A Comparison of Albuterol Administered by Metered Dose Inhaler (and Holding Chamber) or Wet Nebulizer in Acute Asthma*

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Background: Comparative studies of albuterol by wet nebulizer or metered dose inhaler have tested fixed doses of medications. We compared the dose-response relationship to albuterol by wet nebulization or metered dose inhaler in acute asthma.

Methods: Randomized, double-blind, placebo-controlled trial. Patients with acute asthma received either albuterol, 0.4 mg, by metered dose inhaler (and holding chamber) or albuterol, 2.5 mg, by wet nebulizer every 30 min until maximal bronchodilation. Forty patients (forced expiratory volume in 1 s [FEV_1]: 1.15±0.43 L; 36±12 percent predicted) received metered dose inhaler and 40 others (FEV_1: 1.08±0.52 L; 35±16 percent predicted) received wet nebulization.

Results: Twenty-six patients (65 percent) receiving metered dose inhaler and 30 (75 percent) receiving wet nebulization achieved maximal bronchodilation after two doses. Almost all reached maximal bronchodilation by four doses. The FEV_1 improved by 0.72±0.49 L for metered dose inhaler and 0.68±0.61 L for wet nebulizer ($p=0.71$). A significant linear relationship was seen in both groups (metered dose inhaler $r=0.94$; wet nebulizer $r=0.98$) between the log dose of albuterol and change in FEV_1. About ⅙ the wet nebulizer dose of albuterol was needed to achieve similar response to the metered dose inhaler.

Conclusions: Albuterol by metered dose inhaler provided similar bronchodilation to that achieved by wet nebulization in patients with acute asthma. The cumulative dose-response technique is applicable in the emergency department setting and is helpful in comparing the relative utility of various bronchodilator regimens.

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DAM = dose above maximal response; MAX = maximal bronchodilation; MDI = metered-dose inhaler; SMBD-JGH = Sir Mortimer B. Davis-Jewish General Hospital; WN = wet nebulization

Inhaled β-agonists are the treatment of choice in acute asthma. These aerosols may be administered by either metered dose inhaler (MDI) or by wet nebulization (WN). Wet nebulization can produce continuous aerosolization of bronchodilator which deposits in the tracheobronchial tree during normal tidal breathing. In contrast, the MDI delivers bronchodilator aerosol in a single dose that is usually inhaled using a deep inspiration followed by a breathhold. Until recently, bronchodilation achieved by WN was considered to be greater than that attainable after MDI use, and therefore the former was the treatment of choice for in-hospital therapy of asthma.[1,2] However, new evidence has suggested that there is little difference between both forms of treatment in acute asthma.[3-7] Nevertheless, The Expert Panel on the Management of Asthma (National Institutes of Health) recommends delivery of aerosolized bronchodilator by wet nebulizer for acute asthma management of adults in emergency departments.[8]

Conventional doses (two puffs) of β-agonists given by MDI (with holding chamber) may not produce optimal bronchodilation. Some authors suggest 4 to 15 puffs[6,7] while the British Thoracic Society suggests 20 to 50 puffs[9] of β-agonists may be required for maximum bronchodilation in patients with acute asthma. To our knowledge, no study has compared either the dose-response relationship or the maximal response to a β-agonist administered by MDI or WN in patients with acute asthma. In this study, we compared the dose-response relationship to albuterol administered by MDI (with holding chamber) and WN in a group of acutely ill adult asthmatics presenting to the Emergency Department. We also compared the maximum responses and ratio of doses yielding equivalent responses using the two methods of therapy.

Methods

Patients

Eighty-five consecutive eligible patients who presented to the Emergency Department of the Sir Mortimer B. Davis-Jewish General Hospital (SMBD-JGH) with a diagnosis of acute asthma were studied.[10] Patients were eligible for study if they were at least 18 years of age, able to perform spirometry, and had an FEV_1 <70 percent of predicted. Those with complicating medical illness such as pneumonia, ischemic heart disease (acute or chronic), frequent ventricular beats, or unstable angina were excluded. Pregnant or nursing mothers or patients who had received any aerosolized or

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parenteral β-agonists in the Emergency Department were also ineligible for study. This study was approved by the ethics committee of the SMBD-JGH. A signed consent was obtained from each patient.

Treatment Protocol

A double-blind, placebo-controlled, randomized and stratified design was used to establish cumulative dose response relationships to inhaled β-agonist by either WN or MDI in patients with acute asthma. The treatment arms were stratified into two groups based on whether there was concurrent use of additional medication (intravenous aminophylline and/or corticosteroids) given at the discretion of the Emergency Department physician.

Eighty-five patients were initially randomized into two groups.

Group 1: Wet Nebulization (WN)—Forty-four individuals received placebo, four puffs, by MDI with a holding chamber (AeroChamber; Boehringer Ingelheim, Burlington, Ontario, Canada). This was immediately followed by albuterol (Ventolin, Glaxo, Mississauga, Ontario, Canada), 2.5 mg (0.5 ml in 2.0 ml normal saline solution) given by a hand-held disposable updraft nebulizer (Diverse Pulmonary Inc, San Dimas, Calif) and face mask driven by oxygen at a flow rate of 5 to 8 L/min. This system produced particles with a mass median diameter of 3.56 ± 0.089 μm.[11]

Group 2: Metered Dose Inhaler and holding chamber (MDI)—Forty-one individuals received albuterol, four puffs (0.4 mg), by MDI and holding chamber (AeroChamber) with mouthpiece followed by placebo (2.5 ml normal saline solution) administered by WN and driven by oxygen at a flow rate of 5 to 8 L/min. The median aerodynamic diameter of albuterol by MDI and holding chamber has been shown previously to be 1.32 μm (geometric standard deviation, 2.36).[12]

When using the MDI, patients in both groups were instructed to take a slow deep inhalation and to hold each inspiration for at least 5 s. This inspiratory capacity maneuver and breathhold was repeated with each of the four puffs of albuterol or placebo at 1-min intervals. The tidal breathing technique was used during WN. When nebulizer tapping did not result in further aerosolization, the mask was removed from the patient.

After baseline pulmonary function measurements, the above regimens were administered, and repeated every 30 min until maximal bronchodilation was achieved. A minimum of two doses was given to all patients, including those who failed to respond to the first dose. Maximal bronchodilation (MAX) was defined as the dose that produced a plateau in response as determined by a less than 100-ml improvement in FEV_1 between two successive determinations. We defined the dose above maximal response (DAM) as being that dose which in retrospect had not produced further bronchodilation. Although by definition, FEV_1 had not improved at DAM, we searched for toxic effects at both MAX and DAM.

Measurements

After the patient's arrival in the Emergency Department, baseline measurements were made. Spirometry was performed (Vitalograph model S with PFT printer, Lenexa, Kan or the Vitalograph Compact, Lenexa, Kan). The FVC, FEV_1, FEV_1/FVC were determined from three maximal expiratory maneuvers using the curve having the best FEV_1.[13]

If the FEV_1 and other eligibility criteria were met and the patient consented to the study, heart rate, respiratory rate, and BP were measured. Dyspnea was evaluated using the modified Borg Scale.[14,15] Hand tremor was assessed as absent, mild, moderate, or severe. All measurements were collected every 30 min (approximately 20 min following the completion of the WN) until a plateau in response (maximal bronchodilation) was achieved.

Statistical Considerations

The sample size calculations for this study were based on previous work done in the Emergency Department.[6] We assumed an α-error equal to 0.05 and β equal to 0.20. The test employed was two tailed. If the standard deviation associated with the increase in FEV_1 was 0.3 L[6] then, at the set power of 80 percent, 72 patients were necessary to detect a difference of 0.2 L between groups. There were 80 patients who completed the protocol described above.

Initial baseline data were compared by the unpaired Student's *t* test. The data for spirometry (FEV_1, FVC, FEV_1 percent predicted, FVC percent predicted), vital signs (BP, pulse, respiratory rate), and dyspnea were grouped and analyzed separately. Since several dependent variables were measured during the study, a multivariate approach was employed followed by univariate analysis where appropriate.[16] Three specific times (doses) of interest were determined: baseline, at maximal bronchodilation (MAX), and following the next dose above maximal response (DAM). These measurements, made on three occasions, were the within-subject factor (time). The main effect was mode of therapy. The interaction term between mode of therapy and the three specific times (baseline, MAX, and DAM) was also determined.

Regression analysis was performed at MAX to predict the rise in response (FEV_1) per unit dose for both modes of therapy. The horizontal separation of these lines was considered to be a measure of the difference in doses necessary to produce a given response. The slopes of these regressions were compared using *t* tests.

Binary outcomes (tremor, number of subjects with an increase in heart rate greater than 20 beats per minute) were analyzed using χ^2 or Fisher's Exact Test.

All tests were two-tailed; p values less than 0.05 were considered statistically significant. All data are presented as mean ± standard deviation unless otherwise specified.

Results

Eighty-five patients initially entered into the study were randomized into two groups (41 to MDI, 44 to WN). Five of these (four WN, one MDI) were later excluded from study. Two patients initially randomized to WN were withdrawn from study because entry criteria were not met (FEV_1 >70 percent predicted). One patient initially randomized to WN had improved clinically and on spirometry (FEV_1 before, 2.26 L, 51 percent predicted; after, 3.60 L, 81 percent predicted) and discharged himself after three doses; in another, a protocol error was detected (baseline data were not collected prior to drug administration) after the patient finished the study. One other patient (FEV_1 before, 1.19 L, 31 percent predicted) randomized to MDI was removed from study after one dose (15 min into study) because of increased cough, shortness of breath, and diaphoresis. The patient then received albuterol, 5.0 mg, plus ipratropium, 0.25 mg, by wet nebulizer in addition to intravenous corticosteroids. His FEV_1 80 min later was 1.91 L (49 percent predicted) and admission to the hospital was necessary.

The demographic characteristics of the 80 patients completing the study are shown in Table 1. Patients randomized to the two groups were well matched at baseline for age, sex, FEV_1, FVC, FEV_1/FVC percent, and dyspnea score. Eight subjects in the MDI group and five in the WN group were treated concurrently with intravenous aminophylline. Five and three pa-

Table 1—*Patient Characteristics (Mean ± SD)*

	MDI	WN
No.	40	40
Sex, F/M	21/19	24/16
Age, yr	41 ± 18	43 ± 19
(Range)	(18-81)	(18-83)
Initial FEV_1, L	1.15 ± 0.43	1.08 ± 0.52
Percent predicted†	36 ± 12	35 ± 16
Initial FVC, L	2.15 ± 0.75	2.05 ± 0.80
Percent predicted†	55 ± 15	54 ± 18
FEV_1/FVC percent	54 ± 12	52 ± 12
Borg Dyspnea Score	5.5 ± 2.1	5.5 ± 2.8
(Range)	(1.5-10)	(0.5-10)
Previous medications‡		
β-agonists	32	32
Anticholinergics	4	6
Inhaled steroids	8	19
Oral steroids	4	4
Theophylline	19	19
Cromolyn sodium	1	. . .
No medications	5	5

MDI = metered dose inhaler; WN = wet nebulizer.

†Morris JF, Koshi A, Johnson LC. Spirometric standards for healthy nonsmoking adults. Am Rev Respir Dis 1971; 103:57-67

‡Most patients were receiving more than one medication.

tients, respectively, received both intravenous aminophylline and intravenous corticosteroids, and three in the WN group were given intravenous corticosteroids only.

The multivariate analysis of variance results for all dependent variables indicated that the treatment groups had similar responses. The p values between treatment groups for spirometry (FEV_1, FVC, FEV_1 percent predicted, FVC percent predicted), vital signs (BP, respiratory rate, heart rate), and dyspnea score were 0.964, 0.165, 0.743, respectively. Thus, there were no significant differences between MDI and WN groups in pulmonary function, dyspnea score, or toxicity throughout the study. A significant time factor ($p<0.001$) was apparent indicating that pulmonary function, dyspnea score, and vital signs all changed significantly following administration of bronchodilator independent of treatment group. The most important effect in the multivariate analysis is the interaction between mode of therapy and time (dose), which was not significant (spirometry, $p=0.994$; vital signs, $p=0.096$; dyspnea, $p=0.716$), indicating that both methods of therapy achieved similar magnitude of change at MAX and DAM.

The univariate analysis for each dependent variable measured resulted in findings similar to the multivariate analysis. Following treatment, each group achieved significant bronchodilation ($p<0.001$) and a decrease in dyspnea ($p<0.001$) at MAX and DAM compared with baseline (Fig 1 and 2). The changes in FEV_1 from baseline for both groups were similar (MDI, 0.72 ± 0.49 L, 23 ± 16 percent predicted); (WN, 0.68 ± 0.61 L, 22 ± 19 percent predicted). Although

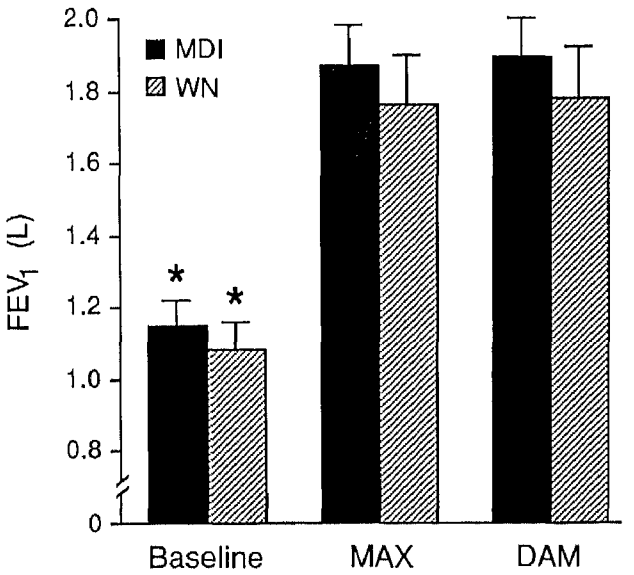

FIGURE 1. Mean FEV_1 (± SEM) was similar for MDI and WN groups at baseline, maximal bronchodilation (MAX), and one dose above maximal bronchodilation (DAM). Both groups showed significant increases at MAX and DAM compared with baseline values. Asterisk = $p<0.001$.

only data for FEV_1 are reported, the FVC response is similar and the changes are also statistically significant.

The changes in respiratory rate, BP, and pulse were small and considered to be clinically insignificant. Although the mean pulse rate increased only slightly, this was statistically significant ($p<0.05$) at DAM in the WN group (Table 2); moreover, there were four patients in the MDI group compared with ten receiving WN who had an increase in pulse of greater than

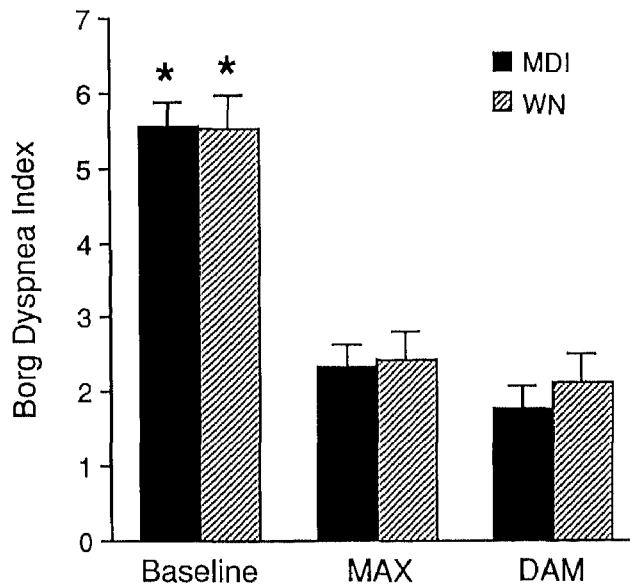

FIGURE 2. Patients treated with albuterol delivered by MDI and WN recorded similar scores in the Borg Dyspnea Index (± SEM) at baseline, MAX, and DAM. Dyspnea decreased significantly from baseline values at MAX and DAM for both MDI and WN groups. Asterisk = $p<0.001$.

Table 2—*Vital Signs Before and After Albuterol*

	MDI			WN		
	Baseline	MAX	DAM	Baseline	MAX	DAM
Respiratory Rate	22 (19-24)	19† (17-20)	19† (17-21)	23 (21-25)	20† (17-22)	19† (17-21)
Pulse	94 (88-100)	93 (87-99)	95 (89-101)	93 (87-98)	97 (91-103)	100† (94-106)
Systolic pressure	131 (126-136)	127† (123-131)	127† (123-132)	123 (116-130)	123 (116-130)	122 (116-127)
Diastolic pressure	85 (82-88)	82† (79-84)	82† (79-84)	82 (79-85)	79† (75-82)	76† (72-79)

MDI = metered dose inhaler; WN = wet nebulizer; MAX = dose producing maximal bronchodilation; DAM = one dose above maximal bronchodilation. Ninety-five percent confidence limits are shown in parentheses.
†$p<0.05$, respiratory rate, pulse, and BP are significantly different from baseline values.

20 beats per minute at DAM ($p=0.07$). There were no arrhythmias detected, although this was not assessed by constant ECG monitoring.

There was an increase in tremor noted after administration of albuterol by either MDI or WN; however, this was usually mild in degree. Two patients receiving treatment by MDI had moderate or severe tremor at baseline. At MAX and DAM, there were five patients with this degree of tremor at each of these points. For WN, the corresponding figures for moderate/severe tremor were 0, 3, and 4 at baseline, MAX, and DAM.

Figure 3 shows the number of doses required in each treatment group to reach maximal bronchodilation. About half of all patients (17/40 [43 percent] in MDI, 20/40 [50 percent] in WN) achieved maximal bronchodilation after albuterol, 0.4 mg by MDI or 2.5 mg by WN. After three doses, 90 percent of MDI patients and 83 percent of WN patients had achieved maximal bronchodilation. Only two patients in the WN group needed more than four doses to achieve maximal bronchodilation.

The relationship between the cumulative dose of albuterol and the change in FEV_1 expressed as percent predicted was examined. There was no significant serial correlation between the responses to different doses of albuterol (Durbin-Watson Test = 2.27). This implies that individuals who responded well to the initial dose of albuterol did not necessarily continue to do so after other doses. We therefore were able to use the cumulative data on all patients for each dose until maximal bronchodilation was achieved for the construction of the dose-response relationships. A significant linear relationship ($p<0.05$) was observed for both MDI and WN (MDI; $r=0.94$) (WN; $r=0.98$) (Fig 4). The slopes of the regression lines (MDI = 48.45 logx; WN = 47.98 logx; $p>0.1$) were no different

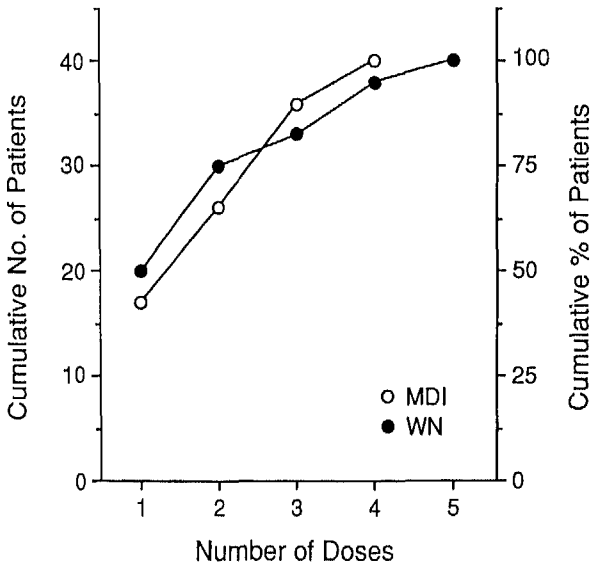

FIGURE 3. Number and percentage of patients achieving maximal bronchodilation after each (cumulative) dose of albuterol (0.4 mg, 0.8 mg, 1.2 mg, and 1.6 mg for MDI and 2.5 mg, 5.0 mg, 7.5 mg, 10 mg, and 12.5 mg for WN). A similar number of patients in both treatment groups achieved maximal FEV_1 after each dose.

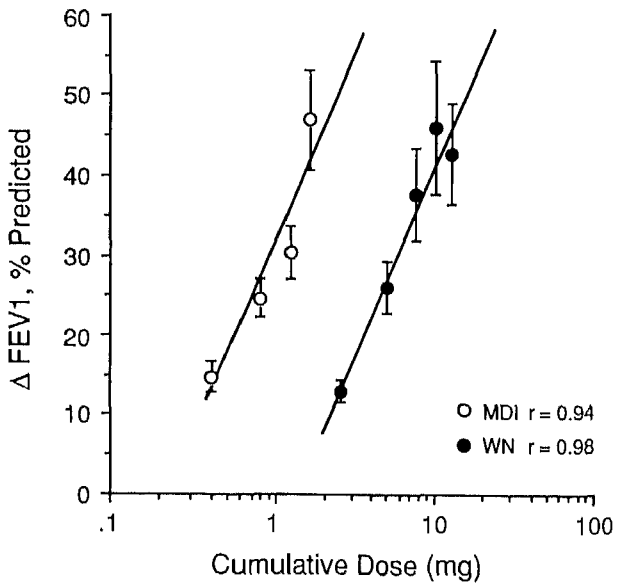

FIGURE 4. The relationship between the change in FEV_1 expressed as percent predicted, plotted against the cumulative dose of albuterol. A relative potency of 6 to 1 in favor of MDI is reflected by the parallel position of the regression lines.

indicating that the increase in FEV_1 per dose was similar in both groups. Using common logarithms and the assumed common slope of 48, we determined that a dose ratio of 6.09 in favor of MDI was needed to obtain equivalent bronchodilation.

Discussion

This study assessed the efficacy of two delivery systems (MDI and WN) for administering inhaled albuterol in patients with acute asthma. Cumulative dose-response curves were used to compare maximal effects. The two forms of therapy are effective with no significant difference in bronchodilation, dyspnea relief, or toxicity.

Patients with acute asthma presenting to the Emergency Department expect the traditional in-hospital treatment of WN as the form of aerosol therapy. However, the idea of using MDIs to replace WN has been under serious consideration.[9,17,18] Both devices are equally effective in the treatment of acute or unstable asthma or COPD.[3-6,19-25] This study confirms that equal bronchodilation and dyspnea relief may be achieved either by MDI (with holding chamber) or WN. Use of MDI in hospital produces potential cost savings, faster access to therapy, and more efficient use of paramedical staff time.[18,26,27] Administration of albuterol by MDI according to this protocol would take 3 min for each treatment compared with 10 to 15 min for WN. This might be beneficial in an Emergency Department where only limited human resources are available.

Our results on the bronchodilator efficacy of MDI in acute asthma are in agreement with others.[3-6] However, it remains difficult to compare this study with others using fixed doses, different agents, or small sample sizes (potentially large β error) to compare methods of delivery.[3,7] In the study most comparable to ours, Tarala et al[6] developed dose-response relationships to albuterol by MDI in 17 patients with acute asthma. After maximal bronchodilation by MDI, an additional 5 mg of albuterol was given by WN. The small increment in FEV_1 after WN (0.043 ± 0.085 L) was statistically significant but clinically unimportant. We did not use the indirect evidence of no further bronchodilation following WN but used a randomized double-blind design to determine the response to MDI and WN.

Differences in reports comparing the efficacy of WN to MDI may be explained in several ways.[20,28] In this study, equivalent bronchodilation occurred with a 6:1 ratio favoring MDI. Hodder et al[7] compared albuterol by MDI (0.8 mg; 0.2 mg every 2 min) and WN (2.5 mg) in the initial treatment of asthma. Fifteen minutes after treatment, the MDI group had achieved superior bronchodilation and a significant decrease in heart rate compared with WN. Considering the equivalent response with a dose by WN six times that of MDI in our study, the dose (0.8 mg) of albuterol by MDI in the study of Hodder et al[7] was high relative to that of WN (2.5 mg). Therefore, it would be expected that superior bronchodilation occurred after MDI. In contrast, with an albuterol dose ratio >6:1, WN is superior to MDI.[29] The WN dose administered by Morley et al[29] was nine times that given by MDI (MDI, 0.270 mg—WN, 2.5 mg of albuterol), and accordingly the former produced superior results.

The optimal dosage for producing maximal bronchodilation varies between individuals independent of the method of administration. We showed that about 50 percent of asthmatics reach maximal bronchodilation after a single dose of albuterol. Those not achieving maximal response may improve further after additional β-agonist therapy. However, many patients will attain maximal responses after relatively small doses of β-agonists and greater bronchodilation may be achieved only with other therapy (anticholinergics, steroids, etc).

Approximately 14 percent of asthmatics need substantially more albuterol to achieve maximal response (16 puffs by MDI: 1.6 mg—4 to 5 doses by WN: 10 to 12.5 mg). The results of Tarala et al[6] suggested that 0.4 to 0.8 mg (range, 0.4 to 1.4 mg) of albuterol by MDI was sufficient to provide maximal bronchodilation in most patients. The British Thoracic Society statement on the management of asthma suggests doses by MDI of 2.0 to 5.0 mg (20 to 50 puffs, 5 at a time).[9] This dose was probably selected with the assumption that response per milligram was equivalent by WN and MDI, an estimate that is not confirmed in our study. We found that substantially less albuterol is needed and that 90 percent will have achieved maximal response after 1.2 mg (three doses). Therefore, a fixed dose by MDI may not provide optimal benefit for all individuals, and very high doses may have potential toxicity.

Figure 4 shows the dose-response relationship for those patients who continued to respond to albuterol. The rise in response per dose was similar for both methods. The regression equations (MDI $Y = 31.77 + 48.45 \log x$: WN $Y = -5.9 + 47.98 \log x$) show that for every 1 mg of albuterol by MDI, 6 mg are needed from a WN to have equal response. This difference in bronchodilator effect per delivered dose using MDI and WN is well known and is directly related to the delivery of aerosol to the tracheobronchial tree.[30] The majority of aerosol delivered by WN never reaches the respiratory tract as it is nebulized during expiration, remains in the nebulizer tubing, or impacts in the oropharynx and is swallowed. Additionally, aerosols delivered by ultrasonic nebulizers may actually cause bronchoconstriction.[31] Most of the medication delivered by MDI also impacts in the holding chamber

or oropharynx, but this is quantitatively less than the wastage encountered with WN.

This study evaluated the dose-response relationship by the cumulative technique using albuterol every 30 min. The cumulative technique in stable asthma produced greater bronchodilation than an equivalent single dose of aerosolized bronchodilator.[32] This method probably produced greater bronchodilation than a single large dose would have in our patients as well. In contrast, it is possible that the cumulative dose was not truly cumulative, particularly in those patients receiving four to five doses over 2 h. This population with severe obstruction likely had down-regulation of β-receptors and therefore some of the drug effect may have been lost from earlier doses. Although this study could have randomly assigned a single treatment with several different doses by MDI or WN, we believed this was not practical as a much larger patient population would have been required.

We chose a 30-min interval between doses rather than the 10 to 20-min interval[8,33,34] that is sometimes suggested. The study mechanics required approximately 15 min to do spirometry and administer medications. Therefore, a shorter interval between doses was not feasible. Nevertheless, the pharmacodynamics of inhaled albuterol suggest that testing at 30 min is appropriate to determine peak bronchodilator effect.[35,36]

Although toxicity was considered as minor in both groups, more patients in the WN group had an increase in heart rate >20 beats/min ($p=0.07$) at DAM. This difference was not statistically significant yet it raises the question about potential toxicity of higher doses of albuterol delivered by WN.

In stable patients with good hand breath coordination, the addition of a holding chamber to the MDI has not been shown to be more advantageous than the MDI alone.[37] We suspect, however, that these holding chambers are extremely important in the acute setting. The anxious patient with increased respiratory distress may benefit from MDIs that are breath activated or from holding chambers. In this study, the Aero-Chamber was used as the holding chamber and hand-breath coordination was not necessary. Without this, the dose-response relationship to MDI may possibly have shifted to the right, thereby decreasing the potency ratio between the modes of therapy. Unfortunately, there are no studies that have tested this hypothesis of superior efficacy of MDI when combined with a spacer or holding chamber in acute asthma.

In summary, using a cumulative dose-response technique, there was equivalent bronchodilation after albuterol administered by either MDI or WN in patients with acute asthma. This technique is recommended for comparison of relative bronchodilator efficacy of different medications or delivery devices, as fixed dose studies may yield incomplete and potentially misleading results.

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