Treatment of Bronchospasm by Metered-Dose Inhaler Albuterol in Mechanically Ventilated Patients*

Constantine A. Manthous, MD; Wissam Chatila, MD; Gregory A. Schmidt, MD; and Jesse B. Hall, MD

β₂-agonist bronchodilators delivered by metered-dose inhalers (MDI) are commonly used in the treatment of bronchospasm in both intubated and nonintubated patients. Substantial data support the effectiveness of MDI delivery systems in nonintubated patients. However, few studies have examined the effectiveness of MDIs in intubated, mechanically ventilated patients. MDIs are often used in conjunction with a spacing device that may enhance delivery of drug to the airways, but few in vivo data have demonstrated efficacy of this delivery method in ventilated patients. We studied ten critically ill patients who had a peak (Ppeak) to pause (Ppause) gradient of more than 15 cm H₂O during sedated, quiet breathing on assist control ventilation. We administered 5, 10, and 15 puffs (90 μg per puff) of MDI albuterol through a specific spacer (Aerovent) at 30-min intervals, while measuring resistive pressure (defined as Ppeak–Ppause) before and after treatments. Resistive airway pressure after 5 puffs decreased in nine of ten patients, from 25.1±7.2 to 20.8±5.6 cm H₂O (p<0.01). The addition of 10 more puffs further reduced resistive pressure in nine of nine patients from 20.8±5.6 to 19.0±4.4 (p<0.01). Fifteen more puffs (30 cumulative puffs) did not result in further improvement (p>0.5). A toxic reaction occurred in one patient (systolic blood pressure decreased 20 mm Hg) after 5 puffs of albuterol. We conclude that MDI administered through this specific spacer is effective in mechanically ventilated patients in doses up to 15 puffs, and that therapy should be titrated to effectiveness and toxicity. (Chest 1995; 107:210-13)

Nebulizers (NEBs) and metered-dose inhalers (MDIs) are commonly used to deliver bronchodilators to intubated, mechanically ventilated patients. Many studies have substantiated that MDIs and NEBs are equally effective in the treatment of bronchospasm in nonintubated patients.1-5 Few studies have examined the effectiveness of aerosolized bronchodilators in intubated patients.5-8 We recently reported that MDI albuterol delivered by endotracheal tube adapter was ineffective in doses of up to 100 puffs while airway resistance decreased after 2.5 and 5.0 mg of NEB albuterol.5 Many institutions use MDI delivered by in-line spacing devices to improve the delivery of aerosol to the airways of intubated patients, though few in vivo data support this practice. Accordingly, we determined the efficacy of MDI albuterol delivered by a commonly used spacer.

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Key words: aerosol; albuterol; bronchospasm; intubated; metered-dose inhaler; nebulization; spacer

METHODS

All patients admitted to the Bridgeport Hospital intensive care units (ICUs) in July and August of 1993 who required mechanical ventilation and had a greater than 15 cm H₂O difference between peak (Ppeak) and pause (Ppause) airway pressures on tidal volume inflation (see below) were included in this study. All patients were heavily sedated with less than five triggered breaths per minute on ventilators (Puritan Bennett 7200 [PB7200]). Tidal volumes were delivered with an inspiratory flow rate of 60 L/min and a square waveform. Patients were excluded if they had a history of symptomatic coronary artery disease in the 6 months prior to hospital admission or if they had a history of hemodynamically significant arrhythmias. Patient profiles are provided in Table 1; all patients had 7- or 8-mm endotracheal tubes. The study protocol was approved by the Bridgeport Hospital Institutional Review Board.

Routine tracheal suctioning was performed 15 to 30 min before the trial. Patients received MDI albuterol in doses of 5, 10, and 15 puffs (90 μg per puff) administered at 30-min intervals via a specific spacer (Aeroven) placed less than 10 cm proximal to the y-piece in the inspiratory limb of the ventilator circuit. The y-piece was connected directly to the endotracheal tube. Treatments were stopped if a toxic reaction occurred, defined by the following: (1) heart rate increment of 20/min; (2) more than four premature ventricular contractions or premature atrial contractions per minute; (3) tremulousness; (4) nausea; or (5) reduced systolic blood pressure of more than 20 mm Hg. Tidal volumes, respiratory rates, and flow rates remained constant throughout the treatment and measurement periods. The MDI cannister was shaken at least every ten breaths or more often if an adequate cloud of aerosol was not observed after each actuation performed.
Table 1—Profiles of Ten Sedated Mechanically Ventilated Patients Treated With Albuterol*

<table>
<thead>
<tr>
<th>No./Age, yr/Sex</th>
<th>Ventilator</th>
<th>Diseases</th>
<th>RF</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/72/M</td>
<td>12/600</td>
<td>COPD, diffuse pneumonia</td>
<td>1</td>
<td></td>
</tr>
<tr>
<td>2/57/M</td>
<td>24/500</td>
<td>Asthma</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>5/39/F</td>
<td>14/400</td>
<td>Asthma</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>4/62/M</td>
<td>14/550</td>
<td>Aspiration pneumonia</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>5/77/F</td>
<td>12/600</td>
<td>s/p fractured hip, COPD</td>
<td>3</td>
<td></td>
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<tr>
<td>6/75/F</td>
<td>10/500</td>
<td>s/p esophagectomy, COPD</td>
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<td></td>
</tr>
<tr>
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<td>16/600</td>
<td>Sepsis, COPD</td>
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<td></td>
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<tr>
<td>8/70/F</td>
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<td>Exacerbation, COPD</td>
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<td></td>
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<tr>
<td>9/69/F</td>
<td>14/500</td>
<td>Exacerbation, COPD</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>10/41/F</td>
<td>14/400</td>
<td>Asthma</td>
<td>2</td>
<td></td>
</tr>
</tbody>
</table>

*Ventilator=respiratory rate/tidal volume; RF type=respiratory failure type; 1=hypoxemic respiratory failure; 2=ventilatory failure; 3=perioperative respiratory failure.

at end-expiration into the spacer.

Inspiratory airway pressures were measured before and 30 min after each administration. $P_{\text{peak}}$ was measured using the digital display. $P_{\text{pa}}$ was measured on the first breath after application of a 0.5- to 1.0-s end-inspiratory pause, as read from the digital airway pressure display. When patients were receiving mechanical ventilatory assistance with the previously mentioned ventilator with software capable of measuring static airway resistance by the occlusion method, this value was also obtained as a second concurrent measure of airway resistance. The resistive pressures ($P_{\text{peak}}-P_{\text{pa}}$) were determined before treatment and pretreatment values were compared with those at each dose by paired t test, (Bonferroni) corrected for multiple comparisons. Statistical significance was indicated by a p<0.05.

RESULTS

The dose response curves for MDI-delivered albuterol are presented in Figure 1. Five puffs (0.45 mg) of albuterol delivered by MDI/spacer reduced airway resistance in nine of ten patients from 25.1 ± 7.2 to 20.8 ± 5.6 (p<0.12 after Bonferroni correction for three comparisons). Patient 4, whose resistance improved after 5 puffs, did not receive 10 puffs because his systolic blood pressure decreased by 20 mm Hg. After 10 additional puffs (15 cumulative puffs, 1.35 mg), airway resistance was reduced in nine of nine patients, from 20.8 ± 5.6 to 19.0 ± 4.4 (p<0.01). The addition of 15 more puffs (30 cumulative puffs) reduced resistive airway pressure in four of nine patients, but the improvement was not statistically significant (p>0.5). Patient 5 had no response to a cumulative doses of 30 puffs. The magnitude of improvement after 15 cumulative puffs correlated with the magnitude of pretreatment resistive pressure ($R^2=0.66$, p<0.01). Resistance also decreased to a similar degree ($R^2=0.8$, p<0.05) when measured by the occlusion technique (p<0.05 at 15 cumulative puffs) in patients 1, 2, 4, 5, 6, and 7 whose resistive pressures were measured by this second technique. Statistical significance (p<0.05) was maintained even when patient 10, who had a very large reduction of resistive pressure, was excluded from analysis.

Hypotension occurred in patient 4 after five puffs of albuterol, but his blood pressure was noted to be labile prior to therapy. No other toxic reactions were noted.

DISCUSSION

These data indicate that MDI albuterol administered through the spacer (Aeroven) reduces inspiratory airflow resistance in ventilated patients with airflow obstruction. The patients we studied had a variety of diseases requiring mechanical ventilation, though most had COPD or asthma (Table 1). Since 6 cm H$_2$O or more can be attributed to the (8 mm) endotracheal tube and ventilator circuit, 9 cumulative puffs of albuterol led to a 32% reduction in airway resistance. Since the person administering the albuterol in this study also made the measurements, observer bias is possible. However, we were careful to verify that our measures were accurate by performing them manually and with the ventilator’s mechanics package when it was available. The reductions in airways resistance noted herein after MDI/spacer are comparable in magnitude to those noted after nebulized albuterol. 5 This study suggests that 5 puffs (through a spacer), commonly used in many ICUs, may be suboptimal but that there is little additional benefit beyond 15 puffs of MDI/spacer albuterol. Our findings also confirm that aerosolized bronchodilators can be safely titrated to efficacy and toxicity. 5

Accordingly, we suggest that β$_2$-agonist be titrated to the minimal airway resistive pressure that does not lead to toxic reactions, whether nebulized or MDI/spacer is used. Some patients may have toxic reactions at relatively low doses of medication (see patient 4), and some seem to have additional benefit without toxic reactions even at higher doses than 15 cumulative puffs of albuterol (see patients 2, 7, and 8). Delivery of aerosolized medications to the airways of mechanically ventilated patients is highly variable due to particle impaction in the ventilator tubing, endotracheal tube adapter, and endotracheal tube. Thus, there is a distinction between the administered and the delivered doses; only a fraction of the administered dose is delivered to the airways. Most of the administered dose remains in the ventilator circuit and endotracheal tube. 10 Devices used to generate and deliver aerosols differ in efficiency. Newhouse and Fuller 11 have suggested that clinicians should not assume that a device is effective without confirmatory data; devices should be validated both in vitro and in vivo. Furthermore, other determinants of aerosol delivery, such as anatomy of the patient’s airways and ventilator parameters, 12,13 also
affect the efficiency of aerosol delivery. Therefore, it is not surprising to find considerable variation in the optimally effective administered dose. If clinicians titrate aerosols to therapeutic effect and toxicity, these problems are obviated; the present and previous studies offer methods/devices that are effective when therapeutic titration is applied.

Some patients with elevated airway resistance do not respond to β-agonist bronchodilators, even titrated to very high doses (see patients 3 and 9). Inhospitated bronchial secretions or elevated endotracheal tube resistance (due to kinking or secretions), which are not responsive to β-agonist therapy, are possible causes of the elevated airway resistance. It is also conceivable that a subset of patients, especially those with COPD, might have bronchospasm that further improves with inhaled atropine derivatives. Lastly, in many patients with airway inflammation and edema, such as bronchitis and asthma, these contributions to airway resistance may respond more slowly (over days) to systemically administered corticosteroids.

We have suggested from informal polls that approximately one-third of ICUs utilize MDI without a spacer, one-third utilize MDI with a spacer, and the remainder use nebulized aerosols for treatments in mechanically ventilated patients. We have shown that the first method may be ineffective using conventional ventilator settings while titrated nebulized albuterol is extremely effective. Several studies of radiolabeled aerosol deposition have suggested that MDI aerosols may be delivered in ventilator lung models and in patients. Fuller et al determined the efficiency of delivery of radioactively labeled β-agonist to ventilated patients by MDI administered through several devices. The use of an in-line spacer was most efficient but was approximately half as efficient as delivery in nonintubated patients; thus a reasonable approach would be to administer four puffs to mechanically ventilated patients. Why then do our data suggest that in many cases more than five puffs are required to achieve maximal bronchodilation? First, the spacers and ventilator settings used to administer the MDI were different (the efficiencies of the devices could differ). More importantly, the data of Fuller et al suggest that two puffs through a spacer in ventilated patients provide equivalent delivery to one puff in a spontaneously breathing patient. The “standard” dose in nonintubated patients is two puffs; since this does not ensure maximal bronchodilation, it is likely that higher doses might lead to optimal treatment. Accordingly, our finding that titration to higher doses (10 to 15 puffs) causes more bronchodilation does not contradict their findings.

Two preliminary communications have suggested that MDI/spacer albuterol may be effective in alleviating bronchospasm in mechanically ventilated patients. Our study confirms that the spacer used in this study allows for the effective administration of MDI. In the absence of the spacing device, MDI-administered particles likely impact on narrow wetted surfaces, such as the endotracheal tube and adapter, before they can be accelerated (with a breath) to the patient. Our previous study suggested that MDI delivered through an endotracheal tube side-port adapter at end-expiration was not clinically effective. Fuller et al have suggested that MDI can be delivered through a side-port adapter at reasonable (4%) efficiencies if actuated only during inspiration.

Other methods of MDI delivery may also be effective. In 18 ventilated patients, MDI-albuterol (3 puffs of 90 µg each) was delivered by slow manual inflation of the lungs that were held at an increased volume for several seconds before mechanical ventilation was resumed. The passive expiratory flow at constant respiratory recoil pressure increased by 0.1 L/s after MDI, and this reduction in expiratory resistance was similar to that produced in the same patients by 2.5 mg of nebulized albuterol. A third study in 20 ventilated patients with COPD demonstrated that MDI (0.2 mg salbutamol) administered by slow bag-delivered inflations significantly reduced resistive pressure. Therefore, slow bag inflation of the lungs after actuation into a spacer also appears to be effective. However, such a labor-intensive approach may not be practical for general ICU use, and this technique is not widely utilized. Another study demonstrated efficacy of MDI ipratropium using an adapter that was not well described and, to our
knowledge, is not available for clinical use. In addition, intraendotracheal tube catheters, which have been shown to deliver large amounts of aerosols to lung models, may also be effective in ventilated patients, though this remains speculative.

In mechanically ventilated patients, we believe that β-agonist bronchodilators should be given to effect or toxicity, rather than by prescribing an arbitrary number of puffs. Based on our data, we recommend starting at 5 to 10 puffs of MDI/spacer or 2.5 mg of NEB (albuterol, or equivalent dose of metaproterenol). Resistive airway pressures should be measured before and 30 min after treatments. If airway resistance remains over 15 cm H2O L/s and there is no toxic reaction, treatment should be repeated at the same or higher dose. Once an effective dose is determined by a reduction in resistive pressure, this dose can be repeated at 2- to 6-h intervals depending on the severity of the bronchospasm and the half-life of the bronchodilator used. If a patient does not respond to one delivery method, we administer β-agonist by the alternate method. In those patients who do not respond to high doses (eg, 20 puffs of MDI or triple dose NEB) of β-agonist, we administer a NEB or MDI atropine derivative (glycopyrrolate or ipratropium). In patients who do not respond to aerosols, we consider inflamed airways that may be amenable to systemic corticosteroids or increased endotracheal tube resistance.

REFERENCES

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