

DEPOSITION IN THREE NASAL CAST MODELS USING RETRINOSE CONCEPT

In this article, Laurent Vecellio, PhD, Research Engineer, CEPR, INSERM U1100, University of Tours, and Scientific Director, Nemera; Déborah Le Pennec, Research Technician, CEPR, INSERM U1100, University of Tours; Guillaume Grevin, Senior Design Engineer, Nemera; and Alain Regard, Technology Product Manager, Nemera; discuss a study conducted to test particle deposition characteristics of the RetroNose device prototype for nasal drug delivery.

INTRODUCTION

Nasal drug delivery is linked with interest in three fields of pharmaceutical targeting:

- Topical
- Systemic
- Central nervous system.

The clinical efficacy of a nasal treatment depends on how it is deposited in the nose, because the pharmaceutical target (local,

systemic, brain) is directly related to a specific nasal anatomical site. A recent study on chronic rhinosinusitis (CRS) patients has shown how the deposition distribution of corticosteroids in the nasal cavities can have an impact on clinical outcomes.¹ This study has demonstrated the importance of homogenous deposition in the different target regions of the nasal cavity for treating CRS. The turbinates, the maxillary sinuses and the ethmoid regions have been identified as important drug delivery target

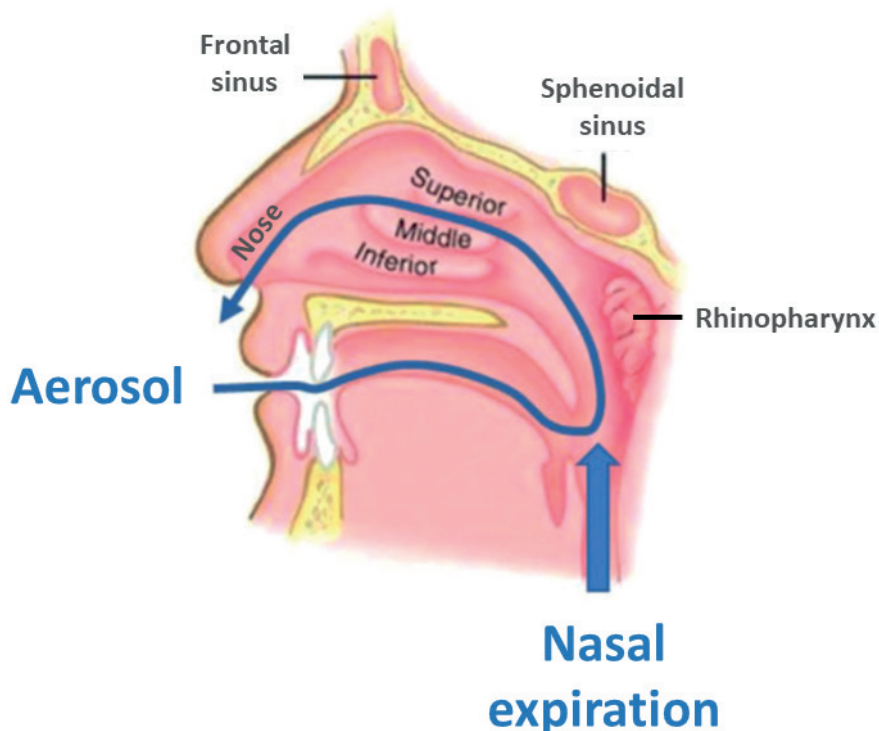


Figure 1: The RetroNose concept: drug delivery through the buccal cavity during the nasal expiratory phase, causes drug particles to enter the nasal cavities through the rhinopharynx.

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“This new device, RetroNose, uses a pMDI to administer the drug through the buccal cavity during the nasal expiratory phase.”

Figure 2: RetroNose prototype device examples.



sites for local treatment of inflammation and infection in rhinological pathologies.² Systemic delivery is enhanced by exposing the drug to the middle and inferior turbinates and the septum which have a high vascularisation and large surface area (around 150 cm²).

An alternate nasal delivery device concept, RetroNose, has been developed to achieve better drug deposition in the different regions of the nose (Figure 1).³⁻⁴ RetroNose (Figure 2) uses a pressurised metered dose inhaler (pMDI) to administer the drug through the buccal cavity during the nasal expiratory phase. Drug particles enter the nasal cavities through the rhinopharynx, which has a significant impact on drug deposition profile. A recent study has already presented data from five asthmatic patients with rhinosinusitis treated with an aerosol therapy exhaled through the nose⁵⁻⁶ using a similar concept.

The evaluation of nasal drug delivery device performance is traditionally done via regulatory *in vitro* tests:

- The dose delivery is measured and gives information about the consistency of dose delivered to the patient.
- The droplet size informs about the particle size distribution and potential lung penetration.

- Spray plume and spray pattern give information about the geometry of the spray.

Although these measurements are relevant for describing the *in vitro* characteristics produced by a nasal sprays pump, they are not adapted for the RetroNose device, as the medication is administered orally. Instead, anatomical models such as cadaver heads,⁷ nasal cavity replicas⁸ or nasal casts⁹ are used to measure drug deposition across anatomical regions. Nasal casts are consequently more adapted for performance evaluation of the RetroNose device.

The main objective of the study discussed hereafter was to compare the deposition obtained by the RetroNose prototype with a nasal spray pump using three different nasal casts.

MATERIAL AND METHODS

The RetroNose prototype device was a pMDI (Inhalia®, Nemera, France) filled with HFA 134a gas (no surfactant) and a 12 µm active compound (API-1) particle size, resulting in a 14.8 ±0.4 µm mass median aerodynamic diameter measured by cascade impactor. A standard nasal pump (Flixonase®, France, GSK) was filled with API-1 solution, resulting in a 48 ±2 µm volume mean diameter measured by laser diffraction (n=3).

API-1 deposition in the nasal casts was studied using three different anatomical models, one developed by the Virginia Commonwealth University (VCU, Richmond, VA, US),¹⁰ and two 3D-printed models recently obtained from females (FANI 1 & FANI 2, CEPR, INSERM U1100, University of Tours, Tours, France).

“A high variability in deposition was observed for the nasal spray compared with the RetroNose prototype device for the different regions of nasal cavities, except for in the middle part.”

Nasal casts were connected to a mouth and a lung model, including a filter to measure potential drug penetration in the lungs.

Different regions of interest were defined in the nasal casts:

- Mouth
- Nose
- Upper part of the nasal cavity
- Middle part of the nasal cavity
- Lower part of the nasal cavity
- Rhinopharynx.

Three additional regions of interests were added for the FANI 1 & 2 nasal casts (maxillary sinuses, frontal sinuses, sphenoids). The different regions were washed with different volumes of sodium hydroxide using syringes. API-1 was assayed by a spectrophotometric method.

An additional experiment was performed using a second active product (API-2). A Flixotide® (125 µg fluticasone, GSK, France) pMDI was used in the RetroNose prototype and was radiolabelled with Tc99m, as previously described by Chand *et al.*¹¹ Nasal administration was performed on the VCU model. Deposition was imaged using a gamma camera and was fused with a nasal cast scan.

RESULTS

Results from the experiments demonstrated the following:

- No active compound was detected in the lung model for nasal spray and RetroNose.
- About 50% of the drug was deposited in the nose for the nasal spray.
- About 50% of the drug was deposited into the mouth using the RetroNose prototype.
- Less than 5% of the delivered dose was exhaled in ambient air using the RetroNose device.
- Results showed a major deposition in the middle part of the nasal cavity using the RetroNose device, in contrast to the nasal spray which emphasised deposition in the front of the nose.
- Greater depositions in maxillary sinuses, sphenoids and frontal sinuses were detected when using the RetroNose device compared with the nasal spray.

A high variability in deposition was observed for the nasal spray compared with the RetroNose prototype device for the

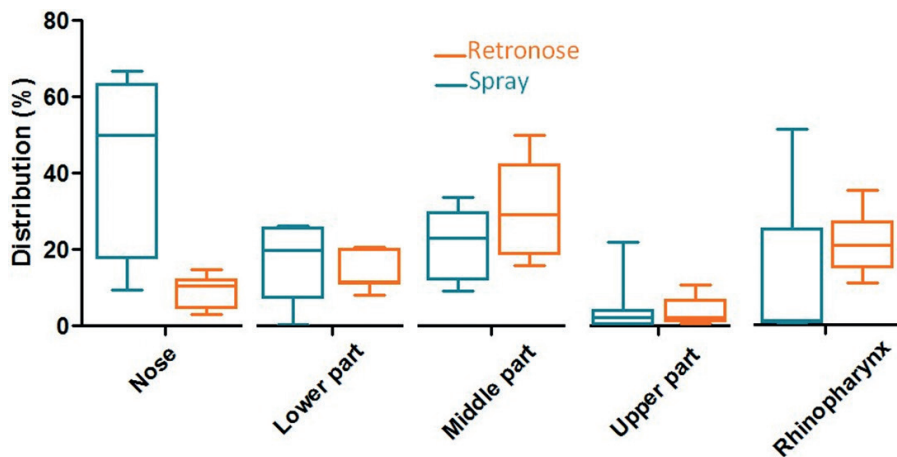


Figure 3: Drug deposition in the different regions of the nasal cavities (upper airway model) using three different nasal cast models for a standard nasal spray (A) and RetroNose (B). (Results expressed in terms of deposited fraction in nasal cavity, n=3 for each nasal cast.)

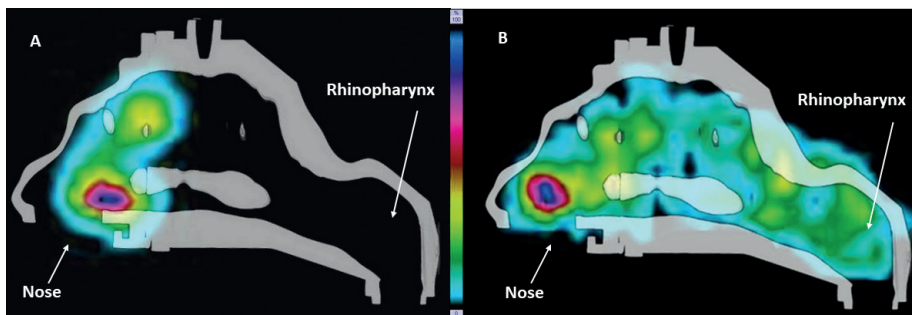


Figure 4: Radioactive deposition of fluticasone in the VCU model with Flixonase® nasal spray (A), and Flixotide® RetroNose prototype device (B).

different regions of nasal cavities, except for in the middle part (Figure 3). This variability should be more important for a nasal spray where the angle and penetration is not

controlled during spray administration. For a nasal spray, drug particles are not likely to reach the rhinopharynx region, whereas a significant deposition rate is consistently observed when using the RetroNose device.

Deposition images show a more distal and homogeneous deposition in the VCU nasal model when using the RetroNose device compared with a nasal spray (Figure 4).

DISCUSSION

The deposition differences between a nasal spray and the RetroNose device can be explained by the particle size and the route of administration. The particle size generated by the RetroNose device is smaller (12 μm) than the nasal spray (47 μm) and therefore the kinetics of the

particles in the nasal cavities is different, resulting in different deposition between the two. Administration through the mouth also induces a difference in air humidity compared with nasal administration, which can increase the size of the particles. Particle intake from the oropharynx instead of the nose can also explain the difference in terms of penetration and deposition in the different regions of the nasal cavities. Depositions in the mouth and oropharynx using the RetroNose device can be explained by the particle velocity generated by the pMDI. Similar deposition has been reported when using commercialised pMDIs for inhalation.

The homogenous deposition (Figure 3) obtained with the RetroNose prototype device demonstrates its ability to administer the corticosteroid directly into the different anatomical regions of interest, including the sinuses. This deposition pattern is very different to that of the nasal spray, where the drug is deposited in the first centimetres of the nose. Similar homogenous depositions have been reported using a nebuliser, and have demonstrated increased drug retention in the nasal cavities and higher clinical efficacy than a nasal spray.¹ In this study, the RetroNose device used a pMDI as an aerosol generator and can be defined as a portable, multidose device for nasal delivery without lung deposition.

CONCLUSION

This study has shown promising results with regard to a new method of nasal drug administration for producing a more homogenous deposition distribution than a standard nasal spray. The RetroNose device demonstrated potential to be of interest for local, vaccine and systemic nasal drug delivery.

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