Understanding the Relationship Between In Vitro Nasal Spray Characteristics and Intranasal Deposition in the Adult and Pediatric Populations

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PURPOSE

In vitro studies are included as part of the recommendations to establish bioequivalence (BE) of suspension nasal sprays [1]. While the in vitro studies generally are sensitive to detect performance differences, their clinical relevance may be limited. Additionally, differences in nasal anatomy, both between and among adult and pediatric patients, can further complicate evaluating regional nasal deposition using standard in vitro methods.

To address the concerns regarding clinical relevance of in vitro studies and intersubject variability, other potential performance metrics such as regional nasal deposition can be explored using in vitro anatomical nasal models of adults and pediatric subjects.

OBJECTIVE

Develop in vitro anatomical nasal models of pediatric patients and evaluate the sensitivity of these models in detecting performance differences for nasal suspension products, as compared to previously developed in vitro adult nasal models.

METHODS

Models

Three healthy adult and three healthy pediatric anatomically realistic rapid prototyped computed tomography (CT)-based nasal airway models, selected out of 40 adult and 40 pediatric nasal cavities, were used (21–75 years old, half female and half ≥ 50 years old for adults, and for pediatric subjects 2-11 years old, half female and half ≤ 6 years old).

These models were selected to represent three main levels of nasal spray drug deposition: Low posterior deposition (PD) (L models, Figure 1), medium PD (M models, Figure 2), and high PD (H models, Figure 3).

The selected cavities were cut into **six regions**, including the **anterior** region and five regions comprising the posterior region: **front**, **inferior**, **middle**, **superior meatuses**, and **nasopharynx**.

Products

Three triamcinolone acetonide (TA) nasal spray products, including one reference listed drug (RLD) product and two approved generics, T1 and T2, were used.

In Vitro Tests

Conducted in vitro studies were spray characterization, including droplet size distribution (DSD), plume geometry and spray pattern, and in vitro deposition studies (Figure 4) in all six models through a controlled administration method.

Drug Extraction and Assay

Following actuation, the models were dismantled, and each region was separately rinsed with the solvent to collect the drug. A high-performance liquid chromatography (HPLC) method was developed and used to analyze the deposited drug.

The procedure was repeated for all three products using three different batches and three units per batch.

Population Bioequivalence (PBE) Statistical Analysis

After obtaining the deposition percentage in each region, the total PD was calculated and used to perform the population bioequivalence (PBE) analyses for both generic products in all six nasal models [1].

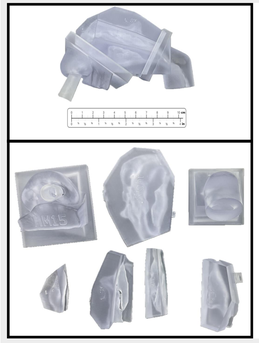

Figure 1 – Child L model and its associated regions.

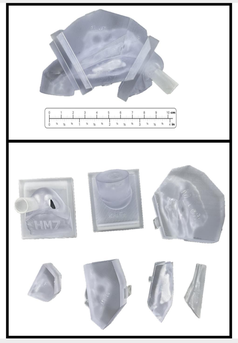

Figure 2 – Child M model and its associated regions.

Figure 3 – Child H model and its associated regions.

Figure 4 – Experimental setup of the controlled administration method. The nasopharynx component is connected to a filter, which is connected to a breathing machine via blue ventilator tubing.

RESULTS

The results of spray characterization (Table 1) confirm a relatively small difference between the RLD, T1 and T2 products, as could be expected based on the established BE from approval with the U.S. Food and Drug Administration.

Despite this similarity, anterior and posterior deposition are quite different for both the adult and pediatric nasal models (Table 2).

- In the region of interest (i.e., posterior), only 4 of the conducted 12 analyses were determined to meet the PBE criteria (Table 3).
- Considering the three main levels and comparing the pediatric and adult groups demonstrated that a conclusion for PBE for one age group cannot be translated to the other. However, L models are an exception here (Table 3).
- Within an age group, L, M and H models show different PBE outcomes with each other, which may indicate the importance of accounting for intersubject variability in PBE analysis (Table 3).

Table 1 – Spray characterization at two different distances from the spray orifice, mean ± SD of 1 batch (3 units) of each spray.

Spray and distance	DSD				Plume Geometry		Spray Pattern				
	D_{10}	D_{50}	D_{90}	Span [a]	Angle (°)	Width (mm)	D_{min} [b] (mm)	D_{max} [c] (mm)	Ovality [d]	Perimeter (mm)	Area (mm²)
RLD Product 3 cm	14.64±1.02	32.77±0.49	76.59±1.63	1.89±0.02	58.72±0.7	33.80±0.52	23.39±0.35	27.47±1.55	1.17±0.06	81.82±3.05	494.69±17.32
T1 Product 3 cm	14.93±0.32	35.72±1.26	81.02±2.1	1.85±0.02	56.8±0.97	32.51±0.62	23.43±2.01	28.09±2.82	1.2±0.02	81.83±6.74	502.43±77.85
T2 Product 3 cm	15.00±0.21	37.20±1.27	82.10±1.34	1.80±0.03	58.42±1.69	33.70±1.12	22.73±2.65	27.09±2.77	1.19±0.05	80.02±8.70	488.12±95.89
RLD product 6 cm	18.36±1.06	33.71±0.71	62.79±3.52	1.32±0.1	46.81±2.12	52.10±2.57	34.82±3.54	47.36±4.61	1.36±0.08	143.26±15.72	1378.42±281.78
T1 Product 6 cm	19.08±0.77	35.64±0.8	68.45±1.53	1.38±0.02	50.14±1.47	56.24±1.82	33.22±2.47	39.47±2.98	1.19±0.04	118.63±8.47	1030.24±155.88
T2 Product 6 cm	19.56±1.66	36.93±0.71	71.51±1.64	1.41±0.07	50.74±2.58	57.09±3.25	33.28±5.21	38.97±6.08	1.2±0.05	117.47±16.94	1027.73±314.63

a. $Span = (D_{90} - D_{10})/D_{50}$
b. *Minimum diameter of the spray pattern*
c. *Maximum diameter of the spray pattern*
d. *Ratio of* D_{max}/D_{min}

Table 2 – Mean ± SD of percentage of the drug deposited in the anterior and posterior of three nasal sprays for 3 batches and 3 units per batch.

Spray and Model	Anterior Deposition (%)	Posterior Deposition (%)
RLD Product Child L Model	65.67±4.88	34.33±4.88
T1 Product Child L Model	55.02±4.52	44.98±4.52
T2 Product Child L Model	61.42±4.40	38.58±4.40
RLD Product Child M Model	44.02±4.31	55.98±4.31
T1 Product Child M Model	46.94±2.13	53.06±2.13
T2 Product Child M Model	50.62±4.62	49.38±4.62
RLD Product Child H Model	17.20±3.82	82.80±3.82
T1 Product Child H Model	11.86±3.51	88.14±3.51
T2 Product Child H Model	16.40±7.11	83.60±7.11
RLD Product Adult L Model	80.37±2.85	19.63±2.85
T1 Product Adult L Model	76.04±6.44	23.96±6.44
T2 Product Adult L Model	77.13±3.85	22.87±3.85
RLD Product Adult M Model	55.49±4.84	44.51±4.84
T1 Product Adult M Model	43.89±3.83	56.11±3.83
T2 Product Adult M Model	40.96±4.78	59.04±4.78
RLD Product Adult H Model	28.92±3.97	71.08±3.97
T1 Product Adult H Model	25.98±2.78	74.02±2.78
T2 Product Adult H Model	19.44±4.71	80.56±4.70

Table 3 – Is PBE established in the posterior region in comparison with RLD?

Model	Age Group	T1 Product	T2 Product
L Model	Child	No	No
	Adult	No	No
M Model	Child	Yes	No
	Adult	No	No
H Model	Child	Yes	Yes
	Adult	Yes	No

CONCLUSION

Differences in the PBE determination between products using the adult models as compared to the pediatric models suggest that anatomical differences between the adult and pediatric population could impact in vitro regional deposition performance between nasal suspension products with similar in vitro characteristics.

Further studies are needed to evaluate whether such differences with in vitro nasal deposition are indicative of similar performance differences in vivo.

ACKNOWLEDGEMENTS

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