Equivalence of Continuous Flow Nebulizer and Metered-Dose Inhaler with Reservoir Bag for Treatment of Acute Airflow Obstruction*

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Traditionally, patients with acute airflow obstruction are treated with bronchodilator aerosols delivered by continuous flow nebulizers. While bronchodilator administration with the metered dose inhaler (MDI) and reservoir or spacer attachment is as effective as administration with the nebulizer in most settings, the former has not been widely accepted for treatment of acute airway obstruction in the emergency room. We compared the efficacy of the continuous flow nebulizer to that of the MDI with InspirEase (reservoir spacer) in 75 patients (45 men and 30 women), ages 18-73 (χ 44 years) who presented to the emergency room with acute asthma and COPD. Subjects in each group (22 COPD and 53 asthma) were randomly assigned to treatment with three puffs of metaproterenol (0.65 mg/puff) via the MDI with InspirEase plus nebulizer with placebo, or placebo MDI with InspirEase plus nebulizer with 15 mg metaproterenol in double blind fashion. Either treatment was given three times at 30 min intervals. The FEV_1 and dyspnea scores according to the Borg scale were measured at baseline, 30 min after the first treatment, and 30 min after the third. There was no significant outcome difference between the two treatments in either diagnostic group. There also was no significant outcome difference for patients with baseline FEV_1 <0.9L. Serum theophylline levels, the need for concomitant therapy with corticosteroids, or additional emergency room therapy after the study, hospitalizations and treatment side effects did not differ between treatment groups. We conclude that there is no demonstrable advantage of a continuous flow nebulizer over an MDI with InspirEase for the treatment of acute airflow obstruction.

Several devices are generally advocated to provide aerosolized medications for inhalation. They are metered-dose inhalers (MDI), tube, pear or reservoir bag spacer attachments that can be used with the MDI, and the continuous flow (wet) nebulizer.[1]

Nebulizers have traditionally been recommended for administering bronchodilator aerosol medications to patients with asthma or chronic obstructive pulmonary disease (COPD) who present to the emergency room.[2,3] Because nebulizers are used in the emergency room, patients assume that the devices are superior to the MDI for bronchodilator delivery and often request them for home use. However, nebulizer treatments are expensive,[4] require cumbersome electric compressors or compressed gas power sources, utilize up to ten times more bronchodilator drugs than the MDI, and the equipment must be regularly changed or cleaned to prevent contamination.

Several investigators[5-11] have reported that the MDI with tube or pear-shaped spacer is equivalent to the nebulizer for the treatment of stable asthma. The former devices are more portable, less expensive, and require less maintenance than nebulizers. They have been advocated for adults with poor MDI technique, and children less than five years of age,[1] but have not been accepted for emergency treatment of acute airflow obstruction. The purpose of the present study was to determine if the MDI with a 700 ml collapsible reservoir bag spacer (InspirEase, Key Pharmaceuticals, Inc) is an effective alternative to the nebulizer for the treatment of acute airflow obstruction in the emergency room.

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Material and Methods

Subjects

The study was conducted in the emergency room of San Francisco General Hospital, a 582-bed acute care facility. Seventy-five patients (45 men and 30 women), mean age 44 ± 16, who presented with acute airflow obstruction (mean FEV_1 1.06 L ± 0.47) were prospectively assigned into COPD and asthma groups according to the following criteria:

COPD—≥10 pack-years smoking *and* onset of symptoms ≥age 30

Asthma—<10 pack-years smoking *or* onset of symptoms <age 30

Patients were excluded from the study if they were less than 18 years of age or older than 75 years, unable or unwilling to provide informed consent, presented with suspected acute myocardial infarction, congestive heart failure, or respiratory failure requiring intubation. Also excluded were those unable to perform an FEV_1 maneuver, suspected of having an allergy to metaproterenol, or pregnant.

Study Design

The study was approved by the Committee on Human Research of the University of California, San Francisco. After the patients had provided informed consent and had been assigned to a diagnostic group (COPD or asthma), the following baseline evaluations were measured: serum theophylline level, blood pressure, apical pulse, respiratory rate, FEV_1 (best of three forced exhalations with Breon spirometer, patient seated without nose clip), and dyspnea evaluation with the modified Borg scale. The modified Borg scale[12] is an interval scale that contains numbers from 0 to 10 and statements along the numerical scale such as "nothing at all, slight, severe, very severe, maximum." Patients were asked to indicate the degree of their dyspnea on the scale and the numeric score was noted. Once the baseline evaluations were completed, patients were randomized in double-blind fashion to treatment with: 1) metaproterenol MDI with InspirEase and nebulizer with normal saline solution, or 2) placebo MDI with InspirEase and nebulizer with metaproterenol. All patients were positioned on a gurney with the backrest elevated approximately 90°. Based on data from Shim and Williams[13] on the effects of inhaled metaproterenol in stable outpatients, metaproterenol doses of 1.95 mg via MDI were considered equivalent to 15 mg via nebulizer. Three puffs of metaproterenol (650 μg/puff) or placebo were inhaled from the InspirEase after the MDI was activated. Subjects were instructed to fill the InspirEase reservoir bag with air, actuate the MDI aerosol into the bag, inhale slowly so that the reed in the mouthpiece did not make a noise, hold their breath for a count of 5, breathe out into the bag, inhale again, and hold their breath for a count of 5. They then took the InspirEase mouthpiece out of their mouth and repeated the maneuvers again after two and four minutes. Immediately after administration of metaproterenol via the MDI with InspirEase, the patients received 2.5 ml normal saline solution via nebulizer, or 15 mg metaproterenol diluted with normal saline solution to a volume of 2.5 ml (unit dose preparation) if they received placebo via the MDI. Nebulizer treatments were delivered with a compressor-operated Acorn II nebulizer (Marquest Medical, Englewood, CO) with 7" tubing, mouthpiece, and 5½" flextube on the exhalation port. Metaproterenol solution and normal saline solution for nebulization were prepared in sterile syringes and refrigerated before the study. Each nebulizer treatment lasted approximately six minutes. Each subject received three treatments with the nebulizer and three with the MDI and InspirEase at 30-minute intervals. Just before the second treatment and 30 minutes after the third treatment, subjects repeated the dyspnea assessment on the Borg scale and three FEV_1 maneuvers. Blood pressure level, pulse and respiratory rates were measured 30 minutes after the third treatment. At the end of the study, patients were questioned about palpitations, tremulousness, or other possible treatment side effects. They were given supplemental oxygen and intravenous steroids at the discretion of the emergency room physician who was not involved in the study. Intravenous and oral theophylline were withheld before and during the study period. All subjects were managed by the emergency room physician after the study was completed.

Statistical Analysis

Data for subjects with asthma were analyzed separately from those with COPD. A p value of less than 0.05 was considered to be significant. Mean changes in measured variables before and after treatment within treatment groups, for the subgroup of patients with a baseline $FEV_1 < 0.9$ L and dyspnea scores ≥5 were analyzed with Student's *t* test for paired data and the two-way analysis of variance with the Newman-Keul's multiple range test. Mean changes between treatment groups were compared with Student's *t* test for nonpaired samples. The comparative frequency of concomitant corticosteroid therapy, treatment side effects, post-study emergency room therapy, and hospitalizations was assessed with Fisher's exact probability test.

Results

There were 101 subjects evaluated for participation in the study, but 26 were excluded because they did not meet the entry criteria or had participated in the study during a previous emergency room visit. Subjects randomized to the two treatments were well matched at baseline within the diagnostic groups for age, sex, pack years of smoking, serum theophylline levels, FEV_1, and dyspnea scores (Table 1), as well as pulse rate, respiratory rate, and blood pressure (Table 2). In the 53 patients considered to have asthma by our entry criteria, FEV_1 and dyspnea score improved significantly at 30 and 90 minutes after the start of treatment in both treatment groups (Fig 1). Values for FEV_1 and for dyspnea score were not significantly different between the treatment groups at either time point. In the 22 patients considered to have COPD, the dyspnea score improved significantly at 30 and 90 minutes in both treatment groups. The FEV_1 improved significantly at 30 minutes only in the patients treated with metaproterenol by wet nebulizer and in both treatment groups at 90 minutes (Fig 2). Nonetheless, as for patients with asthma, there was no significant difference between treatment groups for any variable at any time point studied. In patients most severely breathless at baseline (dyspnea score ≥5) the mean dyspnea scores were also not significantly different after treatment. The mean outcome score for severely breathless patients with COPD treated with the MDI was 2.4 and 3.5 for those treated with the nebulizer ($p = 0.26$), and 3.3 and 2.5 for patients with asthma treated with the MDI and nebulizer respectively ($p = 0.29$). In patients with asthma with the most severe airway obstruction (baseline $FEV_1 < 0.9$ L), the dyspnea score improved significantly at 30 and 90 min, but FEV_1 improved significantly only at 90 min (Fig 3). For all data points representing significant improvements, values were again not significantly different between treatment groups.

The comparison between baseline and post-study pulse rate, respiratory rate, and blood pressure is presented in Table 2. The mean systolic and diastolic blood pressure dropped in all groups; however, the decrease in diastolic pressure was not significant for patients with COPD treated with the MDI because of one subject with a post-study diastolic pressure of 120 mm Hg. The mean pulse rate decreased after treatment in all groups except for patients with COPD treated with the nebulizer. However, the decrease was significant compared to baseline only for patients with COPD treated with the MDI. The respiratory rate decreased after treatment in all groups and was significant for all except patients with COPD treated with the nebulizer where there was a larger standard deviation. The only statistically significant difference between treatment groups was a greater fall in pulse rate in

Table 1—*Selected Baseline Characteristics According to Treatment and Diagnostic Groups ± SEM*

Group	N	Sex % male	Age	Cigarettes, Pack Years	Theophylline Level (mg/L)	FEV_1 (L)	Dyspnea Score (Borg Scale)
COPD							
MDI with InspirEase	10	70	55±4	40±0.7	10.2±2.7	1.1±0.1	5.7±0.8
Nebulizer	12	69	57±3	43±0.8	8.9±2.2	0.9±0.1	5.2±0.8
p value			NS*	NS	NS	NS	NS
Asthma							
MDI with InspirEase	27	56	38±3	6±0.2	6.9±1.6	1.2±0.1	5.0±0.4
Nebulizer	26	56	39±3	9±0.3	5.3±1.1	1.1±0.1	5.2±0.5
p value			NS	NS	NS	NS	NS

*NS = not significant.

patients with COPD treated with the MDI compared with patients treated with the nebulizer (Table 2).

Also, there was no significant difference between treatment groups in the number of post-study complaints of palpitations, tremulousness, or other side effects; in the need for concomitant corticosteroid therapy; in the need for additional bronchodilator therapy after the study; and in the number of patients who required hospitalization (Table 3).

Discussion

We were unable to demonstrate that bronchodilator therapy with the nebulizer was preferable to the MDI with reservoir spacer for the administration of metaproterenol aerosol to subjects who presented to the emergency room with acute asthma or COPD. The results of the present study indicate that the MDI with InspirEase and the compressor driven nebulizer produce not only equivalent bronchodilation, but also equivalent improvement in dyspnea. Furthermore, the two methods of delivery resulted in equivalent rates of hospital admission and were equally tolerated by patients in both diagnostic groups. Even patients with asthma who had very severe airway obstruction (initial FEV_1 <0.9 L), a group commonly provided with home nebulizers, responded equally well to both modes of aerosol delivery. The significantly higher heart rate noted in COPD subjects treated with the nebulizer may have resulted from the larger dose of metaproterenol that was administered.

We prospectively stratified our subjects into COPD and asthma groups according to smoking history and age of onset of symptoms because we did not have previous records and documented histories for all the patients who presented to the emergency room. We suspect that this is the case in many emergency rooms where treatment must be instituted without detailed background information.

We selected the InspirEase for use with the MDI for several reasons. It is conveniently portable and requires little maintenance. The manufacturer's recommendation is that the bag be changed approximately every three weeks. The InspirEase mouthpiece contains a reed that makes a noise if the inspiratory flow rate exceeds 0.3 L/s, thus encouraging patients to maintain an inspiratory flow rate slow enough to reduce air turbulence and impaction of the aerosol in the upper airway. The device does not contain a one-way valve that may stick, as does the Nebuhaler.[14] When they use the InspirEase, patients need hold their breath only five seconds after inhaling the aerosol. They may then exhale into the bag one time without activating the MDI and rebreathe any remaining suspended particles.

Because of the small number of subjects with severe obstruction and the slight trend toward more improvement with the nebulizer, we cannot exclude the possibility that the nebulizer may be preferable in this group. On the other hand, it is possible that we underestimated the potential bronchodilator effect that could be achieved with the MDI and InspirEase. We studied only one dose of MDI-delivered metaproterenol (1.95 mg×3) and it is conceivable that bronchodilation could have been enhanced with a

Table 2—*Change in Vital Signs after Treatment ± SEM*

Group	N	Pulse B	Pulse A	Respirations B	Respirations A	Systolic BP B	Systolic BP A	Diastolic BP B	Diastolic BP A
COPD									
MDI with InspirEase	10	93±4	86±4†*	26±2	22±1*	142±5	136±4*	92±6	83±7
Nebulizer	12	104±5	104±3	28±3	23±2	155±10	130±3*	92±6	77±3*
Asthma									
MDI with InspirEase	27	97±4	93±3	24±2	21±1*	140±4	126±3*	87±3	80±3*
Nebulizer	26	103±5	100±4	25±2	19±1*	131±4	126±3*	84±3	77±2*

B = Before treatment; A = 30 min after third treatment; † = significantly less than nebulizer treatment ($p<.05$); * = significantly less than baseline ($p<.05$).

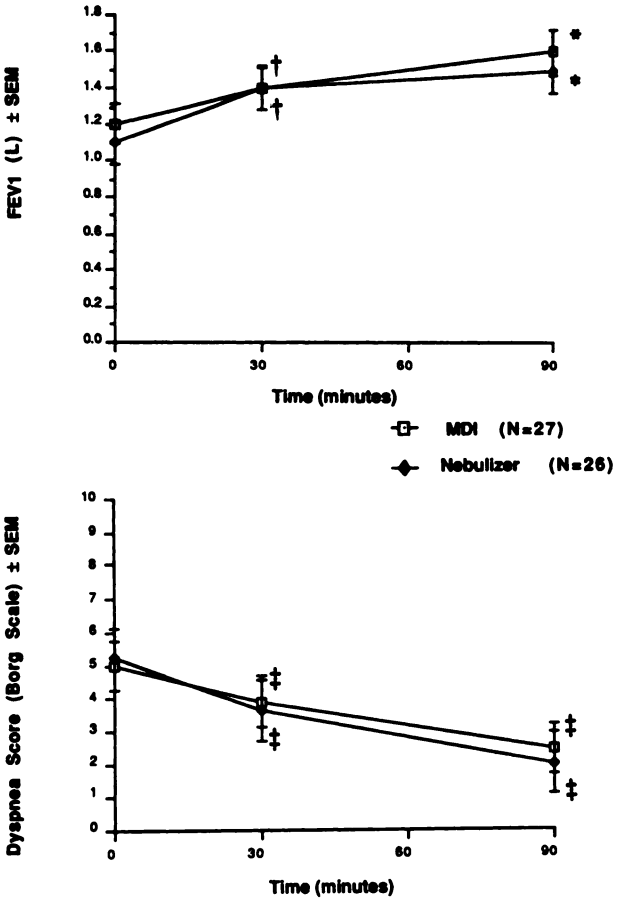

FIGURE 1. Mean values for FEV_1 (±SEM) (*upper panel*) and dyspnea score (*lower panel*) in 27 patients with asthma treated with metaproterenol via MDI and InspirEase and in 26 patients with asthma treated with metaproterenol via nebulizer. * = significantly different from baseline ($p \leq .001$); † = significantly different from baseline ($p < .05$); ‡ = significantly different from baseline ($p = .005$).

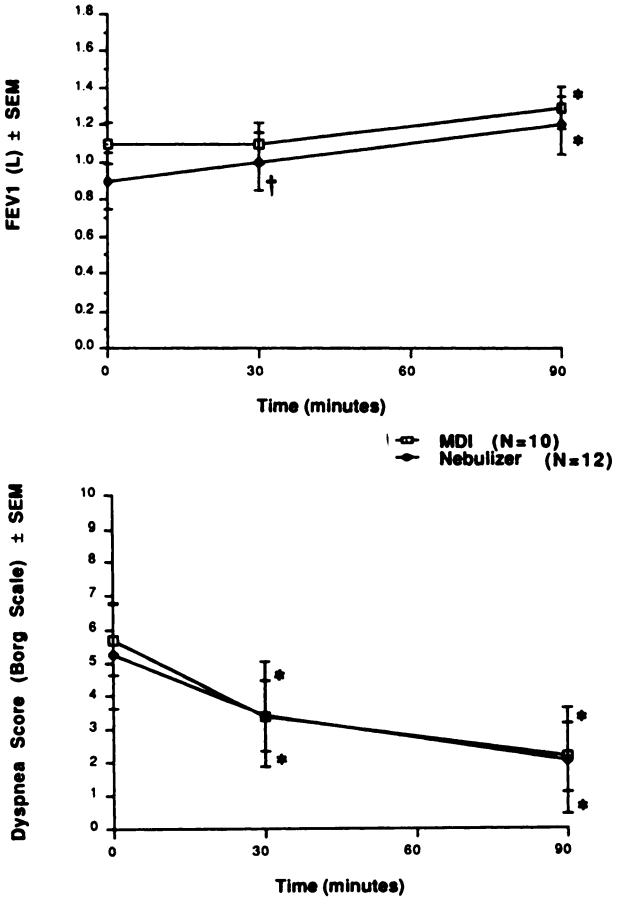

FIGURE 2. Mean values for FEV_1 (±SEM) (*upper panel*) and dyspnea score (*lower panel*) in 10 patients with COPD treated with metaproterenol via MDI and InspirEase and in 12 patients with COPD treated with metaproterenol via nebulizer. * = significantly different from baseline ($p \leq .005$); † = significantly different from baseline ($p < .05$).

larger dose. Additional studies with larger numbers of subjects and higher doses of MDI-delivered bronchodilator would be necessary to firmly establish that the MDI with spacer and nebulizer are equivalent for patients with severe obstruction.

Our findings are consistent with previous studies comparing nebulizers with the MDI with tube- and pear-shaped spacers in asthmatic subjects referred to in the introduction to this article and three other studies comparing the nebulizer and MDI alone for patients with stable COPD. One study[15] showed that the MDI alone was superior to the nebulizer for subjects with chronic COPD with obstruction comparable to that of subjects in our study. Two other studies performed in a double-blind fashion[13,17] showed that the MDI and nebulizer were equivalent in subjects with chronic airflow obstruction comparable to the subgroup in our study with a baseline FEV_1 of less than 0.9 L. In another study[4] no difference was found between the tube-shaped spacer and MDI compared with the nebulizer in hospitalized patients who were prescribed aerosolized bronchodilators. The diagnoses of the subjects were not reported, however, so we could not adequately compare the results with our study. Two previous studies in asthmatic patients with acute obstruction were not performed double-blind and revealed conflicting results. One group[16] reported that the MDI with pear spacer (Nebuhaler) was equivalent to the nebulizer, while the other[14] reported that the nebulizer was superior. In the latter study, Nebuhaler spacer aerosol delivery was impaired by a one-way valve that patients with acute obstruction were unable to close.

Nevertheless, compressor-driven nebulizers continue to be widely prescribed for outpatients, in part because of the widespread belief that they are more effective than metered-dose inhalers in treating acute exacerbations of airway obstruction. This belief is largely due to the common clinical observation that patients come to the emergency room having used their MDI without apparent benefit and are often promptly relieved by inhalation of the same bronchodilator drug delivered by compressor-driven nebulizer. Indeed, many of the subjects in our study

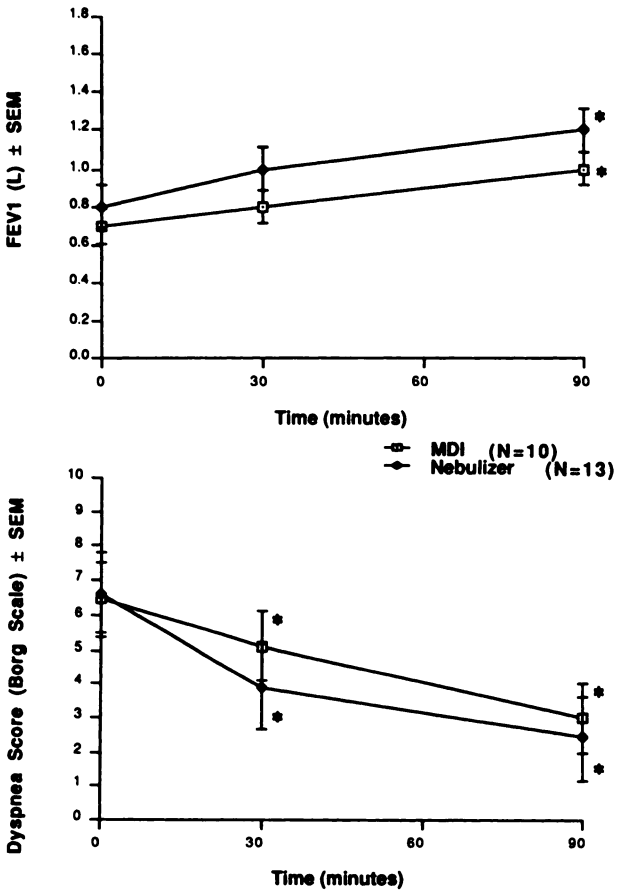

FIGURE 3. Mean values for FEV_1 (±SEM) (*upper panel*) and dyspnea score (*lower panel*) in 10 patients with severe obstruction with asthma treated with metaproterenol via MDI and InspirEase, and in 13 patients with severe obstruction with asthma treated with metaproterenol via nebulizer. * = significantly different from baseline (p = .025).

had been using their MDIs without benefit before arrival in the emergency room. However, the results of the present study suggest that the subsequent improvement in lung function in the emergency room was not due to the superior effects of the compressor-driven nebulizer. We suspect (but cannot prove) that patients failed to respond to inhaled bronchodilator medications before arrival in the emergency room because they either used too low a dose or failed to adequately coordinate their breathing with activation of their inhalers. Both problems were overcome by the protocol for MDI with InspirEase used in this study. As in our study, other investigators have found the MDI to be effective for patients with acute obstruction when the doses of bronchodilator drug administered are as much as six times those routinely advocated.[7,13,16] These doses are still significantly lower than those recommended for administration via nebulizer.

We conclude that the reservoir bag spacer can eliminate concerns about the ability of patients with acute obstruction to use the MDI effectively and can be used in emergency rooms in place of the nebulizer. Also, it is important that proper use of the MDI be reinforced before discharge when the patient's condition has stabilized. Staff time is necessary, however, to train patients to use the MDI with spacer attachment properly and it may be more practical to use nebulizers in some emergency rooms where compressed gases are easily accessible. However, in most circumstances, the MDI with spacer is more convenient, less expensive, and as effective as the nebulizer for the treatment of acute airflow obstruction. This mode of therapy should therefore obviate the need for pressure-driven nebulizers for treatment of acute airflow obstruction in the home, clinic, physician's office, and other settings where a source of compressed gas is not readily available.

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Table 3—*Other Study Variables*

	Side Effects N* (%)	Concomitant Corticosteroids N* (%)	Additional Therapy after Study N* (%)	Hospitalizations N* (%)
COPD				
MDI and InspirEase	0	3 (30)	6 (60)	2 (20)
Nebulizer	2 (17)	4 (33)	7 (64)	2 (17)
p value	NS†	NS	NS	NS
Asthma				
MDI and InspirEase	7 (25)	4 (14)	18 (64)	4 (14)
Nebulizer	3 (12)	2 (8)	15 (58)	5 (19)
p value	NS	NS	NS	NS

*N = number of subjects
†NS = not significant

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