Understanding the Impact of Disease on Pediatric Regional Intranasal Drug Delivery with Nasal Sprays

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INTRODUCTION AND OBJECTIVES

- Drug deposition in 40 healthy pediatric nasal cavities was previously studied, and three representative models, low (L), mean (M), and high (H), were selected based on the amount of drug deposited in the posterior region of nasal cavity [1,2]. However, the impact of disease on pediatric intranasal regional drug deposition is not well studied.
- In this study, we aimed to study the in vitro regional drug deposition in eight nasal cavities, based on the left and right cavities of four subjects, with diseased nasal airways. The effect of disease type on deposition pattern and on the ability of currently developed representative models, L, M, and H to represent the diseased nasal airways were evaluated.

METHODS

Prototyping Nasal Models

- Diseased nasal airways of four subjects aged 5-10 years (Table 1) were obtained from CT scans.
- Nasal models were prototyped based on the 8 cavities (the left and right cavities of 4 subjects), and segmented into six regions: anterior, front, inferior, middle and superior turbinate, as well as nasopharynx (Figure 1).

In Vitro Drug Deposition Study

- Nasal models were placed on an automatic actuator and connected to a breathing simulator.
- Three units of the same batch of Nasacort 24HR nasal spray were used.
- Sprays were actuated at the beginning of the inhalation phase.

Drug Assay and Statistical Analysis

- Each piece of the nasal models was rinsed in a separate tray using a known amount of diluent.
- Samples were taken and drug was assayed using HPLC.
- T-test was used to compare A) both sides of a model, and B) healthy and diseased models.

Table 1 – Models and Subjects Information.

Diseased Model (DM) Number	Age (years)	Sex	Type of Disease
DM1	5	Male	Significant airway edema, chronic rhinosinusitis (CRS), minor nasal septal deviation (NSD)
DM2	7	Female	CRS, significant left hypertrophy, NSD
DM3	8	Male	Significant NSD
DM4	10	Female	Severe CRS

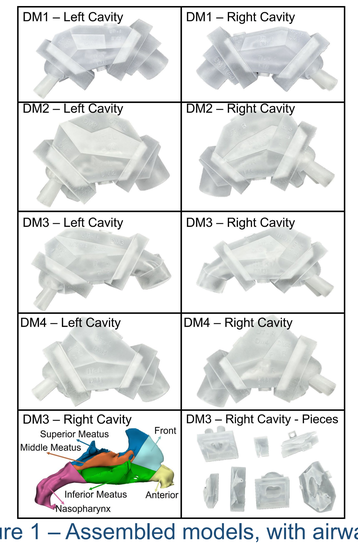

Figure 1 – Assembled models, with airway and pieces of DM3

RESULTS

- Similar to the healthy airway models, more than 90% of drug deposited in three regions: anterior, front, and inferior turbinate. Considering this, Figure 2 shows the percentage of recovered drug deposited only in these three regions for diseased and healthy models, L, M, and H.

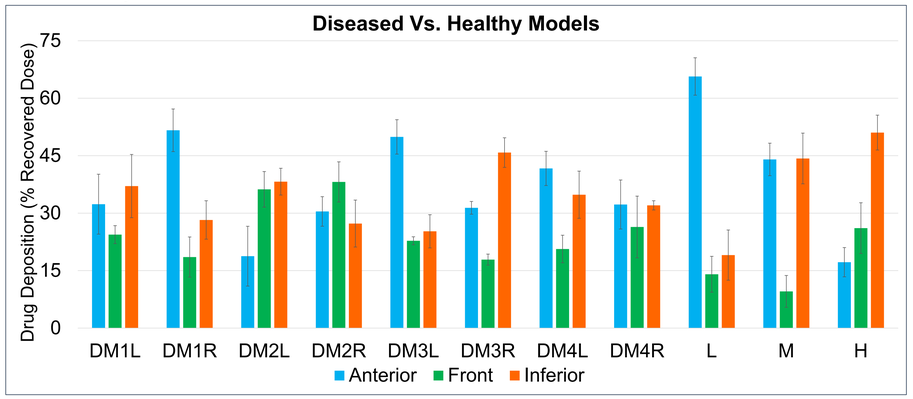

Figure 2 – Percentage regional drug deposition in child L, M, H and diseased models. N=3 for diseased models and n = 27 for healthy models. Error bars are standard deviation.

- Deposition in the front region is overall higher in the diseased models. Figure 3 shows the mean ratio of deposition in the front to inferior turbinate regions.

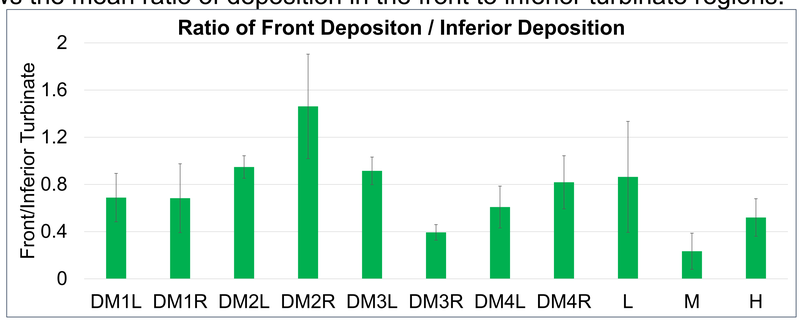

Figure 3 – Front/Inferior ratio for diseased and healthy models. Error bars are standard deviation.

- This ratio in some cases, i.e., DM2 Left and Right and DM4 Right, was close or even greater than 1, but for child L, M and H models the corresponding ratios were 0.74, 0.22 and 0.51, respectively.
- Table 2 shows the *p*-values of the performed *t*-tests to compare the left and right of the diseased models. It also presents the *p*-values of *t*-tests for comparing the diseased and healthy models.

Table 2 - P-values from t-test performed to compare both sides of each model in different regions, as well as the comparison for all 8 diseased models with the three healthy models.

Region	DM1 – Right vs Left	DM2 – Right vs Left	DM3 – Right vs Left	DM4 – Right vs Left	DM1-4 vs L, M, H models
Anterior	**0.030***	0.105	**0.0056***	0.113	0.1832
Front	0.183	0.658	**0.0055***	0.347	**0.0004***
Inferior	0.203	0.070	**0.0019***	0.519	0.1807
Fr/Inf [a]	0.981	0.177	**0.0029***	0.277	**0.0115***

Asterisks (*) show statistically significant difference (α = 0.05).
a – Front deposition / inferior deposition ratio.

CONCLUSION

- Among the considered diseases, significant NSD caused the most significant impact on the deposition pattern, when comparing the two sides of a subject.
- The case with significant hypertrophy in the left side nasal cavity, in addition to CRS and NSD, showed the most dissimilar deposition pattern to healthy models. The front deposition in both sides of this model was higher than other models, healthy or diseased.
- Given that no significant difference in nasal deposition was observed for the inferior turbinate region between the healthy and diseased nasal models, this study suggests the child L, M and H models may provide reasonable estimates for in vitro nasal deposition for both the healthy and diseased population.

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