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Improving Nasal Drug Delivery with HFA Nasal Aerosols – Dispelling Myths and Meeting Patient Preferences

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Introduction

- There was a staged phase out of chlorofluorocarbon (CFC) propellants following the Montreal Protocol [1] and IPACT I and II [2,3] for oral aerosol products.
- CFC nasal aerosols were phased out immediately.
- The aqueous (AQ) nasal spray has since dominated the nasal marketplace, however the FDA have now approved two hydrofluoroalkane (HFA) nasal aerosols, Zetonna ® and QNASL® [4,5].
- Based on historical experiences with CFC nasal aerosols, concerns regarding forceful sprays and the 'cold-Freon' effect persist.
- However, it has been shown that patients prefer the nasal aerosol device over an AQ spray device: the nasal aerosol is easy to use, delivers a no-drip, 'dry' spray of a good force and no aftertaste [6].

In this study, *in-vitro* data are presented to compare the plume force of HFA nasal aerosols to historical CFC oral and nasal aerosols, and *in-vivo* data are presented to compare deposition and retention of a HFA nasal aerosol to an AQ nasal spray.

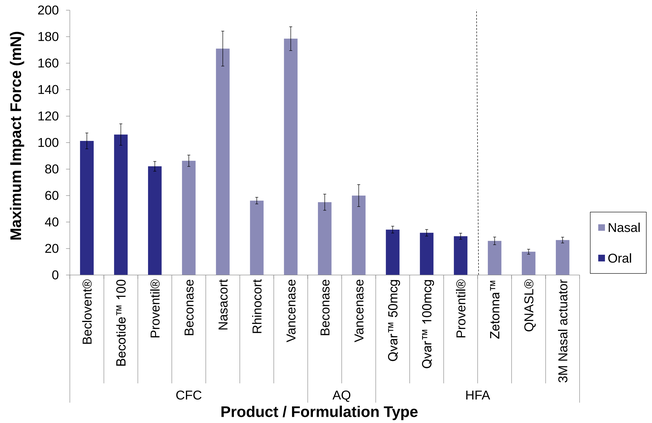
In-Vitro Assessment of the Deposition from HFA Nasal Aerosols

It is generally accepted that to minimize the 'cold freon' effect a softer and warmer plume is desirable, and Gabrio et al have shown that HFA oral aerosols generate softer and warmer plumes than historical CFC oral aerosols [9]. In a previous study by Gabrio et al [9] the plume force and temperature of a number of systems, including CFC oral and nasal aerosols, HFA oral aerosols and AQ nasal products was presented. This follow-up study has been undertaken to evaluate the plume force of HFA nasal aerosols and to understand where these products sit in comparison.

- Plume force testing was performed using an Instron 5544 tensile tester, which both actuated the inhaler and measured the resultant force produced by the spray.
- The 10N load cell was connected to the Tensile Tester for data recording and visually positioned in the same axis as the nose piece of the test actuator approximately at the tip, and therefore measured the maximum force at the point the spray leaves the actuator.
- Five or 10 nasal aerosols of each product were tested and 10 replicates were assessed per nasal aerosol.
- The HFA products tested were Zetonna, QNASL and an alternative 3M nasal actuator with integrated dose counter utilizing a placebo formulation containing propellant 134a and dehydrated alcohol, in line with the approved formulations. The 3M nasal actuator has similar critical dimensions to the commercial nasal actuators.

- Plume force data from Gabrio et al [9] and for the new HFA aerosols are presented in Figure 1.
- Although the method of plume force determination is not identical, the data for HFA nasal aerosols from the present study are comparable to the previously generated data for HFA oral aerosols.
- The data generated for HFA nasal products (Zetonna, QNASL, and 3M nasal actuator, Figure 1) demonstrates that HFA nasal aerosols have a considerably softer plume than the old CFC nasal aerosols, which is in line with the data presented in Gabrio et al for oral aerosols.
- The data in Figure 1 also indicate that the force of HFA nasal aerosols is lower than that of the AQ nasal products tested.

Figure 1 – Plume Force for a Selection of CFC, HFA and AQ Products



In-Vivo Assessment of the Deposition from HFA Nasal Aerosol and AQ Nasal Spray

An *in-vivo* assessment of the nasal and pulmonary deposition of a single dose of ciclesonide HFA nasal aerosol (74µg/actuation) versus AQ nasal spray (50µg/actuation, Omnaris) has been performed [7].

- In an open-label, single-dose, single-site, non-randomized study in 10 healthy subjects, the initial deposition of a ^{99m}Tc sodium pertechnetate radio-labelled dose from each product was compared to evaluate the deposition of both products by gamma scintigraphy.
- MRI scans were taken prior to the dosing visits to provide lateral outlines of the nasal cavity on which the scintigraphic images were overlaid.
- Scintigraphy data were corrected for background radiation, radioactive decay and tissue attenuation.
- Each subject received a fixed treatment sequence, consisting of a single dose (one 50µL actuation per nostril) of ciclesonide HFA nasal aerosol (total 148µg ex-actuator, containing ≤5MBq ^{99m}Tc per 2 actuations), followed by a single dose (two 70µL actuations per nostril) of ciclesonide AQ nasal spray (total 200µg ex-actuator, containing ≤5MBq ^{99m}Tc per 4 actuations), which were separated by a washout period of at least 72 h.
- Both devices were administered with gentle nasal inhalation and an upright orientation was maintained during and after dosing.
- Initial deposition of radioactivity was quantified by scintigraphy (% of delivered dose, summarized in Table 1) in the nasal cavity, nasopharynx, lungs, swallowed (i.e. sum of radioactivity within esophagus plus stomach), and on nasal wipes (i.e. sum of radioactivity deposited on tissues, gloves and apron), immediately after dosing (within 1 to 4 minutes).

Table 1 – Initial Deposition Pattern as a Percentage of Delivered Dose

		Mean	Range (Min - Max)	SD
Nasal Cavity	HFA	98.4	97.0 – 99.7	1.1
	AQ	76.4	27.0 – 99.1	22.9
Nasopharynx	HFA	0.2	0.1 – 0.5	0.1
	AQ	0.3	0.0 – 0.7	0.3
Lungs	HFA	1.4	0.2 – 2.9	1.0
	AQ	0.6	0.0 – 1.2	0.5
Swallowed	HFA	0.0	0.0 – 0.1	0.0
	AQ	0.0	0.0 – 0.0	0.0
Nasal Wipes	HFA	0.0	0.0 – 0.2	0.1
	AO	22.7	0.8 – 72.9	23.2

- The HFA nasal aerosol resulted in deposition of almost the entire delivered dose consistently within the nasal cavity, negligible deposition in the lungs and minimal deposition in the nasopharynx
- The AQ nasal spray resulted in majority of deposition within the nasal cavity, but with higher variability, with the remainder mainly exiting the nose via dripping externally.
- These data are comparable with published data comparing ciclesonide HFA nasal aerosol and mometasone furoate AQ nasal spray [8].

Conclusions

- The *in-vitro* data presented dispel the myths and concerns about HFA nasal aerosols, demonstrating that they are not a forceful spray.
- The results from *in-vivo* studies demonstrate the improved initial deposition and retention of the dose delivered from a HFA nasal aerosol compared to that from an AQ nasal spray, with less external and post nasal drip (meaning no aftertaste or odor).
  - These advantages are in line with those which are desired by patients [6].
  - Softer plumes from HFA nasal aerosols are expected to be warmer than historical CFC aerosols [9].
- The CFC nasal products were popular prior to being phased out, and these data, combined with the patient preference study [6] provide reassurance that the HFA nasal product is a better alternative.

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