In vitro performance characteristics of the A2A Spacer

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Summary

Valved holding chamber (VHC) spacers are recommended for users unable to coordinate actuation of the pMDI with inhalation of aerosolized drug and/or to avoid potential drug-related events (eg. high-dose inhaled corticosteroid-induced oral candidiasis). VHC use is commonplace among young children, and national/international recommendations exist for their use. Drug manufacturers routinely validate VHCs against their aerosol products to provide guidance and recommendations. A similar *in vitro* evaluation of the new Clement Clarke A2A Spacer® VHC (A2A) has been conducted at an independent laboratory. A2A is differentiated from other VHCs by inclusion of an anti-microbial additive throughout the device- and interchangeable mask-polymers that also confers considerable anti-static properties. A2A has been investigated inter- and intra-sample, through lifetime, and compared with AeroChamber® VHC and pMDI without spacer; determining the aerosol characteristics of Ventolin® HFA. Particle size, GSD, total dose delivered, and respirable, coarse, fine and ultra-fine particle fraction data were determined using an Andersen Cascade Impactor operated to FDA methodology. There were no significant differences between A2A samples for any aerosol characteristic (F-statistic < 4.74, ns). A2A passed all functional and visual lifetime tests, with no significant post-test differences in aerosol characteristics (t < 2.78, ns). Both VHCs significantly affected total delivered dose and coarse particle fraction - an expected outcome, with the VHCs trapping the larger non-respirable particles. The data indicate that A2A will be a useful additional VHC choice with bacterio- and fungi-static properties.

Introduction

The terms ‘spacer’ and ‘chamber’ are often used interchangeably to describe the pressurized metered dose inhaler (pMDI) aids. Spacers create a ‘temporal space’ between pMDI actuation and inhalation, and a greater physical space between the high-speed drug plume and oropharynx. As such, they can be simple tube-like devices. Chamber devices include an enclosed space, usually valved, which enables the patient to capture and inhale the drug particle cloud over successive breaths. These more sophisticated spacers are known as valved holding chambers or VHCs. The two main advantages of VHCs are (i) that the intermediary chamber removes the requirement for actuation-inhalation coordination and (ii) the reduction in oropharyngeal drug deposition and potential for improved lung deposition. Spacer use is recommended, for example, alongside high-dose inhaled corticosteroids. Governed by need and compliance, the UK National Institute for Health and Clinical Excellence recommends spacer use across all asthma age groups and for COPD patients [1], and it is recommended that inhaled drug-product manufacturers identify at least one spacer or VHC that has been validated with their product [2]. The main considerations thereafter become patient preference, cost and re-imbursement.

There are several prescription VHCs available in the UK: the A2A Spacer® and Able Spacer® (Clement Clarke International Ltd), AeroChamber Plus® and Volumatic® (GSK), Optichamber Diamond (Philips Respironics), Pocket Chamber (nSpire Health Ltd), Space Chamber Plus® (Medical Developments UK Ltd), and Vortex® (PARI Medical Ltd) [3]. One of the newest of these is the A2A (Aerosol to Airways) Spacer, introduced in 2012 [4].

The main features of VHCs are: one-way valve, collapsible or small-volume chamber to aid portability (exception, Volumatic), varying face-mask sizes, regimens to avoid static and drug-product build-up, and a 12-month life. Most chamber bodies are constructed from an anti-static transparent polymer (metal, Vortex) to aid visualization of the drug particles. The A2A Spacer (A2A) has the added advantage of achieving its anti-static effect through the use of a polymer additive that additionally confers both anti-microbial (data on file) and anti-static properties, extending the hygiene profile. It was, therefore, of particular interest to undertake our own evaluation of the A2A with a significant pMDI respiratory drug.

Methods and Materials

The effect of the A2A was determined, *in vitro,* on the aerosol characteristics of salbutamol sulphate (Ventolin® HFA; 90μg ex-mouthpiece and 108μg ex-valve). The study comprised three parts: intra- and inter-sample, comparative, and lifetime testing. The A2A is telescopic, opening to 208mL (Figure 1) and is, with the exception of the valve, constructed entirely from anti-microbial, anti-static polymers [4].

pMDIs were operated according to manufacturer’s instructions, and no two actuations of a pMDI occurred less than 30 seconds apart. pMDI boots were solvent-rinsed, washed in soapy water, distilled water-rinsed and allowed to air dry. VHCs were cleaned with soapy water and allowed to air dry, without rinsing. A silicon sleeve air-tight connection was formed between the A2A (or other devices) and a 7-stage Andersen Cascade Impactor (filter paper, 8th stage) mounted with an induction port [5] operated at a continuous 28L.min^{-1} flow rate. Twelve samples of drug material were extracted from the apparatus using HPLC-grade drug-appropriate solvents: pMDI boot fitting port/10mL, boot inner surfaces/20mL, chamber inner surfaces/30mL, induction port/30mL and each of

the eight Impactor stages/5-10mL. Particle size, geometric standard deviation and dose-fractions expressed as percent of valve label (total dose delivered, and respirable 0.5-5.0μm, coarse particle >4.7μm, fine particle <4.7μm and ultra-fine particle <1.0μm fractions) were determined using standard analytical techniques. Analysis of Variance and Student's t-test were used, respectively, to detect differences between the sample data and between the lifetime data. 95% confidence intervals were calculated for the comparative test data.

Figure 1 - A2A Spacer in opened position, plus pMDI

Intra- and inter-sample testing - Three samples of A2A were drawn at random from a recent production run. Each sample was tested three times with Ventolin HFA (n=9 tests).
Comparative testing - Three samples of A2A and of AeroChamber Plus Z Stat® (GSK) VHC were each tested once with Ventolin HFA (n=6 tests). The drug pMDI without a VHC attachment was also tested three times (n=3 tests). A2A data for this test were drawn from the sample testing protocol.
Lifetime testing - Three A2A samples were used from the sample testing protocol. The lifetime test procedures, with Pass/Fail outcomes, were disassembly, re-assembly, visual check, and pMDI-fit. These were conducted a total of four times: under ambient conditions before and after exposure to serial storage and stress environments (-21°C/4%RH for 24h, +62°C/95%RH for 24h, a 1m three-orientation concrete drop-test and 30 full cycles of connection plus four actuations through the Impactor) and, following this exposure, repeated twice to determine cold function (+2°C/5%RH for 4h) and hot function (+42°C/95%RH for 4h). Thereafter, the three A2As were tested once through the Impactor using Ventolin HFA (n=3 tests). For comparative purposes, the pre-lifetime Impactor data were drawn from the first Ventolin HFA pMDI of the sample testing protocol.

Results

The main results (particle size, total dose delivered and respirable fraction) for Ventolin across all testing protocols are presented in Table 1. There was no significant difference between the three A2A samples for particle size, total dose or respirable fraction ($F < 4.74$, not significant) or any other aerosol characteristic (data not shown). The A2A passed all the functional and visual lifetime tests, and there were no significant differences in any aerosol characteristic ($t < 2.78$, not significant) following the lifetime procedures. The A2A was comparable with the pMDI alone and with the brand-leading AeroChamber [6] in terms of particle size and respirable fractions. The 0.5-5.0μm respirable dose delivered by the pMDI alone in this study (42.18μg ± 4.11 [95% CI 37.54 – 46.83]) is comparable with published data for the Ventolin® [7] and Airomir® [8] HFA products, although it is recognised that the use of a non-USP induction port and the multi stage liquid impinger (MSLI), respectively, in the generation of the published data will have contributed to the small differences [9]. Both VHCs significantly affected total delivered dose and coarse particle fraction (latter data not shown) with neither confidence interval overlapping that of the pMDI alone. The outcome was to be expected, with the VHCs trapping the larger non-respirable particles. In all instances the data findings were typical for the devices being measured.

Conclusion

The data from this study confirm current UK recommendations regarding the use of A2A and AeroChamber with Ventolin HFA pMDI [10], with neither VHC adversely affecting the inhalation aerosol characteristics compared with pMDI alone. There are very few studies investigating the effect of cleaning on, or the potential for adverse effects from, spacer contamination but research does indicate that four out of 10 spacers have a bacterial/fungal contamination, with a possible link to pneumonial infection in children [11]. Cleaning has a variable effect, and is frequently omitted or incorrectly carried out [11-12]. It is hoped that the anti-microbial properties of A2A combined with a comparable low-static delivery is a positive addition to VHC choice. We plan to conduct similar in-clinic culture sample studies with A2A.

References

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Table 1 – Ventolin HFA aerosol characteristics

TEST	COMPARATIVE TEST			LIFETIME TEST	
			SAMPLE TEST		
	Commercial pMDI	**AeroChamber Plus Z Stat**	**A2A samples (1-3) combined**	**pre lifetime A2A (sample 1)**	**post lifetime A2A**
MMAD particle size (mean, μm)					
mean	1.80	1.60	1.70	1.67	1.53
SD	0.10	0.10	0.09	0.06	0.12
95% CI	1.69 - 1.91	1.49 - 1.71	1.60 - 1.80	1.60 - 1.73	
statistic			$F = 0.37$	$t = 1.79$	
Total dose (mean, % valve)					
mean	96.1	46.9	45.6	42.3	46.2
SD	0.9	5.2	5.0	7.7	3.2
95% CI	95.1 - 97.1	41.0 - 52.8	40.0 - 51.2	44.6 - 50.9	
statistic			$F = 1.32$	$t = 0.83$	
Respirable fraction 0.5 – 5.0μm (mean, % valve)					
mean	39.1	41.9	39.5	36.5	38.0
SD	3.8	5.4	4.7	7.4	2.4
95% CI	34.8 - 43.4	35.8 - 48.1	34.1 - 44.9	28.1 - 44.9	
statistic			$F = 1.05$	$t = 0.33$	