Effect of formoterol/budesonide combination on arterial blood gases in patients with acute exacerbation of COPD

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Received 18 April 2005; accepted 21 April 2005

Summary
Background: Patients with severe chronic airway obstruction might suffer dangerous hypoxemia after administration of a \(\beta\)-agonist despite bronchodilation.
Methods: We first compared the acute effects on gas exchange of two doses of formoterol Turbuhaler (9 and 18 \(\mu\)g) in 10 patients with acute exacerbation of COPD. Afterwards, we compared the acute effects of formoterol Turbuhaler 9 \(\mu\)g with those of formoterol/budesonide combination in a single inhaler (Turbuhaler) 9/320 \(\mu\)g in 10 other patients with acute exacerbation of COPD. Finally, we compared the changes in \(P_{aO_2}\) induced by formoterol Turbuhaler 9 \(\mu\)g or formoterol/budesonide combination in a single inhaler (Turbuhaler) 9/320 \(\mu\)g with those in \(FEV_1\) in 10 other patients with acute exacerbation of COPD. Each agent was given on separate days, and the patients’ arterial blood gases were measured at baseline and at intervals of 120 min.
Results: Small but statistically significant declines in \(P_{aO_2}\) were found after administration of both formoterol 9 and 18 \(\mu\)g. In the second group of patients, formoterol 9 \(\mu\)g alone again induced a significant decrease in \(P_{aO_2}\). However, the simultaneous administration of budesonide 320 \(\mu\)g significantly reduced the acute effect of formoterol on \(P_{aO_2}\). In a third group of 10 patients we confirmed a small but significant decrease in \(P_{aO_2}\) after formoterol alone and the reduction of this effect when budesonide was administered simultaneously. Moreover, we also documented that addition of budesonide amplified the fast onset of action of formoterol.
Conclusions: These results suggest that when treating patients suffering from acute exacerbation of COPD with formoterol, it is prudent to check their arterial blood gases.

KEYWORDS
Formoterol; Budesonide; Acute exacerbation; COPD

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gases. In any case, combined administration of formoterol and budesonide reduces the potential for acute effects of formoterol on blood-gas tensions. © 2009 Elsevier Ltd. All rights reserved.

Introduction

In most patients with acute exacerbations of COPD, there appears to be a component of the worsened airflow obstruction that is particularly responsive to bronchodilators. Therefore, when airway obstruction increases, the therapeutic option is to add a short-acting inhaled $\beta_2$ agonist, for a rapid relief of bronchospasm. Obviously, this bronchodilator should be titrated to maximal effect when possible, monitoring closely for adverse effects of the larger-than-usual doses that are sometimes necessary to relieve airway obstruction.

Recently, we have suggested long-acting $\beta_2$ agonists, formoterol and salmeterol, as potential option in the treatment of acute exacerbations of COPD, although these agents are currently not approved for use in this pathologic condition because they must be intended for maintenance treatment and not immediate symptomatic relief. This opinion was supported by results of several small clinical trials. In particular, in a selected group of patients with mild acute exacerbations of COPD, formoterol via Turbuhaler induced a fast bronchodilation that was dose dependent and not significantly different from that caused by salbutamol. In general, a delivered dose of 18-μg formoterol seemed to induce clinically relevant effect in many patients suffering from acute exacerbation of COPD. Interestingly, formoterol did not induce significant modifications in $SpO_2$ in these patients. However, some subjects presented a decrease in $SpO_2$ under 90%. This finding was not a real surprise because the administration of $\beta$-adrenergic agents to patients with airways obstruction often results in a transient decrease in $PaO_2$ despite concomitant bronchodilation. This has been attributed to the pulmonary vasodilator action of these agents, increasing blood flow to poorly ventilated lung regions and thus increasing ventilation-perfusion inequality, a shunt-like effect.

Since this effect could be potentially dangerous for patients suffering from acute exacerbation of COPD and hypoxemia, we aimed to investigate the acute effects of formoterol inhalation on the arterial blood gas tensions of hospitalized patients with acute exacerbation of COPD. We also investigated the influence of the acute addition of budesonide on the acute effects of formoterol in this type of patients in view of the documented capacity of budesonide to influence the effects of formoterol, and the possibility of treating patients with acute exacerbations of COPD with this inhaled corticosteroid.

Patients and methods

Study population

Thirty patients admitted to our Unit were recruited on the basis of having an exacerbation of COPD requiring hospitalization, an age of more than 50 years, a smoking history of more than 20-pack years, an FEV1 of less than 70% predicted for age and height, a $PaO_2$ of less than 70 mmHg. The presence of a COPD exacerbation was diagnosed when physician observed a sustained worsening of the patient’s condition, from the stable state and beyond normal day-to-day variations, necessitating a change in regular medication in a patient with underlying COPD. Exacerbations were considered severe because patient/physician recognised obvious and/or rapid deterioration in condition, requiring hospitalisation. The exclusion criteria were: personal or family history of asthma, atopy, allergic disease, presence of eosinophilia, use of systemic steroids within the preceding month, presence of severe hypertension, or uncontrolled (or difficult to control) diabetes mellitus, or if a specific cause for the exacerbation, such as pneumonia, pneumothorax, or heart failure, was diagnosed. Patients were also excluded if they were at risk of imminent acute respiratory failure requiring mechanical ventilation or admission to the intensive care unit (pH <7.30 and/or $PaCO_2 > 70$ mmHg, and/or $PaO_2 < 50$ mmHg despite supplemental oxygen). The study was approved by the ethics committee and all patients gave written informed consent.

Study protocol

This was a three-step study. In the first step, 10 patients received formoterol Turbuhaler 9 μg (1 inhalation)+placebo (1 inhalation) or formoterol Turbuhaler 18 μg (2 inhalations) in 2 consecutive days under randomized, cross-over, double-blind
conditions. In the second and third step, 20 other patients (10 for each step) received formoterol Turbuhaler 9 µg (1 inhalation)+placebo (1 inhalation) or formoterol 9 µg+budesonide 320 µg in a single Turbuhaler (2 inhalations of 4.5/160-µg) in 2 consecutive days, always under randomized, crossover, double-blind conditions.

Oral bronchodilators were not permitted during the study. Short-acting inhaled β₂-agonists were permitted soon after each test when required. Due to ethical considerations and the recommendations of current guidelines for the hospital management of exacerbations of COPD, all patients were treated with oral prednisolone 30-mg daily and supplemental oxygen, when required, soon after the end of each session. All patients also received a treatment with an oral antibiotic (co-amoxiclav or levofloxacin). Patients were asked not to consume cola drinks, coffee or tea and not to smoke in the hours before and during the investigation.

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 PaO₂, PaCO₂, and pH with a blood gas analyzer. The machine output was checked daily with a standard test sample. During the study period, the SD values were ±0.6 mmHg for PaO₂, ±0.5 mmHg for PaCO₂, and ±0.011 for pH). Blood gas analysis was repeated at 10, 20, 30, 60, 90, and 120 min, always on room air. In the third group of patients, spirometry was performed at the same time intervals.

The change in PaO₂ after each treatment, from the baseline obtained on that day, was the primary outcome variable. The magnitude of changes in blood-gas tensions and spirometric values at each analysis time was 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

The changes in PaO₂ values following formoterol administration in the first step of the study (Fig. 1) showed a small but statistically significant decrease from baseline after each dose. The magnitude of decline in PaO₂ did not significantly increase with the highest dose, the greatest mean change being −4.0 mmHg (95% CI: −6.7 to −1.3) at 30 min after formoterol 9 µg, and −5.5 mmHg (95% CI: −7.9 to −3.1) at 60 min after formoterol 18 µg. Moreover, at 120 min the magnitude of decline was −2.2 mmHg (95% CI: −5.0 to 0.6) after formoterol 9 µg and −4.0 mmHg (95% CI: −6.8 to −1.2) after formoterol 18 µg. Both formoterol 9 and 18 µg induced a decrease in PaCO₂ (Fig. 1), but the effect was higher (−2.9 mmHg; 95% CI: −5.8 to 0.1, at 60 min) after formoterol 9 µg than (−1.4 mmHg; 95% CI: −3.0 to 0.2, at 10 min) after formoterol 18 µg.

In the second group of patients, formoterol 9 µg alone again induced a significant decrease in PaO₂, with the greatest mean change being −5.3 mmHg (95% CI: −8.9 to −1.7) at 60 min, and a fall of −2.4 mmHg (95% CI: −6.1 to −1.3) at 120 min (Fig. 2). However, the simultaneous administration of budesonide 320 µg significantly reduced the acute effect of formoterol on PaO₂, the greatest mean change being −1.7 mmHg (95% CI: −3.4 to 0.0) at 20 min (Fig. 2). Also, in this group of patients, the administration of formoterol 9 µg induced a decrease in PaCO₂ with a maximum fall (−5.3 mmHg; 95% CI: −9.0 to −1.6) recorded after 20 min (Fig. 2). The inhalation of the fixed
combination formoterol 9 µg/budesonide 320 µg reduced the size of this decrease (−2.1 mmHg; 95% CI: −4.1 to −0.0) at 30 min.

As expected, formoterol 9 µg caused a fall in PaO₂ also in the third group of patients, with a maximum decrease (−5.7 mmHg; 95% CI: −8.5 to −2.9) observed after 60 min (Fig. 3). Again, the simultaneous administration of budesonide 320 µg reduced the acute effect of formoterol on blood-gas tensions. These findings suggest that the use of formoterol in the treatment of acute exacerbations of COPD must always be cautious, but there is room for exploring the use of higher than customary doses of the combination formoterol/budesonide in this pathological condition.

It is not easy to justify why the addition of budesonide can reduce the acute effect of formoterol on blood gases. Increased blood flow to increased ventilated lung regions and, thus, decreased ventilation–perfusion inequality might be a possibility. This explanation is based on the fact that formoterol induces a stimulation of pulmonary vessels in areas that are rapidly opened due to the facilitated broncholytic action of formoterol driven by budesonide. In other words, we are suggesting the opening of vessels in lung areas that are better

Discussion

In this study, formoterol, taken in recommended dosages, resulted in a significant decline in PaO₂ that could be attributed to its pulmonary vasodilator effects mediated via β₂-adrenoceptors on vascular smooth muscle. However, the addition of budesonide reduced the acute effect of formoterol on blood-gas tensions. These findings suggest that the use of formoterol in the treatment of acute exacerbations of COPD must always be cautious, but there is room for exploring the use of higher than customary doses of the combination formoterol/budesonide in this pathological condition.
ventilated due to the more rapid broncholytic activity of the combination formoterol/budesonide when compared to formoterol alone.

Actually, results of the present study have confirmed and enlarged our previous documentation that the addition of budesonide to formoterol amplifies the fast onset of action of formoterol on airways, at least when the two drugs are administered via a single inhaler. In particular, in the present study, we have observed that this action is possible even in patients suffering from acute exacerbation of COPD.

Another possible explanation of the interference of budesonide on the acute effect of formoterol on blood gases is linked to the documented potential of inhaled corticosteroids to exert an acute reduction of bronchial blood flow. Apparently, budesonide is particularly active in reducing airway blood flow. 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: uptake2). This could consequently increase noradrenaline concentration at a-adrenergic receptor sites of the bronchial vascular smooth muscle. The pulmonary vasculature expresses a-adrenoceptors. The stimulation of these receptors induces produces vasoconstriction. This effect might divert blood flow away from poorly ventilated alveoli to the regions that are better ventilated, thereby optimising ventilation/perfusion ratio matching, and maintaining an adequate systemic PaO2.

It is likely that the facilitating action of budesonide was due to a nongenomic effect. In fact, it appeared almost instantaneously, and certainly within a time frame that precluded significant modifications of gene expression. Although many nongenomic effects might also occur over a time scale that might include genomic action, one of the main characteristics supporting a genomic-mediated steroid effect is the prolonged period between the initial application of the agent and the onset of the cellular response. For most steroids, including glucocorticoids, the typical latency time ranges from 30 min to several hours or even days. Recent evidence indicates that corticosteroids can act at the membrane to exert rapid nongenomic effects. The documentation that increased budesonide inhibited allergic reaction within 10 min in guinea pigs sensitised with ovalbumin and challenged with the same antigen given by aerosol, which would preclude genomic-mediated responses that normally takes several hours to occur, is really intriguing. Equally intriguing is the documentation that uptake2 is inhibited by steroid hormones through a nongenomic action.

In conclusion, our results suggest that when treating patients suffering from acute exacerbation of COPD with formoterol, it is prudent to check their arterial blood gases because this bronchodilator can worsen pretreatment hypoxemia. However, combined administration of formoterol and budesonide reduces the potential for acute effects of formoterol on blood-gas tensions. This finding indicates the possibility of exploring the impact of high than customary doses of formoterol/budesonide combination in the treatment of this pathologic condition.

Acknowledgements

This paper was not supported by any Drug Company.

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