Clinically Appropriate Testing of Different Valved Holding Chamber (VHC)-Facemask Combinations investigating Delivered Mass to Carina for a Widely Prescribed Inhaled Corticosteroid Delivered by Pressurized Metered-Dose Inhaler (pMDI)

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Summary

Background: Laboratory evaluation of VHC-facemask add-ons is ideally undertaken simulating conditions-of-use. We report a study in which VHCs for small child use (n=3/group) (AeroChamber Plus® Flow-Vu® anti-static/child mask (aAC+); PocketChamber® (POC); Vortex® (VOR); SpaceChamber Plus® (SP); A2A Spacer® (A2A); Able Spacer™-2 (AB2)) were evaluated using an anatomical face/ 4-year child oropharynx model (ADAM-III).
Materials and Methods: Each VHC was evaluated out-of-package (OOP), but the non-anti-static devices were also washed with mild detergent / drip-drying (W). Performance was evaluated by breathing simulator (tidal volume = 155-mL, inspiratory: expiratory (I:E) ratio = 1:2, rate/min = 25 cycles). The facemask was attached to the model face following a 2-s coordination delay post pMDI actuation. The airway was coupled directly to the breathing simulator via an exit filter capturing fine particles that could theoretically penetrate as far as the carina in a patient (FP_{carina}). 5-actuations of fluticasone propionate (50 µg FP/actuation ex actuator) were delivered at 30-s intervals. Recovered FP was assayed by HPLC-UV spectrophotometry.
Results: Values of FP_{carina} (µg/actuation; mean±SD) were 10.5±1.0 (aAC+/OOP); 4.0±1.7 (POC/OOP); 0.7±1.1 (VOR/OOP); 1.0±0.3 (SP/OOP); 5.0±1.4 (SP/W); 0.6±0.1 (A2A/OOP); 4.1±0.9 (A2A/W); 0.3 ± 0.1 (AB2/OOP);4.8 ± 0.9 (AB2/W).
Conclusions: Significantly more FP was delivered to the model 'carina' from the aAC+ VHC (1-way ANOVA; $p < 0.001$); associated primarily with decreased VHC retention of medication. Large differences in delivery efficiency may exist when using different VHC-facemask delivery systems. Some of the difference can be eliminated by pre-conditioning non-anti-static devices before first use, however even when this is performed significant differences still exist.

Introduction

Valved holding chambers (VHCs) are widely prescribed for patients requiring inhaled medications via the pressurized metered-dose inhaler (pMDI) route who are unable to coordinate the onset of inhalation with inhaler actuation [1] and to reduce oropharyngeal deposition of medication. They are particularly necessary for infants and small children who are unable to use a mouthpiece as the patient interface, and must instead have their medication delivered via a facemask [2]. The laboratory evaluation of VHCs is a key part of the design process, in that it serves as a demonstration that the various components making up the device are functioning as intended [3]. In particular, it is important to establish that the delivery of the therapeutically beneficial fine particle component of the inhaled medication (typically taken as particles < 5 µm aerodynamic diameter [4]) capable of reaching receptors located along the airways of the lungs distal to the carina [5], has been optimized. The existing compendial methods for the assessment of pMDIs [4,6] are intentionally rudimentary in nature, because their primary purpose is to assure the consistent quality of the inhaler. For this purpose, it is sufficient to sample the aerosol at a fixed flow rate from the inhaler either into a dose uniformity sampling apparatus or cascade impactor for the determination of total emitted dose (mass) and aerosol aerodynamic particle size distribution respectively. However, more sophisticated laboratory evaluation techniques are required when the intention is to examine and quantify how the add-on device is likely to perform in the hand of the patient or caregiver [7]. In particular, it is essential to be able to quantify how the fine particle component emitted is reduced as the result of processes taking place within the chamber (*i.e.* gravitational sedimentation, deposition due to electrostatic charge etc.) when there is a delay between pMDI actuation and inhalation [8]. Furthermore, mimicking the continuously varying flow-time waveform associated with tidal-breathing is more likely to be representative of patient use than sampling at a constant flow rate [9]. Finally, added realism can be provided to the testing by using anatomically correct (to the intended patient population) face and upper airway models. The goal of the present study was to establish how a selection of similar-sized VHCs equipped with their associated facemasks performed in terms of fine particle delivery to the carina, simulating inhalation by a 4-year old child.

Materials and Methods

The following VHC types (n=3/group) were evaluated:

1. AeroChamber Plus® Flow-Vu® anti-static VHC (aAC+): Trudell Medical International, London, Canada;
2. PocketChamber® anti-static VHC (POC): nSpire Health Ltd., Hertford, UK;
3. Vortex® anti-static VHC (VOR): PARI Respiratory Equipment Inc., Midlothian, VA, USA;
4. SpaceChamber Plus® VHC (SP): Medical Developments International Ltd., Victoria, Australia;
5. A2A Spacer (A2A): Clement Clarke International Ltd., Harlow, UK.
6. Able Spacer™-2 VHC (AB2): Clement Clarke International Ltd., Harlow, UK.

Each device type was intended for small child use and was therefore tested with its appropriate sized facemask supplied by the manufacturer (Figure 1).

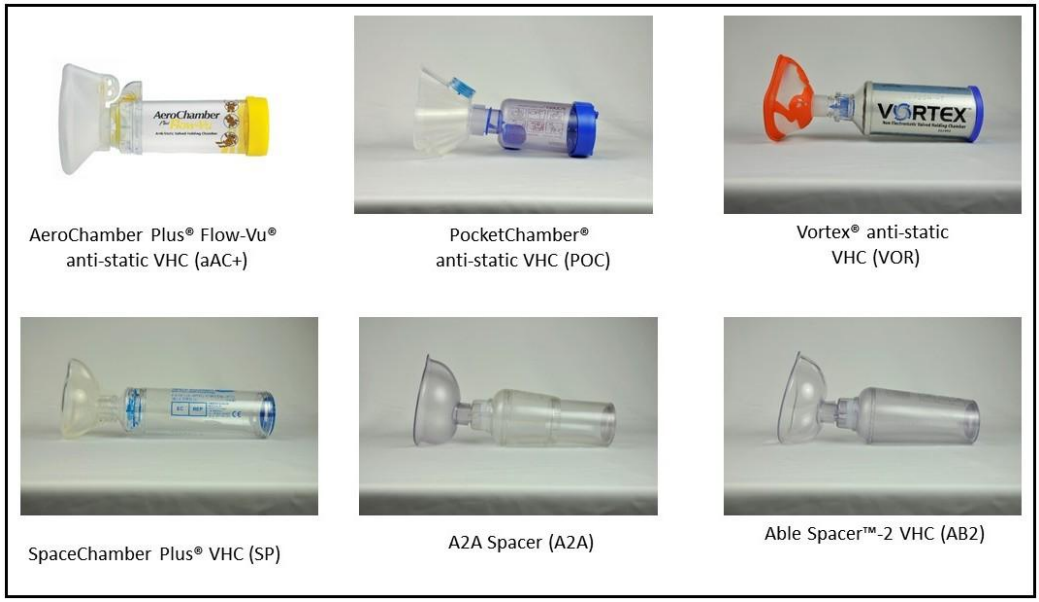

Figure 1: The VHCs Examined in the Investigation

Each of the VHCs evaluated (n = 3/group) were tested out-of-package (OOP) as would be the likely in use scenario, however, the non-anti-static devices were also evaluated after washing with mild detergent and drip-drying (W) in line with their recommended instructions for use. The manufacturer of the Able Spacer™-2 VHC claims it to be a 'low static' device so as it was uncertain if this chamber was an anti-static device, the device was evaluated OOP and also after pre-washing. *In vitro* performance was evaluated by breathing simulator (ASL5000), mimicking a 2-s coordination delay post pMDI actuation, followed by tidal breathing (tidal volume = 155-mL, inspiratory: expiratory (I:E) ratio = 1:2, rate/min = 25 cycles [10]). The facemask was attached to the Aerosol Delivery to Anatomic Model (ADAM-III) 4 year old small child face equipped with oropharynx (Figure 2). The airway was coupled directly to the breathing simulator via an exit filter to capture fine particles that would penetrate as far as the carina in a patient (FP_{carina}). 5-actuations of fluticasone propionate (50 µg FP/actuation; GSK Inc., Canada) were delivered at 30-s intervals. Recovered FP was assayed by HPLC-UV spectrophotometry.

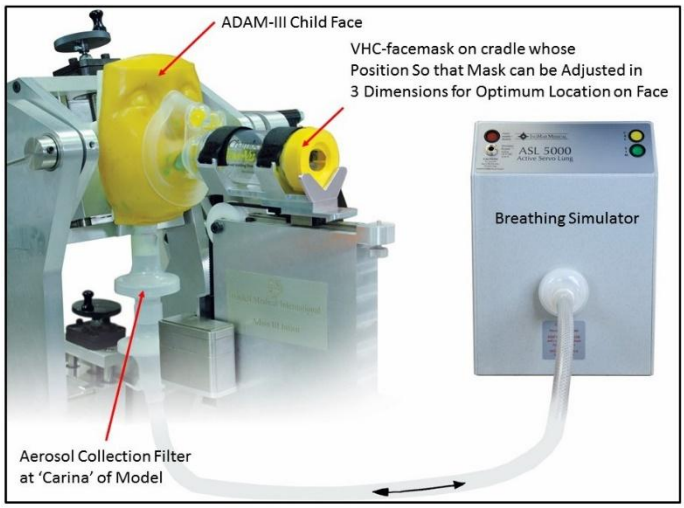

Figure 2: ADAM-III Small Child Face/Oropharynx Model with Breathing Simulator, Showing Position of Filter at Distal End of Oropharynx Mimicking Delivery of Medication at the Carina

Results

The distribution of recovered FP (µg/actuation; mean ± SD) emitted from each type of VHC is summarized in Table 1. Significantly more FP was delivered to the model 'carina' from the aAC+ VHC compared with any of the other anti-static devices evaluated, and also regardless of device pre-treatment modality in the case of the non-conducting SP and A2A VHCs (1-way ANOVA; $p < 0.001$). Given that the methodology incorporated a 2 second coordination delay between MDI actuation and placing the mask on the face for inhalation, the test system could not be enclosed in entirety. This fact, in addition to the variability of the pMDI itself, resulted in some variability in mass balances across the different devices tested, however, as the aAC+ device exhibited the lowest overall mass balance, the observed difference in model 'Carina' delivery is, if anything, minimized.

VHC Type	aAC+	POC	VOR	SP		A2A		AB2	
VHC conditioning	OOP	OOP	OOP	OOP	W	OOP	W	OOP	W
Retained by VHC	17.5 ± 1.6	36.6 ± 0.2	36.2 ± 3.8	40.1 ± 1.3	27.0 ± 1.8	37.8 ± 2.5	28.3 ± 2.8	37.5 ± 5.3	23.6 ± 3.6
Retained by pMDI	9.0 ± 0.7	12.5 ± 2.0	8.9 ± 0.8	9.1 ± 1.1	10.7 ± 0.9	7.1 ± 0.3	10.9 ± 1.4	8.3 ± 0.6	12.5 ± 0.4
Deposited on Face & Facemask	2.0 ± 0.6	2.1 ± 0.8	0.5 ± 0.8	0.5 ± 0.1	3.1 ± 2.0	0.0 ± 0.0	0.2 ± 0.1	0.1 ± 0.0	0.4 ± 0.4
Deposited in Model Oropharynx	1.1 ± 0.2	0.4 ± 0.2	0.3 ± 0.1	0.1 ± 0.1	0.5 ± 0.1	0.1 ± 0.1	0.4 ± 0.1	0.3 ± 0.3	0.5 ± 0.1
Filter at 'Carina' of model	10.5 ± 1.0	4.0 ± 1.7	0.7 ± 1.1	1.0 ± 0.3	5.0 ± 1.4	0.6 ± 0.1	4.1 ± 0.9	0.3 ± 0.1	4.8 ± 0.9

Table 1: Distribution of recovered FP (µg/actuation; mean ± SD) for each type of VHC

Discussion:

There are many factors that may affect the way in which a given VHC may perform, even when used correctly by the patient or care-giver [8,11]. Attraction of the pMDI generated aerosols to the VHC due to electrostatic forces is one factor. Pre-washing devices that are manufactured from non-conducting materials in a mild (ionic) detergent followed by drip-drying in air, as was done for some devices in this investigation, can coat the surfaces with a conducting monolayer of surfactant that may allow surface charges to drain to ground [12]. The slightly but significantly increased mass recovered from the 'carina' from the pre-washed SP, A2A and AB2 devices (paired t-test for each device type; $p < 0.001$) therefore reflects the expected improvement in delivery following such pre-treatment. However, in each case, the magnitude of improvement was not sufficient to match the delivery from the anti-static aAC+ VHC. This outcome suggests that additional factors must also be responsible for controlling the delivery of FP. The increased FP mass recovered from the filter at 'carina' location for the aAC+ VHC compared with values from the other devices was coincidental to a decreased retention of medication within the VHC itself for this particular VHC type. Other differences were observed at the various drug collection stages, however these were not of the same magnitude as the difference in VHC retention. Although the experiment was not designed specifically to identify the relative magnitude of such factors, there is ample evidence from previously published work that inefficient inhalation (and exhalation) VHC valve function [13], as well as the presence of even small leakage pathways from the facemask-face contact [14] can result in significant reduction in medication delivery efficiency. Differences in dead volume across the various facemasks may also have influenced drug delivery, although mask leakage has the potential to be a more significant factor [14,15]. In all cases, facemask-to-face leakage was therefore minimized during testing by careful positioning of the facemask on the model using the purpose-built cradle to support the VHC-on-test at an appropriate angle to the mouth and nose of the face, however it is expected that differences in the ability to seal with the face of the model would still be present due to the different designs of each mask. The relatively small delivered mass to the 'carina' for VOR was unexpected given that it is an antistatic VHC. Low values were observed for all three VOR devices tested and, following investigation, analytical abnormalities were ruled out. Given the large effect of even a small leakage on medication delivery reported by Esposito-Festen *et al*., it is speculated that facemask-to-face leakage may have been a cause, however further investigation would be required to fully understand the reason for this behavior. The small FP_{carina} mass from the AB2 when evaluated OOP was also a surprise, as it had been thought that the manufacturer claimed 'low-static' nature of the VHC and its supply within an, apparently, anti-static bag would have conferred improved performance. Instead, it behaved like the non-conducting VHCs, with a small but significant increase in FP after washing (paired t-test, $p < 0.001$). The 2 second delay from pMDI actuation to onset of inhalation, simulating real life use, would likely accentuate differences in VHC performance with respect to the ability to hold the particles in suspension ready for inhalation.

Conclusions:

The mass of FP delivered to the 'carina' of the model represents medication potentially available for therapeutic effect in the airways of the lungs. There was significantly more drug mass recovered from this location using the aAC+ VHC compared to the other devices (1-way ANOVA; $p < 0.001$) and it was related to a decreased retention of medication within the VHC. These results show the importance of such clinically relevant *in*-vitro testing during the development of VHCs and their associated facemasks. Large differences in delivery efficiency may exist between different devices and this may be even more pronounced when a facemask is present. When not able to immediately titrate the dose based upon response, such as with steroid delivery, then the risk of under-dosing is clearly possible.

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