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SPECT Imaging of Direct Nose-to-Brain Transfer of MAG-3 in Man.

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PURPOSE

Summary:
This study compares the direct-nose-to-brain delivery capabilities of a traditional nasal pump and Impel NeuroPharma's Precision Olfactory Delivery (POD) device using Single Photon Emission Computed Tomography (SPECT) imaging data generated from administration of MAG3, a radiolabeled tri-peptide tracer.

Background and Objective:
In multiple species, intranasal administration of drug has been shown to bypass the blood-brain-barrier and deliver drugs directly to the central nervous system (CNS). This route of delivery has the potential to enable many therapeutics, including peptide and proteins, to reach the CNS in effective concentrations and could have a significant impact in the treatment of CNS diseases.

The objective of this study was to determine if increased drug targeting to the upper nasal cavity would lead to increased CNS concentrations and direct nose-to-brain delivery. In this study, SPECT imaging was used to visualize this direct nose-to-brain transfer in man for the first time.

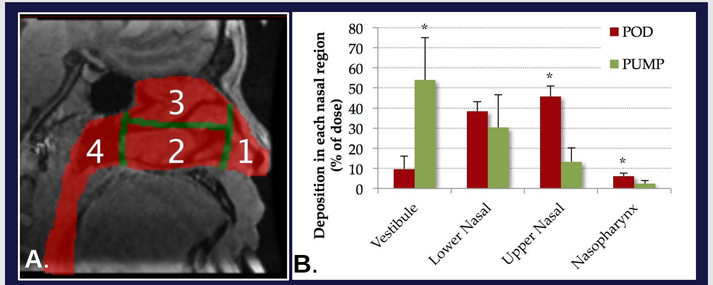


Fig 3.
A. For the determination of nasal deposition the nasal cavity was sectioned into the nasal vestibule (1), the lower turbinate region (2), the upper turbinate/olfactory region (3), and the nasopharynx (4). These sections were defined based on the nasal anatomy observed in the MRI images.
B: Nasal deposition quantitation. The POD device led to significantly higher deposition in the upper nasal cavity / olfactory region (Upper Nasal) compared to the traditional nasal pump (PUMP). A majority of the PUMP dose was administered into the vestibule region. (*=P<0.05).

METHODS

Study Design
Seven subjects were enrolled in this study. MAG-3, a technetium-99m labeled peptide, was delivered as the radiotracer. This study used a two arm cross-over design to investigate MAG-3 administration with Impel's POD nasal device in comparison with a traditional nasal pump. Imaging was performed on two separate days, one week apart. After tracer administration, 2D SPECT (Siemens ECAM) imaging was performed for 5 minutes. Then, 3D SPECT(Siemens ECAM) was acquired for 8 minutes starting at 10 minutes after tracer administration. An MRI (GE Signa Excite) scan was also acquired to provide detailed anatomical information. Pixel analysis (VivoQuant) by nasal region of interest was used to quantify radioactivity in each target nasal deposition region (MATLAB). MAG-3 in the 3D scan regions of interest was quantified using VivoQuant Software (Invicro). Regional radioactivity signal was compared using a paired two tailed Students t-test. The clinical study was conducted at Lovelace Respiratory Research Institute.

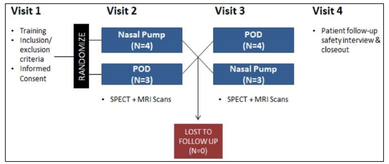
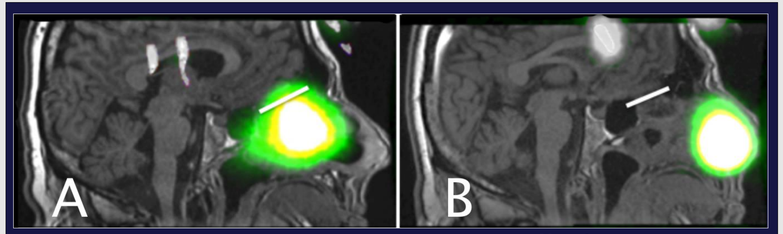


Fig1: Schematic of the study design.



POD **Nasal pump**

Fig 2.This representative 2D SPECT sagittal image shows the nasal deposition of the POD device (A) as compared to a standard nasal pump (B).The white bar identifies the cribriform plate where the nasal cavity is in direct contact with the CNS.

RESULTS

- The POD nasal device resulted in a large fraction of dose being deposited in the upper third of the nasal cavity after administration.
- The traditional nasal pump resulted in a majority of the dose being deposited in the vestibule portion of the nasal cavity. With the traditional nasal pump there was no observable transfer of the MAG3 peptide tracer from the nasal cavity to the central nervous system.
- With POD administration the tracer could be observed in the basal membranes of the brain and other brain regions in a distribution pattern similar to what has been observed in several preclinical studies on nose-to-brain transport.
- No significant amount of tracer was observed in muscle tissue, indicating a direct nose-to-brain transfer.

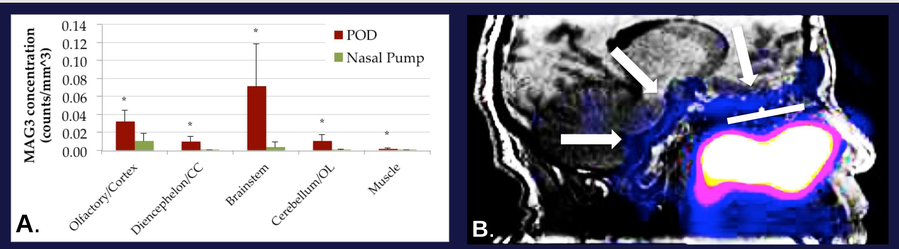


Fig 4. A. Regional MAG3 distribution in the CNS. POD administration led to significantly higher MAG3 signal in all brain regions examined. The high levels of MAG3 observed in Olfactory/Cortex and Brainstem regions are indicative of direct nose-to-brain transport. (* = P < 0.05).
B: Representative 3D SPECT visualization of MAG3 in the CNS of a single subject after POD administration. After administration with the POD device, MAG3 was visualized in the basal portion of the brain with concentrated regions near the olfactory bulb and cerebellum/brainstem regions. This pattern of distribution is indicative of direct nose-to-brain transport. The white bar indicates the location of the cribriform plate (the nose/brain interface).

CONCLUSIONS

The Impel POD device was superior in depositing the peptide tracer into the upper third of the nasal cavity where connections exist between the nasal cavity and the CNS. This nasal distribution appears critical to enable direct transfer of compound from the nasal cavity to the central nervous system along the nose-to-brain distribution pathways. This study indicates a nose-to-brain transport pathway in humans using SPECT imaging and validates the continued study of this pathway to deliver biologic therapeutics to the CNS.