Effect of pMDI Orifice Diameter on Regional Extrathoracic Deposition in an Idealized Child Airway

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BACKGROUND

RATIONALE

- Extrathoracic (ET) deposition from pressurized metered dose inhalers (pMDIs) is known to be influenced by several factors including the spray pattern from the inhaler, inhalation flow rate and size of particles delivered to the patient [1,2].
- High ET deposition results in decreased delivery to lungs, can cause undesirable side effects in the ET airways [3], and is primary a source of variability in lung deposition [4].
- Ruzycki *et al.* recently demonstrated that actuator orifice diameter (OD) significantly influences regional ET deposition of an epinephrine suspension pMDI in the adult Alberta Idealized Throat (AIT) [5].
- Inhalation maneuvers and airway size for children are different than in adults [6]. While total ET deposition in children from pMDIs has been previously investigated [7], less is known about the influence of device characteristics, such as OD, on regional ET deposition.

OBJECTIVE

- To investigate the influence of orifice diameter, inhalation flow rate and inhaler orientation on regional ET deposition for a suspension epinephrine pMDI in the Alberta Idealized Child Throat (AICT).
- To assess the robustness of orifice diameter effects on regional ET deposition subject to varying ambient temperature and humidity conditions.

METHODS

EXPERIMENTAL PROCEDURE

- A sectioned version of the AICT (s-AICT), divided into analogues of the oral cavity, the pharynx/larynx, and the upper trachea was used in a series of experiments to explore the influence of several factors on regional deposition of a commercially available suspension of epinephrine in the ET airways of children.
- Previously established methods [2, 5] were used to evaluate deposition from pMDIs in the s-AICT using actuators with two ODs. The small OD was 0.22 mm (Bespak, Consort Medical), and the large OD, evaluated using precision steel pin gages, was 0.42 mm (Primatene MIST, Amphastar Pharmaceuticals Inc).
- A suspension epinephrine formulation was used for testing (Primatene MIST; label claim of 125 µg). Three actuations were used per test, giving a total nominal dose of 375 µg.
- Following device actuation and inhalation, components were disassembled, and the mass of drug in each section was quantified through ultraviolet (UV) spectroscopy of analytes obtained with a solvent of 1:1 methanol and 0.1 N hydrochloric acid. Two-tailed Student's T-tests were performed (α = 0.05) across 3 repetitions (n = 3) on the results for each experimental condition .

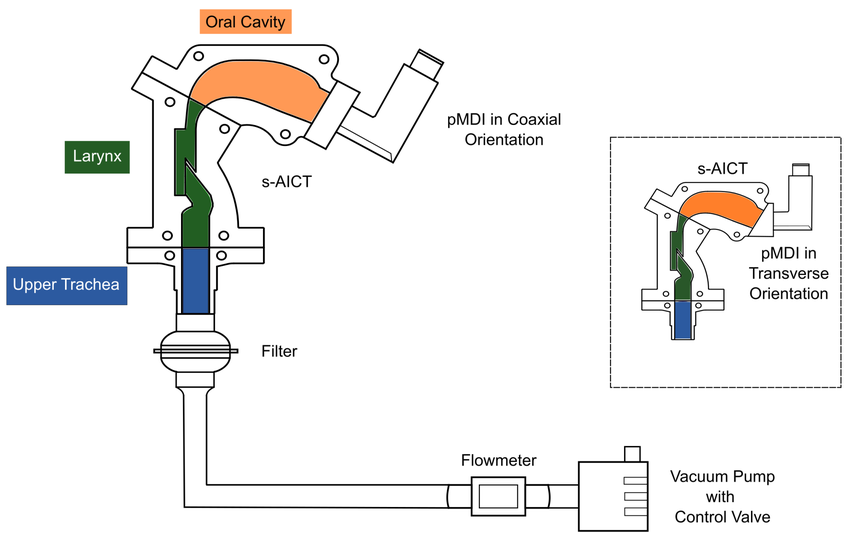

Figure 1. Experimental setup for measuring regional deposition in the s-AICT from pMDIs with different orifice diameters. The ET model used during testing was a sectioned version of the Alberta Idealized Child Throat.

REGIONAL DEPOSITION TESTS EXPLORING INFLUENCE OF OD AND INHALER ORIENTATION

A full factorial study was conducted exploring regional ET deposition in an environment at room temperature (20 – 22°C) with low ambient humidity (1.6 - 19.5% RH, approx. 2 g H_2O /m^3 dry air). The following factors were incorporated into the analysis:

- Two actuators with different orifice diameters (0.22 and 0.42 mm)
- Two inhaler orientations (transverse and coaxial)
- Four inhalation flow rates (10, 30, 60 and 100 L/min)

EFFECT OF HUMIDITY ON REGIONAL DEPOSITION IN THE S-AICT

An auxiliary study investigating the effect of ambient humidity on regional deposition was conducted using

- A single inhalation flow rate (30 L/min)
- Two actuators with different orifice diameters (0.22 and 0.42 mm)
- Two inhaler orientations (transverse and coaxial)
- Two additional humidity conditions:
    1. Mid at 21.5 – 22 °C with 65 – 73 %RH (approx. 13.4 g H_2O /m^3 dry air)
    2. High at 29.8 – 30.7 °C with 81 -85 %RH (approx. 25.2 g H_2O /m^3 dry air)

EFFECT OF ORIFICE DIAMETER ON PARTICLE SIZE MEASUREMENTS DOWNSTREAM OF ET AIRWAYS

Tests were performed to investigate the influence of orifice size on residual particle size distributions measured downstream of the s-AICT, following previously described methods from our group [4]. A Next Generation Impactor was placed downstream of the s-AICT instead of the filter, with a 30 L/min flow rate drawn through the system. Mass median aerodynamic diameter (MMAD) and geometric standard deviation (GSD) were calculated via linear interpolation on measured particle size distributions following standard approaches.

RESULTS AND DISCUSSION

REGIONAL DEPOSITION TESTS EXPLORING INFLUENCE OF OD AND INHALER ORIENTATION

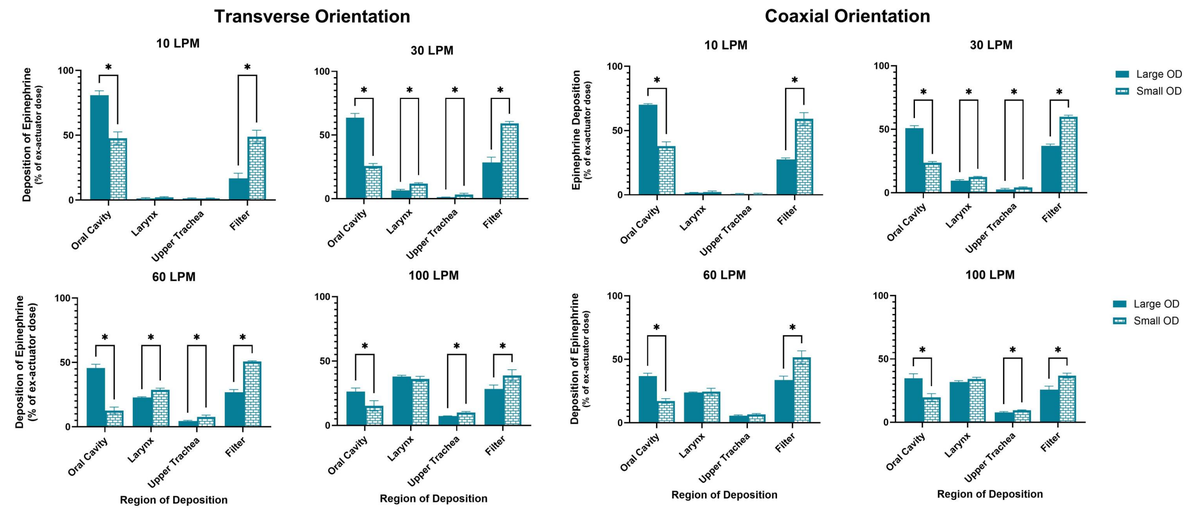

Figure 2. The results from the primary study exploring the influence of orifice diameter (OD), inhaler orientation and inhalation flow rate on regional ET deposition of inhaled epinephrine in the s-AICT are displayed. Statistical significance is indicated with an asterisk (*).

- Tests with the small OD inhaler displayed lower oral cavity deposition (10.2 – 52.6%) across all flow rates and inhaler orientations compared to the large OD inhaler (22.4 – 85.7%).
- Inhaler orientation had no significant effects on deposition for the small OD inhaler while 7 of 16 test conditions for the large OD inhaler were significantly affected by orientation.
- Trends are consistent with deposition patterns measured in the comparative adult study by Ruzycki *et al.* [5] across both orientations.

EFFECT OF HUMIDITY ON REGIONAL DEPOSITION IN THE S-AICT

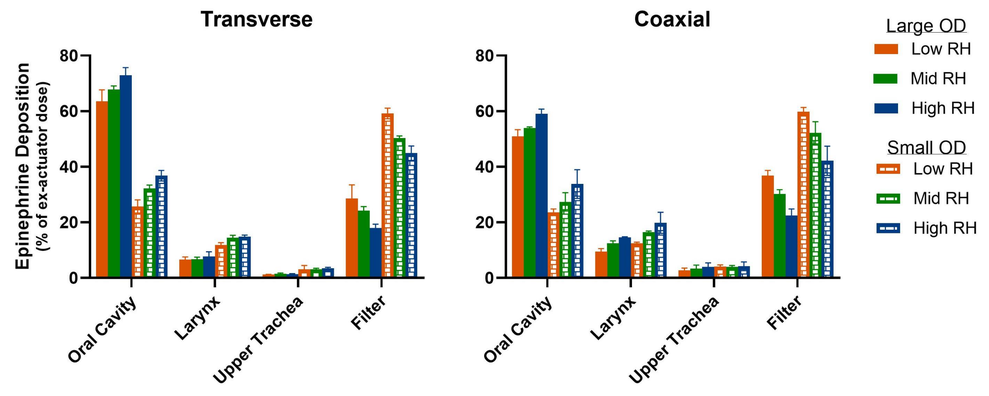

Figure 3. Regional deposition of epinephrine at different humidity conditions using both inhaler orientations with a 30 L/min flow rate. The low and mid humidity experiments were performed at room temperature, while high humidity experiments were conducted at increased temperature and ambient humidity.

- Statistical analysis showed that all differences between the two inhalers shown in Figure 3 are statistically significant ($p<0.05$) except for deposition in the upper trachea.
- Despite changes to humidity inhaler orientation continued to have no impact on regional deposition for the small OD inhaler, and had similarly significant effects of orientation as noted earlier for the large OD inhaler (for 5/8 measurements).

EFFECT OF ORIFICE DIAMETER ON PARTICLE SIZE MEASUREMENTS DOWNSTREAM OF ET AIRWAYS

Table 1. Comparison between MMAD and GSD from epinephrine pMDIs with a large and small OD downstream of the s-AICT. Results are presented as averages across 3 tests with the standard deviation in brackets.

	Large OD	Small OD
MMAD (µm)	1.76 (0.00)	1.83 (0.03)
GSD	1.66 (0.01)	1.68 (0.01)

- Changes in particle size downstream of the s-AICT due to changes in orifice size were negligible. This implies that observed differences in ET deposition patterns were more likely due to spray patterns and the geometry of the aerosolized drug plume than differences in particle size.

CONCLUSIONS

- Regional deposition measurements performed in the s-AICT indicate that use of the small OD actuator resulted in reduced oral cavity deposition and increased *in vitro* lung deposition, compared to the large OD actuator.
- While increased ambient humidity and temperature caused an increase in oral and laryngeal deposition, along with concomitantly decreased deposition in the lung region, the influence of these environmental changes had a minor effect on regional deposition patterns when compared with changes to actuator OD.

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