A Laboratory Investigation into the Performance of a Valved Holding Chamber with the Respimat† Soft Mist Inhaler using an Adult Oropharynx Model and Breathing Simulation

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INTRODUCTION

- The Respimat† Soft Mist Inhaler (SMI) (Boehringer Ingelheim, Germany) delivers medication in the form of a standing cloud of micrometer-sized droplets
- However, as with pressurized Metered Dose Inhalers (pMDIs), if there is poor coordination between actuation and inhalation, the effectiveness of aerosol delivery can be compromised, even though the SMI has a longer discharge time than a typical propellant-driven pMDI
- Valved Holding Chambers (VHCs) are widely prescribed for use with pMDIs as they conserve the aerosolized medication following actuation for subsequent inhalation by patients who have poor coordination
- Both plume velocity and shape are different for pMDI- and SMI-generated aerosols, so there is interest in investigating whether the use of a chamber with a SMI is associated with comparable mass of medication available for delivery to the lungs
- This laboratory study, mimicking adult use, examined the hypothesis that adding a VHC to the mouthpiece of a Respimat† SMI would result in a similar dose of medication available for lung deposition. It was assumed that the control SMI alone use would be perfectly coordinated.

MATERIALS AND METHODS

- Respimat† SMIs (n = 5/group)
  - Spiriva†: 2.5 µg Tiotropium Bromide
  - Combivent†: 100 µg Albuterol Sulfate +20 µg Ipratropium Bromide
  - Inspiolto†: 2.5 µg Tiotropium Bromide and 2.5 µg Olodaterol Hydrochloride

Part 1

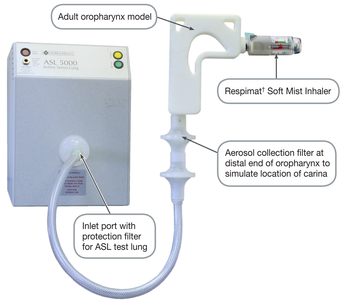


Figure 1: Test setup with ASL 5000 breathing simulator *(IngMar Medical)* and ADAM (Aerosol Delivery to Anatomic Model) an anatomically correct adult oropharyngeal model *(Trudell Medical International)*

- The mouthpiece of each SMI was directly connected to a breathing simulator (ASL 5000, IngMar Medical, Pittsburgh, PA) via an anatomically correct adult oropharyngeal model (Figure 1)
- An aerosol filter collected the medication at the exit from the model's upper airway, representing medication likely to penetrate beyond the carinal ridge to reach the lungs
- A tidally breathing adult was mimicked
  - Tidal volume = 770 mL
  - Rate/min = 12
  - Inspiratory: expiratory ratio = 1:2
- Five actuations were each delivered at the beginning of an inhalation, with a six-breathing cycle sampling period in between each actuation

Part 2

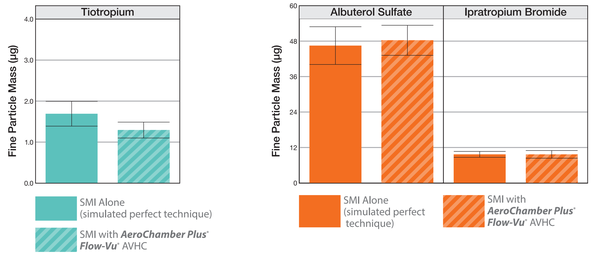
- The measurements were repeated with the ***AeroChamber Plus**** ***Flow-Vu**** VHC downstream of the SMI-on-test
- In both parts of the study the mass of active pharmaceutical ingredient(s) recovered from each filter, including its housing, was determined by an internally validated HPLC-spectrophotometric procedure

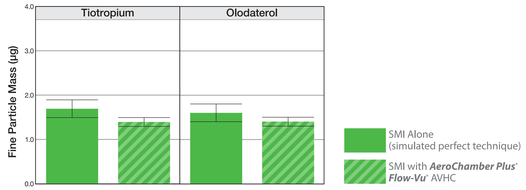
RESULTS

Mass of API (µg/actuation) Recovered Downstream of an ADAM Oropharyngeal Model

	Spiriva† SMI		Combivent† SMI				Inspiolto† SMI			
	Tiotropium		Albuterol Sulfate		Ipratropium Bromide		Tiotropium		Olodaterol	
	Alone	VHC	Alone	VHC	Alone	VHC	Alone	VHC	Alone	VHC
Chamber	N/A	1.3±0.1	N/A	32.9±7.7	N/A	6.0±1.5	N/A	0.9±0.1	N/A	0.9±0.1
Oropharynx	0.9±0.2	0.4±0.1	31.5±3.7	12.2±1.9	6.6±0.8	2.1±0.4	0.4±0.5	0.4±0.1	0.9±0.0	0.4±0.2
Filter ('carina')	1.7±0.3	1.3±0.2	46.6±6.4	48.4±5.1	9.7±1.0	9.7±1.3	1.7±0.2	1.4±0.1	1.6±0.2	1.4±0.1
Total	2.7±0.2	3.0±0.1	78.1±8.8	93.5±4.6	16.3±1.8	17.8±1.1	2.0±0.5	2.7±0.1	2.6±0.2	2.6±0.1

Filter or 'Carina' Values Illustrated Graphically





DISCUSSION

- Mean values of total drug mass recovered ex SMI mouthpiece were within ±20% label claim for all three products
- In general, the mass of each active pharmaceutical ingredient deposited in the model oropharynx was significantly reduced when the VHC was present (paired t-test, $p < 0.001$)
  - The exception was the tiotropium component of the Inspiolto† product, where we saw no difference (a finding perhaps confounded because we were close to the limit of detection)
- Significant deposition of all APIs within the VHC was evident
  - In general, this additional deposition was associated with an increase in the total mass recovered, the exception being the olodaterol component of the Inspiolto† product where no change was observed
- The mass of API recovered from the filter, representing the portion of the inhaled dose likely to reach the carina, and therefore available for delivery to the lungs, was similar with or without the chamber present for all three products

CONCLUSIONS

- The study, modeling adult use, confirmed the hypothesis that the addition of the ***AeroChamber Plus**** ***Flow-Vu**** VHC to the three different Respimat† SMI products did not appreciably affect delivery of the portion of each API penetrating the model carina, and therefore available for lung deposition
- In general, the use of the VHC also reduced the amount of medication deposited in the oropharynx

API = active pharmaceutical ingredient

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