Performance of Large-Volume versus Small-Volume Holding Chambers with Chlorofluorocarbon-Albuterol and Hydrofluoroalkane-Albuterol Sulfate

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BACKGROUND: The recent development of non-chlorofluorocarbon propellant formulations for pressurized metered-dose inhalers prompts the need for the comparative evaluation of dose delivery by small- versus large-volume holding chambers (HCs). The performance of 2 representative large- and small-volume HCs has been investigated with chlorofluorocarbon-formulated albuterol (Ventolin) and hydrofluoroalkane-formulated albuterol sulfate (Airomir) with the objective of studying the influence of chamber capacity on so-called “fine-particle” dose and total dose. Three AeroChamber and a similar number of Volumatic HCs were tested with each formulation. METHODS: An 8-stage Andersen cascade impactor was used to determine mass-weighted size distributions of drug delivered at the mouthpiece of each HC. The mass of albuterol (Ventolin) or albuterol sulfate (Airomir) collected in the impactor was assayed by high performance liquid chromatography with ultraviolet detection in order to measure both fine-particle dose (<4.7-μm aerodynamic diameter) and total dose. RESULTS: For Ventolin, the fine-particle and total doses were 45.4 ± 0.3 μg and 47.2 ± 0.1 μg, respectively, for the AeroChamber HC and 63.8 ± 2.3 μg and 66.1 ± 3.0 μg, respectively, for the Volumatic HC. For Airomir, the fine-particle and total doses expressed as albuterol base equivalent were 62.0 ± 2.9 μg and 64.2 ± 3.0 μg, respectively, for the AeroChamber HC and 67.9 ± 2.5 μg and 69.7 ± 3.4 μg, respectively, for the Volumatic HC. CONCLUSIONS: There was a significant difference in both fine-particle and total dose between large- and small-volume HCs with Ventolin (unpaired t test, p < 0.001). However, both HCs performed similarly with Airomir (p = 0.056). In all cases, the available dose from the HCs comprised >95% of fine particles. [Respir Care 1999;44(1):38–44] Key words: Aerosol propellants, albuterol, bronchodilator aerosols, chlorofluorocarbon, hydrofluoroalkane, drug delivery, holding chambers, in vitro studies, metered dose inhalers.

Background

Pressurized metered-dose inhalers (pMDIs), which were introduced in the late 1950s, offer a convenient method for

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*Suppliers of commercial products are listed in the Product Sources section at the end of the text.

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the delivery of inhaled aerosolized medications.1 Previously, pMDIs have utilized chlorofluorocarbon (CFC) propellants for the generation of aerosol drug particles. In 1987, the United Nations Environmental Programme developed the Montréal Protocol on Substances that Deplete the Ozone Layer, which initially called for a 50% reduction in CFC production, which was to be followed by an eventual ban by 1996. As a result, pharmaceutical manufacturers have been forced to seek alternatives to CFC-based propellants for use in pMDIs. Hydrofluoroalkanes (HFA) share many of the attractive properties of CFCs without the propensity for damaging the atmospheric ozone
layer. A new formulation of the adrenergic bronchodilator, albuterol sulfate, incorporates the HFA propellant 134a and was first released outside the U.S. as Airomir® in 1995 and subsequently as Proventil HFA (Key Pharmaceuticals, Kenilworth, NJ).

It has been well established with CFC formulations that larger-volume holding chambers (HCs; eg, those with a 700- to 1000-mL capacity) deliver significantly more drug than smaller-volume HCs.2– 4 However, preliminary work by us5 and Barry and O’Callaghan6 suggest that the change from CFC to HFA propellants may decrease the importance of HC volume on dose delivery. The purpose of this study was to investigate the performance of 2 representative large- and small-volume HCs with CFC-formulated albuterol (Ventolin) and HFA-formulated albuterol sulfate (Airomir), both of which deliver a nominal unit dose of 90 μg albuterol from the mouthpiece of the manufacturer’s actuator. Our objective was to study the influence of chamber capacity on both total dose and fine-particle dose. In this study, fine particles have been defined as having an aerodynamic diameter of < 4.7 μm (based on the cut point of the impactor stage closest to the 5-μm aerodynamic diameter limit associated with improved penetration beyond the upper respiratory tract).7

Methods

Large-volume holding chambers were represented by the Volumatic HC, and small-volume devices were represented by the AeroChamber HC.

Both AeroChamber and Volumatic HCs were washed in mild detergent and allowed to dry naturally prior to testing to minimize interference from electrostatic effects.8 Each device was then connected in turn to the United States Pharmacopeia induction port (throat) of the cascade impactor operated at 28.3 ± 0.5 L/min (Fig. 1). A rubber coupling piece was used between the HC and impactor induction port to ensure a leak-tight fit. Prior to testing the device with drug, we measured the flow through the impactor by coupling a calibrated Timeter RT200 reference flow meter to the chamber in place of the pMDI actuator. One measurement was made using each of 3 HCs of each type with Ventolin, actuating the pMDI canister 3 times to waste immediately before use. In each test, 5 doses were dispensed at 30-s intervals into the HC, with the impactor operating continuously. The pMDI canister was left in place for at least 20 s after actuation to permit all of the drug to reach the device and impactor, and then it was shaken and reinserted into the manufacturer’s actuator. The HC was then removed from the impactor, and...
the induction port and glass collection plates were washed with 100% vol/vol methanol to a constant volume, from which 2-mL samples were removed for high-performance liquid chromatography-ultraviolet spectrophotometric assay for albuterol at a wavelength of 276 nm. The after filter of the impactor was agitated in pure methanol in a glass tube, and the drug was extracted in solution for assay by high-performance liquid chromatography. All measurements were made at room ambient temperature (22° ± 2°C) at a relative humidity close to 50%.

Next, a further series of measurements with each holding chamber was undertaken with Airomir, following the procedure described above. After we obtained these measurements, we repeated the procedure above, actuating each pMDI directly into the induction port of the impactor (pMDI alone condition) in order to provide a reference with which to compare the performance of both types of HC.

Statistical interpretation of the data obtained with each formulation was undertaken using tests for significance (SigmaStat), and differences were deemed significant when p was < 0.05.

Results

Size distribution data (mean ± 1 SD) for the measurements using Ventolin with AeroChamber HC, Volumatic HC, and pMDI alone are presented in Figure 2, and equivalent data obtained using Airomir are given in Figure 3. Fine-particle and total doses per actuation are summarized in Tables 1 (Ventolin) and 2 (Airomir), with the data for Airomir expressed as albuterol base equivalent, with 108 μg albuterol sulfate containing 90 μg albuterol base equivalent. These data represent the mass of aerosol that collected within the impactor. The balance of the unit dose exited from the pMDI actuator mouthpiece (pMDI without HC) or from the mouthpiece of the holding chamber and was collected in the United States Pharmacopeia induction port. Material collecting in the induction port comprised particles larger than the cut-point size of the first impact stage (aerodynamic diameter of 9 μm). Thus, in the case of measurements with pMDI without HC, ~58% of the unit dose from Ventolin and ~53% of the unit dose from Airomir were contained in particles larger than this size. The mass median aerodynamic diameter (MMAD) of the total aerosol from either formulation was therefore > 9 μm. However, if the mass that collected in the induction port (representing particulate not likely to penetrate beyond the oropharyngeal region) is removed from the size analysis, these MMAD values would have been close to those obtained using either of the holding chambers.

In the measurements made with Ventolin, the unit fine-particle dose from the 145-mL AeroChamber HC (45.4 ± 0.3 μg) was marginally greater than the equivalent dose delivered by the pMDI without HC (42.0 ± 1.4 μg). Al-
though this difference was statistically significant (unpaired t test, \( p = 0.013 \)), it represents a difference of only 3.4 \( \mu \text{g} \) per actuation and is unlikely to be of clinical relevance. On the other hand, the unit fine-particle dose via the 750-mL Volumatic (63.8 \( \pm \) 2.3 \( \mu \text{g} \)) is 52% greater than that from the pMDI alone, illustrating the improved drug delivery potentially achievable with the larger-volume HC with this CFC-based formulation. The aerosols delivered by both types of HC comprised 96% fine particles by mass, with similar MMADs (aerodynamic diameters close to 2.3 \( \mu \text{m} \); see Fig. 2).

In the case of Airomir, both the AeroChamber (62.0 \( \pm \) 2.9 \( \mu \text{g} \)) and Volumatic (67.9 \( \pm \) 2.5 \( \mu \text{g} \)) HCs delivered significantly larger fine-particle doses than the pMDI alone (38.7 \( \pm \) 2.2 \( \mu \text{g} \)) (one-way analysis of variance, \( p < 0.001 \)). Of interest, the difference in drug delivery (5.9 \( \mu \text{g} \)) between the two types of HC was much smaller for this HFA-based formulation than that measured with Ventolin, and it was statistically insignificant (\( p = 0.056 \)). Again, >96% of the unit doses from both types of HC consisted of fine particles, and the MMAD of the aerosol from both HCs was similar, with aerodynamic diameter ranges of 2.4–2.6 \( \mu \text{m} \) (see Fig. 3).

**Discussion**

Several factors, including chamber shape and inhalation/exhalation valve operation, can affect the performance of HCs. However, chamber volume has been shown in in
vitro studies by Dolovich with a CFC-formulated placebo containing fluorescent particles to be an important influence on both fine-particle and total unit dose. In Dolovich’s study, the amount of available drug increased with increasing volume to ~140 mL, but little further increase was measured with greater chamber volume. However, the fine-particle fraction (mass contained in the range from 1- to 5-μm aerodynamic diameter) continued to increase toward 100% of the total dose with HC volumes in excess of ~400 mL. Barry and O’Callaghan also noted a similar correlation between the volume of cylindrical spacers and fine-particle (<5-μm aerodynamic diameter) drug output when tested with CFC-formulated sodium cromoglycate, but significant increases in available drug were also evident with increasing spacer volume beyond 500 mL. The present study therefore focused on the behavior of 2 HCs that represent small-capacity (145 mL) and large-capacity (750 mL) devices with albuterol delivered with either HFA or CFC as propellant. It is likely that the exact relationship between HC or spacer volume and drug output depends on the precise formulation (eg, propellant type, metered volume, drug and excipient content) that results in a particular aerosol plume geometry following actuation. It is therefore recognized that the findings from this study may not be applicable beyond the formulations examined or with other designs of HC or spacer.

In vitro studies characterizing aerosol delivery with pMDIs formulated using HFA propellants are beginning to appear in the literature. Barry and O’Callaghan and others have observed that the aerosol produced from the CFC-formulated Ventolin emerges at a higher velocity from the manufacturer’s actuator mouthpiece than does that from the HFA-formulated Airomir. Their high-speed video analysis of the aerosol plume showed that the leading edge of the Airomir aerosol had a velocity approximately one-half that of the Ventolin aerosol cloud at both 10 ms and 60 ms after pMDI discharge. In addition, the analysis revealed that the volume occupied by the Airomir aerosol was 251 cm³ on average, compared with 695 cm³ for the Ventolin aerosol.

Barry and O’Callaghan also compared the delivery of Ventolin and Airomir via AeroChamber with that from a 700-mL, large-volume HC (Nebuhaler), which had a capacity comparable to that of the Volumatic HC. Measurements were obtained for new, unwashed HCs and for the Nebuhaler after coating the interior surfaces of the HC with antistatic paint. The fine-particle doses from the untreated Nebuhaler ranged from 24.6 μg (Ventolin) to 42.1 μg (Airomir); These doses were much lower than the equivalent values obtained in the present study with the Volumatic HC, which had a similar capacity (750 mL). However, when the influence of electrostatic charge was removed from the Nebuhaler, the fine-particle dose increased to 68.5 μg (Ventolin) and 74.8 μg (Airomir). These results were much closer to those obtained in the present study with the Volumatic HC (63.8 ± 2.3 μg with Ventolin; 67.9 ± 2.5 μg with Airomir), which had been pre-washed with ionic detergent and dried in ambient air to minimize the influence of electrostatic charge in accordance with the recommendations of Wildhaber et al.

In another in vitro study, Wildhaber et al examined HFA-albuterol delivery in pediatric ventilator circuits, including the AeroChamber-MV and the Nebuhaler HC. Measurements were made before and after the removal of electrostatic charge on the delivery devices, and drug amounts from each device were reported as percentages of the nominal unit dose from the pMDI. With the elimination of electrostatic charge, the AeroChamber-MV and the larger Nebuhaler delivered 63% and 72%, respectively, of the dose as particles finer than 6.8-μm aerodynamic diameter. These data are in good agreement with findings with Airomir in the present study, in which the AeroChamber and Volumatic HCs delivered 69% and 75%, respectively, of the nominal dose leaving the mouthpiece of the manufacturer’s actuator (90 μg) (based on particles finer than 4.7 μm aerodynamic diameter). Therefore, both studies support the conclusion that increases in chamber volume between ~140 and 750 mL have little if any impact on the mass of albuterol delivered as fine particles from these devices when using HFA-formulated albuterol.

In what is probably the closest comparison with the present study, Schulz et al compared, using (as we did) an Andersen cascade impactor, the in vitro delivery of HFA- and CFC-formulated albuterol via small- and large-volume HCs (unspecified). They reported fine-particle (<4.7-μm aerodynamic diameter) and total doses that were, in most cases, comparable with those found in the present study. For example, their fine-particle doses for the small-volume HC (50.3 ± 2.8 μg for CFC-albuterol and 64.5 ± 1.1 μg for HFA-albuterol) compare with doses of 45.4 ± 0.3 μg (Ventolin) and 62.0 ± 2.9 μg (Airomir) for the AeroChamber. However, for the larger HC, they reported fine-particle doses of 72.3 ± 2.2 μg (CFC-albuterol) and 77.7 ± 2.7 μg (HFA-albuterol), which are slightly greater than the doses obtained with the Volumatic HC in the present study (63.8 ± 2.3 μg for Ventolin and 67.9 ± 2.5 μg for Airomir). Nevertheless, both investigations show that the difference in performance between large- and small-volume HCs (based on fine-particle dose) was markedly smaller with the HFA-formulated albuterol. On the basis of this comparison, it is reasonable to speculate that if particles in the plume from the CFC formulation have greater velocities at the time of pMDI actuation, they would be more likely to impact on the walls of a smaller-volume HC than on a chamber of larger capacity. The walls of the smaller HC are closer to the axis of plume generation, where particle-wall interactions would be expected to increase. In contrast, the slower plume velocity and smaller
volume occupied by the aerosol from the HFA formulation would be expected to result in reduced particle-wall interactions within the smaller-volume HC. In the larger HC, the walls are further from the axis of plume generation and therefore less involved with the inertial deposition process.

The safety of inhaled HFA-134a propellant on a short-term basis has been demonstrated by Donnell et al. They investigated the acute patient response in 12 healthy male subjects to cumulative doses of 1, 2, 4, 8, and 16 inhalations of either HFA-134a propellant without drug and CFC-propelled albuterol (salbutamol). Their study found no differences in pulmonary function, cardiovascular performance (heart rate and blood pressure), tremor, or serum potassium following each incremental dose. Longer-term clinical experience with the CFC-free propellant should provide additional data on patient response and the safety profile for HFA-propellant use.

The equivalence of bronchodilator effects between HFA-formulated albuterol and the CFC formulation has also been established in preliminary studies. For instance, Nogami-Itoh et al. compared the bioequivalence of HFA-formulated albuterol with the CFC formulation for the prevention of histamine-induced bronchospasm in the anesthetized dog. They concluded that both formulations provided equivalent dose-related inhibitory effects. In another study with 20 asthmatic subjects with exercise-induced bronchospasm, Dockhorn et al. found equivalent changes in forced expiratory volume 1 s after exercise challenge with either Proventil-HFA or Ventolin. Side effects, which were monitored through changes in heart rate, blood pressure, and electrocardiographic QT intervals, were similar. Kleerup et al. found that HFA-134a and CFC-11/12 salbutamol (albuterol) sulfate produced clinically and statistically similar airway responses and side effects in a randomized crossover study with 24 stable, mild-to-moderate asthmatic subjects. However, none of these in vivo studies indicated that a spacer or HC had been used in the administration of the aerosol.

The improved delivery seen with the typical small-volume HC (represented by AeroChamber HC in both our study and that of Schulz et al.) may have implications for clinical dosing with HFA-formulated albuterol, requiring further dose-response investigations in subjects who use HCs for bronchodilator administration. In association with fine particles in the 3 samples of AeroChamber that were tested, we found an average increase in mass of 16.6 mg, representing a 37% increase in dose compared with that from CFC-formulated albuterol. If in fact the dose-response to HFA-formulated albuterol is equivalent to that for the CFC formulation, as indicated in the preliminary studies, this increase may allow for fewer doses per treatment in either acute or maintenance conditions. Further clinical investigation is therefore needed to quantify the dose-response relationship to HFA-formulated albuterol when inhaled with a small-volume HC.

**Conclusions**

Preliminary investigation of HFA-formulated albuterol sulfate delivery by a large- and small-volume HC using cascade impaction testing of particle sizes revealed that both HCs almost eliminate particles larger than 4.7-μm aerodynamic diameter. Total and fine-particle unit doses were increased for both large- and small-volume HCs with HFA-formulated albuterol sulfate compared with the CFC formulation. In addition, there was no significant difference in dose delivery of HFA-formulated albuterol between the large- and small-volume HCs, allowing use of the more convenient smaller-volume HC with no loss of dose compared with the larger HC.

**PRODUCT SOURCES**

**Holding Chambers (HCs):**
- AeroChamber® valved HC with FLOWSIGnal™, Monaghan Medical Corp., Plattsburgh NY
- Volumatic™ HC, Allen & Hanburys Ltd., Stockley Park UK

**Drugs:**
- Ventolin®, GlaxoSmithKline (Canada) Inc., Mississauga Ontario Canada
- Airomir™, 3M HealthCare, Loughborough UK

**Cascade Impactor:**
- 1 ACFM (Mk-II) nonviable ambient particle sizing sampler, Graseby Andersen, Smyrna GA

**Reference Flowmeter:**
- Model RT200, Timeter Instrument Corp, St. Louis MO

**Drug Assay:**
- Star HPLC System, Varian Associates Inc, Walnut Creek CA

**Statistical Software:**
- SigmaStat, SPSS Inc, Chicago IL

**REFERENCES**