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COMPARISON OF SALBUTAMOL DELIVERED BY NEBULIZER OR METERED-DOSE INHALER WITH A PEAR-SHAPED SPACER IN ACUTE ASTHMA

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ABSTRACT

In severe acute asthma, beta-agonist bronchodilator aerosols are the standard first line of treatment. More controversial are the method of delivery and the dose. The purpose of this study was to compare the efficacy of salbutamol delivered by jet nebulizer with that of salbutamol delivered by metered-dose inhaler (MDI) attached to a pear-shaped spacer. Doses were calculated on the basis of the percentage of total dose that reaches the lower airway. Ninety-seven patients, ages 18 to 50 years, with acute bronchial asthma previously treated at a hospital emergency room, were enrolled in this randomized, double-blind, placebo-controlled trial. The MDI-spacer group received salbutamol, delivered via MDI into a spacer device, in four puffs actuated in rapid succession (100 μg per actuation) at 10-minute intervals. The nebulized group was treated with nebulized salbutamol, 1.5 mg, via nebulizer at 15-minute intervals. The final mean dose was 5.61 mg for the MDI-spacer group and 11.8 mg for the nebulized group (2:1 dose ratio). Hospitalization was mandatory if the total treatment time exceeded 6 hours. The spirometric values in both groups improved in a similar manner. There were no differences between groups for any variable at any point studied. The duration of emergency room treatment was 2.17 ± 1.69 hours in the MDI-spacer group and 1.94 ± 1.49 hours in the nebulized group ($P = 0.68$). The hospital admission rate was similar in both groups (10.2% and 8.33%, respectively; $P = 0.95$). There were no differences between groups when patients admitted or discharged were examined separately. Similar patterns were seen in patients with severe airway obstruction (forced expiratory volume in 1 second < 0.9 L). The final mean doses of salbutamol delivered by the nebulizer or the MDI-spacer were equivalent when they were calculated on the basis of the percentage of total dose that reaches the lower airway. Both the MDI-spacer and nebulized regimens provided similar rates of spirometric and clinical improvements. We conclude that there is no demonstrable advantage in a jet nebulizer over an MDI with a spacer for treating acute asthma in the emergency room.

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INTRODUCTION

In severe acute asthma, beta-agonist bronchodilator aerosols are the standard first line of treatment.[1] More controversial are the dose, frequency of treatment, and method of delivery associated with optimal bronchodilation. Generally, hand-held nebulizers are most commonly used for emergency room patients, while metered-dose inhalers (MDI) have been used primarily in outpatients.[2] Consequently, many physicians assume that nebulizer treatment is superior to MDI treatment with or without a spacer. More important, a constant question for many clinicians is what dose of beta-agonist by MDI is equivalent to that by nebulizer.[3] Numerous studies[4–13] have compared the bronchodilator efficacy of beta-agonist aerosols inhaled from MDIs or jet nebulizers. Healthy adults and patients with asthma, ranging from stable to severe acute or chronic asthma, have been tested. Although there have been conflicting reports, recent studies seem to demonstrate similar therapeutic responses with both methods of drug delivery. However, there are a number of problems in correctly interpreting these data. Most of the studies excluded patients with severe obstruction, which is one of the main indications for use of a nebulizer, and the doses used varied widely. Previous studies have reported equipotent dose ratios of beta-agonists delivered by MDI and by nebulizer ranging from 1:1 to 10:1. From a different point of view, Blake et al[14] compared the effects of salbutamol given by MDI or nebulizer on airway reactivity as assessed by the (pre:post) dose ratio of the histamine PC_{20} (concentration required to decrease forced expiratory volume in 1 second [FEV_1] by 20%) before and after drug administration. The data suggested that administering 10 puffs from an MDI is likely to deliver approximately the same amount of salbutamol as administering 2.5 mg of the nebulizer solution (2:5 dose ratio).

The purpose of our study was to compare the efficacy of salbutamol delivered by jet nebulizer with that of salbutamol delivered by MDI attached to a pear-shaped spacer. Doses were calculated on the basis of the percentage of total dose that reaches the lower airway with each method.

PATIENTS AND METHODS

Ninety-seven patients with acute exacerbation of asthma who were treated at the Emergency Room of Military Hospital, Montevideo, were enrolled in the trial. All patients met the criteria of the American Thoracic Society.[15] Patients between ages 18 and 50 years with a peak expiratory flow (PEF) and a FEV_1 below 50% of predicted value were eligible for the study. Patients with history of chronic cough, or cardiac, hepatic, renal, or other medical disease were excluded, as were pregnant women. An expressed willingness to participate in the study was required, and all patients pro-

vided written informed consent. The study was approved by the Hospital Ethics Committee.

Patients were assigned by random number allocation to one of two treatment groups. Patients in the first group (n = 49) were given salbutamol delivered by an MDI into a spacer device* in four puffs actuated one at a time 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 μm.[16] The Volumatic* spacer is a pear-shaped extension tube of 750-ml volume and 22-cm length with a one-way inhalation valve. Each puff was followed by two deep inhalations from the spacer. Patients in the second group (n = 48) were treated with nebulized salbutamol, 0.3 ml (1.5 mg) diluted in 4 ml of normal saline solution, via a jet nebulizer† driven by 100% oxygen at a flow rate of 8 L/min at 15-minute intervals. A mouthpiece was used. The nebulization time was approximately 10 minutes and nebulization was terminated when no solution was visible in the reservoir. Both treatments were administered by emergency room physicians who were not involved in the study.

The MMAD of the particles generated by the nebulizer was about 2.0 μm (data obtained from the manufacturer). With MDI and a pear-shaped spacer, the dose that reaches the lungs ranges from 15% to 20% of the total dose.[17,18] Jet nebulizers, however, deposit only between 8% and 10% of the total dose.[19] We administered 26 puffs/hr, or 2.6 mg. Assuming a 15% to 20% rate of deposition in the lungs, the total delivery of salbutamol to the lungs would be between 390 μg/hr and 520 μg/hr. Based on these data, a salbutamol dose of 6 mg/hr via nebulizer was considered approximately equivalent to 2.6 mg/hr via MDI. Assuming an 8% to 10% rate of lung deposition, the total lung delivery of salbutamol via nebulizer would be between 480 μg/hr and 600 μg/hr.

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 an Ava-Neb jet nebulizer driven by 100% oxygen at a flow of 8 L/min at 15-minute intervals. The nebulization time was approximately 10 minutes. Patients in the nebulized group received four puffs from an identical MDI that contained only propellant at 10-minute intervals. Each patient was given oxygen by nasal prongs at a rate of 4 L/min. The condition of each patient was reassessed every 30 minutes after the initial hour of therapy, and the decision for continued treatment or discharge from the emergency room was made at that time.

Within the first 6 hours after each patient was admitted to the emergency room, the following variables were measured, immediately before starting treatment and at 30-minute intervals until discharge or hospital

* Trademark: Volumatic® (Allen & Hanburys Ltd, Greenford, United Kingdom).
† Trademark: Ava-Neb® No. 1782 jet nebulizer (Hudson Respiratory Care Inc., Temecula, California).

admission: heart rate, respiratory rate, systolic and diastolic blood pressures, PEF, FEV_1, forced vital capacity (FVC), accessory muscle use, dyspnea, and wheezing. Heart rate was measured by continuous electrocardiogram. The PEF was measured with a mini-Wright peak flow meter (Clement Clarke Inc., Columbus, Ohio). The highest of three values was recorded. Because the accuracy of the mini-Wright meter deteriorates after 200 uses,[20] we changed it periodically. FEV_1 and FVC were measured using a Vitalograph Compact spirometer (Vitalograph Ltd., Maids Moreton House, Buckingham, United Kingdom) that was calibrated daily using a test syringe. 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.[21] Before treatment, serum theophylline concentrations were measured in all patients, and the patients were asked to describe their symptoms using a four-point scale on which 0 = none, 1 = mild, 2 = moderate, and 3 = severe.[22] All measures were made by one of the authors.

Patients were discharged from the emergency room when they were free of dyspnea, when accessory muscle use abated, and when wheezing was judged to be minimal or completely resolved. All patients with persistent wheezing, dyspnea, or accessory muscle use at rest despite 6 hours of emergency room treatment were admitted to the hospital. The decision to discharge or admit a patient was made by senior emergency room staff members who were unaware of the treatment group assignment. Oral steroids (a 5-day taper starting at 40 mg of prednisone daily) were prescribed for all discharged patients. At the end of the therapy, patients were asked whether they had experienced nausea, palpitations, tremor, anxiety, or headache.

Statistical Analysis

The Mann-Whitney U-test, chi-square test with Yates correction, and unpaired Student's *t* test were used to compare groups. Changes in PEF, FVC, and FEV_1 were evaluated using a one-way analysis of variance (ANOVA) with the Newman-Keul's multiple range test. All probabilities reported were two-tailed. All data are expressed as mean ± 1 standard deviation (SD). $P < 0.05$ was considered statistically significant.

RESULTS

The two treatment groups were comparable with respect to age, sex, weight, height, heart rate, respiratory rate, blood pressure, PEF, FVC, FEV_1, theophylline blood levels, subjective symptom index, corticosteroids used within the past 7 days, and duration of attack (Table I). Twenty-four (50%) patients in the nebulized group and 24 (48.9%) in the MDI-spacer

Table I. Patient characteristics at study entry. (Values are expressed as mean ± SD.)

	Nebulized Group (n = 48)	MDI-Spacer Group (n = 49)	P
Age (yr)	31.9 ± 12.0	32.4 ± 12.1	0.86
Sex			
Male	22	24	
Female	26	25	
Weight (kg)	65.6 ± 14.0	55.3 ± 10.2	0.89
Height (m)	1.6 ± 0.13	1.6 ± 0.18	0.41
Heart rate (beats/min)	105.0 ± 17.1	102.7 ± 16.3	0.65
Blood pressure (mmHg)			
Systolic	125.5 ± 17.6	126.4 ± 16.5	0.60
Diastolic	77.1 ± 15.6	79.3 ± 16.2	0.58
Respiration rate (breaths/min)	20.7 ± 5.61	21.6 ± 5.08	0.22
Predicted PEF (L/min)	523.7 ± 70.4	538.7 ± 69.7	0.64
PEF (mean % of predicted)	31.7 ± 11.6	32.2 ± 9.59	0.97
PEF (L/min)	166.5 ± 60.5	172.9 ± 51.0	0.71
Predicted FVC (L)	3.9 ± 0.86	4.1 ± 0.83	0.23
FVC (mean % of predicted)	48.0 ± 16.1	47.5 ± 13.7	0.85
FVC (L)	1.8 ± 0.62	1.9 ± 0.58	0.70
Predicted FEV_1 (L)	3.3 ± 0.86	3.4 ± 0.75	0.34
FEV_1 (mean % of predicted)	30.0 ± 10.6	28.6 ± 10.0	0.69
FEV_1 (L)	0.9 ± 0.38	0.9 ± 0.33	0.70
Theophylline (mg/L)	3.0 ± 4.30	2.6 ± 3.22	0.83
Symptom index	1.9 ± 0.32	2.1 ± 0.47	0.22
Duration of attack (hr)	30.2 ± 21.2	27.9 ± 24.2	0.42
Corticosteroids used within past 7 days (% of patients)	37.5 ± 18.0	32.6 ± 16.0	0.44

PEF = peak expiratory flow; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second.

group had self-administered methylxanthines 24 hours before coming to the emergency room ($P = 0.93$). Thirty (62.5%) patients in the nebulized group and 26 (53%) in the MDI-spacer group had been pretreated with beta-agonists ($P = 0.68$).

The effects of each treatment on PEF, FVC, and FEV_1 are shown in Figures 1 through 3. Mean PEF improved significantly over baseline values in both the nebulized and the MDI-spacer groups ($P < 0.001$ by ANOVA). The magnitude of the improvement was significant at 30 minutes (76.8 ± 46.0 L/min in the nebulized group and 83.0 ± 61.3 L/min in the MDI-spacer group; $P < 0.01$) and at the end of treatment (112.3 ± 52.4 L/min in the nebulized group and 118.7 L/min in the MDI-spacer group; $P < 0.001$). Mean FVC improved significantly over pretreatment values in both groups ($P < 0.001$). The nebulized and MDI-spacer improvements were significant at 30 minutes (0.68 ± 0.44 L and 0.74 ± 0.58 L, respectively; $P < 0.01$) and at the end of treatment (0.96 ± 0.58 L and 1.02 ± 0.65 L, respectively; $P < 0.001$). The same pattern held for changes in FEV_1. At 30 minutes, FEV_1 increased 0.51 ± 0.30 L in the nebulized group and 0.58 ± 0.46 L in the MDI-spacer group ($P < 0.01$). At the end of treatment, FEV_1 increased 0.76 ± 0.42 L in the nebulized group and 0.85 ± 0.53 L in the MDI-spacer group ($P < 0.001$). There were no significant differences

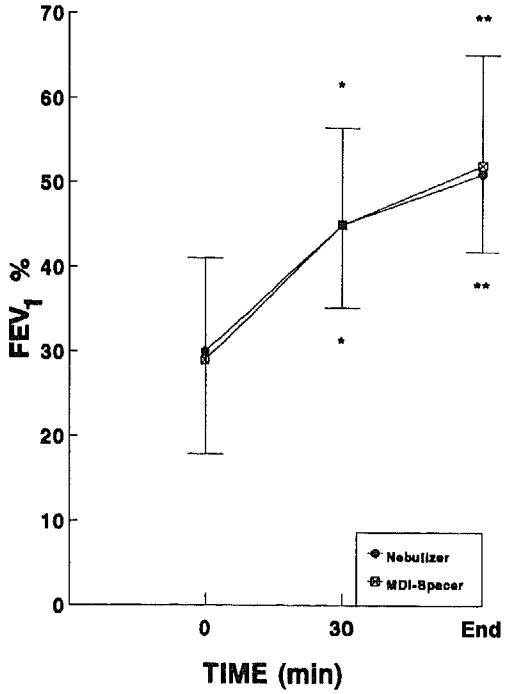

Figure 1. Force expiratory volume in 1 second (FEV_1) response, expressed as mean percent of predicted values. *$P < 0.01$; **$P < 0.001$.

between groups for any variable at any time point nor were there any significant differences at discharge.

The mean duration of emergency room treatment was 1.94 ± 1.49 hours in the nebulized group and 2.19 ± 1.67 hours in the MDI-spacer group ($P = 0.68$). The hospital admission rate was similar in both groups. Of 9 admitted patients, 4 (8.33%) were from the nebulized group and 5 (10.2%) from the MDI-spacer group ($P = 0.95$ by chi-square test). There were no differences between groups for all measured variables.

Similar results were obtained when patients admitted or discharged were examined separately (Tables II and III). The duration of treatment, improvement in PEF, FVC, and FEV_1, and subjective response at final disposition were similar in both the nebulized and the MDI-spacer groups (Table IV).

In asthmatic patients with the most severe airway obstruction (baseline $FEV_1 < 0.9$ L), there were no significant differences in spirometric values between treatment groups (Table V).

The final mean doses of salbutamol in both the nebulized and the MDI-spacer groups were 11.8 ± 9.11 mg and 5.61 ± 4.08 mg, respectively (2:1 ratio). Because jet nebulizers deposit 10% of the total dose, the total

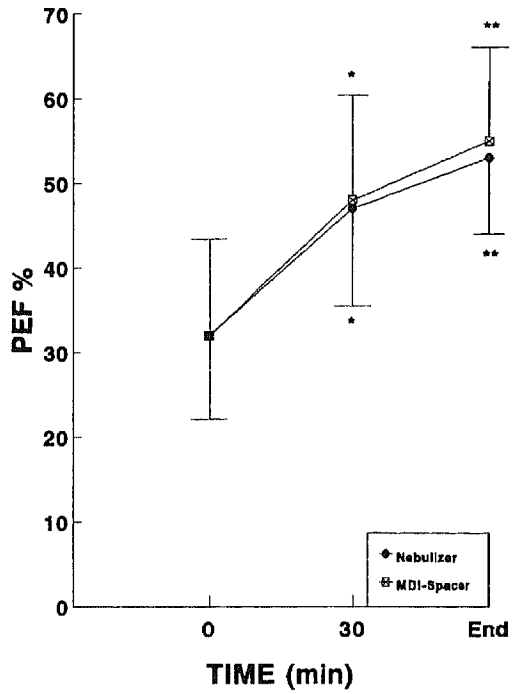

Figure 2. Peak expiratory flow (PEF) response, expressed as mean percent of predicted values. *$P < 0.01$; **$P < 0.001$.

lung delivery of salbutamol would be 1.18 ± 0.91 mg. Assuming that 20% of the dose was deposited in the lungs, the MDI-spacer dose that reached the lungs would be 1.12 ± 0.81 mg ($P = 0.98$).

Tremor was the most frequently observed adverse effect (28% of patients in the nebulized group and 36% in the MDI-spacer group). Patients in the nebulized group reported headache (16%), palpitations (9%), anxiety (9%), and nausea (6%). The rates for these side effects in the MDI-spacer group were 10%, 9%, 9%, and 4%, respectively. There were no significant differences between groups. Nonsignificant decreases in heart rate were seen in both groups. At the end of the treatment, patients in the nebulized group had a decrease in heart rate of −0.44 ± 14.2% and those in the MDI-spacer group had a decrease of −1.32 ± 13.8% from baseline values ($P = 0.99$).

DISCUSSION

Bronchodilator therapy administered via a jet nebulizer for acute asthma is equivalent to that administered with an MDI-spacer. The results of our study indicate that an MDI-with-spacer and a jet-nebulizer produce equiv-

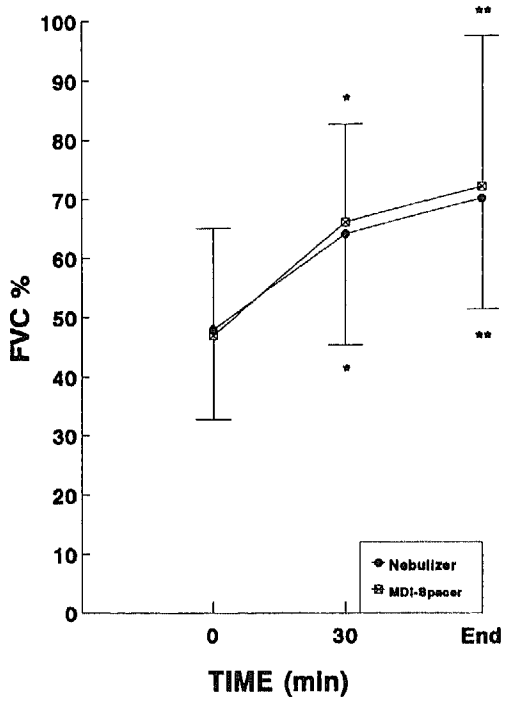

Figure 3. Forced vital capacity (FVC) response, expressed as mean percent of predicted values. *$P < 0.01$; **$P < 0.001$.

alent bronchodilatation and clinical improvement. The two methods resulted in similar rates of hospital admission and were equally well tolerated by patients in both treatment groups. Patients with very severe airway obstruction ($FEV_1 < 0.9$ L), a group commonly treated with nebulizers, responded equally well to both modes of aerosol delivery. However,

Table II. Characteristics of patients at emergency room discharge. (Values are expressed as mean ± SD.)

	Nebulized Group (n = 44)	MDI-Spacer Group (n = 44)	P
PEF (mean % of predicted)	55.2 ± 13.7	57.6 ± 14.0	0.40
PEF (L/min)	287.8 ± 78.8	311.1 ± 84.2	0.21
FVC (mean % of predicted)	72.4 ± 19.4	74.2 ± 14.9	0.87
FVC (L)	2.9 ± 0.91	3.1 ± 0.80	0.52
FEV_1 (mean % of predicted)	53.0 ± 18.1	54.5 ± 15.3	0.53
FEV_1 (L)	1.7 ± 0.58	1.9 ± 0.61	0.94
Duration of emergency room treatment (hr)	1.7 ± 1.02	1.8 ± 1.30	0.94
Confidence interval	1.41–1.99	1.43–2.17	

PEF = peak expiratory flow; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second.

Table III. Characteristics of patients at hospital admission. (Values are expressed as mean ± SD.)

	Nebulized Group (n = 4)	MDI-Spacer Group (n = 5)	P
PEF (mean % of predicted)	32.5 ± 8.18	30.2 ± 12.7	0.56
PEF (L/min)	166.2 ± 42.6	165.0 ± 68.2	0.98
FVC (mean % of predicted)	47.3 ± 6.86	43.7 ± 10.3	0.99
FVC (L)	2.0 ± 0.25	2.1 ± 0.65	0.99
FEV_1 (mean % of predicted)	28.0 ± 3.78	24.1 ± 6.18	0.49
FEV_1 (L)	1.2 ± 0.45	0.9 ± 0.43	0.52
Symptom index	1.2 ± 0.31	1.3 ± 0.46	0.71

PEF = peak expiratory flow; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second.

there are several important differences between our investigation and other studies.

First, many studies exclude patients with severe obstruction. For example, Maguire et al[12] concluded that metaproterenol delivered by nebulizer results in greater spirometric improvement in patients with acute obstructive pulmonary disease than the conventional dosage of metaproterenol delivered by MDI-spacer. At entry, the mean percent of FEV_1 predicted was between 42.8% and 45.6%, which is in contrast to the FEV_1 percentages in our study (28.6% and 30%), suggesting that the patients in the Maguire study[12] were not as severely ill as those in our study. In a similar study, Morley et al[10] reported on patients with a baseline mean percent of FEV_1 predicted to be 39.1% to 51.9%.

Second, beta-agonist doses vary widely among studies, and there is controversy over the equivalent dosage for the two delivery systems. Previous studies comparing inhalation by MDI and nebulizer have used different doses of beta-agonist: 200 or 400 μg of salbutamol by MDI compared with 5 or 10 mg by nebulizer.[23,24] Bronchodilatation was usually greater

Table IV. Characteristics of all patients at final disposition. (Values are expressed as mean ± SD.)

	Nebulized Group (n = 48)	MDI-Spacer Group (n = 49)	P
PEF (mean % of predicted)	53.4 ± 14.7	55.1 ± 16.1	0.44
PEF (L/min)	278.6 ± 81.1	296.7 ± 92.8	0.30
FVC (mean % of predicted)	70.4 ± 19.6	71.8 ± 16.9	0.84
FVC (L)	2.7 ± 0.91	2.9 ± 0.88	0.28
FEV_1 (mean % of predicted)	51.3 ± 18.6	51.6 ± 17.4	0.69
FEV_1 (L)	1.7 ± 0.64	1.8 ± 0.66	0.43
Duration of emergency room treatment (hr)	1.9 ± 1.49	2.1 ± 1.69	0.68
Confidence interval	1.55–2.33	1.72–2.66	
Hospital admission rate (% of patients)	4.0 ± 8.33	5.0 ± 10.2	0.95

PEF = peak expiratory flow; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second.

Table V. Characteristics of patients with severe airway obstruction ($FEV_1 < 0.9$ L). (Values are expressed as mean ± SD.)

FEV_1	Nebulized Group (n = 20)	MDI-Spacer Group (n = 19)	P
Pretreatment (L)	0.6 ± 0.14	0.6 ± 0.17	0.82
Mean % of predicted pretreatment	19.0 ± 6.61	20.5 ± 7.24	0.64
At 30 minutes (L)	1.0 ± 0.27	1.1 ± 0.43	0.44
Mean % of predicted at 30 minutes	32.4 ± 10.2	37.7 ± 14.8	0.36
At end (L)	1.2 ± 0.40	1.3 ± 0.55	0.63
Mean % of predicted at end	38.7 ± 14.5	43.1 ± 17.5	0.32
Duration of emergency room treatment	2.4 ± 0.04	2.3 ± 0.03	0.30
Confidence interval	1.87–2.93	1.77–2.83	

FEV_1 = forced expiratory volume in 1 second.

with nebulized salbutamol, which may have been due to the large disparity in dose. The dose of beta-agonist that reaches the lower airway probably is substantially smaller when conventional doses of salbutamol are administered by MDI than by nebulizer. The amount of drug that enters the lung from the nebulizer depends on the type of nebulizer (specifically, the aerodynamic mass median diameter) and the way in which it is used. With the Ava-Neb jet nebulizer used in our study, approximately 10% of the dose leaving the nebulizer entered the lungs.[19] With the MDI-with-spacer, approximately 20% of the dose is deposited in the lungs.[17,18] Thus it is not unexpected that Morley et al[10] found that nebulizer therapy was superior to an MDI-spacer in the initial phase of status asthmaticus when they compared 270 μg of salbutamol delivered by MDI-spacer (20% = 54 μg) with 2.5 mg of salbutamol nebulized (10% = 250 μg). However, in our study, the final doses of salbutamol delivered by both the nebulizer and the MDI-spacer were equivalent when they were calculated on the basis of percentage of total dose to reach the lower airway with each method.

Third, the methods used in our study differ substantially from those of other studies.[8–10] We did not give a fixed number of doses to all patients, but instead continued treatment until symptoms were eliminated. Thus we were able to assess length of stay in the emergency room and discharge outcome for the two treatment groups. The mean duration of treatment was 1.94 ± 1.49 hours in the nebulized group and 2.19 ± 1.67 hours in the MDI-spacer group. Of 9 admitted patients, 4 were from the nebulizer group and 5 from the MDI-spacer group.

Our data agree with those of Blake et al.[14] Using a bioassay method and administration technique, they 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 (2:7 dose ratio). This ratio is similar to ours (2:1).

Finally, we did not confirm the results of Idris et al,[13] who reported

that patients with the most severe obstruction ($FEV_1 < 0.9$ L) showed a trend toward greater improvement with the MDI system.

Our data indicate that there is no demonstrable advantage to delivering salbutamol by nebulizer rather than by MDI-spacer in the treatment of acute asthma in the emergency room, as long as the doses used are calculated on the basis of the percentage of total drug that reaches the lower airway. We also found that frequent administration of beta-agonists by either system is associated with only minimal signs or symptoms of drug toxicity. Studies comparing the efficacy of MDIs or nebulizers in acute asthma are valid only if equivalent doses are used for each method. Nebulizer therapy is expensive and a potential source of pulmonary infection in the hospital and home. The development of patient- and task-specific MDI accessory devices in recent years has allowed easier, less expensive, and more reliable administration of most aerosol medications. Thus nebulizer therapy is virtually obsolete, except for delivery of drugs available only as liquid solutions or suspensions.[25]

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