



The effect of a holding chamber on albuterol metered-dose inhaler product differences

Jennifer L.H. Johnson, PhD^{*}; Danielle Guthrie, BS^{*}; Joel Hyde, BS^{*}; Thomas Hanson, BS^{*,†}; Kelly Karlage, BS[‡]; Paul B. Myrdal, PhD[‡]

^{*} Thayer Medical Corporation, Tucson, Arizona

[†] Department of Pharmacy Practice and Sciences, The University of Arizona College of Pharmacy, Tucson, Arizona

[‡] Department of Pharmaceutical Sciences, The University of Arizona College of Pharmacy, Tucson, Arizona

ARTICLE INFO

Article history:

Received for publication April 29, 2016.

Received in revised form July 8, 2016.

Accepted for publication July 13, 2016.

ABSTRACT

Background: Three albuterol sulfate metered-dose inhaled (MDI) products (Ventolin HFA, Proventil HFA, and ProAir HFA) are marketed in the United States to provide the same total dose of albuterol sulfate. However, it is widely known that the fine particle dose ($<5 \mu\text{m}$) is the portion of the particle distribution that actually reaches the lungs and provides therapeutic benefit.

Objective: To examine the differences in particle size between products and how a valved holding chamber (VHC) can mitigate possible adverse effects.

Methods: Particle size distributions in each product were measured, with and without a VHC, and were analyzed by high-performance liquid chromatography.

Results: The only significant mean (SD) difference in total dose was between Proventil (75 [21] μg) and ProAir (107 [12] μg) ($P < .01$). The fine particle doses of all 3 products were significantly different: 21 (5) μg of albuterol sulfate for Ventolin, 40 (4) μg of albuterol sulfate for Proventil, and 64 (7) μg of albuterol sulfate for ProAir ($P < .001$ for all 3 cases). The VHC successfully removed the larger particle dose delivered by all 3 products ($P \leq .01$) without reducing the fine particle dose ($P > .05$).

Conclusion: Ventolin, Proventil, and ProAir should not be considered interchangeable products. In this study, the dose of albuterol sulfate likely to reach the lungs with Proventil or ProAir is 2 to 3 times that of Ventolin. As such, patients with asthma may require 3 additional puffs of Ventolin to achieve a clinical benefit similar to Proventil or ProAir. Because all 3 products contain 200 actuations, it also follows that Proventil or ProAir products may last a user 2 to 3 times longer than Ventolin.

© 2016 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

Introduction

Inhalation therapy has become the delivery system of choice for treatment of asthma because it allows faster symptom relief with smaller doses of corticosteroids and β_2 -agonists delivered directly to the intended site of action (the lungs) and it avoids large systemic doses that occur with oral administration and are commonly associated with adverse effects.^{1–3} Albuterol is a short-acting β_2 -adrenergic receptor agonist administered by pressurized meter-dose inhaler (MDI) to optimize drug delivery to the lungs. Albuterol is generally used as a rescue treatment during an acute

asthma attack because it can provide rapid relief to the patient. Systemic adrenergic adverse effects are mostly avoided via inhalation of the drug as long as the particles are of the right size to reach the lungs.⁴ When a substantial portion of the dose deposits in the mouth and throat, there can be a delay in symptom relief (or in some cases no symptom relief) and a consequential increase in systemic adverse effects. Some of these adverse effects include decrease in potassium serum levels, heart rate increase, finger tremors, and reduction in T-wave amplitude.⁵

There are currently 3 racemic albuterol sulfate pressurized MDI products on the market in the United States: Ventolin HFA (GlaxoSmithKline, Philadelphia, Pennsylvania), Proventil HFA (3M Health Care Ltd, Key Pharmaceuticals, and Merck & Co, Kenilworth, New Jersey), and ProAir HFA (Teva Respiratory, LLC, and IVAX Pharmaceuticals, North Wales, Pennsylvania). They all contain enough product for 200 actuations, and each actuation is reported to deliver 108 μg of albuterol sulfate (90 μg of albuterol base) from the mouthpiece of the actuator.^{6–8} Furthermore, they all use the

Reprints: Jennifer L. H. Johnson, PhD, Thayer Medical Corporation, 4575 S Palo Verde Rd, Ste 337, Tucson, AZ 85714; E-mail: jenny.johnson@thayermedical.com.

Disclosures: Dr Johnson, Ms Guthrie, and Messrs Hyde and Hanson are employees of Thayer Medical Corporation, the manufacturer of the LiteAir valved holding chamber discussed in this article.

Funding Sources: Thayer Medical Corporation supplied the drug products, devices, and consumables used in testing. No other funding was supplied.

<http://dx.doi.org/10.1016/j.anai.2016.07.016>

1081-1206/© 2016 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc. All rights reserved.

same hydrofluoroalkane (HFA) as their propellant: HFA-134a. The only differences in the 3 products exist in their inactive ingredients and in their canister designs (ie, proprietary valving systems vary). In addition to the albuterol sulfate and the HFA propellant, Proventil HFA and ProAir HFA both contain ethanol, and Proventil HFA also contains oleic acid. Ventolin HFA consists of albuterol sulfate and the HFA propellant alone.

It is well established that the portion of the dose from an MDI that is therapeutically relevant is the portion that is of a particle size small enough to be aerodynamically transported into the lungs. The cut-off particle size threshold is roughly $5\ \mu\text{m}$ in effective aerodynamic diameter.^{3,9,10} Particles larger than approximately $5\ \mu\text{m}$ are known to deposit quickly on the immediate surrounding surfaces, whereas particles less than approximately $5\ \mu\text{m}$ are known to have the advantage of following the flight path of the inhaled breath into the lungs. Therefore, the nominal total dose of albuterol sulfate emitted from the actuator is much less important than the portion of that dose that is aerodynamically less than $5\ \mu\text{m}$. This study was designed to investigate the performance of the 3 albuterol sulfate MDI products and the effect a holding chamber can have on their drug delivery.

Methods

Experiment

Ventolin HFA (lot 3ZP0173), Proventil HFA (lot 130461), and ProAir HFA (lot DAA77A) products were each purchased in triplicate from a local pharmacy. USP grade albuterol sulfate was purchased from Spectrum Chemical (Brunswick, New Jersey) (product AL156) for the preparation of standards.

The aerodynamic particle size distribution of each of the 3 MDI products was established in sextuplicate without a spacer or holding chamber. Each experiment was performed using a nonviable 8-stage Anderson Cascade Impactor (ACI) with a USP throat model and a mean (SD) air flow rate of 28.3 (0.5) mL/min.

Next, LiteAir valved holding chambers (VHCs; Thayer Medical Corporation, Tucson, Arizona [Fig 1]) were positioned between the MDI, and the ACI induction port and aerodynamic particle size distribution of albuterol sulfate in each drug product was redetermined 6 times. In all cases, the analysis of albuterol sulfate deposition on each stage of the ACI was performed using high-performance liquid chromatography (HPLC) with UV detection at 276 nm.

HPLC Assay

An Agilent 1100 HPLC system was used to quantitate the albuterol sulfate in each sample and each standard. The system included a binary pump, a degasser, an autosampler, a column heater, and a diode array detector. Chemstation software (Agilent Technologies, Santa Clara, California) was used to collect and analyze the data. A Synergi Fusion-RP (Phenomenex, Torrance, California) (inside diameter, 150 mm length $\times$ 4.6 mm; particle size, $4\ \mu\text{m}$; pore size, $80\ \text{\AA}$) column was used with an isocratic mobile phase of 0.01 M ammonium acetate/isopropanol (95/5) (pH adjusted to 4.5) at a flow rate of 1 mL/min to elute the albuterol sulfate. UV absorbance detection at 276 nm was used to measure the albuterol sulfate peak areas. The injection volume was $10\ \mu\text{L}$, and the column temperature was controlled at 30°C . The run time was 5 minutes, and the albuterol sulfate peak eluted at 3.0 minutes.

The HPLC assay was validated for accuracy, precision, specificity, sensitivity, linearity, and range and limits of quantitation and detection. The stability of albuterol sulfate was also established in the intended solvent system for 72 hours. Specificity was revealed in the observation that no interfering or coeluting peaks had the same retention time as albuterol sulfate. The limit of detection and



Figure 1. The LiteAir Dual Valved Holding Chamber displayed flat (lower left) and in its pop-up form (lower right) (Thayer Medical Corporation).

limit of quantitation were determined to be $0.002465\ \mu\text{g}$ and $0.00493\ \mu\text{g}$ of albuterol sulfate on column, respectively. The standard curve contained 6 levels, which ranged from 0.001 to 0.666 mg/mL of albuterol sulfate. Linearity and accuracy of the standard curve were shown through reproducibility ($R^2 > 0.98$) and measured concentrations being 100% to 105% of their known concentrations. Interday and intraday precision of peak area and retention time were demonstrated because the coefficients of variation ranged from 0.1% to 3.5% for peak areas and from 0.1% to 1.9% for retention times.

Statistical Analysis

Data were statistically analyzed using Minitab software, version 16.2.4 (Minitab Inc, State College, Pennsylvania). Analysis of variance was used when 3 or more groups were being compared, and *t* tests were used when only 2 groups were being compared. Post hoc pairwise testing was applied where analysis of variance $P < .05$. $P < .05$ was considered significant.

Results

Table 1 gives the summarized data obtained for all 36 ACI runs (18 with and 18 without using a VHC).

MDI Without a VHC

Figure 2 shows the results of testing all 3 albuterol sulfate MDI products by ACI without a spacer or holding chamber. A mean (SD) of 66 (16) μg of albuterol sulfate of the total dose of Ventolin HFA was nonrespirable (recovered from the induction port through plate 2), whereas the respirable dose was 21 (5) μg of albuterol sulfate (recovered from plate 3 through the filter). Proventil HFA and ProAir HFA had higher mean (SD) respirable doses at 40 (4) μg and 64 (7) μg , respectively, and lower nonrespirable doses at 35 (21) μg and 42 (9) μg , respectively. This implies that a patient taking Ventolin HFA might only be expected to receive a portion of the dose (particles small enough to reach the lungs) of albuterol sulfate compared with administration of Proventil HFA and ProAir HFA. In addition, without a spacer or holding chamber, the patient taking Ventolin HFA is likely to receive a comparably high deposition of albuterol sulfate in the mouth and throat.

Figure 3 shows the significance of the differences between the total doses and respirable doses for each product when no spacer or holding chamber was used. All 3 products produced total doses that

Table 1
Mean (SD) Amount of Albuterol Sulfate Obtained From Each Stage of an Andersen Cascade Impactor and Resulting Summary Parameters for 6 Separate Runs of 3 Different MDI Products With and Without Using a Valved Holding Chamber

Deposit location	MDI alone			MDI with valved holding chamber		
	ProAir HFA (n = 6)	Proventil HFA (n = 6)	Ventolin HFA (n = 6)	ProAir HFA (n = 6)	Proventil HFA (n = 6)	Ventolin HFA (n = 6)
Canister stem	1.79 (0.21)	4.82 (1.09)	7.39 (1.51)	2.46 (0.73)	4.15 (0.84)	6.66 (2.01)
Actuator	10.01 (3.93)	21.98 (5.24)	19.18 (1.54)	6.19 (2.58)	11.27 (1.46)	15.23 (2.13)
Induction port	38.90 (7.41)	34.29 (20.65)	61.57 (14.86)	3.07 ^b	4.78 ^b	2.79 (0.34)
Plate						
0	1.29 (0.53)	0.57 (0.04)	1.69 (1.07)	BLOQ ^a	BLOQ ^a	0.50 ^b
1	0.93 (0.30)	BLOQ ^a	1.24 (0.37)	BLOQ ^a	BLOQ ^a	0.58 ^b
2	1.78 (0.82)	0.64 (0.12)	1.58 (0.76)	1.29 (0.55)	0.65 (0.18)	0.77 (0.24)
3	12.45 (4.13)	5.41 (1.64)	4.26 (2.03)	10.48 (3.49)	6.74 (2.72)	3.32 (1.76)
4	26.56 (3.14)	16.67 (2.07)	6.93 (3.10)	25.93 (2.02)	23.62 (2.23)	8.98 (2.98)
5	14.69 (6.07)	12.61 (3.26)	5.73 (1.87)	12.29 (3.80)	16.54 (3.21)	7.71 (2.85)
6	1.80 (0.41)	2.16 (0.42)	0.87 (0.16)	1.83 (0.49)	2.17 (0.31)	1.04 (0.13)
7	0.88 (0.16)	0.74 (0.14)	BLOQ ^a	0.94 (0.13)	0.81 (0.14)	BLOQ ^a
Filter	8.03 (1.71)	2.45 (0.64)	3.11 (0.91)	9.95 (1.57)	2.62 (0.79)	3.77 (0.88)
Total dose, μg	106.73 (11.89)	75.04 (20.83)	86.50 (20.80)	63.23 (3.65)	53.84 (5.10)	26.32 (6.53)
Respirable dose, μg (plate 3 – filter)	64.41 (6.85)	40.05 (4.16)	20.90 (4.84)	61.42 (2.48)	52.50 (3.91)	24.83 (6.55)
Respirable dose, %	61 (5)	58 (19)	24 (1)	97 (2)	98 (4)	94 (6)
Nonrespirable dose, μg (induction port – plate 2)	42.32 (8.94)	34.99 (20.76)	65.61 (16.07)	1.80 (1.49)	1.33 (2.17) ^c	1.50 (1.34)
Nonrespirable dose, %	39 (5)	42 (19)	76 (1)	3 (2)	2 (4) ^c	6 (6)
MMAD ^d	2.42 (0.20)	2.22 (0.16)	2.48 (0.52)	2.33 (0.16)	2.26 (0.15)	2.08 (0.23)
GSD ^d	1.53 (0.06)	1.57 (0.20)	1.77 (0.18)	1.48 (0.04)	1.41 (0.03)	1.71 (0.23)

Abbreviations: BLOQ, below the limit of quantitation; GSD, geometric SD; MDI, metered-dose inhaler; MMAD, mass medium aerodynamic diameter.

^aAll 6 samples were BLOQ.

^bOnly 1 of 6 samples was above the limit of quantitation, so an SD could not be calculated.

^cMean value not significantly different from 0 ($P > .05$).

^dCalculated using www.mmadacalculator.com. Equations based on International Organization for Standardization No. 24727.

were significantly larger than their respirable doses ($P < .001$ for ProAir HFA, $P = .009$ for Proventil HFA, and $P < .001$ for Ventolin HFA). As such, 39% to 76% of the aerosol in all 3 products are defined as nonrespirable.

Without a spacer or holding chamber, ProAir HFA gives a mean (SD) total dose of 107 (12) μg of albuterol sulfate with a respirable dose of 64 (7) μg of albuterol sulfate, which means the respirable fraction is 61% (5%) of the dose. Without a spacer or holding chamber, Proventil HFA gives a total dose of 75 (21) μg of albuterol sulfate with a respirable dose of 40 (4) μg of albuterol sulfate, which means the respirable fraction is 58% (19%) of the dose. Without a spacer or holding chamber, Ventolin HFA gives a total dose of 87 (21) μg of albuterol sulfate with a respirable dose of 21 (5) μg of albuterol sulfate, which means the respirable fraction is only 24% (1%) of the dose.

ProAir HFA was found to produce a total dose closest to manufacturers' report of 108 μg per actuation. Measurements for Proventil HFA and Ventolin HFA were lower, but the large error bars on these measurements revealed no significant difference between the total doses of ProAir HFA and Ventolin HFA ($P = .36$) or between the total doses of Proventil HFA and Ventolin HFA ($P = .07$). However, the difference between the total doses of ProAir HFA and Proventil HFA is significant ($P = .009$).

MDI With a VHC

Figure 4 shows the results of testing all 3 albuterol sulfate MDI products by ACI when a VHC is used. It can be seen that the VHC removed almost all the nonrespirable dose from the 3 products.

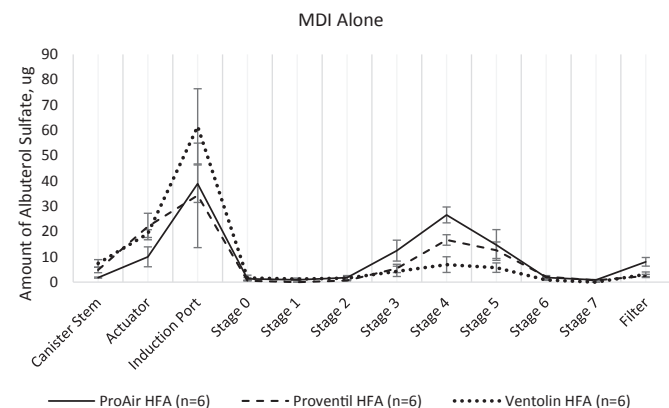


Figure 2. The Andersen stage distributions of the 3 metered-dose inhaler (MDI) products actuated without holding chambers: ProAir HFA (solid line), Proventil HFA (dashed line) and Ventolin HFA (dotted line). The error bars represent 1 SD of the mean (n = 6).

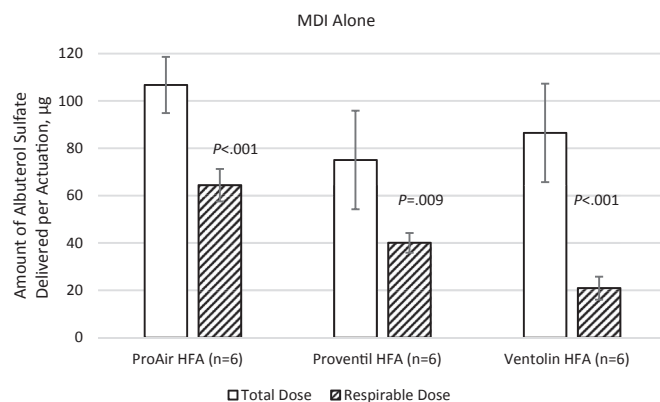


Figure 3. The means (SDs) (error bars) of the total doses (open rectangles) and respirable doses (striped rectangles) of albuterol sulfate emitted per actuation of 3 metered-dose inhaler (MDI) products (Ventolin HFA, ProAir HFA, and Proventil HFA). The P values represent the significance of the difference between the total dose and the respirable dose. Note that ProAir HFA was measured to produce an albuterol sulfate dose closest to manufacturers' report of 108 μg per actuation.

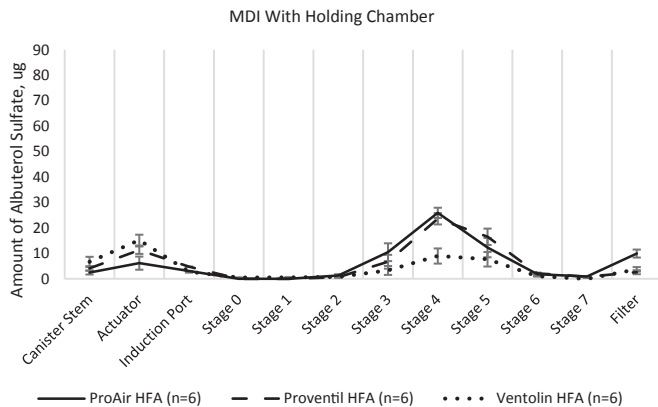


Figure 4. The Andersen stage distributions of the 3 metered-dose inhaler (MDI) products actuated through a valved holding chamber VHC (LiteAire). The error bars represent the SDs of the means. Note that the VHC removes all the nonrespirable particles for all 3 products such that their total doses of albuterol sulfate are now equivalent to their respirable doses. Note that Ventolin HFA is shown to deliver a significantly lower dose of albuterol sulfate than Proventil HFA and ProAir HFA.

Most notably, the drug collected in the induction port was reduced to negligible amounts ($P < .02$), whereas no reduction was observed in the respirable dose for all products tested ($P > .20$). This is optimal performance for a holding chamber.

Figure 5 shows the relative respirable doses compared with the total doses emitted per actuation when the VHC is used. It can be seen that the VHC renders the total dose equivalent to the respirable dose for all 3 drug products ($P = .47$ for ProAir HFA, $P = .62$ for Proventil HFA, and $P = .70$ for Ventolin HFA). ProAir HFA gives a mean (SD) total dose of 63 (4) μg of albuterol sulfate with a respirable dose of 61 (3) μg of albuterol sulfate, which brings the respirable fraction up to 97% (2%). Proventil HFA gives a mean (SD) total dose of 54 (5) μg of albuterol sulfate with a respirable dose of 53 (4) μg of albuterol sulfate, which brings the respirable fraction up to 98% (4%). Ventolin HFA gives a mean (SD) total dose of 26 (7) μg of albuterol sulfate with a respirable dose of 25 (7) μg of albuterol sulfate, which brings the respirable fraction up to 94% (6%).

Discussion

Disparities of 3 Albuterol Sulfate MDI Products

Previously, other researchers have found clinically relevant differences among MDI products that are marketed by their manufacturers to be equivalent in drug substance and dose. As a matter of fact, because of some of these known differences, the Medicines and Healthcare Products Regulatory Agency (MHRA) in the United Kingdom has asked physicians to specify the brand of the MDI product rather than allowing an “equivalent” replacement.¹¹

All 3 of the products we studied have significant *in vitro* differences that may be clinically relevant. In 2012, McCabe et al¹² published that ProAir HFA delivers a softer and warmer plume that lingers longer than that of Ventolin HFA. They also reported that the respirable dose in ProAir HFA (53 [4] μg per actuation) was notably higher than that in Ventolin HFA (26 [2] μg per actuation). DeBacker et al¹³ found roughly 3 times the lung deposition of albuterol sulfate in 3-dimensional airway models of patients with asthma using ProAir HFA compared with Ventolin HFA. Hautmann et al¹⁴ compared all 3 albuterol sulfate products and found that, with or without a VHC, ProAir HFA and Proventil HFA delivered significantly more albuterol sulfate per actuation than Ventolin HFA. Furthermore, the US Food and Drug Administration lists the 3 albuterol sulfate products as having therapeutic equivalence codes

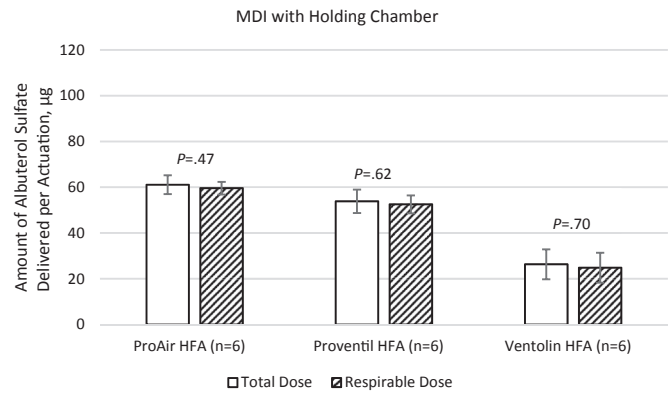


Figure 5. The means (SDs) (error bars) of the total doses (open rectangles) and respirable doses (striped rectangles) of albuterol sulfate emitted per actuation of 3 metered-dose inhaler (MDI) products (Ventolin HFA, ProAir HFA, and Proventil HFA) when a valved holding chamber is used. The P values represent the significance of the difference between the total dose and the respirable dose.

of BX, which means they are presumed to be therapeutically inequivalent because of insufficient data to the contrary.¹⁵

The Importance of a VHC

Ideally, an MDI product would directly deliver 100% respirable drug with every actuation. If this were achievable, a spacer would not be necessary. Spacers for MDI delivery only offer one benefit to the user. They provide a chamber through which the aerosol plume must travel before reaching the patient's mouth. Within that space, the larger, nonrespirable (less aerodynamic) particles deposit on the walls of the spacer and do not travel into the patient's mouth. Thus, spacers allow the patient to avoid potential adverse effects and discomfort associated with drug delivery to the mouth and throat surfaces.^{16,17}

Holding chambers were initially developed as an improvement over spacers. They also provide a chamber to remove the non-respirable particles, but in addition, they are valved, which allows the aerosol plume to be held in the chamber until the patient is prepared to inhale the dose. A second improvement was to also provide an exhalation valve system that prevented a patient from exhaling back into the chamber and disrupting the intended dose. These valves become important for children and older adults who have either not developed the ability or lost the coordination to slowly inhale while actuating the MDI and to continue to inhale until the plume has been consumed. In addition, oral exhalation without a VHC requires the patient to remove the MDI actuator mouthpiece from the patient's mouth. This is another level of coordination that becomes difficult for the very young and the elderly.^{16,17} If a patient exhales while the aerosol plume is still inside a spacer, the plume would be (at least partially) redirected back toward the MDI actuator. In some cases, the dose can be wasted as it is blown backwards out of the spacer or deposited in and around the actuator. The purpose of the valve system in the VHC is to prevent exhaled air from entering the chamber but to allow inhaled air to come through the chamber.¹⁸

Originally, spacers and VHCs were only thought to be necessary for inhaled corticosteroids because of the additional systemic exposure and the development of secondary yeast infections of the oropharynx. Now it is widely published that most inhaled MDI medications can benefit from the use of a VHC for the following reasons.^{3,11,18–23} First, MDI products with standard actuators, strictly from a physics perspective, simply cannot avoid oropharyngeal deposition. Second, all medications can cause adverse

effects, especially when delivered in excess. Third, clinical benefit depends more on patient technique of use than on the MDI device itself. Removing the need for the patient (regardless of age) to properly coordinate MDI actuation with slow inhalation; hence, consuming the entire dose better ensures dose uniformity and expected clinical outcome.³

The present study reveals how a VHC (in this case the LiteAir collapsible paperboard VHC) can remove the nonrespirable dose without reducing the respirable dose. Table 1, Figure 3, and Figure 4 provide clear evidence of such. For all 3 drug products, the VHC removed the nonrespirable particles to the point that there were no significant differences between the total doses and the respirable doses: ProAir HFA became up to 99% respirable, Proventil HFA became up to 100% respirable, and Ventolin HFA became up to 100% respirable. Furthermore, there were no reductions in the respirable doses delivered through the VHC compared with respirable doses delivered directly from the MDI alone.

Interestingly, there was one increase in the respirable dose of albuterol sulfate delivered through the VHC compared with the respirable dose obtained from the MDI alone. Proventil HFA produced a respirable dose of 40 (4) μg of albuterol sulfate per actuation from the MDI alone. With the addition of the VHC, the respirable dose went up significantly to 53 (4) μg of albuterol sulfate per actuation ($P < .001$). The reason for this is unknown but when similar observations were made in a previous study the increase was attributed to lack of static attraction.²⁴ In the present case, it could be also attributed to the inherent static dissipative nature of the paperboard VHC (surface resistance of $5 \times 10^9 \pm 1 \times 10^9 \Omega$) and/or plume geometry of Proventil HFA in relation to the internal geometry of the VHC. Hautmann et al.¹⁴ used a high-speed infrared camera to image the varying plume geometries of the same 3 albuterol sulfate products. They found that the diameter of the Proventil HFA plume is larger than the plumes of ProAir HFA and Ventolin HFA immediately outside the actuator. Preliminary in-house measurements of all 3 products also revealed that Proventil HFA had the largest plume diameter upon exiting the actuator. When an MDI is actuated into an opening narrower than the plume diameter, such as might be the case with Proventil HFA and a USP throat model, some of the respirable dose will likely directly affect and deposit on the walls. On the other hand, a VHC with an inside diameter wider than the plume might allow more of the respirable dose to pass through, improving respiratory delivery. This possible explanation for an apparent increase in respirable dose with a VHC should be evaluated in a future study.

Further study is warranted with the LiteAir because it is unique among VHCs in its shape and paperboard construction. To better understand the increase in the Proventil HFA fine particle dose with the VHC, the performance of the LiteAir relative to other VHCs should be evaluated with a special focus on plume geometry. In addition, the possibility that the paperboard nature of the LiteAir may offer an advantage in drug delivery compared with non-antistatic plastic VHCs should be investigated by comparing fine particle dose delivery.

A weakness of the present study is the lack of in vivo data to accompany the in vitro findings. It is not possible to state whether the in vitro differences found herein translate to similar clinical differences. Furthermore, it may be more clinically predictive to add simulation of patient breathing and delays between inhalation and actuation of the MDI. Other researchers have found the combined effect of uncoordinated breathing and breath flow rate with an antistatic VHC.²⁵ Additional studies on these parameters are planned; nevertheless, researchers have also found clinical differences between 2 of the same products (ProAir HFA and Ventolin

HFA), which reflect the in vitro differences discovered in this study.¹³

It appears that the respirable doses of ProAir HFA, Proventil HFA, and Ventolin HFA are not substantially equivalent. Implications are that a manufacturer's reported total dose delivered for an MDI may be an inadequate way to predict an expected clinical response and that the value of using a VHC as standard practice cannot be overlooked.

References

- [1] Jackson D, Blair J, Gerbes M, Savery S, Scott J. Metered-dose inhaler prescribing patterns and patient education quality among healthcare providers in New York State [abstract]. *J Am Acad Physician Assistants*. 2015;28:1.
- [2] Breuer O, Shoseyov D, Kerem E, Brooks R. Implementation of a policy change: replacement of nebulizers by spacers for the treatment of asthma in children. *Isr Med Assoc J*. 2015;17:421–424.
- [3] Brocklebank D, Ram F, Wright J, et al. Comparison of the effectiveness of inhaler devices in asthma and chronic obstructive airways disease: a systematic review of the literature. *Health Technol Assess*. 2001;5:1–149.
- [4] Kung M, Croley SW, Phillips BA. Systemic cardiovascular and metabolic effects associated with the inhalation of an increased dose of albuterol. *Chest*. 1987;91:382–387.
- [5] Newnham DM, Lipworth BJ. Nebulizer performance, pharmacokinetics, airways and systemic effects of salbutamol given via a novel nebulizer delivery system. *Thorax*. 1994;49:762–770.
- [6] ProAir® HFA [package insert]. North Wales, PA: Teva Respiratory, LLC, and IVAX Pharmaceuticals; 2012.
- [7] Proventil® HFA [package insert]. Kenilworth, NJ: 3M Health Care Ltd, Key Pharmaceuticals, and Merck & Co; 2012.
- [8] Ventolin® HFA [package insert]. Philadelphia, PA: GlaxoSmithKline; 2012.
- [9] Vidgren P, Vidgren M, Laurikainen K, Pietila T, Silvasti M, Paronen P. In vitro deposition and clinical efficacy of two sodium cromoglycate inhalation powders. *Int J Clin Pharmacol Ther Toxicol*. 1991;29:108–112.
- [10] Vidgren P, Silvasti M, Vidgren M, Paronen P, Tukiainen H, Lehti H. In vitro inhalation behavior and therapeutic response of salbutamol particles administered from two metered dose aerosols. *Pharmazie*. 1991;46:41–43.
- [11] Chrystyn H, Price D. Not all asthma inhalers are the same: factors to consider when prescribing an inhaler. *Prim Care Respir J*. 2009;18:243–249.
- [12] McCabe JC, Koppenhagen F, Blair J, Zeng XM. ProAir® HFA delivers warmer, lower-impact, longer-duration plumes containing higher fine particle dose than Ventolin® HFA. *J Aerosol Med Pulm Drug Delivery*. 2012;25:104–109.
- [13] DeBacker J, Vinchurkar S, DeBacker WA, Zeng XM. Functional imaging using computational fluid dynamics to compare ProAir with Truflow actuator and Ventolin in asthmatic patients [abstract]. *Respir Crit Care Med*. 2011;183:A4431.
- [14] Hautmann J, Godoy SE, Marshik P, et al. Effect of time between actuation on the dose variability for three metered dose inhalers. *Respir Drug Delivery Eur*. 2013;2:429–434.
- [15] US Food and Drug Administration, Center for Drug Evaluation and Research. Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations. www.accessdata.fda.gov/scripts/cder/ob/default.cfm. Accessed February 3, 2015.
- [16] Johnson A, Wolf BL. Transition to albuterol HFA: are all inhalers interchangeable? *J Nurse Pract*. 2009;5:585–588.
- [17] Laube BL, Janssens HM, de Jong FHC, et al. What the pulmonary specialist should know about the new inhalation therapies. *Eur Respir J*. 2011;37:1308–1331.
- [18] Ahrens R, Lux C, Bahl T, Han SH. Choosing the metered-dose inhaler spacer or holding chamber that matches the patient's need: evidence that the specific drug being delivered is an important consideration. *J Allergy Clin Immunol*. 1995;96:288–294.
- [19] Al-Showair RAM, Pearson SB, Chrystyn H. The potential of a 2Tone trainer to help patients use their metered-dose inhalers. *Chest*. 2007;131:1776–1782.
- [20] Barry PW, O'Callaghan C. The effect of delay, multiple actuations and spacer static charge on the in vitro delivery of budesonide from the Nebuhaler. *Br J Clin Pharmacol*. 1995;40:76–78.
- [21] Price D, Thomas M. Breaking new ground: challenging existing asthma guidelines. *BMC Pulmonary Med*. 2006;6(suppl 1):S6.
- [22] Dolovich MB, Ahrens RC, Hess DR, et al. Device selection and outcomes of aerosol therapy: evidence-based guidelines. *Chest*. 2005;127:335–371.
- [23] Lavorini F, Fontana G. Targeting drugs to the airways: the role of spacer devices. *Expert Opin Drug Deliv*. 2009;6:91–102.
- [24] Hatley RHM, von Hollen D, Sandell D, Slator L. In vitro characterization of the OptiChamber Diamond valved holding chamber. *J Aerosol Med Pulm Drug Deliv*. 2014;27(suppl 1):S24–S36.
- [25] Slator L, von Hollen D, Sandell D, Hatley RHM. In vitro comparison of the effect of inhalation delay and flow rate on the emitted dose from three valved holding chambers. *J Aerosol Med Pulm Drug Deliv*. 2014;27(suppl 1):S37–S43.