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Effects of formoterol and tiotropium bromide on mucus clearance in patients with COPD

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KEYWORDS
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Summary
Background: Lung mucociliary clearance is impaired in patients with chronic obstructive pulmonary disease (COPD). Treatment guidelines recommend that patients with COPD receive maintenance therapy with long-acting beta-agonists and anticholinergic agents.
Methods: Twenty-four patients with mild to moderate COPD received formoterol (12 μg, twice daily from Turbuhaler® dry powder inhaler (DPI)) or tiotropium (18 μg, once daily from Handihaler® DPI) for 14 days. They also received single doses of formoterol, tiotropium, salbutamol (200 μg) and placebo. A radioaerosol technique was used to assess the effects on mucus clearance of 14 days treatment with formoterol or tiotropium, as well as single doses of these drugs.
Results: The 4 h whole lung retention of radioaerosol was significantly higher after 14 days treatment with tiotropium ($P = 0.016$), but not after 14 days treatment with formoterol. However, patients bronchodilated after 14 days treatment with both drugs, so that the deposited radioaerosol may have had an increased distance to travel in order to be cleared by mucociliary action. A single dose of formoterol enhanced radioaerosol clearance significantly compared to other single dose treatments ($P < 0.05$).
Conclusion: Formoterol (12 μg) enhances mucus clearance in patients with mild to moderate COPD when given as a single dose, and may do so when given for 14 days. Studies of longer

Abbreviations: COPD, Chronic obstructive pulmonary disease; FEV_1, Forced expiratory volume in 1 s; FVC, Forced vital capacity; Kr, Krypton; RV, Residual volume; Tc, Technetium.

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duration would be needed in order to assess the effects of the study drugs on mucus clearance when they are used for long-term maintenance therapy.

Introduction

Treatment guidelines recommend that patients with moderate or severe chronic obstructive pulmonary disease (COPD) are given maintenance therapy with long-acting inhaled bronchodilators.[1] Both long-acting beta-agonists (e.g. formoterol and salmeterol) and long-acting anticholinergic agents (e.g. tiotropium bromide) are effective in the management of COPD,[2] and can enhance quality of life.

Mucociliary clearance is a natural lung defence mechanism,[3] which helps to maintain a healthy environment in the lungs. Mucociliary clearance is impaired in COPD patients,[4] especially in the larger more central airways of the lungs.[5] Patients may compensate for ineffective mucociliary clearance of pulmonary secretions by increasing the amount of mucus they clear by cough.[6,7] Bronchodilating drugs may influence mucus clearance,[8,9] but the nature of the effects depend on the type of drug and the length of time for which it is administered. While tertiary ammonium compounds such as atropine may slow mucociliary clearance,[9,10] quaternary ammonium compounds such as ipratropium bromide[11] and tiotropium bromide[12] have been reported not do so. Beta-agonists including fenoterol,[13] salbutamol,[14] and formoterol[15] have been reported to enhance mucus clearance in patients, or to increase ciliary beat frequency in animal models.[16]

The effect of a bronchodilator on mucus clearance may differ according to whether it is given continuously over several weeks, or as a single dose. The objectives of this study were to assess the effect on mucus clearance of (a) treatment for 14 days with either formoterol or tiotropium, and (b) single inhalations of formoterol or tiotropium. The latter assessment used the short-acting beta-agonist salbutamol as a comparator, and placebo as a control. Formoterol and tiotropium were given by dry powder inhalers (DPIs). Mucus clearance was assessed from the retention of inhaled radioaerosol particles in the lungs.

Methods

Study population

Patients with an established clinical diagnosis of COPD, having severities I (mild) or II (moderate) according to the guidelines of the Global Initiative for COPD,[1] were included in the study. All patients had a cigarette smoking history, which was defined by current or previous smoking of more than 10 pack-years. An additional inclusion criterion was the requirement for at least 4 weeks' therapy on a stable medication regimen before the screening visit. All patients gave informed consent in writing, and the study was approved by the local ethics committee and by the federal office for radiation protection in Germany.

Unpublished data from patients with COPD who had inhaled a radioaerosol in order to assess mucus clearance were used to estimate the required number of subjects. These data indicated a mean whole lung retention of radiolabeled particles after 2 h of 82% (standard deviation (SD) 8%). Considering a two-sided, two sample *t*-test, a sample size of 18 subjects was required (alpha = 5%, power = 80%). In order to obtain a balanced sample, 24 subjects were to be investigated.

Study design and treatment

The study was open-label, single-centre, randomised, and cross-over in design. It was designed in order to allow the effects of both 14 days therapy with either formoterol or tiotropium, and single doses of the same drugs, to be determined (Figs. 1 and 2). After the initial screening visit (visit 1) and a 2–7 day run-in period, patients were randomly assigned to receive for 14 days either formoterol (metered dose 12 μg, Oxis®, AstraZeneca) inhaled twice daily via Turbuhaler® DPI, or tiotropium (capsule dose 18 μg, Spiriva®, Boehringer Ingelheim) inhaled once daily via HandiHaler® DPI. Each patient was given two devices, such that patients receiving formoterol also inhaled from a Handihaler containing empty capsules, while patients receiving tiotropium also inhaled from an empty Turbuhaler. After a one week wash-out period, each patient crossed over onto the other active treatment. Mucus clearance was measured using a radioaerosol technique before and after each two week treatment period (visits 2, 3, 4 and 5). The whole lung retention of the radioaerosol after 2 h and 4 h was used as a measure of mucus clearance, in order to assess the effects of the 14 day treatments.

The single dose study involved inhalation of either formoterol (12 μg, Oxis®, AstraZeneca), tiotropium (18 μg, Spiriva®, Boehringer Ingelheim), salbutamol (200 μg, Evohaler®, GlaxoSmithKline) or placebo (empty Handihaler capsules) at visits 2, 3, 4 and 5. Administration of the single doses of drug or placebo took place 4 h after inhalation of the radioaerosol, and was block-randomised across the four visits using a Latin square design (Fig. 2). The whole lung retentions of the radioaerosol after 4 h and 6 h were used as measures of mucus clearance, in order to assess the effects of single dose treatments.

Patients were trained in the correct use the Turbuhaler® for inhalation of formoterol, Handihaler® for inhalation of tiotropium, and pressurised metred dose inhaler (pMDI) for inhalation of salbutamol, according to the manufacturer's instructions.

Permitted concomitant therapy during the study period included short-acting theophylline, oral steroids, and salbutamol. Therapies with long-acting anticholinergic agents (other than the study medication), long-acting beta-agonists (other than the study medication), long-acting theophylline, and inhaled corticosteroids were not permitted for at least 48 h before visit 2, until completion of visit 5. During each 6 h mucus clearance measurement,