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Chronic inhalation of nebulized levalbuterol does not increase mucociliary clearance in healthy subjects

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Abstract

Acute inhalations of β_2-adrenergic receptor agonists increase mucociliary clearance (MCC). Less is known about the effect of long-term inhalations of these agents on MCC, or cough clearance (CC). We hypothesized that chronic inhalations of nebulized levalbuterol, the R-isomer of albuterol, would enhance MCC and/or CC in healthy subjects, compared to albuterol or placebo. This was a randomized, double-blind, placebo-controlled trial in ten healthy, adult subjects who inhaled nebulized levalbuterol (1.25 mg), albuterol (2.5 mg), or placebo for 7 days, three times daily. MCC and CC were measured 6–7 h after the last dose of drug on the 7th day of treatment. These were quantified from gamma camera images of the lungs following inhalation of an aerosol containing the isotope ^{99m}technetium. Levalbuterol did not improve MCC or CC. MCC averaged ($\pm$SD) 12.3$\pm$8.3%, 9.2$\pm$4.7% and 10.0$\pm$9.6% with placebo, albuterol and levalbuterol, respectively. CC averaged 3.9$\pm$6.8%, 4.9$\pm$4.3% and 3.8$\pm$6.4% with placebo, albuterol and levalbuterol, respectively. These results indicate that chronic inhalations of nebulized levalbuterol for 1 week do not increase MCC or CC in healthy subjects, compared to albuterol or placebo.

Keywords: Aerosols; β_2-adrenergic receptor agonists; Mucociliary clearance

1. Introduction

In healthy lungs, inhaled insoluble materials such as bacteria, viruses, antigens, and toxins deposit in the tracheobronchial airway mucus and are removed from the lung in a matter of hours by mucociliary clearance (MCC). When MCC is overwhelmed or impaired, some mucus can be removed by mechanical, or cough clearance (CC). Impairment of MCC typically leads to the accumulation of mucus in the airways, and this in turn is associated with acute infections, chronic bacterial colonization and chronic inflammation [1–3].

Acute doses of inhaled β-adrenergic receptor agonists have been shown to stimulate MCC. For example, several studies in healthy individuals show that MCC is stimulated after inhaling acute doses of terbutaline sulfate [4,5], salbutamol (albuterol) [6], isoproterenol [7–9], isoetharine hydrochloride [8], or fenoterol [10]. Acute doses of inhaled fenoterol [11] and salbutamol [6] and oral doses of terbutaline [12] also enhance MCC in patients with chronic bronchitis. Based on these results, clinicians often instruct their patients with airway disease to inhale a β-adrenergic receptor agonist several times a day, thinking this therapeutic approach will not only improve lung function, but will also improve MCC throughout the day.

Nevertheless, it is unclear if long-term treatment with a β-adrenergic receptor agonist several times a day improves the removal of mucus. The few studies of the effect of chronic, multiple administrations of these drugs on MCC have produced mixed results. Two studies showed no significant difference in MCC after 1 week of daily, multiple treatments with inhaled or oral terbutaline, compared to placebo, in patients with chronic bronchitis [13,14] and Perry and Smaldone [9] found no increase in MCC in healthy subjects after 1 week of daily, inhalations of albuterol, compared to placebo. In contrast, oral doses of both fenoterol and tulobuterol resulted in a significant improvement in MCC after 1 week of chronic, multiple treatments, in patients with chronic bronchitis [15].

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The racemic form of albuterol has been available for years and contains two optical isomers: levo (R) and dextro (S). Analysis of these two isomers indicates that the S-isomer lacks significant β_2-adrenergic receptor affinity and it is thought that this binding is necessary to stimulate MCC [16]. If this is the case, one might speculate that drug containing only the R-isomer would stimulate MCC to a greater extent than drug containing the S-isomer as well. This hypothesis is supported by *in vitro* data reported by Frohock and colleagues [17]. They quantified ciliary beat frequency, an integral part of MCC, in single ovine airway epithelial cells that were exposed to racemic albuterol, the R-isomer alone, or the S-isomer alone. Results from that study demonstrated that the R-isomer had a greater stimulatory effect on ciliary beat frequency than either racemic albuterol, or the S-isomer alone. This was despite the same amount of R-isomer being present in both the racemic form and the single-isomer form [17]. The hypothesis is also supported by results from another study of mucociliary transport in a calf trachea model, which showed that the R-isomer is a log more potent than its racemate in terms of increasing mucociliary transport velocity (Y. Schwartz, Sepracor, unpublished data).

Another study reported that the S-isomer has a 12-fold slower rate of metabolism compared to the R-isomer, leading to a longer retention time in the lung [18]. This difference in retention may not be important with acute inhalations, but could lead to desensitization to the racemate with daily, multiple dosing and desensitization could be one explanation for the lack of stimulation observed when racemic albuterol was administered four times daily for a week to healthy subjects [9].

Since levalbuterol, the R-isomer of albuterol, is now available for inhalation, we decided to repeat the study by Perry and Smaldone [9] with levalbuterol, hypothesizing that chronic, multiple inhalations of nebulized levalbuterol would stimulate MCC and/or CC to a greater extent than either racemic albuterol, or placebo.

2. Material and methods

2.1. Study subjects

Ten non-smoking, healthy males and non-pregnant females, $\geqslant$18 years of age completed the protocol. A sample size of ten healthy subjects was calculated to provide 80% or greater power to detect a change in MCC of 12% between visits, if the standard deviation (SD) for the change in MCC between visits was 10% or less. In addition, a previous study in our laboratory in lung transplant patients indicated that significant improvement in MCC could be detected in a sample as small as seven individuals, following an acute inhalation of 180 μg racemic albuterol by metered dose inhaler [19]. Based on these results and our power calculation, we reasoned that a sample size of ten healthy subjects should be sufficient to detect significant differences in MCC following chronic administration of the more potent R-isomer of albuterol. Altogether 14 patients enrolled in the study. However, four patients did not complete the study for personal reasons.

Although patients with asthma, or chronic obstructive pulmonary disease (COPD), are the target population for this drug, these patients are likely to have damaged epithelial cells, due to the inflammation associated with the disease process, and that damage could mask the inherent effects of the drug on MCC. To eliminate this possibility, we decided to quantify the MCC response in healthy subjects. All subjects gave informed, signed consent, as approved by the Johns Hopkins School of Medicine Institutional Review Board.

2.2. Study design

This was a randomized, double-blind, placebo-controlled trial. The CONSORT guidelines [20] were followed (ClinicalTrials.govIdentifier: NCT00325767). There was one screening visit and three study visits. Prior to each study visit, subjects were treated with one of three study drugs for 7 days. There was a washout period (no drug) of at least 1 week after treatment weeks 1 and 2. The primary outcomes of MCC and CC were quantified on the 7th day of each treatment week.

2.3. Distribution of study drug

Blinded stocks of albuterol, levalbuterol and placebo were supplied by Sepracor, Inc. (Waterford, MA) and distributed to subjects in coded containers by Johns Hopkins Research Pharmacy personnel. The order of drug administration was also randomized by our research pharmacy, which used the Block Stratified Randomization (version 5.0) computer program. The pseudorandom number generator was a linear congruential algorithm of Park and Miller with Bays-Durham shuffling.

2.4. Drug doses

Subjects were instructed to inhale aerosol three times daily for 7 days. Each dose of placebo aerosol consisted of 3 ml of drug vehicle. The dose of racemic albuterol was 2.5 mg/3 ml, which is the standard clinical dose that is routinely administered to patients with asthma to relieve their bronchospasm. The dose of levalbuterol was 1.25 mg/3 ml, which is also a standard clinical dose. In a previous study of daily, multiple administrations in patients with asthma, this dose was well-tolerated and resulted in clinically significant increases in pulmonary function measurements up to 8 h after the last dose of drug was administered [21].

2.5. Drug administration

Aerosolized drug was generated by an LC Plus nebulizer (PARI Respiratory Equipment, Inc., Midlothian, VA)