In Vitro Comparison of Particle Size Distribution/Respirable Dose for LiteAire Spacer versus Misty Max – 10 Nebulizer Using Albuterol.

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Introduction

Despite tremendous variability in the number of MDI actuations (2-12) used in studies comparing beta agonist delivery via MDI/spacer and one unit dose ampule with a nebulizer, there is increasing literature support based on clinical trials for the use of 6 MDI actuations. As delivery systems influence the inhaled dose, it would be prudent to determine the in vitro dose outputs using the two systems prior to conducting a clinical efficacy comparison study between MDI/Spacer and nebulizer. In a prior in-vitro study, we have demonstrated no significant difference in the β-agonist total dose output between 6 actuations of MDI with LiteAire Spacer versus 1 unit dose ampule with a nebulizer. However, as particle size distribution was investigated with the two delivery systems, respirable dose output equivalency between the two systems remains undetermined. Therefore, the objective of this study is to compare the emitted dose particle size distribution and effective respirable dose between 6 actuations of albuterol MDI with LiteAire Spacer versus 1 unit dose ampule of a nebulizer.

Materials and Methods

To determine the total dose output, a test device was attached to a USP throat model feeding into a filter connected to a Michigan Instrument Dual Test Lung System. The lung was driven by a Puritan Bennet 7200 Ventilator set at 14 breaths/minute, tidal volume (TV) of 600 ml and inspiratory to expiratory (I:E) ratio of 1:4. With LiteAire, an albuterol MDI (CFC Inhalation Aerosol – IVAX Pharmaceuticals, Inc.) was actuated at the beginning of inhalation for 6 respiratory cycles (n=6 actuations) and with the nebulizer (Misty Max 10), one 3-ml vial (0.833mg/ml) of albuterol solution was delivered over five minutes. O2 to the Nebulizer was set at a pressure of 50-Psi and a flow of 8 LPM. Each filter was washed with 0.05mM KCl with 1 % acetic acid buffer to collect the deposited drug. Dosage was determined using a UV spectrophotometer, at a wavelength of 276 nm. Both devices were tested 3 times each.

Particle size was determined using an Andersen 8-Stage Cascade Impactor (ACI) with USP throat. The ACI was operated at 28.3 LPM. A filter for collection of particle was placed after the last plate of the ACI instead of a terminal filter inside the impactor. A TSI flow meter was connected between the ACI and vacuum pump. For the spacer unit (Figure 1), the vacuum pump was turned on for at least 60 seconds. Six doses of medication were dispensed at the rate of one actuation of albuterol MDI every ten seconds. For the T-nebulizer, setup using the Misty Max 10 (Figure 2), the vacuum pump was turned on for at least 60 seconds and one 3-ml vial (0.833mg/ml) albuterol solution was delivered over five minute period using O2 at 8 L/min to the nebulizer. Each plate and the filter were washed separately with 10ml of 0.05 mM KCl with 1% acetic acid solution to obtain 9 samples. The 9 samples underwent analysis to quantify the dose of albuterol using a UV spectrophotometer (λ=276 nm). The above experiment was repeated for a total of three times (N=3), for both devices.

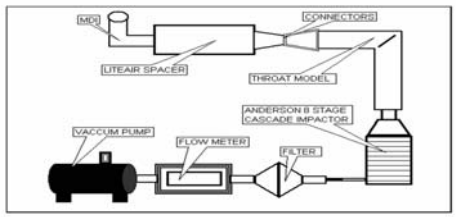

Figure 1: Set up for LiteAire Spacer with MDI.

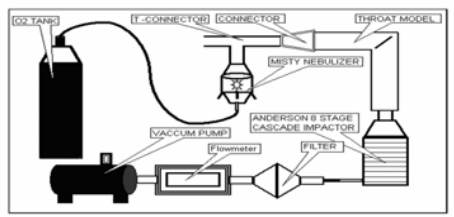

Figure 2: Set up for Misty Max-10 Nebulizer.

Results

The total dose output was found to be 175.9±27.0 µg for 6 actuations of albuterol delivered to a LiteAire Spacer via MDI versus 219.8±13.6 µg for a Misty Max 10 with T-piece. The percent respirable fraction (defined as the total mass on plates # 3-7 indicating a size range of 4.7-0.4 µm) was found to be 90.26±1.51% for LiteAire and 81.68±0.66% for the Misty Max 10 (p<0.001).. The particle size distributions are shown in Figure 3. Table 1 summarizes the ACI results. The MMAD was 2.05±0.03 for the LiteAire versus 1.49 ± 0.05 for the Misty Max 10 (p<0.0001) and the GSD was 1.64±0.03 for the LiteAire versus 2.25±0.06 for the Misty Max 10 (p<0.001). The effective respirable dose (total dose output from the breath simulation studies * respirable fraction in micrograms) was 158.79+24.38 micrograms with the LiteAire vs. 179.57+11.11 micrograms for the Misty Max 10 (p=0.27)

	LITEAIRE	MISTY MAX-10
MMAD ± SD	2.05 ± 0.03	1.49 ± 0.05
GSD ± SD	1.64 ± 0.03	2.25 ± 0.06
Effective Respirable Dose (micrograms albuterol)	158.79±24.38	179.57±11.11

Table 1: Characterization of Particle Size Distribution.

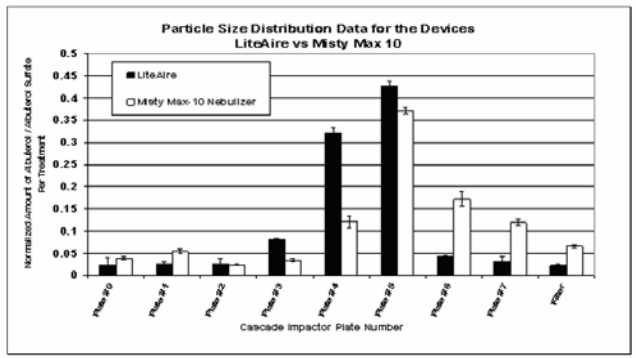

Figure 3: Graph of particle size distribution.

Discussion

This study demonstrates that using the breath simulation technique there is no significant difference in the total dose output using 6 actuation of albuterol MDI spacer versus 1 unit dose of nebulizer albuterol. Even though the difference in the respirable fraction between the two modes of delivery using ACI was significant, there was no difference in the total dose output in the effective respirable dose calculated using the breath simulation studies. We also determined that the total dose deposition using ACI with the two modes of delivery was not significantly different and well in line with the method using the breath simulated techniques.

We used Oxygen at a flow rate of 8 LPM for nebulizing albuterol, a standard practice for acute asthma in the emergency department. We determined that the impact of using oxygen instead of room air on the cut off diameter in the ACI is negligible. The cut off diameters for the ACI are dependant on the viscosities of gas used with the impactor. The viscosity of air is 0.018centiPoise while that of 100% oxygen is 0.020centiPoise. The concentration of oxygen and the respective viscosity when delivered at 8 LPM, with ACI operating at 28.3LPM flow was 43% and 0.019centiPoise, respectively. Hence, the difference in viscosities of the two gases used for the two modes of delivery (MDI /Spacer vs. Nebulizer) would be 0.001centiPoise. The impact of this difference on the cutoff diameters of ACI and therefore the respiratory particle size would be negligible.

The optimal time for nebulization has been reported in the literature. In a study by Malone et al, it was determined that aerosolization past the sputtering point did not increase albuterol delivery. The study observed an abrupt decline in aerosol output that always corresponded to the nebulizer sputtering with no change in the albuterol output between 30 to 60 seconds after the sputtering time for three different volumes (1.5 ml, 2.5 ml, and 3.5 ml albuterol solutions). We chose 5 minutes nebulization time in our study as this was one minute past the sputtering time.

Conclusion

When conducting a clinical efficacy study comparing MDI/Spacer and one unit dose of albuterol delivered via nebulization, we recommend using 6 albuterol MDI actuations with spacer as the in vitro dose outputs with the two modes are comparable.