A Comparison of Responses to Albuterol Delivered by Two Aerosol Devices*

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Nineteen outpatients with stable obstructive pulmonary disease (mean forced expiratory volume in one second [FEV1], 1.00 ± 0.10 L) were evaluated for airway response to albuterol (salbutamol) administered by metered-dose inhaler and Bosch ultrasonic nebulizer (BUSN). Albuterol administered by metered-dose inhaler but not by nebulizer caused a significant increase in FEV1, and the mean forced expiratory flow over the middle half of the forced vital capacity (FEF25-75%) (p < 0.02). Absolute increase from baseline of FEV1 and FEF25-75% was significantly greater for metered-dose inhaler (0.21 ± 0.05 L; 0.32 ± 0.13 L/sec) compared to ultrasonic nebulizer (0.07 ± 0.03 L; 0.05 ± 0.04 L/sec) (p < 0.02). In 11 subjects (mean FEV1, 1.06 ± 0.14 L), the placebo effect of inhalation of the diluent from the metered-dose inhaler (Freon) and the ultrasonic nebulizer (isotonic saline solution) was determined. Freon produced the mean increase of 1.5 percent, whereas the ultrasonic aerosol of isotonic saline solution resulted in a mean decrease of 8 percent in FEV1. Therefore, the inferior response to albuterol administered by ultrasonic nebulizer was at least in part due to the superimposed bronchoconstriction occurring with ultrasonically administered saline solution. The metered-dose inhaler was more effective than the ultrasonic nebulizer for administration of albuterol in stable obstructive pulmonary disease, and the latter device is not recommended. A specific ultrasonic nebulizer should be prescribed only if its superiority to a metered-dose inhaler can be objectively documented.

The efficacy of bronchodilator drugs administered by metered-dose inhalers depends on adherence to proper technique. Alternate devices for delivery, including spacers and ultrasonic and air-compressor nebulizers, have been proposed for use in ambulatory patients. These devices are being prescribed for patients who either have difficulty in using a metered-dose inhaler or have inadequate control by standard therapy, including bronchodilators administered by metered-dose inhaler.

In this study, we compared the bronchodilator response to albuterol (salbutamol) delivered by metered-dose inhaler and ultrasonic nebulizer in subjects with moderately severe stable obstructive pulmonary disease.

Materials and Methods

Subjects

Nineteen outpatients (13 male and six female subjects; mean age, 61 years) with stable obstructive pulmonary disease were studied. Six were asthmatic, and 13 had chronic obstructive pulmonary disease (COPD) (criteria of American Thoracic Society). Twelve were taking theophylline, nine ipratropium, eight inhaled steroids, and seven oral steroids. All subjects had been taking oral or inhaled β-adrenergic agonists. The baseline value for forced vital capacity (FVC) was 1.58 ± 0.11 L (± SE), for forced expiratory volume in one second (FEV1) was 1.00 ± 0.10 L (45 percent of predicted), and for the mean forced expiratory flow over the middle half of the FVC (FEF25-75%) was 0.62 ± 0.10 L/sec. No subject had previously used an ultrasonic or air-compressor nebulizer. Subjects abstained from bronchodilator therapy for eight hours prior to study. Oral steroids were administered as usual. Informed consent was obtained from each patient.

Experimental Protocol

The two regimens tested were 200μg of albuterol (Ventolin) in two puffs by metered-dose inhaler and 2.5 mg of albuterol in 1.5 ml of isotonic saline solution by ultrasonic nebulizer (Bosch Halomed model S). The nebulizer's output was 1.4 ± 0.3 ml/min (± SD) when 5 ml of solution was nebulized by continuous flow for two minutes. The mass median diameter was 7.5μ. Using tidal breathing, the patients inhaled the solution nebulized during inspiration via a face mask.

On the first day, spirometric testing was done in triplicate from a recording spirometer (Vitalograph model S). The FVC, FEV1, and FEF25-75% were measured from the best spirogram (sum of FEV1, plus FVC). The subjects then inhaled albuterol from a metered-dose inhaler using the closed-mouth technique with a ten-second breathhold. Spirometry was repeated 30 minutes later.

All subjects then underwent a two-week trial at home with the ultrasonic nebulizer administering albuterol four times daily. On day 14, spirometry was repeated before and after inhalation of albuterol by nebulizer. Patients evaluated the 14-day trial of the ultrasonic nebulizer by comparing it with their previous experience with the metered-dose inhaler.

Responders

Subjects with an increase in FEV1 of 15 percent or more 30 minutes after albuterol delivered by either metered-dose inhaler or ultrasonic nebulizer were considered to be responders. Subjects were classified as responders to metered-dose inhaler, as responders to ultrasonic nebulizer, or as nonresponders.

Placebo Effect

Eleven subjects who volunteered to undergo further testing (eight

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392 Responses to Albuterol by Aerosol Devices (Olivenstein et al)

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Table 1—Data on Pulmonary Function (19 Subjects)*

<table>
<thead>
<tr>
<th>Data</th>
<th>Metered-Dose Inhaler</th>
<th>Ultrasonic Nebulizer</th>
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<tbody>
<tr>
<td></td>
<td>Before Albuterol</td>
<td>After Albuterol</td>
</tr>
<tr>
<td>FVC, L</td>
<td>1.62±0.13</td>
<td>1.82±0.22</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>1.00±0.10</td>
<td>1.21±0.12‡</td>
</tr>
<tr>
<td>FEF25-75%, L/sec</td>
<td>0.66±0.08</td>
<td>0.98±0.18‡</td>
</tr>
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</table>

*Mean ± SE.
†Significantly different from prebronchodilator values.
‡Absolute increase from prebronchodilator values significantly different from ultrasonic nebulizer.

male and three female subjects) were reevaluated to determine the placebo effect of aerosol by metered-dose inhaler and ultrasonic nebulizer. A Freon propellant (two puffs) or isotonic saline solution (2.0 ml) was administered in a randomized crossover single-blind fashion on two separate days at the same time of day. Data obtained after placebo were compared to those obtained previously in these 11 subjects before and after administration of albuterol.

Statistical Analysis
The paired t-test was used to evaluate the significance of differences between observations.

RESULTS
There was no significant difference before the bronchodilator drug on the two testing days (Table 1). After the bronchodilator drug, only the metered-dose inhaler produced significant increases in FEV₁ and FEF25-75% (p <0.02). Furthermore, the absolute change from prebronchodilator values of FEV₁ and FEF25-75% was significantly greater for the metered-dose inhaler compared to the ultrasonic nebulizer (p <0.02).

![Figure 1](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21538/)

**Figure 1.** Identity plot of percentage of change in FEV₁ from baseline values after inhaled albuterol in 19 subjects. Each point represents data from single subject. Only four subjects had greater percentage of change in FEV₁ with ultrasonic nebulizer (BUSN) compared to metered-dose inhaler (MDI).

![Figure 2](http://journal.publications.chestnet.org/pdfaccess.ashx?url=/data/journals/chest/21538/)

**Figure 2.** Responses (FEV₁≥15 percent from baseline values) to albuterol by metered-dose inhaler (MDI) and ultrasonic nebulizer (BUSN). Fourteen subjects were responders, and five subjects were nonresponders. Three subjects were responders to both metered-dose inhaler and ultrasonic nebulizer. Only one subject responded to nebulizer and not to metered-dose inhaler.

An identity plot of the percentage of change in FEV₁ after administration of albuterol by metered-dose inhaler and ultrasonic nebulizer is shown in Figure 1. Greater bronchodilation occurred in most patients after using the metered-dose inhaler. Only four patients (21 percent) had a better response to the ultrasonic nebulizer.

Fourteen subjects (74 percent) were responders to albuterol (Fig 2). Thirteen subjects were responders to the metered-dose inhalers, and only one subject was a responder to the ultrasonic nebulizer without responding to the metered-dose inhaler.

Baseline FEV₁ in 11 subjects evaluated for the placebo effect of aerosol delivery was 1.08±0.14 L (± SE) for the metered-dose inhaler and 1.16±0.16 L for the ultrasonic nebulizer. These values did not differ significantly from those of the group as a whole on albuterol testing days. In these patients, albuterol administered by metered-dose inhaler, but not by nebulizer had significantly increased FEV₁ (0.19±0.07 vs 0.05±0.04 L) (p <0.05) (Table 2). The reduction in FEV₁ after saline solution by ultrasonic nebulizer was almost twice as great as that seen after Freon (0.07±0.05 vs 0.04±0.06), but this difference did not reach statistical significance. Expressed as percent change, the effect of the saline solution was even more pronounced.

Table 2—Change in FEV₁ from Baseline

<table>
<thead>
<tr>
<th>Data</th>
<th>Albuterol</th>
<th>Placebo</th>
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<tbody>
<tr>
<td>Metered-dose inhaler</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in FEV₁, L</td>
<td>0.19±0.07*</td>
<td>-0.04±0.06</td>
</tr>
<tr>
<td>Change in FEV₁, percent</td>
<td>17.1±6.4</td>
<td>1.5±4.7</td>
</tr>
<tr>
<td>Ultrasonic nebulizer</td>
<td></td>
<td></td>
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<tr>
<td>Change in FEV₁, L</td>
<td>0.05±0.04</td>
<td>-0.07±0.05</td>
</tr>
<tr>
<td>Change in FEV₁, percent</td>
<td>3.2±3.3</td>
<td>-8.0±4.7</td>
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*p <0.05.
There was a 12:4 preference for the metered-dose inhaler over the ultrasonic nebulizer, while three subjects rated both equally. Ten subjects (53 percent) found the nebulizer inconvenient due to its lack of portability in pocket or purse. Seven subjects (37 percent) experienced minor side effects with the ultrasonic nebulizer, including facial irritation (two subjects), bad taste (two subjects), and cheilosis (two subjects).

**DISCUSSION**

In this study, the metered-dose inhaler was more effective than the ultrasonic nebulizer for delivery of albuterol. Furthermore, those patients whose condition was refractory to bronchodilator administered by metered-dose inhaler did not improve with the ultrasonic nebulizer. The difference in response to the metered-dose inhaler and ultrasonic nebulizer may have been at least partially due to bronchoconstriction after inhaling ultrasonic saline particles.

The clinical setting in which a nebulizer should replace the metered-dose inhaler remains controversial. The metered-dose inhaler is more convenient, portable, and inexpensive than the ultrasonic nebulizer. Moreover, aerosol delivery by nebulizer is unpredictable and depends on the technique of delivery.

The dose of albuterol used with the ultrasonic nebulizer was much larger than that present in the metered-dose inhaler. This factor may account for the marginal advantage demonstrated in some studies using an air-compressor nebulizer. Although pulmonary deposition was not measured, the superiority of the metered-dose inhaler in our study may reflect greater penetration of aerosol with this device.

We evaluated subjects with reversible and irreversible airway obstruction. Of 13 subjects with COPD, seven demonstrated reversibility of obstruction with β-adrenergic agonists delivered by metered-dose inhaler. The remaining six with COPD were unresponsive to albuterol by metered-dose inhaler. Only one of these patients was considerably improved by the ultrasonic nebulizer.

Our results contrast with those of Wilson and Connellan, who demonstrated an improved airway response to nebulized albuterol in patients with severe COPD unresponsive to traditional doses of bronchodilators administered by metered-dose inhaler. This may be due to the smaller dose of albuterol used in our study (2.5 vs 5.0 mg) or due to the different type of nebulizer employed.

The lesser efficacy of the ultrasonic nebulizer may be explained in several ways. The airway response to aerosols can be influenced by aerosol output, particle size, and breathing pattern. Low output by the nebulizer results in decreased deposition of aerosol particles in the lungs. The output of our ultrasonic nebulizer compares favorably with other models of conventional and ultrasonic nebulizers.

The most efficient size of aerosol droplet for pulmonary deposition is 1µ to 4µ. Only approximately 50 percent of the aerosol droplets produced by the specific ultrasonic nebulizer (Bosch Halomed) are less than 4µ. This figure compares somewhat unfavorably with other nebulizers. Presumably, the number of particles penetrating into the lungs would be reduced using this particular model, but the clinical consequence is difficult to predict. Ryan et al showed that the nebulizer’s output and inspiratory time altered the bronchial response to inhaled methacholine, while the influence of particle size was less apparent.

The inspiratory flow rates used by our patients were not measured. It is unlikely that our patients with severe obstruction exceeded the inspiratory flow of 1 L/sec required for optimal deposition of aerosol.

During the two-week trial at home, our subjects received a greater dose of albuterol by the ultrasonic nebulizer than they had previously been inhaling from the metered-dose inhaler (2.5 vs 0.2 mg four times daily). Short-term tachyphylaxis to this greater dose of albuterol could possibly account for the poorer bronchodilator response to the ultrasonic nebulizer immediately following the domiciliary trial; however, several studies have not confirmed significant tolerance to long-term or short-term administration of β-adrenergic agonists. We therefore do not believe that tachyphylaxis was an important factor in our study.

Ultrasonically generated isotonic saline solution produced greater bronchoconstriction in our subjects than Freon propellant administered by metered-dose inhaler. Therefore, albuterol-induced bronchodilation may have been masked by an accompanying bronchoconstriction induced by the ultrasonic saline particles. This constrictor effect may be due to ultrasonically generated particles, isotonic saline solution, or a combination of both. The net effect of aerosol administration of albuterol by the ultrasonic nebulizer is only slight bronchodilation.

Proper instruction in the use and maintenance of home nebulizers is necessary, as the procedure involves several maneuvers, including dispensing the correct amount of solution into a reservoir and assembling the nebulizer’s components. These considerations might be of practical importance in the population of patients in whom use of a nebulizer is often considered, ie, the elderly, children, and patients with difficulty in coordinating administration by a metered-dose inhaler.

We conclude that the metered-dose inhaler was more effective than the ultrasonic nebulizer as a technique for delivery of albuterol in patients with stable, moderately severe obstructive pulmonary dis-
ease. The ultrasonic nebulizer was ineffective even in patients preselected by their inability to use a metered-dose inhaler or poor control of obstructive pulmonary disease using conventional medication including a metered-dose inhaler. The ultrasonic nebulizer is therefore unsuitable for use in patients with obstructive pulmonary disease. Although other ultrasonic nebulizers may be used, they are not necessarily superior to a metered-dose inhaler, and a particular model should be prescribed only if its efficacy can be confirmed objectively.

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