Salmeterol Administration by Metered-Dose Inhaler Alone vs Metered-Dose Inhaler Plus Valved Holding Chamber*

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Study objective: To determine whether a spacer device designed as a valved holding chamber with a flow signal increases the efficacy of the long-acting β₂-agonist, salmeterol, in patients who use incorrect technique with metered-dose inhaler (MDI) alone.

Design: Double-blind, randomized, placebo-controlled study.

Setting: University hospital outpatient rooms.

Patients: Twenty adult outpatients with stable persistent asthma, receiving a daily anti-inflammatory drug.

Interventions: Patients were randomized to either salmeterol MDI (incorrect use: 1 s after actuating MDI, inhale rapidly) and placebo plus spacer (correct use: inhale slowly as MDI is actuated, continue to inhale slowly and deeply) or placebo MDI (incorrect use) and salmeterol plus spacer (correct use). The following week, patients received the opposite treatment. The dose was two puffs from each device on each treatment day; each puff was separated by 1 min.

Measurements and results: After baseline peak expiratory flow (PEF), salmeterol was administered and serial PEF determined (0.5, 1, 2, 3, 4, 6, 8, 10, and 12 h). Administration of salmeterol MDI plus spacer resulted in significantly greater increases in PEF from baseline vs MDI at 4 h (44 L/min vs 10 L/min; p < 0.01) and 6 h (49 L/min vs 24 L/min; p < 0.05). Both methods of administration were equally well tolerated.

Conclusion: We conclude that patients who have poor timing and rapid inhalation with salmeterol MDI alone will have greater increases in PEF at 4 h and 6 h and no additional side effects if the dose is administered with a valved holding chamber that is used correctly. Further study is needed regarding other errors in MDI technique with salmeterol.

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Key words: asthma; metered-dose inhaler; salmeterol; spacer device

Abbreviations: MDI = metered-dose inhaler; PEF = peak expiratory flow; VHC = valved holding chamber

Salmeterol is the first long-acting inhaled β₂-agonist available in the United States with at least a 12-h duration of action. Salmeterol is indicated for the long-term maintenance treatment of asthma, especially nocturnal asthma, as well as prevention of exercise-induced asthma. Compared with albuterol, salmeterol is associated with better control of asthma as measured by peak expiratory flow (PEF) rate, fewer nocturnal awakenings because of asthma symptoms, and a reduced need for supplemental albuterol. Long-acting inhaled β₂-agonists have a prominent place in the National Institutes of Health guidelines for the long-term management of asthma in patients who do not have optimal control with anti-inflammatory agents. Salmeterol metered-dose inhaler (MDI) product literature specifies that safety and efficacy of spacer devices with salmeterol MDI have not been adequately studied. Numerous trials have demonstrated that a large percentage of patients make errors in using MDI, and evaluations of health professionals reveal similar difficulties. Studies have shown that spacer devices provide at least equivalent efficacy in patients with optimal MDI.
Our review of the literature shows no studies comparing salmeterol MDI alone with salmeterol MDI plus a delivery-enhancement or spacer device. This study was an initial step toward demonstrating safety and efficacy of using a spacer device (AeroChamber [Monaghan Medical; Plattsburgh, NY] valved holding chamber [VHC]) with salmeterol MDI. Because use of salmeterol MDI without a spacer is clearly established as being highly efficacious in patients with correct MDI technique, our aim was to evaluate efficacy of salmeterol with a spacer device in patients with incorrect use of MDI.

**Materials and Methods**

**Patients**

Twenty adults (≥ 18 years old) with persistent asthma, per National Institutes of Health criteria, who were receiving maintenance anti-inflammatory therapy were enrolled in this double-blind, randomized, placebo-controlled study. Patients were recruited from prior asthma studies conducted by the investigators and from the university pulmonary medicine clinic. All patients were clinically stable (PEF ≥ 80% of personal best, daily albuterol requirements ≤ 3 times daily, and no severe exacerbations in the 2 weeks before study). History of asthma severity ranged from mildly persistent to severe persistent. Exclusion criteria included chronic bronchitis or emphysema, pregnancy, substance abuse, or inability to use MDI incorrectly per study requirements or to use MDI-AeroChamber VHC correctly.

**Study Design**

After giving written informed consent for this Institutional Review Board-approved study, baseline physical examination, spirometry, ECG, and blood chemistry were performed. On the study days, patients withheld any “as needed” albuterol for 6 h before beginning the study. Patients who were already receiving salmeterol therapy on study enrollment were allowed to continue their usual q12h dosing, inasmuch as tolerance has not been associated with the bronchodilator effect of salmeterol.

Patients were randomized to single-dose salmeterol (two puffs, each puff separated by 1 min) at 8:00 AM with two different inhalation techniques that were separated by 1 week. Patients inhaled two puffs from each device on each treatment day. The two inhalation techniques were (1) salmeterol MDI alone (incorrect inhalation technique; poor timing and rapid inhalation) and matching placebo via AeroChamber VHC (correctly performed); and (2) placebo MDI alone (incorrect as above) and salmeterol MDI via AeroChamber VHC (performed correctly). Poor timing was defined as waiting 1 s after pressing down on the MDI before inhaling. Rapid inhalation was defined as inhaling with the MDI alone at a rate similar to, but faster than, the rate required to activate the AeroChamber flow signal. Other steps with MDI alone were performed correctly. Patients used closed mouth technique similar to that described by Newman et al.27 (shake well, exhale slowly and steadily, place between lips, press down one time and inhale deeply, then hold breath for 10 s). Correct technique with AeroChamber VHC was similar to that defined by the manufacturer’s instructions (shake well and remove caps, place MDI in AeroChamber VHC, exhale slowly and steadily, press down one time at start of a slow, deep inhalation, then hold breath for 10 s). Although verbal instruction of correct and incorrect techniques was provided, demonstrations of these techniques were emphasized, and patients were carefully observed by an investigator during each maneuver.

PEF was determined at baseline, 0.5, 1, 2, 3, 4, 6, 8, 10, and 12 h after both treatments. Symptoms of asthma and possible side effects were also recorded. PEF was performed according to the manufacturer’s instructions (TruZone Peak Flow Meter; Monaghan Medical), consistent with American Thoracic Society guidelines.28 Patients were coached vigorously during the PEF maneuvers by the investigators (eg, fill lungs completely, tight seal with your lips, blast!), and care was taken to avoid the “spitting maneuver” (ie, peak flowmeter placed well into the mouth on top of the tongue).29 The best of three PEF attempts was recorded for data analysis. Before and 3 h after both treatments, a 12-lead ECG was performed. Heart rate was recorded at baseline, 2, 4, 8, and 12 h.

**Statistical Analysis**

PEF and heart rate data, as well as these values expressed as percent change from baseline, were analyzed by repeated analysis of variance. Patients were nested within order, both of which effects were cross-classified with technique and hour. After being tested for significance, the nonsignificant interaction effects of order with technique, order with hour, and order with technique and hour were pooled with the residual term. The pooled within and between patient error term was used as the estimated variance in the denominator of F tests for previously planned contrasts involving each technique and hour.30 All contrasts were previously planned at a significance level of 0.05. PEF was expressed in two ways, in liters per minute and as percent change from baseline. For PEF as percent change from baseline, the number of degrees of freedom for the subplot was 17; for each technique, nine nonorthogonal contrasts were made between the mean percent change at a particular time to the null value of zero. For PEF expressed in liters per minute, the number of degrees of freedom for the subplot was 19; a total of 10 nonorthogonal contrasts were made between the means for the two techniques at the various times. For heart rate, the number of degrees of freedom for the subplot was nine; for each technique, a total of four nonorthogonal contrasts were made between the mean value at a particular time and that at the baseline. If any change from baseline was statistically significant for PEF or heart rate, previously planned contrasts were made between the techniques.

**Results**

A total of 20 patients were enrolled and completed the study. The characteristics of the patients are summarized in Table 1. On the study days in which salmeterol MDI plus spacer and salmeterol MDI alone were used, the mean (± SD) baseline values for PEF were 443 ± 80 L/min and 441 ± 88 L/min, respectively. For salmeterol MDI plus spacer device, PEF expressed as percent change significantly differed from baseline at all times from 2 h through 10 h. In contrast, for salmeterol MDI alone, percent changes in PEF were significant at 3, 6, 8, and 10 h.
With MDI alone, there was a mean decrease of 21 L/min in PEF at 4 h compared with that at 3 h (Fig 1).

Figure 1 shows the mean PEF (in liters per minute) values for 12 h after breathing salmeterol MDI plus spacer device vs salmeterol MDI alone. Administration of salmeterol MDI plus spacer resulted in significantly greater increases in PEF from baseline vs MDI at 4 h (44 L/min vs 10 L/min; \( p < 0.01 \)) and 6 h (49 L/min vs 24 L/min; \( p < 0.05 \)). There were no significant differences at the other times.

On the study days in which salmeterol MDI plus spacer and salmeterol MDI alone were used, the mean (± SD) baseline values for heart rate were 79 ± 11 beats/min and 78 ± 11 beats/min, respectively. There were no ECG changes associated with salmeterol administration by either administration technique. On the day the spacer device was used, two patients had heart rates of 108 beats/min at 12 h after the salmeterol dose, yet at 2 h and 4 h (near peak effect), the heart rates for these two patients were ≤ 88 beats/min. Only one patient reported very slight, transient nervousness and fine hand tremor 2 h after the salmeterol dose on both study days.

**Discussion**

Delivery enhancement devices (ie, spacers) have been advocated for 20 years for patients who have difficulty using MDI alone. These devices have been demonstrated to increase efficacy of short-acting \( \beta_2 \)-agonists in patients with poor inhalation technique.\(^{23-26}\) In a pediatric study,\(^{24}\) errors in 6 of 20 patients included shallow inhalation and failure to breath-hold (2 patients), no inhalation after pressing down on albuterol MDI (1 patient), and actuation of MDI near the end of inhalation (3 patients). In these six patients, the AeroChamber VHC and two other delivery enhancement devices (InspirEase; Schering Key; Kenilworth, NJ; and an aerosol bag) improved pulmonary function significantly compared with MDI alone. In another pediatric study\(^{25}\) adding a spacer (750-mL collapsible tube) to a terbutaline MDI resulted in better PEF in 12 patients. Most of the patients “were unable to use the inhaler in a proper way.” Bloomfield and Crompton\(^{23}\) found that the efficacy of terbutaline administered to adults via a spacer device was not significantly different from that of an MDI used correctly. However, if patients delayed inhaling 2 s after actuating the MDI, the spacer use resulted in greater efficacy. In another adult study,\(^{26}\) it was reported that patients who are “unable to use a pressurized aerosol efficiently” will achieve greater improvement in pulmonary function using terbutaline with a tube spacer vs an MDI alone. Although most clinical evaluations of spacer devices have found that the response to short-acting \( \beta_2 \)-agonists is equivalent to that achieved with correctly performed MDI technique,\(^{15-23}\) one pediatric study found that the MDI plus a 750-mL spacer was superior to correct use of MDI alone.\(^{31}\) One adult study of primarily chronic bronchitis patients also showed that a spacer device provided a better response to a short-acting \( \beta_2 \)-agonist.\(^{32}\)

Spacer devices reduce the need for excellent hand-lung coordination. In addition, spacer devices

### Table 1—Characteristics of Patients*

<table>
<thead>
<tr>
<th>Variables</th>
<th>Data</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>3/17</td>
</tr>
<tr>
<td>Mean age (range), yr</td>
<td>38.7 (22–67)</td>
</tr>
<tr>
<td>Childhood onset asthma/adult onset</td>
<td>12/8</td>
</tr>
<tr>
<td>History of allergic rhinitis</td>
<td>11</td>
</tr>
<tr>
<td>History of GERD</td>
<td>1</td>
</tr>
<tr>
<td>Smoking history</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>17</td>
</tr>
<tr>
<td>Former</td>
<td>31</td>
</tr>
<tr>
<td>Baseline PEF (range), L/min†</td>
<td>442 ± 83 (300–680)</td>
</tr>
<tr>
<td>Baseline HR, beats/min‡</td>
<td>78 ± 11</td>
</tr>
<tr>
<td>Asthma medications</td>
<td></td>
</tr>
<tr>
<td>Inhaled corticosteroids</td>
<td>19</td>
</tr>
<tr>
<td>Leukotriene receptor antagonist</td>
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<tr>
<td>Salmeterol</td>
<td>4</td>
</tr>
<tr>
<td>Theophylline</td>
<td>1</td>
</tr>
</tbody>
</table>

*\( n = 20 \). Data are presented as No. unless otherwise indicated; GERD = gastroesophageal reflux disease; HR = heart rate.
†Three former smokers quit in their 20s.
‡Mean ± SD.

\[^{23}\]^{23}\) \[^{24}\]^{24}\) \[^{25}\]^{25}\) \[^{26}\]^{26}\)
(eg, AeroChamber VHC) that assist patients in achieving slow inspiratory flow rates (ie, device whistles if rate is fast) are helpful. Slow inspiratory flow of < 30 L/min is preferred. Slow inspiratory flow rate enhances efficacy of short-acting \( \beta_2 \)-agonists and cromolyn by reducing impact in the oropharynx and deposition in large central airways, while increasing homogenous deposition in the lung. It is pertinent to note that spacers are also well documented to enhance efficacy of inhaled corticosteroids.

To our knowledge, there have been no clinical trials that have evaluated spacer devices with salmeterol. Because spacer devices are helpful in patients who have poor inhalation technique with short-acting \( \beta_2 \)-agonists, it is logical that the same will be true for long-acting agents. Results of our study suggest that AeroChamber VHC used properly does provide enhanced efficacy of salmeterol in patients who have poor timing and inhale rapidly. On the basis of errors described in other studies, we strongly suspect our PEF results would have shown significance at several more points if we had exaggerated the errors with the MDI alone. For example, if patients had waited 2 s or 3 s (vs 1 s) after actuating the inhaler, greater differences could be anticipated.

Our study included correct inhalation technique with AeroChamber VHC, including coordination of release of the drug and inhalation. It is pertinent to note that delay between pressing down on the MDI and initiating slow inhalation has been evaluated with some spacer devices. With a 1-s delay, there was a marked reduction in available drug with an open tube spacer (82% decrease) vs a VHC (AeroChamber, 38% decrease). Further study could address the response (eg, PEF) to long-acting or short-acting \( \beta_2 \)-agonists when a 1-s delay is used with the AeroChamber. When using large spacer devices (eg, 750 mL), a delay of 1 to 5 s does not appear to significantly reduce response to short-acting \( \beta_2 \)-agonists.

A strength of our study was its design as a double-blind, randomized, placebo-controlled, crossover trial. All patients had well-controlled, persistent asthma and were receiving anti-inflammatory agents on study entry. A study limitation is that PEF is effort dependent, and air leakage can occur around the mouthpiece. As previously mentioned, investigators carefully observed each PEF maneuver and coached patients to help assure good technique. The reason for the mean percentage drop in PEF at 4 h in the MDI alone group was not readily apparent to us.

Regarding other potential errors, if patients had a shallow (vs deep) inhalation or did not breath-hold for 10 s, results would likely be even more in favor of the spacer device. Further studies could help answer these questions. Results from our study suggest that there are no differences in adverse effects with salmeterol MDI alone compared with MDI plus spacer device, including cardiovascular response. For patients who have difficulty using the salmeterol MDI alone correctly, adding a spacer device to the MDI is recommended.

**Conclusion**

We conclude that patients who have poor timing and rapid inhalation with salmeterol MDI alone will have greater increases in PEF at 4 h and 6 h and no additional side effects if the dose is administered with a VHC that is used correctly. Further study is needed regarding other errors in MDI technique with salmeterol.

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