Comparison of Single 7.5-mg Dose Treatment vs Sequential Multidose 2.5-mg Treatments With Nebulized Albuterol in the Treatment of Acute Asthma*

Rita K. Cydulka, MD, MS; E. Regis McFadden, MD; Joshua H. Sarver, BA; and Charles L. Emerman, MD

Study objectives: The purpose of the current trial was to compare the relief of airway obstruction from treatment with a single dose of albuterol, 7.5 mg (single-dose group), with that from three sequential doses of albuterol, 2.5 mg, spaced 20 min apart (multidose group).

Design: Randomized clinical trial designed to test equivalence.

Setting: Urban county hospital emergency department.

Patients or participants: Adult patients between the ages of 18 and 60 years presenting to the emergency department with acute asthma, as defined by the American Thoracic Society criteria, with FEV1 on presentation to the emergency department of < 75% of predicted were included in the study.

Interventions: After the initial evaluation, patients were administered either albuterol, 2.5 mg via nebulizer every 20 min for a total of three doses, or albuterol 7.5 mg via nebulizer in a single dose.

Measurements and results: Ninety-four patients participated, 46 in the single-dose group and 48 in the multidose group. Patients in both groups had severe obstruction on presentation to the emergency department (single-dose group pretreatment FEV1, 45% of predicted [SD, 16% of predicted]; multidose group pretreatment FEV1, 47% of predicted [SD, 17% of predicted]; p = 0.62). The primary outcome measure was the change in FEV1 percent predicted over time. The secondary outcome measures were disposition after treatment (ie, hospitalization or discharge to home) and the incidence of side effects. We noted a 44.5% improvement (SD, 56.2%) in pretreatment to posttreatment FEV1 values in the single-dose group and a 38.1% improvement (SD, 37.3%) in the multidose group (p = 0.52). A similar proportion of patients in both groups required hospitalization (single-dose group, 48%; multidose group, 41%; p = 0.51). There was a trend for the patients in the single-dose group to experience more side effects than patients in the multidose group (patients in the single-dose group patients, 40% [SD, 19%]; multidose group patients, 22% [SD, 10%]; p = 0.06).

Conclusion: A single dose of 7.5 mg nebulized albuterol and sequential doses of 2.5 mg nebulized albuterol are clinically equivalent in the treatment of patients with moderate-to-severe acute asthma and result in similar dispositions from the emergency department.


Key words: albuterol; asthma; emergency

Abbreviation: NAEPP = National Asthma Education and Prevention Program

In 1991, the National Asthma Education and Prevention Program (NAEPP) published the first set of national guidelines for the emergency treatment of patients with asthma. Prior to this publication, physicians treated asthma exacerbation according to personal preference. The current recommendations advise the initiation of albuterol therapy, 2.5 to 5 mg every 20 min for the first hour of treatment, for the treatment of patients with acute asthma exacerbation.
ations.2 Few data exist to substantiate these recommendations. While several investigators have reported sequential increases in pulmonary function in patients given frequent, repeated doses of albuterol,2 there exist few data to support the use of β-agonist therapy using repeated doses.2,3 Emerman and colleagues previously reported no difference in change in pulmonary function and hospital admission rates between asthmatic patients who had been treated with nebulized albuterol, 2.5 mg every 20 min, and those treated with albuterol, 7.5 mg every 20 min.

Single-dose therapy offers several advantages over multidose therapy. It requires less nursing and/or respiratory therapist time and would allow fewer opportunities for medical errors, such as missed, late, or erroneous treatments, to occur. Despite the potential benefits of single-dose therapy, there is little information on the effects of single, high-dose therapy with the effects of multidose therapy on airway function and side effects. The purpose of this trial was to determine whether treatment with a single dose of albuterol, 7.5 mg, (single-dose group) is equivalent to that with three sequential doses of albuterol, 2.5 mg spaced 20 min apart (multidose group).

**Materials and Methods**

This study was conducted in the emergency department of MetroHealth Medical Center, a large, urban, county-owned institution. Consecutive adult patients between the ages of 18 and 60 years presenting to the emergency department with acute asthma, as defined by the American Thoracic Society criteria,3 were enrolled into the study by one of the department’s research nurses. Treating physicians and study investigators were blinded to the study group. Patients were eligible to participate if their FEV1 on presentation to the emergency department was ≤ 75% of predicted. Patients were excluded from this study if they had an FEV1 > 75% of predicted on presentation, had received a previous diagnosis of COPD (according to the American Thoracic Society criteria),3 had a history consistent with chronic bronchitis, had previously undergone lung surgery, or had received a diagnosis of lung carcinoma. Patients also were excluded from the study if they had clinical evidence of pneumonia, pneumothorax, or decompensated congestive heart failure, or if they had a contraindication for receiving oral prednisone. Patients were enrolled in the study only if they were able to perform spirometry.

The primary outcome measure was the change in the percent predicted for FEV1 over time. The secondary outcome measures were disposition after treatment (ie, hospitalization or discharge to home) and the incidence of side effects.

After informed consent was obtained, blood was drawn for the performance of a CBC count and the measurement of serum potassium levels. Pulse oximetry values were obtained, and, if necessary, patients began receiving oxygen by a nasal cannula to maintain an oxygen saturation of > 91%. Spirometry was performed (Spirocan 4000 Fleisch pneumotachograph spirometer; Brentwood Instruments; Portland, OR) with the patient seated and wearing nose clips. The spirometer was calibrated at least three times per week using a 3-L syringe. At least three expiratory maneuvers were performed, with the highest FEV1 value used for analysis.

In a randomized double-blind fashion, patients received albuterol by air-driven nebulizer in a dose of either 2.5 mg every 20 min, for a total of three doses, or 7.5 mg in a single dose. Patients were randomized using a computer-generated, random numbers table. The medication was premixed in three vials by the pharmacy so that patients in the low-dose group received three sequential doses of albuterol, 2.5 mg in 4 mL normal saline solution, while the patients in the high-dose group received a single dose of albuterol, 7.5 mg in 4 mL normal saline solution, followed by 4 mL normal saline solution that were administered from similar appearing vials. The pharmacist was given only the patient number and used the random numbers table to determine which dose of medication to prepare and send to the emergency department. Physicians were asked to assess the patients before and between scheduled treatments to maintain the blinding to group assignment. All treatments were administered by the research nurses via nebulizer (model 646 acorn nebulizer; DeVilbis Health Care; Somerset, PA) in order to minimize drug loss. All patients were given an oral dose of prednisone, 60 mg, at the initiation of treatment. Patients did not receive any other medications during the time course of the study.

Spirometry was performed at 30, 60, and 100 min. Patients were questioned about the occurrence of any side effects from the albuterol treatment including palpitations, anxiety, nausea, vomiting, or headache. Patients were then either discharged from or admitted to the hospital following the performance of the last spirometry at the discretion of the treating physician and using NAEPP guidelines. At all times, the research nurses, patients, and treating physicians were blinded to group assignment.

The study was designed to recruit 88 patients to have 80% power to detect a 15% absolute difference in FEV1 over time at an α of 0.05, given an SD of 25%.4 Clinical equivalence was considered to be an absolute difference of ≤ 12% predicted in FEV1.7

The analysis of categoric variables was performed using the χ² test. The analysis of continuous variables was performed using the Student t test. The effect of the two different albuterol regimens over the course of 100 min was assessed using the generalized estimating equation method for repeated measures with an unstructured covariance matrix. This equation allows for the adjustment of all individual variation over time when comparing the two groups and is more robust than an analysis of variance repeated time analysis. A p value of < 0.05 was considered to indicate statistical significance. All data were expressed as the mean ± SD. All statistical tests were performed using computer software (Stata, version 7.0 for Windows; Stata Corporation; College Station, TX). An intent-to-treat analysis with no dropouts was used. The hospital’s institutional review board approved this study.

**Results**

Ninety-four patients were enrolled in the study, including 31 men and 63 women with a mean age of 33.7 ± 9.2 years. This represents 90% of consecutive eligible patients who were screened for participation. Ten percent of patients who were screened declined to participate.

The groups were similar in terms of demographics, smoking history, history of asthma intensity, medica-
tion use, intensity of airway obstruction, and other physiologic parameters on presentation to the emergency department (Table 1). The mean pretreatment FEV\(_1\) was 46.2 ± 16.4% of predicted. As therapy, 86% of patients reported receiving \(\beta\)-agonist agents, 53% were receiving inhaled corticosteroid agents, 20% were receiving leukotriene antagonist agents, 16% of the patients were receiving theophylline products, 14% were receiving ipratropium, and 9% were receiving prednisone. There was a current history of cigarette use among 44% of the patients, with a mean of 9.3 ± 13.5 pack-years among all patients.

Overall, there was no significant difference in the improvement in FEV\(_1\) between the two groups, when looked at as a whole or when analyzing patients requiring hospital admission separately from those patients who were able to be discharged to home after treatment (Fig 1, 2). We noted a 44.5 ± 56.2% predicted improvement in pretreatment to posttreatment FEV\(_1\) in the single-dose group and a 38.1 ± 37.3% predicted improvement in the multidose group, (\(p = 0.52\)). A similar proportion of patients in both groups required hospitalization (single-dose group, 48%; multidose group, 41%; \(p = 0.52\)). A similar proportion of patients in both groups required hospitalization (single-dose group, 48%; multidose group, 41%; \(p = 0.51\)). Figure 3 demonstrates that the two treatment groups were clinically equivalent overall and at all three points in time. Twice as many patients in the single-dose group experienced side effects that could be attributed to albuterol (ie, tremor, chest pain, headache, palpitations, nausea, and vomiting) compared to patients in the multidose group, although this number did not reach statistical significance (\(p = 0.06\)) [Table 2].

### Table 1—Patient Demographics and Intensity of Disease*

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Single-Dose Group (n = 46)</th>
<th>Multidose Group (n = 48)</th>
<th>(p) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>33.0 ± 9.4</td>
<td>34.5 ± 92</td>
<td>0.45</td>
</tr>
<tr>
<td>Male gender</td>
<td>35</td>
<td>30</td>
<td>0.61</td>
</tr>
<tr>
<td>White race</td>
<td>44</td>
<td>43</td>
<td>0.46</td>
</tr>
<tr>
<td>(\beta)-agonist use</td>
<td>81</td>
<td>91</td>
<td>0.37</td>
</tr>
<tr>
<td>Ipratropium use</td>
<td>17</td>
<td>10</td>
<td>0.33</td>
</tr>
<tr>
<td>Inhaled corticosteroid use</td>
<td>50</td>
<td>57</td>
<td>0.53</td>
</tr>
<tr>
<td>Oral corticosteroid use</td>
<td>9</td>
<td>8</td>
<td>0.62</td>
</tr>
<tr>
<td>Leukotriene antagonist use</td>
<td>21</td>
<td>17</td>
<td>0.35</td>
</tr>
<tr>
<td>Theophylline use</td>
<td>13</td>
<td>20</td>
<td>0.67</td>
</tr>
<tr>
<td>Cigarette use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current</td>
<td>44</td>
<td>44</td>
<td>0.73</td>
</tr>
<tr>
<td>Past</td>
<td>42</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>15</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>Cigarette pack-yr</td>
<td>9 ± 14</td>
<td>9 ± 13</td>
<td>0.90</td>
</tr>
<tr>
<td>History of ICU admissions</td>
<td>31</td>
<td>40</td>
<td>0.36</td>
</tr>
<tr>
<td>History of intubation</td>
<td>8</td>
<td>22</td>
<td>0.06</td>
</tr>
<tr>
<td>Pretreatment FEV(_1), %</td>
<td>45 ± 16</td>
<td>47 ± 17</td>
<td>0.62</td>
</tr>
</tbody>
</table>

*Values given as mean ± SD or %, unless otherwise indicated.

**DISCUSSION**

This study failed to demonstrate a difference between the administration of albuterol, 7.5 mg in a single dose, and the standard administration of albuterol, 2.5 mg every 20 min for three doses. We also found no difference in the hospital admission rate between the two groups.

We previously reported that no difference in the percentage of improvement in FEV\(_1\) or in the hospital admission rate between patients to whom 2.5 mg albuterol had been administered every 20 min for three doses and those to whom 7.5 mg albuterol had been administered in a single dose. Therefore, we concluded that doses of >2.5 mg albuterol given every 20 min offered no improvement in measured outcomes. The current study was designed to determine whether the different timing of delivery (ie, a single 7.5-mg dose or a 2.5-mg dose every 20 min for a total of three doses) provides equivalent outcomes. Our new data suggest that similar outcomes, but with a tendency toward more side effects, may be achieved with only a single dose of 7.5 mg nebulized albuterol. These findings are similar to those from studies comparing continuous delivery systems with intermittent delivery of aerosolized \(\beta\)-agonists. The high hospital admission rate in both groups is likely attributable to the fact that all subjects had moderate or severe airway obstructions on presentation to the emergency department.

The single-dose method in our study offers two significant advantages, as follows: a specialized delivery system is not needed; and the opportunity to miss or delay doses of nebulized albuterol is minimized. This may permit personnel in the emergency department to spend more time on the evaluation and education of the asthmatic patient and less time on manual tasks, such as refilling acorns. This efficiency may be gained, however, at the expense of the patient’s comfort. Unlike terbutaline, another selective \(\beta_2\)-adrenergic agent, the side effect profile of which mimics the cardiovascular profile of nonselective agents as increasing doses are administered, no increase in palpitations was noted with single, high-dose administrations of albuterol. In addition, no patients complaining of chest pain were >40 years of age, making it unlikely, but not impossible, that the chest pain was cardiac in origin. Regardless, the trend toward the increased reporting of side effects...
and its possible effect on the patient perception and acceptance of this method of delivery will need to be closely followed.

We believe that single, high-dose therapy may represent the next logical step in the development of the emergency care of patients with acute asthma. Although emergency treatment has evolved over the past few decades from hourly subcutaneous epinephrine to the frequent sequential or continuous administration of inhaled agents, now including the use of anticholinergic and antiinflammatory agents, the optimum dose for \( \beta_2 \)-agonist administration is still the subject of investigation. Although the NAEPP recommends doses of 2.5 to 5.0 mg every 20 to 30 min up to a total of three doses, there are few data to support this dosing scheme. Some studies indicate that a cumulative dose between 5 and 7.5 mg albuterol yields adequate responses during the emergency treatment of patients with acute asthma. Patients who fail to respond to these doses generally require hosp-
talization. Therefore, further increasing the dose leads to a greater incidence of side effects without a substantial improvement in bronchodilation. The current study supports the contention that there exists a threshold dose of albuterol that can be given as a single bolus and yields comparable bronchodilation to that achieved with the repeated administration of smaller boluses.

There are several limitations to this study. This is a small, single-center study, and our population may not be representative of other sites. Although we have demonstrated clinical equivalence between single-dose and multidose therapy, we had insufficient sample size to determine equivalence among subpopulations of patients.

**Conclusion**

This study supports the contention that the administration of a single dose of albuterol, 7.5 mg, is equivalent to administering sequential doses of albuterol, 2.5 mg, in the treatment of acute bronchospasm in asthma patients with moderate-to-severe airway obstructions. In addition, this dosing scheme minimizes the opportunity for delayed or missed doses. Further studies are needed to confirm both the efficacy and effectiveness of the dosing scheme in the treatment of patients with acute asthma.

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