and functional characteristics of patients.

Patient (*n*)	Sex	Age (years)	Smoking history (pack/year)	Basal FEV_1 (% predicted)	Basal FVC (% predicted)	Basal PaO_2 (mmHg)	Basal $PaCO_2$ (mmHg)	Under regular inhaled corticosteroid
1	M	73	Ex-smoker	25	39	67.3	42.4	Yes
2	M	74	Ex-smoker	47	60	81.6	38.9	Yes
3	M	63	Ex-smoker	59	70	72.2	42.5	No
4	M	81	Ex-smoker	44	53	67.8	42.5	Yes
5	M	74	Ex-smoker	55	66	75.6	39.5	No
6	M	75	Ex-smoker	61	69	67.4	46.4	No
7	M	71	Ex-smoker	51	65	79.1	39.4	No
8	M	70	Ex-smoker	67	81	80.2	39.9	No
9	M	77	Ex-smoker	49	61	81.2	41.6	No
10	M	72	Ex-smoker	42	63	75.4	41.8	Yes
11	M	78	Ex-smoker	70	84	75.6	40.6	No
12	M	59	Smoker (100)	50	72	74.3	36.9	No
13	M	61	Ex-smoker	29	52	71.3	39.1	Yes
14	M	72	Ex-smoker	66	90	81.3	39.7	No
15	M	73	Ex-smoker	61	77	76.4	36.1	No
16	M	64	Ex-smoker	44	56	79.4	38.4	No
17	M	70	Ex-smoker	64	73	70.6	34.4	No
18	M	69	Ex-smoker	33	56	65.7	43.3	Yes
19	M	76	Ex-smoker	22	37	71.2	41.9	Yes
20	F	62	Ex-smoker	24	44	69.8	46.2	Yes
21	M	65	Ex-smoker	32	48	67.2	44.1	Yes
22	M	72	Ex-smoker	27	47	74.0	45.4	Yes
23	M	67	Smoker (50)	58	67	78.6	36.4	No
24	M	63	Ex-smoker	64	74	73.9	38.4	No
25	M	72	Smoker (50)	39	52	74.9	41.3	Yes
26	M	74	Smoker (40)	67	89	82.8	36.3	No
27	M	72	Ex-smoker	58	63	65.7	44.2	No
28	M	71	Ex-smoker	44	73	72.3	41.7	Yes
29	F	71	Ex-smoker	31	58	55.2	49.8	Yes
30	M	76	Ex-smoker	43	60	66.9	48.4	Yes

sRaw decreased (%) by 35, 30, and 32 after tiotropium, salmeterol, and formoterol, respectively. Residual volume (RV) decreased (%) by 16, 13, and 21, and thoracic gas volume (TGV) by 12, 10, and 15, after tiotropium, salmeterol, and formoterol, respectively (Fig. 2). All treatments significantly improved (ml/min/mmHg) DLco by 1.6, 1.8, and 1.6 after tiotropium, salmeterol, and formoterol, respectively (Fig. 2).

No significant changes were observed in $PaCO_2$ after the three different treatments (Fig. 3). However, PaO_2 significantly decreased (mmHg) by 1.7, 4.9, and 4.8 (Fig. 3), and alveolar–arterial difference in oxygen tension [$P(A\text{-}a)O_2$] increased (mmHg) by 2.1, 5.0, and 4.5 (Fig. 3) after tiotropium, salmeterol, and formoterol, respectively. The effects of salmeterol and tiotropium on gas exchange tended to be slower in onset and more prolonged than those of formoterol, with a change that was sustained at 180 min. Nevertheless, the $PaO_2AUC_{0-180\,min}$ was greatest for formoterol (−3.59 mmHg/h), next greatest for salmeterol (−2.83 mmHg/h), and least for tiotropium (−1.03 mmHg/h) and the differences among formoterol or salmeterol and tiotropium with respect to $AUC_{0-180\,min}$ values were statistically significant (Fig. 3).

Discussion

The central finding of this pilot study was that all treatments resulted in significant improvement in lung function and significant but small decreases in PaO_2 and increases in $P(A\text{-}a)O_2$, although the impact of tiotropium on PaO_2 and $P(A\text{-}a)O_2$ was smaller than that induced by salmeterol or formoterol. In any case, the average decreases in PaO_2 and increases in $P(A\text{-}a)O_2$ were quite small and of questionable clinical significance. In fact, the average 5 mmHg decrease in PaO_2 from 75 to 70 mmHg that we observed did not affect oxygen saturation and hence was not clinically relevant.

Our data were in agreement with the results of the few studies that have compared the impact of β_2-agonists and anticholinergic agents on blood gases.[14,16–19] All of them, in fact, reported that anticholinergic bronchodilators only induce small and statistically insignificant effects on gas exchange, whereas β-adrenergic agents result in a statistically significant decrease in the PaO_2 despite concomitant bronchodilation.[20]

The transient decrease in PaO_2 with β-adrenergic agents has been attributed to the pulmonary vasodilator action of these agents[21] due to the activation of β-adrenoceptors that

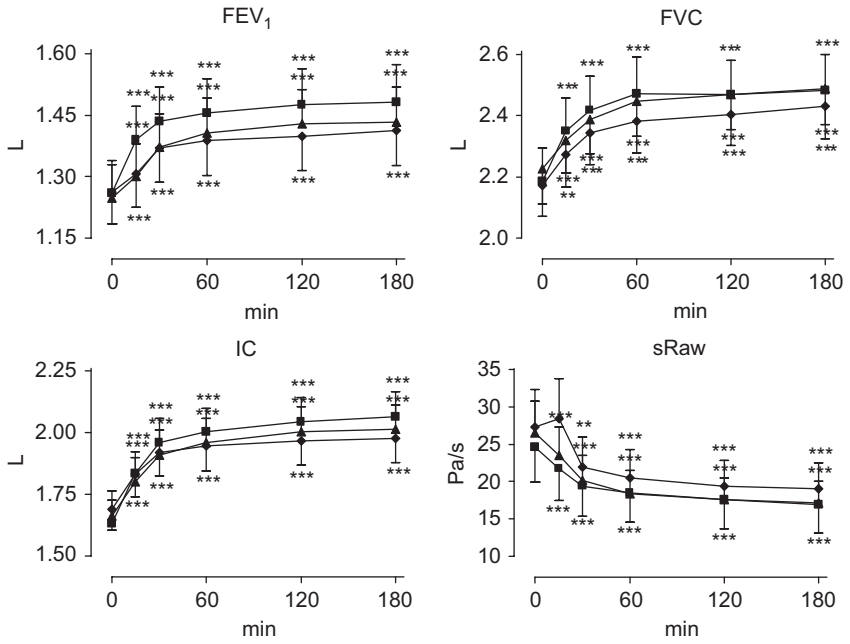

Figure 1 Mean changes (±SE) in FEV_1, FVC, IC, and sRaw with time after administration of formoterol (squares), salmeterol (rhombi), and tiotropium (triangles). $^{**}p<0.01$ and $^{***}p<0.001$ vs. baseline.

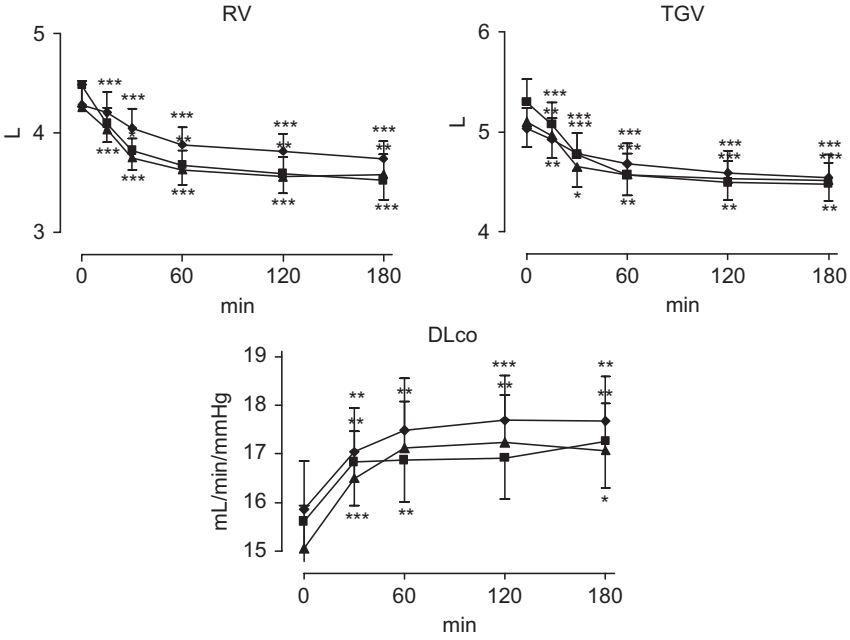

Figure 2 Mean changes (±SE) in RV, TGV, and DLco with time after administration of formoterol (squares), salmeterol (rhombi), and tiotropium (triangles). $^{*}p<0.05$, $^{**}p<0.01$ and $^{***}p<0.001$ vs. baseline.

are present in pulmonary vessels,[22] increasing blood flow to poorly ventilated lung regions and thus increasing ventilation–perfusion (VA/Q) inequality, a shunt-like effect, at least in asthmatic patients.[23,24] The anticholinergic agents act more selectively in bronchial muscle receptors than in myocardium and would be less likely to aggravate the VA/Q disturbance.[25] In effect, compared to adrenergic nerves, the functional significance of cholinergic nerves[26] and the muscarinic receptor subtype(s) involved[27,28] in the regulation of the tone of pulmonary circulation is less clear although, at least in rats, muscarinic M_3 receptor activation is responsible for the pulmonary artery contraction induced by acetylcholine.[29]

It is likely that the small improvement in DLco that we have observed after the inhalation of the three long-acting bronchodilators was related to the diminished pulmonary

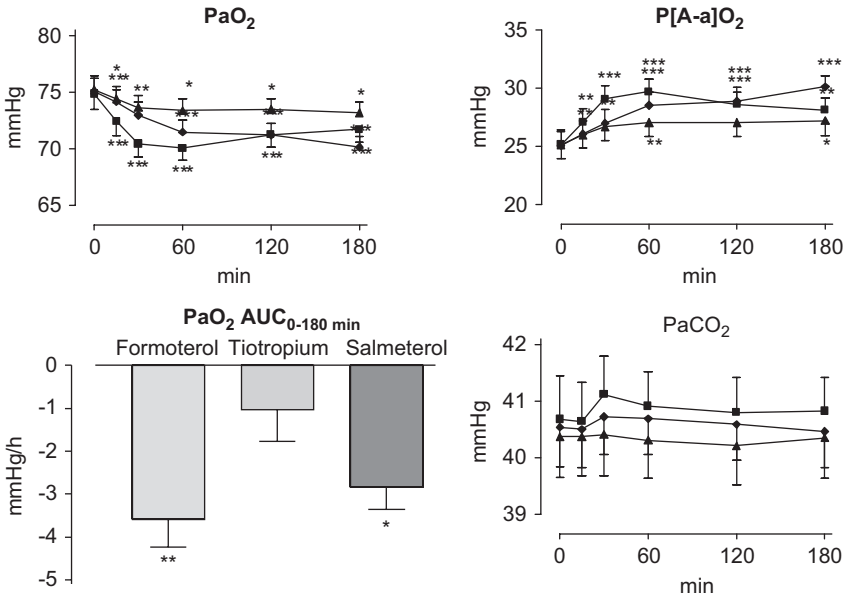

Figure 3 Mean changes ($\pm$SE) in PaO_2, $P(A\text{-}a)O_2$, $PaO_2AUC_{0-180\,min}$, and $PaCO_2$ with time after administration of formoterol (squares), salmeterol (rhombi), and tiotropium (triangles). $^{*}p<0.05$, $^{**}p<0.01$, and $^{***}p<0.001$ vs. baseline, except for $PaO_2AUC_{0-180\,min}$ where $^{*}p<0.05$ and $^{**}p<0.01$ vs. tiotropium.

vascular tone. However, it must be also mentioned that the inter-session variability of DLco in healthy subjects and those with pulmonary disease has been shown to be $\sim$5 ml/min/mmHg over 1 week.[30] In any case, β_2-agonists have been suggested to induce a fall in pulmonary vascular resistance also because of an increase in cardiac output[31,32] and in right ventricular ejection,[32,33] whereas there is no documentation that this is the case for anticholinergic agents.

We must highlight that in our study all patients but one had PaO_2 values greater than 60 mmHg at baseline. This is an important finding because it has been documented that β-agonists cause an increase in VA/Q inequality in patients having PaO_2 values greater than 60 mmHg which results in a moderate fall in the PaO_2, whereas in patients with PaO_2 values less than 60 mmHg, the highest mean sPAP and the poorest spirometric performances demonstrate no significant changes in VA/Q distributions or PaO_2 after β-agonists.[34] It is clear, therefore, that our documentation of drop in PaO_2 after the inhalation of a long-acting bronchodilator cannot be extended to patients with more advanced disease.

In conclusion, in this study, all treatments resulted in significant improvement in lung function and significant but small decreases in PaO_2 and increases in $P(A\text{-}a)O_2$. The mild deterioration of arterial blood gases after long-acting bronchodilators shown in our study indicates a further VA/Q worsening, but also that SaO_2 should not change at all. In any case, tiotropium might be preferable in patients with hypoxemia caused by stable COPD because it seems to carry a smaller risk of worsening systemic hypoxemia.

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