Simulating the Impact of Delayed Inhalation Upon Medication Delivery from Suspension and Solution Pressurized Metered Dose Inhalers Used With and Without a Valved Holding Chamber

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INTRODUCTION

- The present study was designed to investigate, using clinically relevant laboratory testing, potential changes in medication delivery associated with delayed inhalation with Pressurized Metered Dose Inhaler (pMDI)-delivered solution and suspension formulations, with and without the presence of a Valved Holding Chamber (VHC).
- The goals were
  - To understand the relative impact of delayed inhalation
  - To examine the protection to the patient afforded by the VHC

MATERIALS AND METHODS

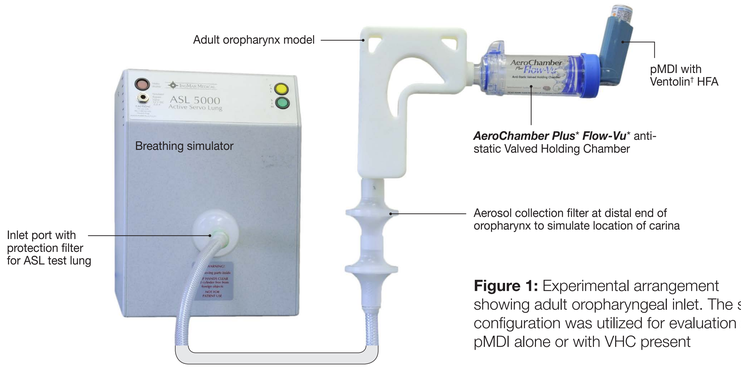

Figure 1: Experimental arrangement showing adult oropharyngeal inlet. The same configuration was utilized for evaluation of pMDI alone or with VHC present

- The large adult model oropharyngeal (OP) airway of the Aerosol Delivery to an Anatomic Model (ADAM) series (Figure 1) was used in order to provide a more clinically relevant laboratory determination of the total mass per actuation of a
  - **Suspension** pMDI (Ventolin†-HFA, 100 µg salbutamol base equivalent/actuation)
  - **Solution** pMDI (Qvar†, 100 µg beclomethasone dipropionate (BDP)/actuation)
- ***AeroChamber Plus*** **Flow-Vu**** antistatic VHC with mouthpiece was used as a representative VHC
  - $n = 3$ devices
  - 1 measurement per device
  - Sampling at a constant flow rate of 30 L/min
- The impact of delayed inhalation was assessed as follows
  - Actuation of pMDI alone with no delay (perfect coordination), 1-s and 2-s delay intervals
  - Actuation of pMDI with VHC with no delay, 2-s, 5-s, 10-s and 15-s delay intervals
- The deposited medication was recovered separately from the mouthpiece of the pMDI, the interior surfaces of the VHC-on-test (when present), the interior surfaces of the model oropharyngeal airway and on the filter (representative of medication available to lungs).
- Assay for either BDP or salbutamol was subsequently undertaken by a validated HPLC-UV spectrophotometric procedure.

RESULTS

Suspension

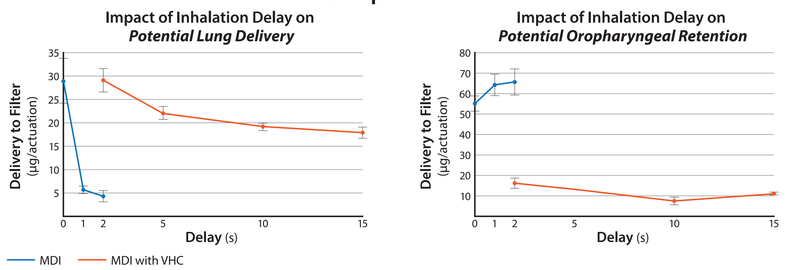

Figure 2: Effect of Inhalation Delay on Salbutamol Suspension-Formulated pMDI-Delivery on Mass of Medication Recovered from (A) Distal Filter of the ADAM Model and (B) the Oropharyngeal Airway

Solution

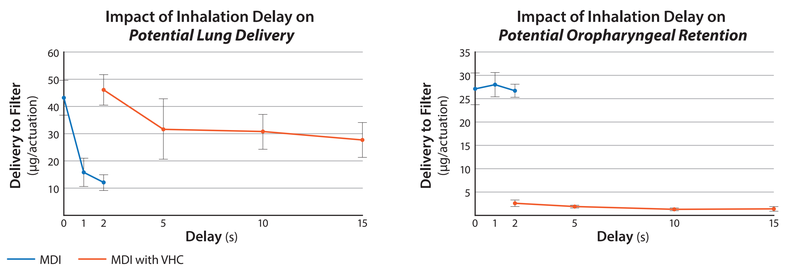

Figure 3: Effect of Inhalation Delay on BDP Solution-Formulated pMDI-Delivery on Mass of Medication Recovered from (A) Distal Filter of the ADAM Model and (B) the Oropharyngeal Airway

Inhalation by	Delay (s)	Location in Model: pMDI mouthpiece	VHC interior	OP airway	Filter	Total Mass
Suspension-formulated Salbutamol (µg/actuation, mean ± SD)						
pMDI alone	0	13.9 ± 2.8		55.1 ± 3.7	29.0 ± 4.8	98.0 ± 5.8
	1	27.7 ± 2.7		64.3 ± 5.2	5.7 ± 0.8	97.7 ± 3.3
	2	31.0 ± 4.2		65.7 ± 6.4	4.3 ± 1.2	101.0 ± 4.3
pMDI with ***AeroChamber Plus*** **Flow-Vu**** aVHC	0	11.4 ± 1.0	21.0 ± 0.9	6.5 ± 1.1	53.6 ± 1.2	92.4 ± 0.6
	2	29.5 ± 2.5	38.6 ± 7.0	16.2 ± 2.5	29.1 ± 2.5	113.9 ± 9.0
	5	28.4 ± 1.3	52.3 ± 1.1	13.2 ± 0.2	22.0 ± 1.4	115.9 ± 0.9
	10	24.9 ± 1.6	42.3 ± 4.0	7.5 ± 1.9	19.2 ± 0.8	93.9 ± 7.9
	15	29.9 ± 2.3	41.2 ± 6.8	11.0 ± 0.7	17.9 ± 1.2	100.0 ± 6.9
Solution-formulated BDP (µg/actuation, mean ± SD)						
pMDI alone	0	22.7 ± 2.1		27.1 ± 3.4	43.2 ± 6.4	93.0 ± 2.3
	1	40.7 ± 3.8		28.0 ± 2.6	15.8 ± 5.2	84.5 ± 2.1
	2	45.1 ± 2.1		26.7 ± 1.4	12.1 ± 2.9	83.8 ± 1.5
pMDI with ***AeroChamber Plus*** **Flow-Vu**** aVHC	0	15.7 ± 0.9	14.3 ± 2.4	2.3 ± 0.6	68.1 ± 2.1	100.4 ± 0.6
	2	23.6 ± 3.0	25.5 ± 7.0	2.6 ± 0.7	46.1 ± 5.6	97.8 ± 4.4
	5	27.5 ± 1.7	36.4 ± 12.8	1.9 ± 0.3	31.6 ± 11.1	97.4 ± 2.9
	10	28.8 ± 4.1	34.4 ± 5.8	1.3 ± 0.3	30.8 ± 6.4	95.4 ± 3.1
	15	29.6 ± 3.3	37.2 ± 4.4	1.4 ± 0.5	27.7 ± 6.4	95.9 ± 0.7

DISCUSSION

- Coordination and oropharyngeal deposition are closely linked. With the salbutamol suspension formulation (Figure 2A), when no VHC was present, any delay to inhalation from inhaler actuation was associated with greatly decreased delivery to the filter, indicative of reduced medication potentially available for lung deposition *in vivo*.
- The situation was only marginally better with the finer droplets associated with the solution aerosol (Figure 3A).
- Less drug (suspension or solution) was deposited in the OP airway when the VHC was present, as the presence of the chamber increased the distance for the ballistic fraction of the emitted mass to expand before entering the model OP.
- Delaying inhalation by as little as 1-s, resulted in decreases of about 80% and 63% in the mass of salbutamol and BDP correspondingly that penetrated as far as the filter, representing potential deposition at the carina. In contrast, when the VHC was present, the mass of either salbutamol (Figure 2A) or BDP (Figure 3A) reaching the filter declined gradually with increased delay, and taking a 2-s delay as representative of a most likely scenario with the poorly coordinated patient, the delivery was comparable with optimum delivery of medication from the pMDI alone with no delay.
- The finer particles emitted from the solution product were less susceptible to gravitational sedimentation-related losses, so that filter collection was more efficient with either a 1-s or 2-s delay when the VHC was absent. Nevertheless, a large percentage decrease in potential lung delivery was still evident, and this decline was significantly reduced when the VHC was present (un-paired t-test for comparison at the 2-s delay interval with/without VHC, $p < 0.001$).

CONCLUSIONS

- This laboratory-based study mimicking adult inhalation of suspension- and solution-formulated pMDI-delivered medications highlighted the potential for even a short delay, following inhaler actuation without a VHC, to reduce markedly the efficiency of aerosol delivery to the carinal region of the airway, potentially available for lung delivery.
- The use of a representative VHC appreciably reduced the impact of inhalation delay with either formulation.
- If one can be assured that the onset of inhalation will coincide with inhaler actuation, it is possible to achieve effective medication delivery to the lungs with either type of pMDI alone. However, it would be clinically prudent to prescribe a VHC regardless of formulation type, given the high likelihood of a delayed inhalation.

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