Salbutamol Treatment of Acute Severe Asthma in the ED: MDI Versus Hand-Held Nebulizer


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The objectives of this study were to compare the efficacy of salbutamol delivered by either metered-dose inhaler plus spacer (MDI-spacer) or by wet nebulization (NEB), and to determine the relationships between physiologic responses and plasma salbutamol concentrations. Asthmatic patients presenting to the emergency department (ED) with acute severe asthma (forced expiratory volume in the first second [FEV1] less than 50% of predicted) were enrolled in a randomized, double-blind, parallel-group study. The MDI-spacer group received salbutamol, delivered via MDI into a spacer device, in four puffs actuated in rapid succession at 10-minute intervals (2.4 mg/h). The NEB group was treated with nebulized salbutamol, 1.5 mg, via nebulizer at 15-minute intervals (6 mg/h). Doses were calculated on the basis of the percentage of total dose that reaches the lower airway with both methods. The protocol involved 3 hours of this treatment. Mean peak expiratory flow rate (PEFR) and FEV1 improved significantly over baseline values for both groups \( P = .01 \). However, there were no significant differences between both groups for PEFR and FEV1 at any point studied. The examination of the relationships between cumulative dose of salbutamol and change in FEV1 showed a significant linear relationship \( P = .01 \) for both methods (MDI \( r = .97 \); NEB \( r = .97 \)). The regression equations showed that for every 1 mg of salbutamol by MDI-spacer, 2.5 mg are needed from nebulization to have equal therapeutic response. At the end of treatment, the salbutamol plasma levels were 10.1 ± 1.6 ng/ml for the MDI-spacer group and 14.4 ± 2.3 ng/ml for the NEB group \( P = .0003 \). Both groups showed a nonsignificant heart rate decrease. A significant group-by-time interaction means that differences between groups increased with time \( P = .04 \). Additionally, the NEB group presented a higher incidence of tremor \( P = .03 \) and anxiety \( P = .04 \), reflecting larger systemic absorption of salbutamol. These data indicate that when doses used are calculated on the basis of the percentage of total drug that reaches the lower airway, there was equivalent bronchodilatation after salbutamol administered by either MDI-spacer or nebulization in patients with acute severe asthma. However, nebulizer therapy produced greater side effects related to the increase in salbutamol absorption and higher plasma level.
Key Words:

Acute severe asthma treatment
metered-dose inhaler
nebulizer.

Beta-agonist bronchodilator aerosols are the treatment of choice for patients with acute asthma presenting to the emergency department (ED). Numerous studies have compared the bronchodilator efficacy of beta-agonist aerosols inhaled from metered-dose inhalers (MDI) or jet nebulizers. Although there have been conflicting reports, recent evidence suggests that there is little difference between both forms of acute asthma treatment and that an MDI with a spacer (MDI-spacer), used in an aggressive manner, provides equal bronchodilatation and relief of symptoms with no increase in side effects. However, this kind of research is notoriously difficult to conduct and interpret because of the unpredictability of delivery systems and because the optimal dose of beta-agonist has not been established.

The dose of beta-agonist, therefore, is empiric at best and should be based on therapeutic response and side effects rather than on the weight or size of patients. There is evidence that patients respond to increasing doses of beta-agonists. The cumulative technique produces greater bronchodilation than an equivalent single large dose aerosolized. However, no studies comparing plasma concentrations of beta-adrenergic agents delivered by MDI or by nebulization have been published.

The objectives of this study were (1) to compare the efficacy of salbutamol delivered by jet nebulizer with that of salbutamol delivered by MDI-spacer and (2) to determine the relationships between physiologic responses and plasma salbutamol concentrations.

METHODS

Patients

Twenty-two patients with acute exacerbations of asthma who were treated at the ED of a large tertiary-care hospital in Montevideo, Uruguay, were enrolled in this trial. All patients met the American Thoracic Society's criteria for the diagnosis of asthma. The inclusion criteria for patients were: (1) age between 18 and 50 years; (2) a forced expiratory volume in the first second (FEV₁) and a peak expiratory flow rate (PEFR) below 50% of predicted value; (3) no history of chronic cough, cardiac, hepatic, renal, or other medical disease, or pregnancy; and (4) an expressed willingness to participate in the study, with written informed consent obtained. The study was approved by the Hospital Ethics Committee.

Treatment Protocol

Patients were assigned by random number allocation to one of two treatment groups. Patients in the first group (MDI-spacer group, n = 11) were given salbutamol delivered by an MDI into a spacer device (Volumatic; Allen & Hanburys Ltd, Greenford, United Kingdom) in 4 puffs at 10-minute intervals (100 µg per actuation). The mass median aerodynamic diameter (MMAD) of MDI salbutamol has been determined to be 2.4 ± 0.3 mum. The Volumatic spacer is a pear-shaped extension tube of 750 mL volume and 22 cm length with one-way inhalation valve. Each puff was followed by two deep inhalations from the spacer. Patients in the second group (NEB group, n = 11) were treated with nebulized salbutamol 0.3 mL (1.5 mg) diluted in 4 mL of normal saline solution via a jet nebulizer (Hudson "T" Up-Draft, Cat No. 1720; Hudson Respiratory Care Inc, Temecula, CA) powered by compressed air at a flow rate of 8 L/min at 15-minute intervals. The nebulization time was approximately 10 minutes and nebulization was terminated when no solution was visible in the reservoir. The MMAD of the particles generated by the nebulizer was 3.2 mm (data obtained from the manufacturer). The protocol involved 3 hours of this treatment (MDI-spacer group 1,200 µg or NEB group 3 mg each 30 minutes). After this time, all patients with poor response received 500 mg hydrocortisone intravenously, in accord with our ED acute
severe asthma current treatment protocol, [22] [23] [24] to avoid a possible interaction effect. Although it is known that parenteral corticosteroids improve pulmonary function after 6 to 12 hours of treatment, [23] Lin et al [26] have shown that the administration of parenteral corticosteroids has a possible early beneficial effect on FEV1 and PEFR, especially in those patients who have received steroids before treatment. Intravenous aminophylline and oxygen treatment were excluded in all patients. In accord with the Ethics Committee recommendations, our protocol included the administration of oxygen if SaO2 decreased to less than 90%; however, during the study, all patients had SaO2 values above 90%. Potassium was not administered.

The drugs were administered in a double-blind manner. As placebo, the patients in the MDI-spacer group received 4 mL of normal saline solution via a Hudson "T" Up-Draft nebulizer driven by compressed air at a flow of 8 L/min at 15-minute intervals. On the other hand, patients in the NEB group received four puffs from an identical MDI that contained only propellant at 10-minute intervals. Treatments were administered by ED physicians who were not involved in the study.

Salbutamol Dosage

Doses were calculated on the basis of the percentage of total dose that reaches the lower airway with both methods. With MDI and spacer, the dose that reaches the lungs ranges from 15% to 20% of the total dose. [27] [28] [29] Jet nebulizers, however, deposit only between 8% and 10% of the total dose. [29] We administered 24 puffs per hour, or 2.4 mg. Assuming a 15% to 20% rate of deposition in the lungs, the total delivery of salbutamol to the lungs would be between 360 mug/h and 480 mug/h. Based on these data, a salbutamol dose of 6 mg/h via nebulizer was considered approximately equivalent to 2.4 mg/h via MDI (2.5:1 dose ratio). Assuming an 8% to 10% rate of lung deposition, the total lung delivery of salbutamol via nebulizer would be between 480 mug/h and 600 mug/h. The reference dose used to calculate NEB dose was 2.4 mg/h via MDI because this dose has been shown previously to produce satisfactory bronchodilation, low serum concentration, and minimal extrapulmonary effects. On the contrary, an increase of 50% of the dose (3.6 mg/h) produces a slightly better therapeutic response but greater side effects related to higher salbutamol serum levels. [12]

Measurements

The following variables were measured in each patient immediately before starting treatment and in 30-minute intervals until 3 hours after presentation. FEV1, PEFR, heart rate, QTc interval, and arterial oxygen saturation (SaO2). Additionally, serum potassium and salbutamol levels were obtained at baseline and at the end of protocol treatment. Before treatment, serum theophylline concentration was determined in all subjects. PEFR was measured with a mini-Wright peak flow meter (Armstrong Industries, Inc, Northbrook, IL). The highest of three values was recorded. FEV1 was measured using a Vitalograph Compact spirometer (Vitalograph Ltd, Maids Moreton House, Buckingham, United Kingdom). Three successive maximal expiratory curves were recorded at each assessment, and the highest value was selected according to the criteria of the American Thoracic Society. [30] Heart rate was measured from continuous electrocardiogram (ECG). The QT interval was calculated as the mean of 5 consecutive beats from a rhythm strip recorded on standard lead II of an ECG at 50 mm/sec. The QT interval was corrected for heart rate (QTc). [31] SaO2 was measured with an ear oximeter (504 pulse oximeter; Criticare Systems Inc, Waukesha, WI). Plasma potassium was assayed by flame photometry (IL 943 analyzer; Instrumentation Laboratories, Warrington, United Kingdom). Finally, serum salbutamol levels were determined by high-performance liquid chromatography. [32] At the end of the therapy, patients were asked to indicate the presence or absence of each of five symptoms (nausea, palpitations, tremor, anxiety, and headache).

Data Analysis

All data were analyzed with an "SPSS PC plus" software package (SPSS Inc, Chicago, IL). In an earlier study, [9] the average FEV1 after 3-hour beta2 treatment was 1.52 ± 0.48. Estimations from power calculations [33] showed that the use of 11 subjects was sufficiently sensitive to detect a 36% difference in FEV1, a 24% difference in heart rate, an 8% difference in QTc, an 11% difference in plasma potassium, a 17% difference in plasma salbutamol, and 2.1% points in SaO2, with alpha = .05 and beta = .20 (ie, with 80% power). Two-way repeated measures analysis of variance (ANOVA) was performed to assess group and time effects. One-way repeated measures ANOVA was used to compare baseline values for each variable. Baseline data of the two groups were compared by Mann-Whitney U test for independent samples or Wilcoxon matched-pairs test for related samples. Fisher's exact test was used for categorical variables. A P < .05 using a two-tailed test was considered significant for all statistical tests. Means are reported with standard deviations in the text.

RESULTS

The demographic characteristics of the 22 patients completing the study are shown in Table 1. Patients randomized to the two groups were well matched at baseline for age, sex, heart rate, FEV1, PEFR, SaO2, QTc interval, previous

| TABLE 1 -- Baseline Characteristics of Patients (Mean ± SD) |
|-------------|-------|-------|-----|
| Variable    | MDI   | NEB   | P   |

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<table>
<thead>
<tr>
<th>Age, yrs</th>
<th>(n = 11)</th>
<th>(n = 11)</th>
<th>.6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male/female</td>
<td>5/6</td>
<td>5/6</td>
<td>1.0</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>66.0 (15.7)</td>
<td>63.8 (13.9)</td>
<td>.9</td>
</tr>
<tr>
<td>Height, m</td>
<td>1.64 (0.08)</td>
<td>1.63 (0.04)</td>
<td>.9</td>
</tr>
<tr>
<td>Heart rate, beats/min</td>
<td>108.6 (20.9)</td>
<td>111.0 (18.1)</td>
<td>.7</td>
</tr>
<tr>
<td>Previous duration of attack, h</td>
<td>26.7 (25.1)</td>
<td>31.0 (24.7)</td>
<td>.5</td>
</tr>
<tr>
<td>Predicted PEFR, L/min</td>
<td>523.0 (71.5)</td>
<td>512.0 (69.2)</td>
<td>.5</td>
</tr>
<tr>
<td>PEFR, % predicted</td>
<td>28.7 (8.7)</td>
<td>31.0 (8.0)</td>
<td>.5</td>
</tr>
<tr>
<td>PEFR, L/min</td>
<td>148.6 (56.7)</td>
<td>160.0 (48.6)</td>
<td>.4</td>
</tr>
<tr>
<td>Predicted FEV₁, L</td>
<td>3.35 (0.73)</td>
<td>3.38 (0.91)</td>
<td>.4</td>
</tr>
<tr>
<td>FEV₁, % predicted</td>
<td>23.1 (9.6)</td>
<td>23.6 (4.4)</td>
<td>.8</td>
</tr>
<tr>
<td>FEV₁, L</td>
<td>0.75 (0.28)</td>
<td>0.78 (0.19)</td>
<td>.8</td>
</tr>
<tr>
<td>QTc, msec</td>
<td>391.9 (33.1)</td>
<td>397.6 (24.2)</td>
<td>.8</td>
</tr>
<tr>
<td>Sa O₂, %</td>
<td>95.8 (1.9)</td>
<td>95.1 (2.0)</td>
<td>.7</td>
</tr>
<tr>
<td>K⁺, mEq/L</td>
<td>4.21 (0.5)</td>
<td>4.09 (0.5)</td>
<td>.4</td>
</tr>
<tr>
<td>Salbutamol, mug/mL</td>
<td>0.37 (0.8)</td>
<td>0.27 (0.6)</td>
<td>.9</td>
</tr>
<tr>
<td>beta₂ used within past 24 hours, %</td>
<td>10</td>
<td>8</td>
<td>.3</td>
</tr>
<tr>
<td>Steroids used within past 7 days, %</td>
<td>3</td>
<td>5</td>
<td>.4</td>
</tr>
<tr>
<td>Theophylline used within 24 hours, %</td>
<td>6</td>
<td>5</td>
<td>.6</td>
</tr>
<tr>
<td>Serum theophylline, mg/L</td>
<td>2.95 (3.23)</td>
<td>3.61 (4.24)</td>
<td>.7</td>
</tr>
</tbody>
</table>

duration of attack, previous medication, and plasma potassium and salbutamol levels.

**Airway Response**

The effects of each treatment on PEFR and FEV₁ are shown in Figures 1 and 2, respectively. Mean PEFR improved significantly over baseline values in both the MDI and the NEB groups (\( P = .001 \) by one-way ANOVA). Although the NEB group showing slight differences over the MDI-spacer group, these differences did not reach statistical significance (\( P = .18 \)). At final disposition the mean percentage of predicted PEFR was 47.5% ± 14.4% (256.1 ± 88.7 L/min) in the MDI group and 57.9% ± 18.7% (305.0 ± 103.9 L/min) in the NEB group.

The same pattern held for changes in FEV₁. There were no significant differences between groups (\( P = .5 \)). A significant time factor (\( P = .001 \)) was apparent, indicating that pulmonary function changed significantly after administration of bronchodilator treatment. After 3 hours of protocol, the mean percentage predicted FEV₁ was 44.3% ± 16.7% (1.48 ± 0.67 L) in the MDI-spacer group and 49.4 ± 21.0% (1.70 ± 0.79 L) in the NEB group.

The relationship between the cumulative dose of salbutamol and the change in FEV₁ expressed as percent predicted was examined. We used data on all patients for each cumulative dose for the construction of the dose-response relationships (Figure 3).

A significant linear relationship (\( P < .01 \)) was observed for both groups (MDI \( r = 0.97 \); NEB \( r = 0.97 \)). The equation of the regression lines (MDI-spacer = 30.7 + 1.97x; NEB = 31.7 + 1.07x) were no different (\( P > .1 \)) indicating that the increase in FEV₁ per dose was similar in both groups. Using these equations, we concluded that a 1:2.5 dose ratio in favor of MDI-spacer was needed to obtain equivalent bronchodilation.
Chronotropic Responses

The changes in heart rate for both groups are shown in Figure 4.

Nonsignificant decreases in heart rate were seen in both groups (P = .9). The final mean heart rate was 97.0 ± 19.7 in the MDI-spacer group and 109.0 ± 19.7 in the NEB group. Three patients presented an increased heart rate (10, 10, and 16 beats/min) in the NEB group. The remaining subjects had reductions at the end of protocol ranging from 1 to 35 beats/min. The repeated measures two-way ANOVA did not show a group effect (P = .5); the MDI-spacer group did not differ from the NEB one at any point studied. However, the group-by-time interaction was significant (P = .04), suggesting that difference between groups increases.
Figure 3. The relationship between FEV1 (mean % of predicted) plotted against the cumulative dose of salbutamol. Bars represent 1 standard deviation of the mean.

Figure 4. Change in heart rate (HR) in response to cumulative doses of inhaled salbutamol. Bars represent 1 standard deviation of the mean.

with time. There were no arrhythmias detected, although this was assessed by constant ECG monitoring.

**QTc**

There was no significant prolongation in the QTc interval of both groups ($P = .7$) (Figure 5). QTc intervals at 180 minutes were $403.1 \pm 25.9$ msec in the MDI-spacer group, and $401.1 \pm 18.0$ msec in the NEB group. There was no difference between both groups at any time ($P$
At the end of treatment, QTc enlargements were seen in six patients in the MDI-spacer group (range 8 to 40) and seven patients in the NEB group (range 7 to 41).

**Figure 5.** Change in QTc interval in response to cumulative doses of inhaled salbutamol. Bars represent 1 standard deviation of the mean.

**Plasma Potassium**

The mean baseline and final serum potassium levels were 4.21 ± 0.5 mEq/L and 3.98 ± 0.6 mEq/L (P = .5) in the MDI-spacer group and 4.09 ± 0.5 mEq/L and 3.92 ± 0.5 mEq/L (P = .2) in the NEB group. Four and five patients showed net decreases in plasma potassium in the MDI-spacer and NEB groups, respectively (Figure 6). There were no differences between the final serum potassium levels in both groups (P = .9). The lowest individual serum potassium values after treatment were 3.0 and 2.8 mEq/L. The normal values are considered to range from 3.5 to 5.0 mEq/L.

**Oxygen Saturation**

Both groups produced nonsignificant increases in mean change in SaO₂ (P = .5) (Figure 7).

The mean final SaO₂ levels were 96.8% ± 1.64% in the MDI-spacer group and 96.1% ± 0.83% in the NEB group. There were no differences between groups at any time point (P = .8).

**Serum Salbutamol**

The mean baseline and end treatment serum salbutamol levels were 0.40 ± 0.8 ng/mL (range, 0 to 2.5 ng/mL) and 10.1 ± 1.6 ng/mL (range, 8 to 14 ng/mL) for the MDI-spacer group (P = .003), and 0.27 ± 0.6 ng/mL (range, 0 to 2 ng/mL) and 14.4 ± 2.3 ng/mL (range, 12 to 20 ng/mL) for the
Figure 6. Baseline and posttreatment potassium levels of each patient.
Figure 7. Change in oxygen saturation in response to cumulative doses of inhaled salbutamol. Bars represent 1 standard deviation of the mean.

Nebulizer (NEB) group (P = .003). At the end of treatment, there was a significant difference between groups (P = .0003).

**Symptoms**

There was a higher incidence of four symptoms (Table 2). However, only anxiety reached a statistical significance.

**DISCUSSION**

This study assessed the efficacy of two delivery systems (MDI-spacer and NEB) for administering inhaled salbutamol in patients with acute severe asthma in the ED setting. The results indicate that an MDI with spacer and a jet nebulizer produce a comparable bronchodilator response, but different side effects related to plasma salbutamol levels.

Beta-agonist doses vary widely among studies, and there is controversy over the equivalent dosage for the two delivery systems. However, comparative drug potency as regard to bronchodilatation is 6-7:1 (nebulizer:MDI) favoring the MDI in two studies to date. [8] [10] Thus, 2.5 mg of salbutamol given by nebulization is equivalent to four puffs (0.4 mg) given by MDI with spacer. This is because less of the aerosol delivered by wet nebulization as compared with MDI and spacer reaches the respiratory tract as it is nebulized during expiration, or it remains in the nebulizer tubing, or it impacts in the oropharynx and is swallowed.

Our data showed a trend toward nebulization delivery being better than MDI-spacer in increasing FEV₁ and PEFR. Nevertheless, these differences did not reach statistical significance. It is possible that a type II error (low power), because of the small sample utilized in this trial, accounted for the failure to show any difference between groups. At 180 minutes, this study had a power of 80% to detect a difference of 0.6 L between groups; to

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>MDI Group (%)</th>
<th>NEB Group (%)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tremor</td>
<td>9.0</td>
<td>54.5</td>
<td>.03</td>
</tr>
<tr>
<td>Nausea</td>
<td>9.0</td>
<td>9.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Anxiety</td>
<td>0.0</td>
<td>36.3</td>
<td>.04</td>
</tr>
<tr>
<td>Headache</td>
<td>9.0</td>
<td>18.1</td>
<td>.6</td>
</tr>
<tr>
<td>Palpitations</td>
<td>10.0</td>
<td>17.6</td>
<td>.3</td>
</tr>
</tbody>
</table>
detect a 0.22-L difference (the observed difference) at the 80% level, 167 patients in each group would have been needed. [33] Consequently, our power analysis demonstrates that there is a possibility that a significant difference was missed by beta error and that a larger sample would have provided more certainty for the results. However, the cumulative dose-response curves used to compare equivalent effects showed that for every 1 mg of salbutamol by MDI and spacer, 2.5 mg are needed from nebulization to have equal therapeutic response. Our data agree with those of Rodrigo and Rodrigo [9] and Blake et al. [34] Rodrigo and Rodrigo, comparing salbutamol delivered by MDI-spacer or nebulizer, found that a salbutamol dose of 6 mg/h via nebulizer was considered equivalent to 2.6 mg/h via MDI (2.3:1 dose-ratio). Similarly, Blake et al, using a bioassay method, estimated that 10 puffs from the MDI (0.9 mg) would deliver approximately the same amount of salbutamol to lung receptors as 2.5 mg of the nebulizer solution (1:2.7 dose-ratio).

Both groups showed a nonsignificant decrease in heart rate. However, the significant group-by-time interaction means that differences between groups increase with time; the nebulized group showed a trend toward an increasing heart rate. Schuh et al [35] demonstrated heart rate increases with serum salbutamol levels of 12.4 to 19.8 ng/ml. Also, Rodrigo and Rodrigo [12] found a significant heart rate increase with a serum salbutamol level of 14.0 ng/ml, but not with 10.4 ng/ml. Jointly, these studies suggest that there may be a serum level threshold at which salbutamol produces tachycardia. Thus, in this study, heart rate presented two different patterns, probably related to the serum salbutamol levels resulting from the two treatment protocols.

The higher incidence of tremor and anxiety likely reflected a larger systemic absorption of salbutamol in the NEB group. Accordingly, there was a significant difference between groups in plasma salbutamol levels, related to the method used. In contrast, cumulative doses of salbutamol administered with MDI-spacer produced low plasma levels of this drug. Spacers decrease particle velocity and reduce the number of large particles. Both of these features reduce oropharyngeal and large-airway deposition, with a consequent reduction in systemic absorption.

Finally, although prolongation of QTc has been observed after high doses of beta-agonists, [36] [37] neither group in our study exhibited a QTc enlargement. Also, SaO2 increased moderately in both groups in our study and serum potassium was moderately reduced, without differences between groups.

In summary, our data indicate that when doses used are calculated on the basis of the percentage of total drug that reaches the lower airway, there was equivalent bronchodilatation after salbutamol administered by either MDI-spacer or nebulizer in patients with acute severe asthma. Also, we found that frequent administration of beta-agonists is associated with minimal signs or symptoms of drug toxicity. The treatment of acute asthma in the ED with salbutamol, 2.4 mg/h, delivered by MDI-spacer (4 puffs at 10-minute intervals), produces similar bronchodilation, low serum salbutamol concentrations, and minimal extrapulmonary effects. On the other hand, nebulizer therapy produced an equivalent therapeutic response with greater side effects likely related to the increase in salbutamol absorption and higher plasma level.

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