

Comparative *in vitro* performance of valved holding chambers with a budesonide/formoterol pressurized metered-dose inhaler

Frank E. Chambers, B.Sc., C.Chem., M.R.S.C., Steven Brown, B.Eng., and Andrew J. Ludzik, B.Sc., C.Chem., M.R.S.C.

ABSTRACT

A combination of budesonide and formoterol in a single pressurized metered-dose inhaler (pMDI) is available in the United States and elsewhere. This study was designed to evaluate the delivered dose and fine particle dose (FPD; mass of particles <4.7-micrometer diameter) using the pMDI with two valved holding chambers (VHCs), using sampling methods reflecting different patient techniques. FPD was measured using an Andersen Cascade Impactor and delivered dose was measured using a disposable filter. Two VHCs, AeroChamber Plus and AeroChamber MAX (Trudell Medical International, London, Ontario, Canada), were evaluated using three sampling methods: (1) immediate collection; (2) collection after up to a 5-second delay; (3) using simulated adult, child, and infant tidal breathing patterns (delivered dose). Decreases in delivered dose were observed using a VHC compared with the pMDI alone. FPD with both VHCs was similar to that with the pMDI alone with minimal delay between actuation and collection. With delays, the antistatic AeroChamber MAX was more resistant than AeroChamber Plus to dose losses. Delivered doses from adult and child profiles were comparable with those after a 1-second delay. The infant profile produced lower delivered doses, probably because more breath cycles are required to empty the VHC. Budesonide/formoterol pMDI can be used effectively with AeroChamber Plus and the antistatic AeroChamber MAX. With minimal delay between actuation and collection, FPD with both VHCs was similar to that with the pMDI alone, giving physicians a choice of administration regimen and taking into account the needs and skills of the patient.

(Allergy Asthma Proc 30:424–432, 2009; doi: 10.2500/aap.2009.30.3252)

Key words: Asthma, budesonide/formoterol, corticosteroid, delivered dose, drug delivery, fine particle dose, long-acting beta₂-adrenergic agonist, pressurized metered-dose inhaler, tidal breathing pattern, valved holding chamber

Inhaled corticosteroids (ICSs) are considered the most effective anti-inflammatory therapy for asthma and remain the backbone of long-term maintenance regimens.¹ In patients with persistent asthma that is not adequately controlled with low- to medium-dose ICS alone, the addition of a long-acting β_2 -adrenergic agonist (LABA) is recommended as a preferred therapy.¹ Formoterol is an effective and well-tolerated LABA with a rapid onset of action and duration of action of at least 12 hours.² A combination of the ICS budesonide and the LABA formoterol (as formoterol fumarate dihydrate) has been available in Europe in a dry powder inhaler (Symbicort Turbuhaler; AstraZeneca, Lund, Sweden) since 2000. Symbicort was

launched in the United States in June 2007 in a pressurized metered-dose inhaler (pMDI) and is also available in this formulation in other countries. It has been shown to be effective and well tolerated in large, randomized clinical trials.^{3,4}

Valved holding chambers (VHCs), often called spacers, are add-on devices that are commonly used with pMDIs to aid delivery of a drug to the lungs. The size of the aerosolized drug particles is important for effective drug delivery. Particles <5 μm in diameter deposit most frequently in the lower airways and represent the fine particle dose (FPD; sometimes referred to as the respirable dose).⁵ Particles of 5–10 μm in diameter are most likely to deposit in the upper airways, whereas large particles >10 μm in diameter are most likely to deposit in the mouth and oropharynx.⁵

The primary use of VHCs is in patients who have difficulty with inhaler technique, particularly the coordination of pMDI actuation with inhalation. However, patients may also have coordination problems with VHCs and inhalation can be more complex for some.^{6,7} This is a crucial issue, because the dose of drug delivered to the lungs may be reduced if the VHC is not used properly.^{6,7}

From AstraZeneca Research and Development, Charnwood, Leicestershire, United Kingdom

All authors are employees of AstraZeneca LP and research reported in this article was funded by AstraZeneca LP

Address correspondence and reprint requests to Frank E. Chambers, B.Sc., C.Chem., M.R.S.C., AstraZeneca R&D Charnwood, Pharmaceutical and Analytical R&D, Bakewell Road, Loughborough, Leicestershire LE11 5RH, U.K.

E-mail address: frank.chambers@astrazeneca.com

Copyright © 2009, OceanSide Publications, Inc., U.S.A.



Figure 1. AeroChamber Plus and AeroChamber MAX valved holding chambers. (Photographs supplied courtesy of Trudell Medical International, London, ON, Canada.)

One aspect of patient VHC technique influencing delivered dose is the delay between actuation and inhalation. Many VHCs acquire electrostatic charge during production, storage, and use.⁸ As the delay between actuation and inhalation increases, this charge significantly impacts the amount of fine particles retained in the VHC because of the continuous, rapid disappearance of the aerosol caused by electrostatic sedimentation.⁹ The half-life of the drug aerosol within the VHC may be as short as 9–10 seconds for different VHC/pMDI combinations.^{10,11} However, the problem can be considerably reduced if the electrostatic charge of the VHC is eliminated,¹² which can be achieved by washing the VHC in detergent and allowing it to drip-dry. Several clinical studies have shown an improved performance of detergent-treated VHCs compared with untreated controls.^{13–15}

A number of different designs of VHCs are available and it cannot be assumed that a particular VHC is compatible with a particular pMDI. Different formulations and actuator designs may have an impact on plume formation of the aerosol cloud and potentially on electrostatic properties. In the United Kingdom, practitioners are advised to use the VHC specifically recommended by the pMDI manufacturer for their inhaler.¹⁶ The Canadian Standards Association¹⁷ and the European regulatory body¹⁸ also recommend that the effect on deposition characteristics of patient technique in terms of delay between actuation and inhalation be determined.

The purpose of this study was to determine the delivered dose, the FPD, and the mass median aerodynamic diameter (MMAD) of the active moieties delivered from the budesonide/formoterol pMDI when used with two VHCs possessing different antistatic properties and using sampling methods that reflect different patient techniques and breathing patterns.

METHODS

Drugs and Devices

Budesonide/formoterol pMDI is a press-and-breathe multiple-dose inhaler. The micronized active moieties are formulated as a suspension in a hydrofluoroalkane (HFA) propellant (HFA-227) with povidone and polyethylene glycol, which act as a suspension stabilizer and valve lubricant, respectively.¹⁹ Two actuations of the inhaler provide the nominal active dose. Two presentations (budesonide/formoterol, 40/4.5 μg /actuation and 160/4.5 μg /actuation) were evaluated using the marketed device that delivers 120 actuations. The 160/4.5- μg /actuation presentation is currently approved for use in the United States,¹⁹ and the 40/4.5- μg /actuation pediatric presentation was the subject of a supplemental New Drug Application in the United States in June 2008.

The pMDIs were compared using two small-volume VHCs, AeroChamber Plus and AeroChamber MAX (Trudell Medical International, London, ON, Canada; Fig. 1), which have been designed for use with HFA pMDIs. AeroChamber Plus is commonly prescribed worldwide, and AeroChamber MAX, currently available in North America, is a newer design manufactured from a new antistatic polymer that is designed to minimize electrostatically induced aerosol deposition onto the walls of the VHC. The AeroChamber Plus and the AeroChamber MAX have an internal volume of ~150 mL and 200 mL, respectively.^{20,21} In accordance with the manufacturer's instructions, both VHC models were washed with a mild detergent solution before use; the AeroChamber Plus was then allowed to dry without rinsing, and the AeroChamber MAX was subsequently rinsed with clean water before being allowed to dry before use.²²

Measurement of Delivered Dose and FPD

Delivered Dose. Delivered dose was evaluated with and without a VHC using a Vital Signs 303 disposable

Table 1 Chromatographic conditions for quantification of delivered dose and fine particle dose

	Delivered Dose	FPD
Mobile phase	2.3 mM of aqueous phosphate buffer:acetonitrile (71:29 v/v)	20 mM of aqueous phosphate buffer pH 6:acetonitrile (65:35 v/v)
Column	Supelcosil LC-Si HPLC column, 5 cm × 4.6 mm, 5- μ m particle size, linked to a Supelcosil LC-18DB HPLC column, 3.3 cm × 4.6 mm, 3- μ m particle size	Fluophase PFP or Discovery F5 HPLC column, 150 × 3.0 mm, 5- μ m particle size
Column oven temperature	22°C	30°C
Injection volume	250 μ L	250 μ L
Flow rate	1.5 mL/min	0.8 mL/min
Run time	10 min	9 min
Wavelength	0–5 min = 214 nm (formoterol detection) 5–10 min = 248 nm (budesonide detection)	0–5 min = 214 nm (formoterol detection) 5–9 min = 248 nm (budesonide detection)

FPD = fine particle dose; HPLC = high-performance liquid chromatograph; PFP = perfluorinated phenyl (Thermo Electron Corp., Billerica, MA); Discovery F5 (Supelco Inc., Bellefonte, PA).

filter (Vital Signs U.K., Ltd., Littlehampton, West Sussex, U.K.). Budesonide and formoterol were recovered from the disposable filter in an ethanol/water mix (28:72 v/v) and quantified using a suitable high-performance liquid chromatograph fitted with an ultraviolet (UV) detector with wavelength switching capability (e.g., HP1100 with UV variable wavelength or Diode array detector; Agilent Technologies U.K., Ltd., Stockport, Cheshire, U.K.). Chromatographic conditions are shown in Table 1. The detection limits for this method are 11.2 ng/mL and 0.5 ng/mL for budesonide and formoterol, respectively.

Fine Particle Dose. An Andersen Cascade Impactor (ACI) (Westech Instruments, Upper Stondon, Bedfordshire, U.K.) was used to evaluate FPD and average MMAD with and without a VHC (Fig. 2). The impactor consisted of a USP 23 induction port with impactor stages 0 through 5, corresponding to aerodynamic cut-off points of 9.0, 5.8, 4.7, 3.3, 2.1, and 1.1 μ m (stages 6 [0.65 μ m] and 7 [0.43 μ m] of the standard ACI stack were removed) and a filter stage for collection of submicron particles. The amount of budesonide and formoterol deposited on each section of the ACI was recovered and quantified by high-performance liquid chromatograph using the parameters described for FPD in Table 1. The detection limits for this method are 1.0 ng/mL for budesonide and 0.24 ng/mL for formoterol. The amount of active drug recovered from each ACI stage was summed to determine the total dose in the impactor. FPD is represented by the sum of active drug recovered from stages 3 through the filter.

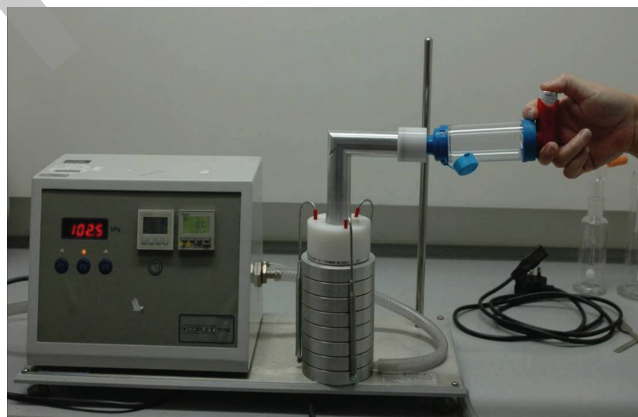


Figure 2. Test apparatus to determine fine particle dose and mass median aerodynamic diameters with the pressurized metered-dose inhaler alone and with valved holding chambers. The test apparatus consists of a pressurized metered-dose inhaler and valved holding chamber attached to an Andersen Cascade Impactor. The Andersen Cascade Impactor is attached to a timing device that controls the delay between actuation and collection of the dose. The apparatus may be used with and without a valved holding chamber.

Sampling Methods

Different sampling methods were evaluated to fully reflect potential patient techniques: (1) comparison of delivered dose and FPD when the pMDI is used with or without the VHC, (2) effect on delivered dose and FPD of introducing a delay time between actuation of the pMDI and inhalation through the VHC, and (3) effect on delivered dose when air is drawn through the VHC using simulated tidal breathing patterns representative of different patient groups.

Table 2 Breathing simulator and dose sampling parameters

Parameter	Breathing Pattern			
	Infant	Child	Adult 1	Adult 2
Tidal volume (mL)	50	155	770	500
Frequency (min ⁻¹)	30	25	12	13
I/E ratio	1:3	1:2	1:2	1:2
Minute volume (mL)	1500	3900	10,000	6000
Dose sampling	15 s (equivalent to 7.5 breath cycles)	15 s (equivalent to 6.25 breath cycles)	6 breath cycles	6 breath cycles

I/E = inspiratory/expiratory.

The delay times and breathing simulator parameters were based on the Canadian Standards Association guideline.¹⁷ Standard test conditions used a delay of 0.01 seconds (referred to for simplicity as no delay), and delay times of 1, 2, and 5 seconds were also evaluated. A Copley TPK-S (Copley Scientific, Nottingham, U.K.) was used to regulate delay times and sampling volumes, and a PARI compass II breath simulator (PARI GmbH, Munich, Germany) was used to simulate the tidal breathing patterns. The infant, child, adult 1, and adult 2 breathing patterns were evaluated; actuations timed to coincide with either the point of inhalation or the exhalation were studied, in line with the Canadian Standards Association guideline.¹⁷ The infant and child patterns simulated the breathing of a 9-month-old infant and a 4-year-old child, respectively, and the two adult patterns encompassed the range of tidal breathing patterns observed in the adult population. The breathing simulator and dose sampling parameters are shown in Table 2. Budesonide/formoterol pMDI has been evaluated in patients ≥ 6 years of age, and the child pattern is the closest profile to this age. The infant pattern data are provided for interest only.

Only delivered dose was evaluated for the tidal breathing simulation studies because the ACI requires a constant flow through the impactor to separate aerosol droplet size ranges and was therefore not appropriate for use in these studies. Six canisters were sampled for delivered dose evaluated without the simulated tidal breathing patterns and five were sampled for FPD evaluation. For delivered dose evaluated with the simulated tidal breathing patterns, three canisters were sampled, with three repeat determinations taken for each canister as described in the Canadian Standards Association guideline.¹⁷ For FPD evaluation, three doses (six actuations) were collected for each determination, the minimum number required to allow accurate quantitation on each impactor stage. Only one dose (two actuations) per determination was required to evaluate delivered dose. In all cases, each individual actuation was collected separately as recommended by

the VHC manufacturer's instructions and British Thoracic Society guidelines.^{16,22}

In this study, FPD was calculated as particles $\leq 4.7 \mu\text{m}$ in diameter expressed as a percentage of the total nominal dose (40 or 160 μg /actuation for budesonide and 4.5 μg /actuation for formoterol). Values for delivered dose are also presented as the percentage of the nominal dose.

Statistical evaluation of the impact of VHC use and delay times on delivered dose and FPD was performed using a one-way analysis of variance (ANOVA; SAS JMP; SAS Institute, Inc., Cary, NC). Values of $p \leq 0.05$ were considered statistically significant. The number of variables (*i.e.*, spacer type, breathing pattern, drug, and product strength) was too many to perform a meaningful statistical analysis of the impact of the tidal breathing patterns on delivered dose, and these data were evaluated descriptively.

RESULTS

As anticipated, there was some loss of total delivered dose with both VHCs, with statistically significant differences ($p < 0.05$) observed between the pMDI alone versus both AeroChamber Plus and AeroChamber MAX for both actives at both product strengths (Table 3). The type of VHC did not influence delivered dose when the dose was collected immediately. However, when a delay was introduced, AeroChamber MAX generally produced a higher delivered dose compared with AeroChamber Plus, with some differences being statistically significant for the 160/4.5- μg /actuation presentation (Table 3).

Without a VHC, the mean FPD for the 40/4.5- μg /actuation presentation was 53.3% and 61.1% of the nominal dose for budesonide and formoterol, respectively, and 48.6% and 57.4% for the 160/4.5- μg /actuation presentation (Table 4). Values for FPD obtained using the VHCs were slightly higher when the dose was collected immediately, with some statistically significant differences compared with the pMDI alone (Table 4). The choice of AeroChamber Plus or Aero-

Table 3 Delivered dose (% nominal dose, mean $\pm$ SD) with and without valved holding chambers and delays between actuation and inhalation

Delay time (s)	pMDI Alone		AeroChamber Plus		AeroChamber MAX	
	Budesonide (n = 6)	Formoterol (n = 6)	Budesonide (n = 6)	Formoterol (n = 6)	Budesonide (n = 6)	Formoterol (n = 6)
40/4.5 μ g/actuation product strength						
0	99.5 $\pm$ 6.1	108.0 $\pm$ 7.1	72.3 $\pm$ 4.0*	77.5 $\pm$ 4.2*	74.2 $\pm$ 3.8*	77.1 $\pm$ 3.6*
1	N/A	N/A	58.2 $\pm$ 3.5	63.1 $\pm$ 4.1	63.3 $\pm$ 5.8	65.5 $\pm$ 3.0
2	N/A	N/A	55.9 $\pm$ 2.7	59.5 $\pm$ 2.5	55.0 $\pm$ 5.2	58.8 $\pm$ 5.2
5	N/A	N/A	49.8 $\pm$ 2.2	53.9 $\pm$ 2.5	51.7 $\pm$ 3.8	54.2 $\pm$ 4.2
160/4.5 μ g/actuation product strength						
0	94.5 $\pm$ 3.5	96.7 $\pm$ 4.3	75.1 $\pm$ 3.2*	79.7 $\pm$ 3.1*	75.3 $\pm$ 2.0*	82.4 $\pm$ 2.5*
1	N/A	N/A	56.1 $\pm$ 2.6	60.1 $\pm$ 2.4	65.8 $\pm$ 1.9#	70.5 $\pm$ 2.0#
2	N/A	N/A	57.4 $\pm$ 3.4	63.0 $\pm$ 3.4	58.4 $\pm$ 2.4	63.2 $\pm$ 2.3
5	N/A	N/A	45.8 $\pm$ 7.1	48.5 $\pm$ 7.6	56.2 $\pm$ 1.7#	59.2 $\pm$ 1.9#

* $p < 0.05$, pMDI alone vs VHC; # $p < 0.05$, AeroChamber Plus vs AeroChamber MAX.

Table 4 Fine particle dose (% nominal dose, mean $\pm$ SD) with and without valved holding chambers and delays between actuation and inhalation

Delay time (s)	pMDI Alone		AeroChamber Plus		AeroChamber MAX	
	Budesonide (n = 5)	Formoterol (n = 5)	Budesonide (n = 5)	Formoterol (n = 5)	Budesonide (n = 5)	Formoterol (n = 5)
40/4.5 μ g/actuation product strength						
0	53.3 $\pm$ 2.3	61.1 $\pm$ 3.2	58.4 $\pm$ 3.1*	65.5 $\pm$ 3.6*	56.4 $\pm$ 2.7*	64.5 $\pm$ 2.2
1	N/A	N/A	51.3 $\pm$ 4.0	56.9 $\pm$ 4.9	52.1 $\pm$ 2.8	60.7 $\pm$ 2.9
2	N/A	N/A	44.9 $\pm$ 2.9	49.8 $\pm$ 3.1	52.9 $\pm$ 3.2#	60.8 $\pm$ 4.0#
5	N/A	N/A	42.7 $\pm$ 3.3	48.4 $\pm$ 3.5	49.1 $\pm$ 1.3#	56.1 $\pm$ 1.4#
160/4.5 μ g/actuation product strength						
0	48.6 $\pm$ 3.5	57.4 $\pm$ 4.3	49.6 $\pm$ 3.0	59.7 $\pm$ 3.0	54.3 $\pm$ 3.0*#	62.9 $\pm$ 1.9*
1	N/A	N/A	39.1 $\pm$ 3.1	46.4 $\pm$ 3.5	45.5 $\pm$ 1.0#	54.0 $\pm$ 1.1#
2	N/A	N/A	42.2 $\pm$ 1.3	51.1 $\pm$ 1.7	45.1 $\pm$ 4.2	52.1 $\pm$ 4.3
5	N/A	N/A	40.8 $\pm$ 1.5	48.0 $\pm$ 0.7	40.2 $\pm$ 2.8	47.2 $\pm$ 2.8

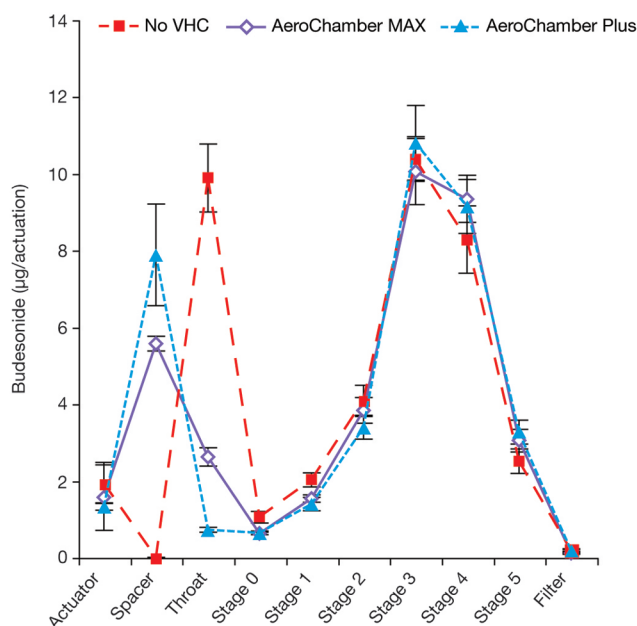
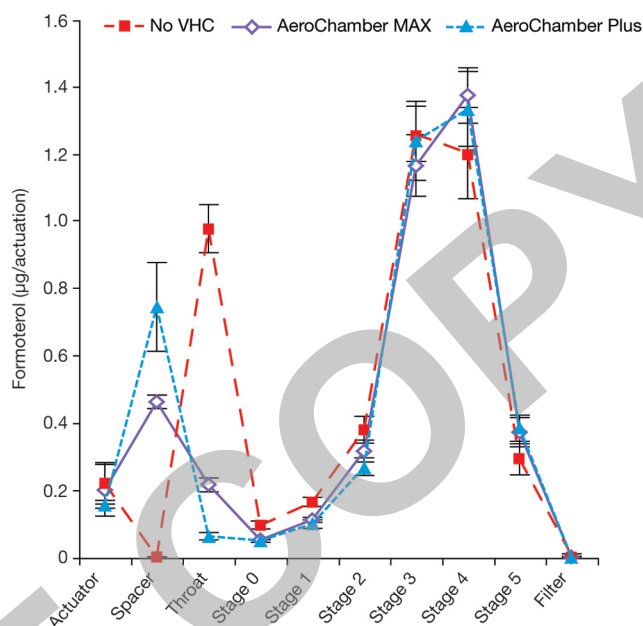
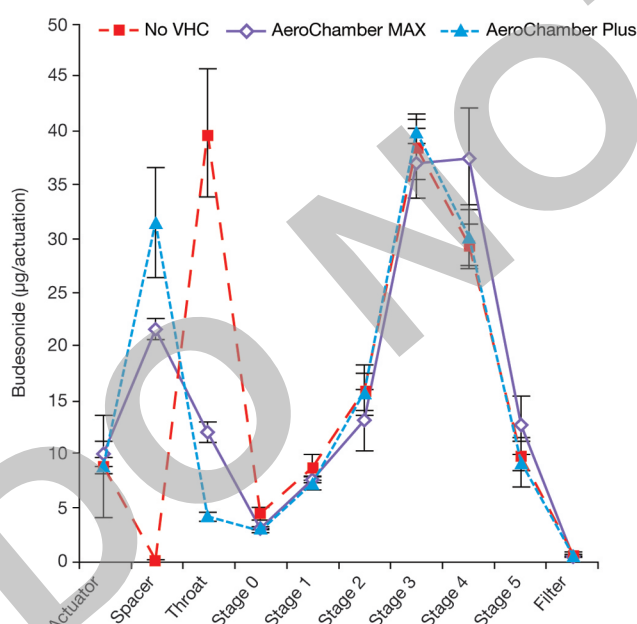
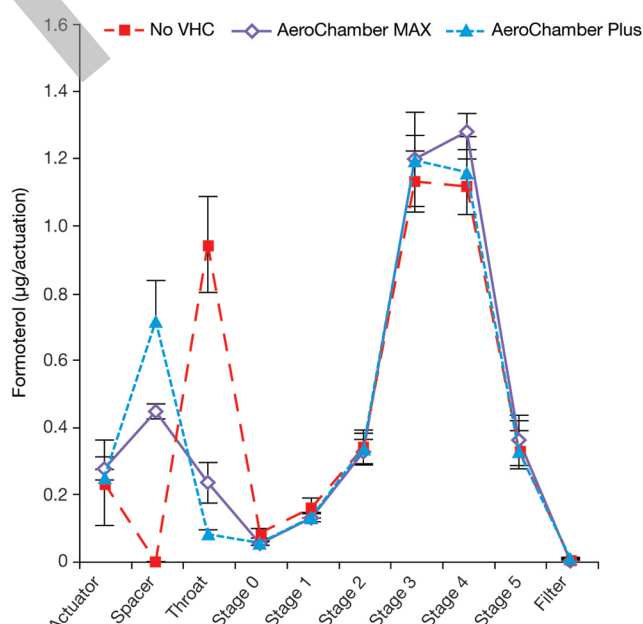
* $p < 0.05$, pMDI alone vs VHC; # $p < 0.05$, AeroChamber Plus vs AeroChamber MAX.

Chamber MAX had very little impact on FPD of either active or strength when the dose was collected immediately, with only the budesonide component of the 160/4.5- μ g/actuation presentation showing a statistically significant difference between the VHCs ($p = 0.034$).

Additionally, the choice of VHC had no impact on the MMAD for either active or strength when the dose was collected immediately. Plots showing the distribution of aerodynamic particle size through the impactor (Fig. 3) show that, with the exception of the throat (induction port), similar profiles were obtained with and without VHCs. It can also be seen that the type of VHC used did not affect particle size distribution within the ACI.

When delays were introduced, there was a general reduction in FPD for both VHCs. As with delivered dose, a reduction in FPD was noticed with as little as a 1-second delay. A difference between the VHCs was observed when delays were introduced, because AeroChamber MAX generally delivered a higher FPD than AeroChamber Plus, again with some statistically significant differences (Table 4).

The delivered doses obtained using the simulated tidal breathing patterns were compared with the delivered doses obtained using the 1-second delay regimen, replicating typical patient usage. Delivered doses obtained with the two adult profiles were at least as good as the delivered doses obtained with the 1-second delay regimen (Fig. 4, A and B). Indeed, there was a

Budesonide 40/4.5 μ g**Formoterol 40/4.5 μ g****Budesonide 160/4.5 μ g****Formoterol 160/4.5 μ g**

Valved holding chamber=VHC

Figure 3. Aerodynamic particle size distribution profiles (mean $\pm$ SD) with and without valved holding chambers. VHC = valved holding chamber.

slightly higher delivered dose with the inhalation profiles for the 40/4.5- μ g/actuation presentation, comparable with the delivered dose obtained with the no-delay regimen. Delivered doses with the child profile were similar or slightly reduced compared with the 1-second delay regimen and the adult breathing patterns, whereas the breathing simulation for the infant patient produced considerably lower delivered doses (Fig. 4, A and B).

DISCUSSION

It is well recognized that total dose loss with VHCs occurs as a result of a selective reduction of the larger particles from the aerosol. This is a positive effect because oropharyngeal drug deposition is reduced without reducing the FPD.^{6,23} Conversely, other factors, including the electrostatic charge of the VHC and patient technique, can reduce the FPD.

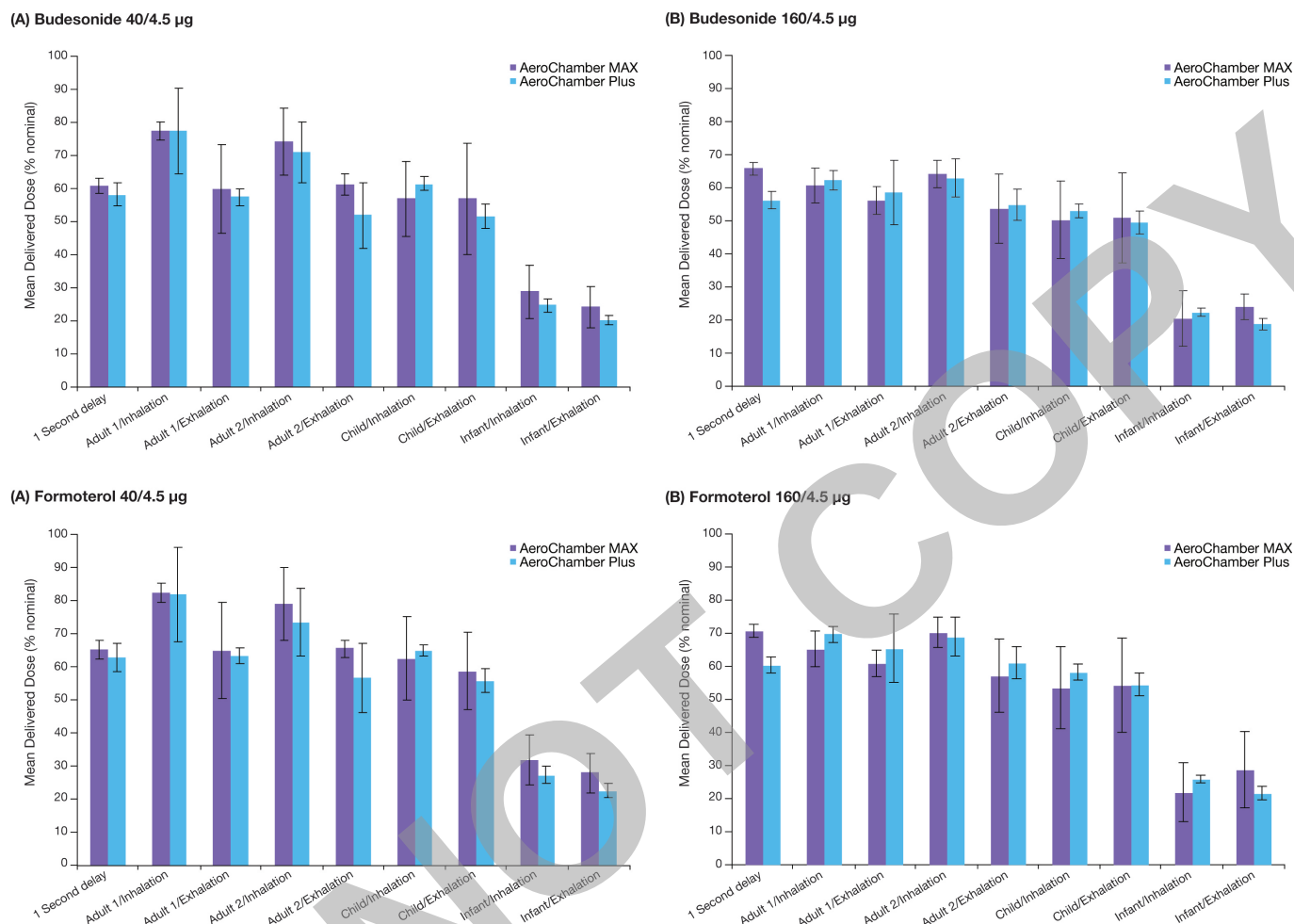


Figure 4. Delivered dose (% nominal dose, mean $\pm$ SD) from each valved holding chamber in combination with different simulated tidal breathing patterns. (A) Budesonide/formoterol, 40/4.5- μ g/actuation presentation and (B) budesonide/formoterol 160/4.5- μ g/actuation presentation.

Although VHCs offer considerable benefits, poor design or inadequate handling and technique may actually lead to reduced or inconsistent delivery of medication to the lungs.^{8,23} It is therefore important to evaluate the compatibility of particular VHCs and pMDIs under different conditions of use, paying particular attention to the FPD.

In this study, the expected loss of delivered dose was seen with both VHCs. However, the FPD was similar with the pMDI alone and with both AeroChamber Plus and AeroChamber MAX when there was no delay between actuation and collection. Differences in FPD values were <10%. Studies of fluticasone, beclomethasone, and salmeterol have also reported that similar FPD values are obtained with a pMDI alone and AeroChamber devices used without a delay between actuation and inhalation.^{24,25} The similarity in the delivered dose and FPD generated from both VHCs suggests that differences in valve design and chamber volume do not significantly influence delivery performance. The results indicate

that the budesonide/formoterol pMDI can be used with a similar efficacy alone and with the two VHCs investigated. Interestingly, the FPD observed in this study was somewhat higher than has been reported with other products. With no delay between actuation and inhalation, mean FPD ranged from 49.6% to 58.4% of the nominal dose with budesonide and 59.7% to 65.5% of the nominal dose with formoterol. This compares with values of ~30–50% with fluticasone, beclomethasone, and salmeterol HFA pMDIs used with VHCs.^{24–26}

There was some reduction in both delivered dose and FPD when delays between actuation and collection were introduced. AeroChamber MAX was generally more resistant than AeroChamber Plus to losses in both delivered dose and FPD when delays were introduced, probably because of the improved antistatic properties of the former. Despite these differences, the approved product specification for the critical FPD parameter was met for both VHCs and product strengths.

Previous studies have also reported dose loss with VHCs after delays and multiple actuations and shown considerable variability between different devices.^{12,27,28} The importance of these findings is recognized in the Canadian Standard guidance, which recommends incorporating a 2-second delay between actuation and collection as part of the *in vitro* evaluation of spacers and holding chambers to account for variations in patient technique.¹⁷ In addition, some guidelines recommend that administration of drugs *via* VHCs should occur by repeated single actuations of the pMDI, each followed immediately by inhalation.¹⁶

The experiments described here using a breathing simulator suggest that good performance will be achieved with the pMDI for patients aged from 6 years to adult using either VHC, especially when the delay between actuation and inhalation is minimized. The 160/4.5- μ g/actuation presentation produced a similar delivered dose in the tests using the adult and child simulated breathing patterns compared with the test where a 1-second delay was introduced between actuation and collection. The 40/4.5- μ g/actuation presentation performed slightly better than the 160/4.5- μ g/actuation presentation. Here, the delivered dose with both simulated adult inhalation patterns (*i.e.*, sampling was timed to coincide with inhalation) was similar to the delivered dose when there was no delay between actuation and collection. With simulated adult exhalation patterns (*i.e.*, actuation was timed to coincide with exhalation), delivered dose was no worse than under conditions where a 1-second delay was introduced. Similar results to the adult exhalation pattern were obtained with the child breathing pattern. There was a significant reduction in delivered dose with the simulated infant breathing pattern; this is likely to be caused by the higher number of breath cycles required to remove the aerosolized dose (three to four for the infant pattern compared with one to two for the adult and child patterns). Because the infant patient group is outside the age range evaluated for this product, these data are presented for interest only. Given the consistent FPD performance of the aerosol under conditions where delays between actuation and inhalation are introduced, the delivered dose is a good surrogate for FPD. The dose delivered from both VHCs was comparable for each simulated breathing pattern evaluated.

It should be noted that our tests have not included use of a face mask with the budesonide/formoterol pMDI and VHCs. Significant variability in delivery of drug to children has been shown depending on the face mask used,²⁹ with *in vitro* data suggesting that leaks between the face mask and the patient's face play an important role.³⁰

The results of this study illustrate the importance of selecting the most appropriate delivery system for the individual patient. Physician assessment of a patient's

ability to use the pMDI with and without a VHC is an essential part of the choice of delivery system.^{31,32} Clinical studies have shown that budesonide/formoterol pMDI is well tolerated and more effective when used in combination than either monocomponent alone.^{3,4} The availability of both drugs in a single inhaler reduces the complexity associated with delivery of different drugs from multiple inhalers and may aid patient compliance, thus providing another factor that the physician must consider when selecting the most appropriate drug and device for a patient.

CONCLUSION

Both AeroChamber Plus and AeroChamber MAX are compatible with budesonide/formoterol pMDI. Use of a VHC had very little effect on the FPD when the delay between actuation and collection was kept to a minimum in accordance with guidelines and the instructions of the VHC manufacturers. The similarity in data generated from both VHCs under conditions of minimal delay between actuation and sampling suggests that the difference in valve designs and chamber volumes do not significantly influence delivery performance. The FPD profile of the AeroChamber MAX was more robust than that of the AeroChamber Plus when delays between actuation and collection were introduced, probably because of the antistatic properties of its construction material. The delivered doses obtained when using the simulated tidal breathing patterns are a useful indicator of FPD performance. Small differences in performance were observed between the product strengths with the adult inhalation cycles. However, the adult profiles and, to a lesser extent, the child profile results were comparable with the delivered doses found when no delay or a 1-second delay between actuation and sampling were introduced. The results from the infant patient profile (~9 months old) produced considerably lower doses, probably because of the increased time required by the infant profile to empty aerosol from the VHC. Thus, budesonide/formoterol pMDI can be used effectively with both VHCs and without a VHC, allowing the physician to decide on the most appropriate administration regimen depending on the needs and skills of the patient.

ACKNOWLEDGMENTS

The authors acknowledge Charlotte Clay, Rajesh Dhingra, and Lynsey Bloomfield (AstraZeneca LP) for their contributions to the study. The authors acknowledge Mary Greenacre, Ph.D. (for Evidence Scientific Solutions, Inc.), for writing assistance funded by AstraZeneca LP.

REFERENCES

1. National Heart, Lung, and Blood Institute. Guidelines for the Diagnosis and Management of Asthma (EPR-3). 2009. Available online at www.nhlbi.nih.gov/guidelines/asthma; last accessed June 3, 2009.

2. Berger WE. The use of inhaled formoterol in the treatment of asthma. *Ann Allergy Asthma Immunol* 97:24–33, 2006.
3. Noonan M, Rosenwasser LJ, Martin P, et al. Efficacy and safety of budesonide and formoterol in one pressurised metered-dose inhaler in adults and adolescents with moderate to severe asthma. A randomised clinical trial. *Drugs* 66:2235–2254, 2006.
4. Corren J, Korenblat PE, Miller CJ, et al. Twelve-week, randomized, placebo-controlled, multicenter study of the efficacy and tolerability of budesonide and formoterol in one metered-dose inhaler compared with budesonide alone and formoterol alone in adolescents and adults with asthma. *Clin Ther* 29:823–843, 2007.
5. Heyder J, Gebhart J, Rudolf G, et al. Deposition of particles in the human respiratory tract in the size range 0.005–15 μm . *J Aerosol Sci* 17:811–825, 1986.
6. Dolovich MB, Ahrens RC, Hess DR, et al. Device selection and outcomes of aerosol therapy: Evidence-based guidelines: American College of Chest Physicians/American College of Asthma, Allergy and Immunology. *Chest* 127:335–371, 2005.
7. Lavorini F, and Fontana GA. Targeting drugs to the airways: The role of spacer devices. *Expert Opin Drug Deliv* 6:91–102, 2009.
8. Mitchell JP, and Nagel MW. Valved holding chambers (VHCs) for use with pressurised metered-dose inhalers (pMDIs): A review of causes of inconsistent medication delivery. *Prim Care Respir J* 16:207–214, 2007.
9. Mitchell JP, Coppolo DP, and Nagel MW. Electrostatics and inhaled medication: Influence on delivery via pressurized metered-dose inhalers and add-on device. *Respir Care* 52:283–300, 2007.
10. Bisgaard H, Anhoj J, Klug B, and Berg E. A non-electrostatic spacer for aerosol delivery. *Arch Dis Child* 73:226–230, 1995.
11. Berg E, Madsen J, and Bisgaard H. In vitro performance of three combinations of spacers and pressurized metered-dose inhalers for treatment of children. *Eur Respir J* 12:472–476, 1998.
12. Barry PW, and 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* 40:76–78, 1995.
13. Piérart F, Wildhaber JH, Vrancken I, et al. Washing plastic spacers in household detergent reduces electrostatic charge and greatly improves delivery. *Eur Respir J* 13:673–678, 1999.
14. Wildhaber JH, Waterer GW, Hall GL, et al. Reducing electrostatic charge on spacer devices and bronchodilator response. *Br J Clin Pharmacol* 50:277–280, 2000.
15. Chuffart AA, Sennhauser FH, and Wildhaber JH. Factors affecting the efficiency of aerosol therapy with pressurised metered-dose inhalers through plastic spacers. *Swiss Med Wkly* 131:14–18, 2001.
16. NHS Clinical Knowledge Summaries. 2009. Available online at www.cks.nhs.uk/asthma/management/detailed_answers/choice_of_inhaled_delivery_system/spacer_devices#30995; last accessed July 9, 2009.
17. Dolovich MB, and Mitchell JP. Canadian Standards Association standard CAN/C5A/Z264.1–02:2002: A new voluntary standard for spacers and holding chambers used with pressurized metered dose inhalers. *Can Respir J* 11:489–495, 2004.
18. European Medicines Agency (EMA). 2007. Guideline on the requirements for clinical documentation for orally inhaled products (OIP) including the requirements for demonstration of therapeutic equivalence between two inhaled products for use in the treatment of asthma and chronic obstructive pulmonary disease (COPD). 2007. Available online at www.emea.europa.eu/pdfs/human/ewp/415100enrev1.pdf; last accessed June 3, 2009.
19. US Food and Drug Administration. 2006, 2007. Symbicort 80/4.5 Symbicort 160/4.5 [PI]. Available online at www.accessdata.fda.gov/drugsatfda_docs/label/2008/021929s0101bl.pdf; last accessed June 3, 2009.
20. Trudell Medical International. 2009. AeroChamber Plus: Valved Holding Chamber. Available online at www.trudellmed.com/healthcare_professionals/hp_aerochamber_plus_vhc.asp; last accessed June 3, 2009.
21. Trudell Medical International. 2009. AeroChamber Max: Valved Holding Chamber. Available online at www.trudellmed.com/healthcare_professionals/hp_aerochamber_max_vhc.asp; last accessed June 3, 2009.
22. Trudell Medical International. 2009. AeroChamber Plus: Valved Holding Chamber Directions for Use [PI]. Available online at www.trudellmed.com/_content/pdfs/hp_aerochamber_plus_amask_cdn_directions.pdf; last accessed June 3, 2009.
23. Dolovich M, MacIntyre NR, Anderson PJ, et al. Consensus statement: Aerosols and delivery devices. *Respir Care* 45:589–596, 2000.
24. Asmus MJ, Coowanitwong I, Kwon SH, et al. In vitro performance of two common valved holding chambers with a chlorofluorocarbon-free beclomethasone metered-dose inhaler. *Pharmacotherapy* 23:1538–1544, 2003.
25. Nagel MW, Wiersema KJ, Bates SL, et al. Performance of large- and small-volume valved holding chambers with a new combination long-term bronchodilator/anti-inflammatory formulation delivered by pressurized metered-dose inhaler. *J Aerosol Med* 15:427–433, 2002.
26. Menzies D, Nair A, Fardon T, et al. An in vivo and in vitro comparison of inhaled steroid delivery via a novel vortex actuator and a conventional valved holding chamber. *Ann Allergy Asthma Immunol* 98:471–479, 2007.
27. Rau JL, Coppolo DP, Nagel MW, et al. The importance of non-electrostatic materials in holding chambers for delivery of hydrofluoroalkane albuterol. *Respir Care* 51:503–510, 2006.
28. Wildhaber JH, Devadason SG, Eber E, et al. Effect of electrostatic charge, flow, delay and multiple actuations on the in vitro delivery of salbutamol from different small volume spacers for infants. *Thorax* 51:985–988, 1996.
29. Hayden JT, Smith N, Woolf DA, et al. A randomized crossover trial of facemask efficacy. *Arch Dis Child* 89:72–73, 2004.
30. Smaldone GC, Berg E, and Nikander K. Variation in pediatric aerosol delivery: Importance of facemask. *J Aerosol Med* 18:354–363, 2005.
31. Chapman KR, Voshaar TH, and Virchow JC. Inhaler choice in primary practice. *Eur Respir Rev* 14:117–122, 2005.
32. Geller DE. Comparing clinical features of the nebulizer, metered-dose inhaler, and dry powder inhaler. *Respir Care* 50:1313–1322, 2005. □

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.