Bronchodilatation with a Metered-Dose Inhaler Plus an Extension, Using Tidal Breathing vs Jet Nebulization

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The bronchodilating response to two doses of 100 µg of salbutamol introduced into an extension device (Aerocam, Bégin et al. 1982), each followed by four tidal breaths, was compared with the nebulization of 2.5 mg of salbutamol in a saline solution during tidal breathing in a crossover study of ten patients with reversible airway obstruction. The forced expiratory volume in one second (FEV₁) and the forced vital capacity 30 min after the drug administration improved significantly with both methods (p < .001). The improvement of FEV₁, with the AC (52.1 percent) compared with the nebulization (55.7 percent) was similar (p > .05).

Topical administration of bronchodilator medications to the airway results in efficient bronchodilatation with minimal side effects. Activation of a metered-dose inhaler (MDI) during a slow inspiration followed by a ten second pause at the end of a full breath allows for optimal deposition and bronchodilatation. Intricate coordination is required and the proportion of patients able to breathe while simultaneously activating the inhaler was only 62 percent in one study. Extension devices have been introduced to minimize problems related to proper timing of activation, but they do not achieve greater bronchodilatation than a correctly used MDI. Some individuals, even with an extension, still have problems because they cannot inhale slowly or perform a sustained end-inspiratory pause. We studied the efficacy of an alternate method of using an extension device by having subjects use repeated tidal breaths and compared it with the continuous nebulization of a bronchodilator with a jet nebulizer, another method not requiring full inspiration or end-inspiratory pause.

Methods

Ten stable asthmatic patients, seven men and three women aged 21 to 61 years of age (mean, 38.8 years), entered the trial (Table 1). Selection criteria included a forced expiratory volume in one second (FEV₁) greater or equal to 1 L with an improvement equal to or greater than 15 percent after the nebulization of 2.5 mg of salbutamol.

All ten were currently using a long-acting theophylline, a β-adrenergic MDI two puffs four times a day with the single-breath technique and none used a nebulizer. Eight also were receiving steroids (four receiving MDI and four receiving prednisone orally). Informed consent was obtained and the subjects were asked to stop their β-adrenergic MDI eight hours before the study while continuing all other medications. Experiments were conducted at 8:30 AM on two consecutive days.

To insure stability, spirometries were measured 30 min after arrival and 30 min later. If spontaneous variations of the FEV₁ exceeded 15 percent of the baseline value or if the baseline on the second day differed by 15 percent or more, the study was delayed to the next morning.

Each day, the patients received an aerosol administered with the MDI plus extension device using repeated tidal breaths and then continuous nebulization with the jet nebulizer. The salbutamol and the placebo were randomly allocated without the patient's knowledge. The subjects were instructed to take four breaths from the Aerocam (AC) (Schering Canada Ltd) at a volume approximating tidal volume immediately after activation of the MDI (100 µg of salbutamol or placebo). The procedure was repeated with a second dose. Expired air was reinserted into room air and not rebreathed as a demand valve prevented reentry into the extension. The patients were observed to ensure that no deep breaths nor pauses were performed.

The nebulization was administered with a Hudson Updraft 1 Nebulizer No. 1700 and an adult Aerosol Face Mask No. 1059 with a constant flow of 6 L/min with either 0.5 cc. (2.5 mg) of salbutamol and 2.5 ml of saline solution or 3.0 ml of saline solution on the placebo day. The nebulization lasted about ten minutes during which the patients used only tidal breaths. After receiving the two modalities the patients were asked how they felt.

Spirometric tests were obtained 30 min after the initial breath in the AC. The baseline values of the FEV₁, forced vital capacity (FVC) and mid maximal expiratory flow rate (MMFR) were compared with the values obtained 30 min later with either method using a Student's paired t test. The percentage improvement with each method was compared with the paired t test and Pearson's coefficient of correlation (R). The confidence interval was calculated using the two-tailed distribution.

Results

Both modalities produced significant improvement of the FEV₁ and FVC (p < .001) and the MMFR (p < .01). With the nebulization, the average increase of FEV₁ was 55.7 percent ± 8.4 (mean ± standard error of mean); the FVC improved by an average of 35.8 percent ± 4.6; and the MMFR, by 79 percent ± 17.8. With the AC, the average increase of FEV₁ was 52.1 percent ± 10.5; that of the FVC, 37.7 percent ± 7.2; and the MMFR, 68.4 percent ± 11.1. The improve-
Table 1—Characteristics of Patients

<table>
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<tr>
<th>Patient</th>
<th>Sex</th>
<th>Age (yr)</th>
<th>Height (cm)</th>
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<th>Baseline FVC*</th>
<th>FEV₁/FVC (%)</th>
<th>Medications†</th>
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<tr>
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<td>Percent Predicted</td>
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<td>Percent Predicted</td>
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*Baseline FEV₁ and FVC on the first study day.
†Medication used at the time of the study: T = long-acting theophylline; B = β-adrenergic by inhaler; St = steroid by inhaler; So = oral steroids.

Discussion

This study shows similar bronchodilatation using tidal breathing in the AC to that obtained after continuous nebulization of a dose of salbutamol 12.5 times greater in ten stable asthmatic patients highly responsive to β-adrenergic medication. The average increases in the FEV₁ with both methods agreed closely. The 95 percent confidence interval of the difference between the two methods did not include values likely to be of any serious clinical significance.

Three patients (1, 3 and 10) presented with an FEV₁ of less than 1 L at the time of the trial after having withheld their β-adrenergic medication for eight hours. Of those, one improved more with the AC while another did better with the nebulization, and the third had almost identical results with the two techniques. Therefore, the relative benefit of the two techniques of administration did not appear to be influenced by the severity of the baseline FEV₁. This suggests a possible use of the AC in the treatment of acute asthma. However, more than two puffs may be needed to achieve the maximal effect when severe obstruction limits drug deposition.

Using radioactively-labelled aerosols and a jet nebulizer, it was shown that roughly 10 percent of the nebulized dose enters the lung. This is similar to the proportion from a MDI with or without an extension using a single-breath technique. While 50 percent to 70 percent of the aerosol volume generated by jet nebulizers driven at a flow rate of 6 L/min contains droplets smaller than 5 μ. 90 percent of all the aerosol particles delivered by the AC are smaller than 2.8 μ aerodynamic diameter. A two-stage process occurs in the AC: high velocity droplets in the initial spray impact on the AC walls and the ones left in suspension evaporate. The available smaller droplets may penetrate more deeply and more evenly, resulting in more...
effective bronchodilatation. The particle size range of less than 5 μm was shown to be more effective than larger fractions in producing bronchodilatation.

We compared both methods using doses of salbutamol currently used. No attempt was made to evaluate airway deposition or the dose-response in our study. The first tidal breath from the AC is likely to remove most of the aerosol present, since one breath is about three to four times greater than the 130-ml volume of the AC. The role of the three subsequent breaths is uncertain. A dose-response comparison between the "mini-neb" nebulizer and a MDI with a single-breath technique showed similar improvements in airway conductance using the same amounts of terbutaline. This suggests that the dose of medication administered to our patients with the jet nebulizer was probably greater than necessary to achieve bronchodilatation. However, this may apply only to a group of subjects highly responsive to β-adrenergic medication as ours.

The possible financial impact of choosing MDI with AC rather than nebulization could be very important. The cost of nebulization including the mask and the nebulizer, the medication, the driving gas and the therapist's time recur with each treatment. The MDI and AC technique includes the cost of medication and that of a reusable AC. However, it is far less time-consuming for the therapist to teach the patient how to use the AC on his own than to repeatedly administer nebulization treatments. At our 984-bed university hospital, a conservative calculation indicates an annual cost of C$32,000.00 Canadian dollars for approximately 85 daily nebulization treatments given to asthmatics and patients with chronic obstructive lung disease. If clinically feasible for all patients, switching from nebulization to MDI and AC could decrease the present expense by approximately 90 percent.

In conclusion, this study demonstrates that repeated tidal breaths through an extension device attached to a MDI is an effective alternative way to deliver medication and to obtain bronchodilatation in a selected asthmatic population. Unexpectedly, using a much lesser dose, it was just as effective as a jet nebulizer.

The low cost, the simplicity and the portability of this method could make it a practical alternative for ambulatory or hospitalized patients requiring aerosol therapy. Further investigation is needed to better define the dose-response relationship of β-adrenergic medication when using jet nebulizers and MDI with extension devices as well as airway particle deposition while using tidal breathing in such devices.

**REFERENCES**