The Effects of an Inhaled β_2-Adrenergic Agonist on Lower Esophageal Function*

A Dose-Response Study

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Study objectives: **Albuterol, a β_2-adrenergic agonist that is commonly used to treat asthma, reduces bronchial smooth muscle tone. The pharmacodynamics of inhaled albuterol on esophageal function were studied in healthy volunteers.**

Design: **A prospective, randomized, placebo-controlled, double-blind crossover design.**

Setting: **An academic medical center.**

Patients: **Nine healthy volunteers (five men, four women; age, 22 to 30 years).**

Interventions: **Albuterol (2.5 to 10 mg) or placebo was given via nebulizer. Volunteers were studied at two sessions, 1 week apart, using a 6-cm manometry assembly and a low-compliance pneumohydraulic pump. The percentage of lower esophageal sphincter (LES) relaxation, the frequency of transient LES relaxations (TLESRs), and the amplitude, duration, and propagation velocity of esophageal contractions were measured at 5 and 10 cm above the LES. Dependent measures were evaluated using two-way, repeated-measures analysis of variance.**

Measurements and results: **Albuterol therapy reduced LES basal tone in a dose-dependent manner (baseline, 17.0 ± 2.6 mm Hg; at 10 mg, 8.9 ± 2.1 mm Hg; $p = 0.01$). The frequency of TLESRs was not different from placebo (not significant). Albuterol reduced the amplitude of esophageal contractions at 5 cm above the LES (baseline, 72.5 ± 18.6 mm Hg; at 10 mg, 48.8 ± 10.0 mm Hg; $p < 0.05$). A significant reduction in esophageal body contractile amplitudes was noted at 10 cm ($F[1,6] = 7.05$; $p < 0.05$).**

Conclusions: **Inhaled albuterol reduced LES basal tone and contractile amplitudes in the smooth muscle esophageal body in a dose-dependent manner. Inhaled β_2-agonists may increase the likelihood of acid reflux in a subset of patients who receive cumulative dosing.**

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Key words: albuterol; asthma; β_2-agonists; esophagus; gastroesophageal reflux; lower esophageal sphincter; transient lower esophageal sphincter relaxations;

Abbreviations: bpm = beats per minute; GER = gastroesophageal reflux; LES = lower esophageal sphincter; LESP = lower esophageal sphincter pressure; TLESR = transient lower esophageal sphincter relaxation; PEF = peak expiratory flow

More than 15 million people in the United States have asthma. A report[1] in 1992 indicated that both the prevalence and severity of asthma may be increasing. Gastroesophageal reflux (GER) disease is a common problem that affects > 20% of the US population on a weekly basis.[2] Osler[3] was one of the first investigators to comment on the association between these two common conditions when he recommended that patients should "... learn to take their daily meal at noon in order to avoid nighttime asthma. ..." Over the last decade, a number of published studies have clarified the relationship between GER and asthma. For example, GER is exceedingly common in patients with asthma. Two studies[4,5] have shown that 77 to 82% of patients with asthma experience GER. In addition, endoscopic examinations of asthmatic patients revealed that 39 to 50% had esophagitis.[6,7] Several studies[5,8] also have shown that GER is not only a precipitating factor in the development of asthma, but that it can worsen ongoing asthma as well.

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Standard pharmacologic agents used in the treatment of asthma include the use of inhaled bronchodilators, inhaled steroids, theophylline, cromolyn sodium, and oral steroids.[1] β_2-adrenergic agonists relax bronchial smooth muscle and relieve symptoms of bronchoconstriction. There is, however, some evidence that these agents reduce lower esophageal sphincter (LES) tone.[9] A reduction in LES tone increases the likelihood that GER will occur. Data on the effects of oral β_2-agonist therapy on LES tone are both limited and contradictory. DiMarino and Cohen[10] demonstrated that an oral dose of the β_2-agonist carbuterol produced a decline in LES tone in healthy volunteers. Their study, however, was limited by the fact that a placebo group was not incorporated into the study. Michoud and coworkers[11] used salbutamol in a placebo-controlled trial to study the effect of this agent on LES tone in 10 healthy volunteers and in 8 patients with asthma. They found that resting LES pressure (LESP) was lower in patients with asthma than in healthy volunteers but that salbutamol had no effect on LESP.

Inhaled β_2-adrenergic agonists, such as albuterol, are more commonly used to treat asthma than are oral agents, although their effect on esophageal function has not been clearly established. Sontag et al[4] previously demonstrated that asthmatic patients have reduced LESPs, greater esophageal acid exposure times, more frequent reflux episodes, and longer esophageal clearance times than control subjects. Twenty-four-hour ambulatory pH probes did not show that bronchodilator use led to an increase in acid reflux. However, esophageal manometry was not performed after bronchodilator use, and LESPs were not measured. The one published study[12] that directly measured the effects of inhaled albuterol found that esophageal motility and LESP were not affected.

The studies published to date do not fully answer the question of whether inhaled β_2-agonists adversely influence LESP for a number of reasons. One, the dose of albuterol used in the study by Schindlbeck et al[12] was quite low, only 1.25 mg total. Most patients treated with an albuterol nebulizer receive 2.5 mg in a single dose. Two, the pharmacodynamics of cumulative dosing of β_2-adrenergic agonists may greatly differ from that of a single dose. This is important to ascertain because self-dosing may result in increased levels of a drug, which then affects esophageal function. This is especially relevant clinically because multiple doses of albuterol often are utilized in emergency situations during acute asthma attacks. Due to the limitations of these studies, we studied the effects of multiple doses of a β_2-adrenergic agonist on esophageal function in healthy volunteers. More specifically, this study was carried out to determine whether the β_2-adrenergic agonist albuterol would exert direct, dose-dependent, cumulative pharmacodynamic influences on lower esophageal smooth muscle function in healthy volunteers.

Materials and Methods

A prospective, randomized, double-blind, placebo-controlled crossover design was used to evaluate the effects of increasing doses of inhaled albuterol (Glaxo-Wellcome; Research Triangle Park, NC), 2.5 to 10 mg, or placebo on LES tone, the percentage of LES relaxation, and the frequency of transient LES relaxations (TLESRs). The amplitude, duration, and propagation velocity of esophageal contractions at 5 and 10 cm above the LES also were measured. Esophageal manometry was completed in nine healthy, asymptomatic volunteers (five men and four women; ages, 22 to 30 years) using a 6-cm, miniaturized manometry assembly (Dentsleeve; Wayville, Australia) and a low-compliance pneumohydraulic pump. Volunteers were randomized to the albuterol group or the placebo group for the first session and then were crossed over to the opposite group for the second session 1 week later. All volunteers received instructions on the use of the nebulizer prior to participating in the study, and a physician investigator conducted all treatments. Following insertion of the esophageal manometry catheter, baseline recordings were obtained for 1 h in order to allow accommodation to occur. Albuterol, 2.5 mg, was dissolved in normal saline solution and then was administered to volunteers via a nebulizer (Vixone model 0209, Westmed; Tucson, AZ) for >10 min. Volunteers were monitored throughout the nebulizer treatment, and nebulizers were checked during the study to ensure that the entire dose was inhaled. A second treatment was given 20 min after the end of the first treatment, for a cumulative dose of 5.0 mg albuterol delivered. A third nebulizer treatment (cumulative dose, 7.5 mg) and then a fourth nebulizer treatment (cumulative dose, 10 mg) each were given 20 min after the end of the preceding treatment. Heart rate and BP were recorded after each dose of medication. Normal saline solution alone was given as a placebo by the same technique in an identical stepwise manner in a separate counterbalanced session.

Esophageal Manometry

Lower esophageal function was measured using a miniaturized manometry catheter (Dentsleeve) with radial, perfused side ports arranged longitudinally 5 cm apart with a 6-cm sleeve positioned on the distal end (outer diameter, 2.5 mm). The individual lumen of the catheter was connected to a low-compliance, pneumohydraulic perfusion system (Mui Scientific; Toronto, Canada) via external pressure transducers and was perfused with water at a rate of 0.5 mL per channel per minute. Fasted patients were studied in a semi-recumbent position reclined to approximately 65° from vertical. Following nasogastric intubation, the LES was identified by station pull-through in 0.5-cm increments. At the pressure inversion point, each pressure sensor was repositioned to maximize abdominal respiratory deflection and the distance from the nare recorded. The sleeve was positioned within the LES with recording ports at 5, 10, and 15 cm above the LES. The catheter was fixed at the nare with tape for the remainder of the study. Each patient then received five 5-mL water swallows beginning at 20 min and at 50 min during the baseline period, and at the end of each 20-min dosing period.

Statistical Analysis

Results are expressed as mean ± SE. Dependent measures were evaluated using two-way, repeated-measures analysis of variance (dose × drug) and the Tukey honestly significant difference *post hoc* pairwise comparisons.

Results

As illustrated in Figure 1, albuterol inhalation produced a dose-dependent reduction in LES basal tone from 17.0 ± 2.6 mm Hg at baseline to 8.9 ± 2.1 mm Hg at the maximum cumulative dose of 10 mg ($F[4,32] = 3.91$; $p = 0.01$) compared to placebo. Reductions in LESP were noted beginning at the cumulative dose of 7.5 mg total ($p = 0.02$) and were maintained through the 10-mg cumulative dose ($p = 0.02$). The frequency of TLESRs decreased from 2.2 ± 1.1 to 1.6 ± 1.8/h but did not reach statistical significance compared to placebo ($p > 0.05$).

A significant effect for dose was noted for the amplitude of esophageal contractions at 5 cm above the LES ($F[4,32] = 6.09$; $p = 0.001$). Albuterol reduced the amplitude of esophageal contractions in a dose-proportional manner. Contractile amplitudes decreased from 72.5 ± 18.6 mm Hg at baseline to 48.8 ± 10.0 mm Hg at the 10-mg cumulative dose. Contractile amplitudes during placebo administration remained essentially unchanged (Fig 2). Significant reductions from placebo were noted beginning with the cumulative dose of 5 mg ($p = 0.04$) and persisted through the higher doses, with reductions in contractile amplitudes noted with the administration of the 7.5-mg cumulative dose ($p = 0.02$) and the 10-mg cumulative dose ($p = 0.01$).

A main effect for trial also was seen for contractile amplitudes at 10 cm ($F[1,6] = 7.05$; $p < 0.05$) above the LES. The amplitude of contractions in the esophageal body decreased over the duration of the trial for both placebo and albuterol, but no significant differences emerged between the two.

The duration of primary esophageal contractions and the propagation velocity were not significantly influenced by albuterol inhalation at any dose tested. Mean contractile duration at 5 cm above the LES decreased from 4.24 ± 0.28 s at baseline to 3.73 ± 0.20 s at the maximum dose tested, although there were no significant differences between the treatment group and the placebo group.

The mean resting heart rate was 65.4 ± 2.4 beats/min (bpm) for the placebo group at the start of the test session and 63.1 ± 2.8 bpm at the end of the session (not significant). The mean resting heart rate for the albuterol group was 65.2 ± 2.8 bpm at the start of the session and 88.6 ± 5.7 bpm after the fourth dose of albuterol (*ie*, the 10-mg cumulative dose; $p = 0.001$). The mean systolic BP for the placebo group was 107.3 ± 4.6 mm Hg at the start of the session, and 104.7 ± 5.3 mm Hg at the end of the session (not significant). The mean systolic BP for the albuterol group was 116.8 ± 5.5 mm Hg at the start of the session and 128.0 ± 6.2 mm Hg at the end of the session. The mean systolic BP was significantly increased in the treatment group compared to the placebo group ($p < 0.05$). All nine patients tolerated

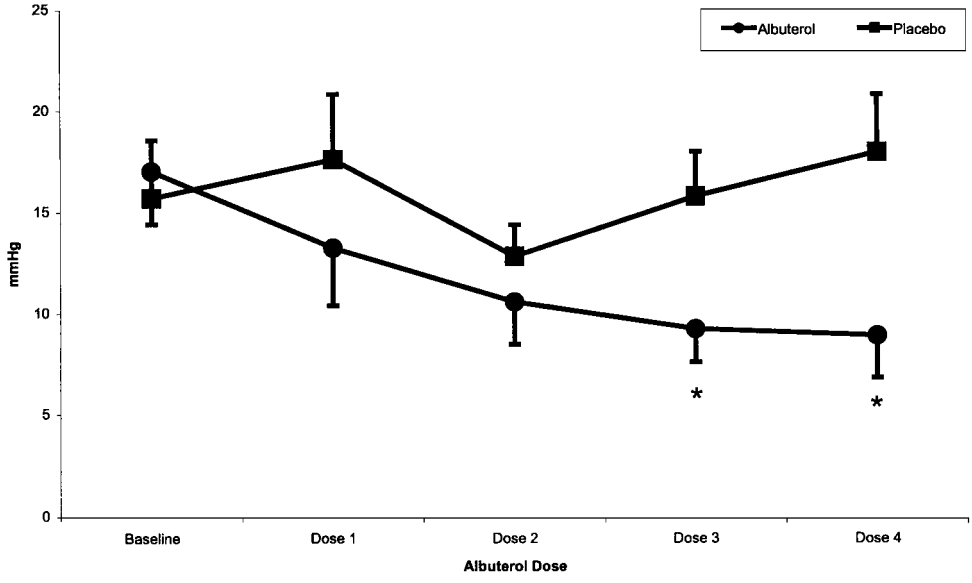

Figure 1. Albuterol inhalation produces a dose-dependent reduction in LES basal tone. Reductions in LES basal tone were statistically significant ($p = 0.02$) at cumulative dose 3 (*ie*, 7.5 mg total) and cumulative dose 4 (*ie*, 10.0 mg total). Error bars represent SE.

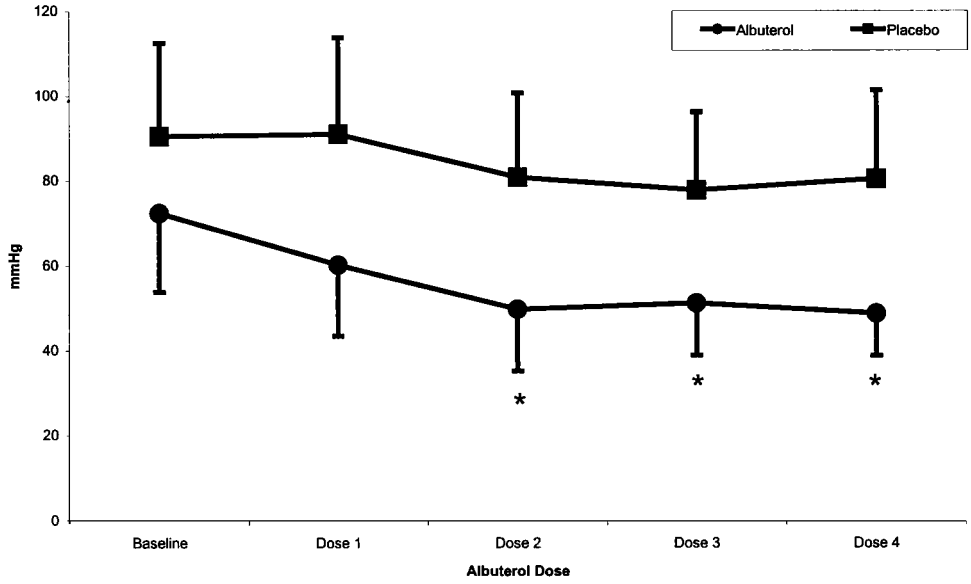

FIGURE 2. Albuterol inhalation reduces contractile amplitudes in the esophageal body, 5 cm above the LES. Reductions were significant at a cumulative dose of 5 mg ($p = 0.04$), a cumulative dose of 7.5 mg ($p = 0.02$), and a cumulative dose 10 mg ($p = 0.01$) compared to placebo. Error bars represent SE.

both trials well. One volunteer had a brief episode of palpitations, which resolved spontaneously after being treated with albuterol.

DISCUSSION

Asthma is a common problem in the United States. It affects approximately 4 to 5% of the US population.[1] Standard outpatient therapy involves the use of inhaled β_2-agonists, inhaled steroids, cromolyn sodium, theophylline, and oral steroids. GER is known to play a significant role in the development and persistence of asthma and is a critical factor in patients with difficult-to-control asthma.[8]

The primary pathophysiologic mechanisms proposed to account for GER are reduced tonic pressures in the LES, frequent TLESRs, and impaired esophageal peristalsis.[13] Patients with asthma have been shown to have lower LES tone than control subjects, in addition to decreased acid clearance time and increased acid exposure.[4] The precise mechanism by which GER induces asthma is widely debated, however, commonly accepted theories include microaspiration of acid into the bronchial tree, an esophagobronchial reflex that produces bronchoconstriction when stimulated, and reflux-induced bronchial hyperreactivity.

Microaspiration of acid from the distal esophagus into the bronchial tree has been reported to produce bronchoconstriction and a reduction in peak expiratory flow (PEF).[14,15] However, other studies using scintigraphy and pharyngeal pH studies have failed to demonstrate this event consistently. For example, Harding and colleagues[16] infused small amounts of acid into the mid-esophagus while monitoring upper and lower esophageal pH and checking spirometry and airway resistance after acid infusion. No significant changes in pulmonary function were noted, which led the authors to believe that microaspiration, leading to bronchoconstriction and reduction in PEF, was not occurring at significant levels. Standard 24-h pH monitoring failed to reveal significant abnormalities of proximal esophageal pH in these patients. To assist researchers in determining the role of microaspiration in pulmonary diseases, new techniques have been proposed to evaluate upper esophageal, pharyngeal, and tracheal acidification for the assessment of these patients.[15,17,18]

Vagovagal reflexes also have been proposed as the primary mechanism responsible for symptoms in this population. The bronchial tree and the esophagus are derived from common embryonic precursors and, as such, are both innervated by the vagus nerve. Acid infused into the distal esophagus causes reflex bronchoconstriction.[19] Intraesophageal acid infusion resulted in a decline in PEF in the absence of microaspiration.[20] Hamamoto and colleagues[21] have reported that local axonal reflexes involving sensory pathways and tachykinin-mediated plasma extravasation of the airways may be responsible for bronchospasm secondary to esophageal acidification. Asth-

matic patients have been shown to have evidence of autonomic dysfunction, and this heightened vagal tone may contribute to an abnormal airway response to acidification of the esophagus.[22] Finally, a recurrent cycle of reflux and bronchoconstriction may exist in many asthma patients.

Reflux of gastric acid can lead to bronchoconstriction and reduced PEF, as described previously. Bronchoconstriction may subsequently induce further acid reflux by increasing airway resistance and decreasing intrathoracic pressures during inspiration. These changes result in an increased gastroesophageal pressure gradient, thus making reflux more likely.

Patients with asthma that is unresponsive to conventional therapy often note an improvement in symptoms if treated for GER. A 4-week course of twice-daily ranitidine improved symptoms in some patients,[23] while a 6-month course of cimetidine (300 mg four times daily) was significantly better than placebo in relieving symptoms.[24] The most significant improvements have occurred with the use of proton pump inhibitors. Meier et al[7] demonstrated that 27% of patients with GER and asthma had a $> 20\%$ improvement in FEV_1 after 6 weeks of treatment with omeprazole. Harding and colleagues[25] found that 73% of patients with asthma and GER had an improvement in symptoms or PEF after 3 months of proton pump inhibitor therapy. Twenty-seven percent of those who responded required > 20 mg omeprazole per day to relieve symptoms or to improve PEF.

Several studies have also shown that antireflux surgery can lead to an improvement in asthma symptoms. Sontag et al[26] demonstrated that in 13 adults with asthma, 6 experienced a cessation of wheezing, 6 noted an improvement in wheezing after antireflux surgery, and 1 patient did not improve. Perrin-Fayolle et al[27] studied 44 patients with asthma who had undergone antireflux surgery an average of 7.9 years earlier. After surgery, 11 patients (25%) noted a total resolution of asthma symptoms, 7 patients (16%) noted marked improvement, and 11 patients (25%) noted moderate improvement. Fifteen patients (34%) failed to report improvement in symptoms following antireflux surgery. Larrain and colleagues[24] reported on the long-term outcomes of 81 patients with adult-onset asthma who were randomized and treated with placebo, cimetidine, or antireflux surgery. Six years after the initial trial, 11 patients (50%) in the surgery group were free of symptoms, while only 1 patient (5%) in the placebo group remained free of symptoms. These studies all support the premise that the treatment of GER in asthmatic patients may improve respiratory function in some patients.

One theoretical concern in the past has been that medications commonly used to treat asthma might actually exacerbate or adversely influence the patient by further decreasing LES tone. If true, this could lead to a vicious cycle, whereby the treatment for an asthma flare (*ie*, nebulized albuterol) might actually increase the severity or the duration of the asthma flare. Oral theophylline has been shown to decrease LES tone in some studies.[28,29] The effects of inhaled β_2-agonists on LES function are less clear. Sontag et al[4] reported that the use of inhaled β_2-agonists did not increase acid reflux, as measured by a 24-h pH probe, while Schindlbeck et al[12] found that low-dose albuterol therapy did not reduce LESP. These studies are incomplete, however, because a low dose of β_2-agonist was used in one study,[12] while the effects of additional or sequential doses of a β_2-agonist on LESP were not measured in the other study.[4]

β_2-Agonists are commonly used to relax bronchial smooth muscle and to treat asthma. One study[10] has demonstrated that oral β_2-agonist therapy decreases LES tone. These compounds, therefore, may contribute to GER and may exacerbate asthma symptoms in susceptible patients. This also may be true with inhalers, as it is well known that a significant portion of an inhaled dose of medication is actually swallowed.

We hypothesized that the β_2-adrenergic agonist albuterol would exert direct pharmacodynamic influences on lower esophageal function, but that the effects might occur in a dose-dependent manner. In support of this hypothesis, we have shown that inhaled albuterol therapy reduced LES basal tone and contractile amplitudes in the smooth muscle esophageal body in a dose-dependent manner. Thus, when administered in higher doses or in frequent sequential doses, β_2-agonists may increase the likelihood of GER and, thus, may increase esophageal acidification in susceptible patients. This could lead to further bronchoconstriction and persistence of asthmatic symptoms. The reduction of LESP may be a critically important step in the persistence of GER, especially when coupled with the ineffective esophageal motility already present in asthmatic patients, and in patients with persistent GER disease, in general.[4,30] Increased esophageal acidification may subsequently contribute to symptoms of asthma under certain treatment conditions. This might commonly occur in the emergency department, where patients with asthma flares are treated aggressively with nebulizers, or at home, when patients with a flare of their asthma are known to self-medicate with frequent doses of their β_2-agonist inhaler.

The current study evaluated the pharmacodynamics of an inhaled β_2-agonist on lower esophageal function in healthy volunteers. Patients with hyper-

sensitive or hyperactive smooth muscle may respond differently to these compounds. Further physiologic studies are needed to evaluate the effects of these agents on patients with asthma and GER.

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