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Bi-Directional Nasal Drug Delivery (Optinose Technology): A Review

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ABSTRACT

In the present study, bi-directional nasal drug delivery is a delivery system where aerodynamics and exhalation technology is involved. The drug can be constrained to a nasal area by an equipment through which exhaling by mouth against resistance leads to closing of soft palate separating nasal and oral cavities and the air leaves by other nostril taking a turn towards septum creating bi-directional flow in the nose. Rapid absorption through nasal mucosa increases the drug action avoiding first pass metabolism. This decreases the deposition of drug in lungs (0.82.0%), whereas, in nasal spray inhalation and nebulizers, deposition in lungs is found out to be more. (22.38.1%).It is used primarily in the treatment of chronic rhinosinusitis and polyposis by constricted to nasal areas and 20% increase in bioavailability of the drug diseases like diphtheria and influenza showed positive immune responses to the drug. It is commonly marketed in the name of 'Optinose's device where the drug can be used in powder form or liquid dosage form. Exhalation technology can play a major role in providing drug constrained to the nasal cavity for an effective treatment. It is feasible to deliver efficiently drugs such as small polar molecules, peptides, large proteins and polysaccharides used in vaccines or DNA plasmids exploited for DNA vaccines. This can be used in the treatment of many nasal constricted problems much better.

INTRODUCTION

Nose is the primary organ for all the pulmonary activity done in the body. The nasal passages are lined by membranes more like linings of lungs called respiratory epithelium which is thin and rich in blood vessels.

Nose is comprised of many bony perturbances that fill the nose which acts as "shelves"(curly shaped turbinate bones)[1]. This convoluted system provides a larger surface area and creates turbulence which slows down the airflow. The epithelium lining this region normally creates a layer of mucus that moistens the nose and in addition have several antibodies and enzymes. Particles will be deposited on mucosa from where mucociliary transport mechanism carries them backward and eventually be swallowed[2]. To ensure successful deposition within nasal cavities, their typical medium particle size should be between 30 and 120 microns. Particle larger than this tends to deposit at front of the nose.[3].

Recent FDA guidance concerned about the particle size of aerosols and dose uniformity of traditionally using mechanical liquid sprays and nebulizers for nasal use, and also about the particle deposition, absorption, and clinical response.[4].

Nebulizers in recent studies have shown 60% of lung deposition and an overdose of the drug in patients treating nasal constricted problems. It has been reported, a drug not being reached to the targeted area especially like nose to brain transport and sinuses. On the other side, nasal sprays reported swelling of nasal membranes and lead to addiction. It is been not effective in rhino-sinusitis and migraine.

By counteracting on all these mechanisms, a new mechanism has been introduced in aerosol generation called "EXHALATION DRUG DELIVERY (EDS)" which is an alternative for all the traditional uses.[4](EDS mainly focuses on the targeted delivery of drugs to upper narrow parts of complex nasal passage housing, the middle meatus where sinuses opening are located as well as regions innervated by olfactory nerve and branches of the trigeminal nerve which is considered essential for the nose to brain transport.[4]

The mechanism of EDS is the exhaled air containing drug enters through one of the nostrils where other nostril is sealed and leaves the drug n nasal membranes and air leaves through other nostril taking a "U" turn through septum creating a "Bi-directional flow".

A United States bases pharmaceutical company "OPTINOSE" developed a way to deliver the right drugs to right places, more reliably, and consistently, allowing us to use known molecules in new ways that address the limitations of other available therapies.[1]

MECHANISM:

Deposition of the drug with nasal drops spray pumps and traditional delivery devices have no significant delivery beyond the nasal valve. Many approaches have been attempted to improve the delivery through traditional devices, but they are generally impractical and yet to be proven. A study tested 7 different head and body positions using traditional nasal sprays and concluded that there is no best method[5,6].

The breath powered bi-directional delivery mechanisms can be implemented in a simple device without electrochemical cost or complexity and overcomes many deficiencies of traditional nasal delivery. Both liquid and powdered drugs can be delivered using such devices, and implementations of each are in active development. This novel nasal delivery concept consists of devices with a flexible mouthpiece and a sealing nosepiece. It is designed to exploit unique aspects of nasal anatomy and physiology to improve extent and reproducibility of drug delivery to target sites in nose beyond nasal valve while avoiding the risk of lung inhalations[5].

The subject is asked to keep the nosepiece into one nostril. The mouthpiece is inserted between the lips, exhalation through mouth creates a positive pressure naturally moving soft palate upright and closing the connection between nasal and oral cavities.

Because of closing one of the nostrils, the airflow and dynamic positive pressure are transferred by the device into the nasal cavity. Where it expands nasal valve ad narrow slit-like passages[5]. The air leaves the drug on nasal valves and escapes through another nostril.

Drug particles are carried posterior by the warmed air in nostril/ beyond the nasal valve and gets deposited and distributed broadly deep into the nasal cavity. This can be seen in **Fig 1**.

Device with a disposable nose piece was developed for patients with sinuses, migraine, and other nasal constricted problems.

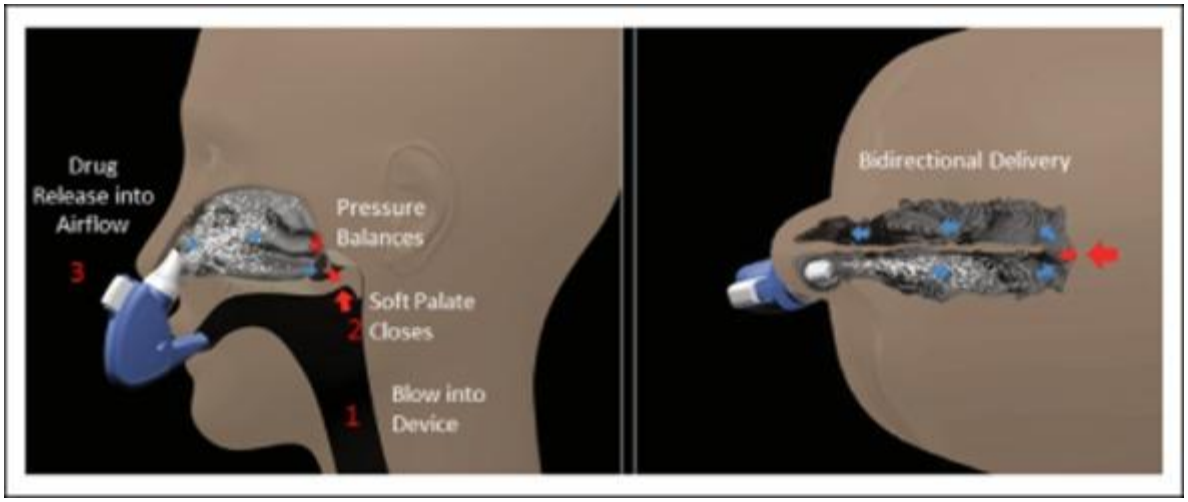

Fig. 1: The mechanism of Bi-directional nasal drug delivery device

TECHNIQUES:

Bidirectional drug delivery has made a revolution by changing the concept into reality, by its effective nasal drug delivery.

OPTINOSE has developed wonderful breath-actuated bi-directional nasal delivery devices as multi-dose liquid device and capsule-based powder multi-use device which are now in phase 3 clinical trials.

LIQUID EXHALATION DELIVERY SYSTEM:

The liquid exhalation drug delivery system consists of a drug containing amber glass vial**(Fig 2)** for liquid drug formulation which is sealed by a metered spray pump enclosed in the liquid subassembly. The nasal spray which is attached to the pump extends to the top of the nosepiece. The nosepiece is designed to create the seal with the nostril.

A patient inserts the nosepiece into one of the nostrils and starts exhaling through the mouthpiece. Simultaneously, the patient presses the amber glass vial upwards to actuate. This causes the coordination-reducing valve to release the exhaled breath concurrently with aerosol spray in “burst" of naturally humidified air.[1]

Fig. 2: liquid exhalation delivery system device

XHANCE is the liquid dosage form drug approved for the Optinose drug delivery systems. XHANCE is for treatment of nasal polyps and it improved in reducing symptoms of nasal polyps.

The active component of XHANCE is "Fluticasone propionate",**(Fig 3)**a corticosteroid, having chemical name S-(fluromethyl) 6α, 9-difluoro-11β,17dihydroxy-16α-methyl-30 oxandrosta-1,4-diene-17β-carbothioate 17propionate.[7]

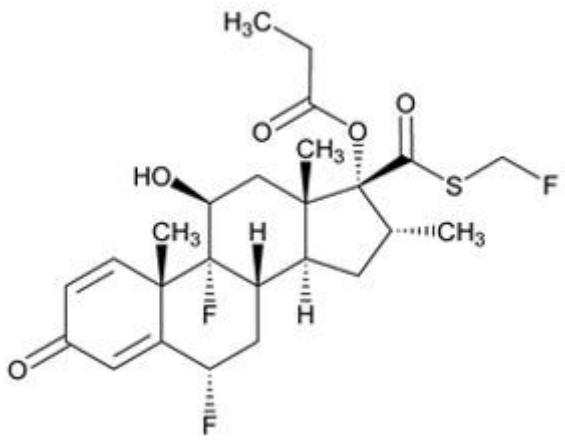

Fig 3: Fluticasone propionate

Molecular weight of 500.5

Empirical formula: $C_{25}H_{31}F_3O_5S$

XHANCE nasal spray, which is taken a standard dose of 93mcg, in the form of aqueous suspension for intranasal administrations.

It is having a micro level particle size distribution in a range of 0 to 5 microns by means of spraying and exhaled breath.

It contains microcrystalline cellulose, carboxymethylcellulose sodium, dextrose, benzalkonium chloride, Polysorbate 80, edentate disodium dehydrate, and water and has Ph between 5 and 7.[7]

The mechanism of fluticasone propionate is associated with inflammatory activity as it is a synthetic triflurinated corticosteroid with anti-inflammatory activity. It effects on several cells such as mast cells, macrophages, eosinophils, neutrophils and cytokines involved in inflammation. Also, the CO_2 present in exhaled breath may influence neuropeptide activity by removing nitric oxide and changing the pH.

ABSORPTION:

The mean (SO) peak exposure (C_{max}) and total exposure ($AUC_{0-\alpha}$) following administration of a dose of 186 mcg of XHANCE during the exhalation were 17.2 ± 7.40 pg/mL and 111 ± 49.75 pg*h/mL respectively.[7]

DISTRIBUTION:

Studies found that fluticasone propionate in intravenous administration showed its initial deposition phase was rapid and high lipid solubility and tissue binding. Fluticasone propionate bound to human plasma proteins was about 99% on average.

METABOLISM:

The derivative of fluticasone propionate 17 derivatives of the fluticasone propionate 17β-carboxylic acid, which is one the byproducts of the CYP3A4 pathway. This had less or negligible pharmacological activity than the parent drug.

EXCRETION:

Fluticasone propionate showed much exponential kinetics and had an elimination half-life of approximately 7.8 hours in intravenous dosing and renal clearance less than 0.02% of the

total. Less than 5% of the radiolabeled oral dose was excreted in urine as metabolites, with the remainder excreted in feces as parent drug and metabolites.[7]

POWDER EXHALATION DELIVERY SYSTEM:

The powder exhalation delivery system (EDS) which consists of a flexible mouthpiece and disposable nosepiece. A white button is placed just beside nose piece for piercing to pierce the medication while blowing.

The disposable nosepieces are provided with pre-filled dry powder formulation and a clear release tablet in a capsule. The piercing button when pressed helps to pierce the capsule and release the powder drug into the nostril along with the pressure attained by blown/exhaled air through the mouthpiece. The patient is asked to take one prefilled nosepiece which is to be attached for one nostril and dispose it after use and use a fresh nosepiece for another nostril. The amount of drug released in two nostrils accounts to be 1 dose to be taken.

A patient is asked to insert the nosepiece deep into one of the nostrils and exhale/blow hard through the adjustable mouthpiece. While blowing, the white button for piercing is been pressed and the drug is released into the nostril through the nosepiece.

The powder device, **(Fig 4)** which is developed, is designed for single-or-multi dose use and will allow the development of powder formulations with greater opportunity for stability to be delivered without the risk of pulmonary deposition.

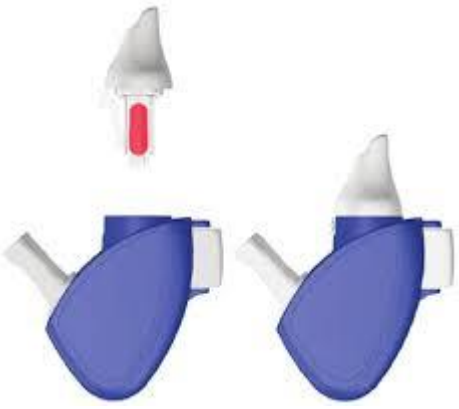

Fig. 4: Powder device

ONZETRA Xsail is the powder drug dosage form which contains an active component of sumatriptan nasal powder. A dry powder of 11mg sumatriptan base is been filled in a

hypromellose capsule in a single disposable nosepiece. 2 nosepieces comprises of 22mg of a dose. This product had shown satisfactory and relieving reports in migraine patients.

Sumatriptan,**(Fig 5)**a selective 5-hydroxytryptamine receptor subtype 1 (5-HT_1) agonist (triptan), as the succinate salt. Sumatriptan succinate is chemically designed as 3-(2-(dimethylamino) ethyl)-N-indole-5-methanesulfonamide succinate (1:1).[8,9]

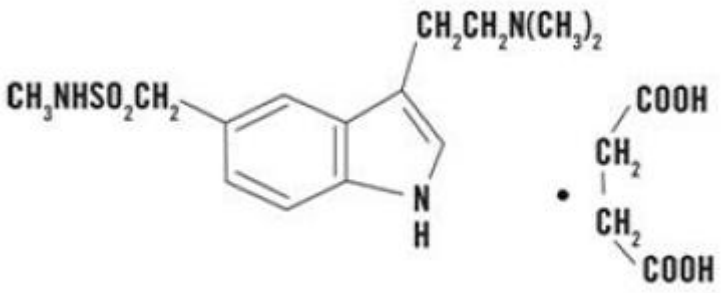

Fig. 5: Sumatriptan

Molecular weight - 413.5

Empirical formula is $C_{14}H_{21}N_3O_2S \bullet C_4H_6O_4$

The Xsail device delivers an average of 10mg of sumatriptan per nosepiece and flow rate of this was estimated to be 30L/min for 4 seconds. When the delivered dose is measured under migraine patients for calculating the efficacy of the product, results found out that each nosepiece delivered the average dose of 7.5-8.1mg, which is the total dose of 15-16.2mg per treatment episode from two nosepieces.[8]

Mechanism of action:

Sumatriptan binds to 5-$HT_{IB/ID}$ receptors and acts as an agonist to it by acting on intracranial blood vessels and sensory nerves of trigeminal system. This leads to cranial vessel constriction and inhibition of pro-inflammatory neuropeptide release.

Absorption:

The mean maximum concentration (C_{max}) following a 22mg nasal dose of ONZETRA Xsail was 21ng/mL and $AUC_{0-\infty}$ was 65 ng*hr/mL. Peak plasma concentration (T_{max}) was average

of 45 minutes. Bioavailability was found out to be 19% when compared to 14% and 15% in liquid sprays and oral administrations respectively.[8]

Distribution:

Protein binding of sumatriptan, when equilibrium dialysis over concentration range graph of 10 to 1000 ng/mL is found out to be 14% to 21% and volume of distribution is found out to be 2.7 L/kg.

Metabolism:

In *in-vitro* studies of sumatriptan showed that it is metabolized by MAO and most of the dose excreted in urine is majorly indole acetic acid (IAA) or IAA glucuronide which are inactive.

Elimination:

Elimination half-life of sumatriptan is found out to be 3 hours. Where 3% dose is excreted unchanged, but 42% of indole acidic acid is excreted. Plasma clearance of sumatriptan was found out to be 1200mL/min.

CLINICAL STUDIES:

XHANCE™

A clinical study conducted on 2 placebo-controlled trials evaluating doses of fluticasone propionate by bi-directional nasal drug delivery devices of 93mg twice daily to 372 mcg twice daily, on about 643 adults subjects suffering from bilateral nasal polyps and nasal congestion. Out of which 161 received 372 mcg twice daily and 161 received placebo. The overall pooled safety included 296(46.0%) female, 347(54.0%) male, 584(90.8%) white, 39(6.1%) black, 9(1.4%) Asian and 11(1.7%) others.[7]

Particularly, by administering fluticasone, an average of 20% of subjects was reported complete elimination of polyps within 3 months. An improvement in polyp score is lower in Optinose delivery when compared to placebo in 4, 8 and 12 weeks. Patients could relatively find improvement in nasal blockage, rhinitis, and sense of smell. Bi-directional delivery device succeeded in the deposition to target sites and has reduced the risk of surgeries, as previous surgery of nasal polyps would take hours together with no impact on efficacy.

Adverse reactions in XHANCE were observed with an incidence < 3% but ≥ 1% and placebo included nasal dryness, sinusitis, toothache, dizziness, abdominal discomfort.5.0% of subjects treated with XHANCE 186 mcg twice daily and 1.2% of subjects treated with 372 mcg twice daily discontinued from the clinical trials prior to the open-label extension because of adverse reactions compared to 4.3% of subjects treated with placebo.[7.] It can be seen from **Table 1**.

Table 1: Effect of XHANCE nasal spray in two randomized, placebo-controlled trials in patients with nasal polyps.

	XHANCE 186 mcg bid	**XHANCE 372 mcg bid**	**PLACEBO**	**Diff. (95% CI) XHANCE 186 mcg bid vs placebo**	**Diff. (95%CI) XHANCE 372 mcg bid vs placebo**
Trial 1 (N)	80	79	82		
baseline nasal congestion LS mean change from baseline in nasal congestion at week 4	2.24 -0.54	2.29 -0.62	2.31 -0.24	-0.30 (-0.48,-0.11)	-0.38 (-0.57,-0.19)
Baseline total polyp grade LS mean change from baseline in total bilateral polyp grade at week 16	3.9 -1.03	3.7 -1.06	3.8 -0.45	-0.59 (-0.93,-0.24)	-0.62 (-0.58,-0.18)
Trial 2 (N)	80	82	79		
Baseline nasal congestion LS mean change from baseline in nasal congestion at week 4	2.20 -0.68	2.25 -0.62	2.29 -0.24	-0.45 (-0.64,-0.25)	-0.38 (-0.58,-0.18)
Baseline total bilateral polyp grade LS mean change from baseline in total bilateral polyp grade at week 16	3.9 -1.22	3.9 -1.41	3.8 -0.61	-0.60 (-0.89,-0.31)	-0.80 (-1.08,-0.51)
Bid=twice daily					

ONZETRA:

The efficacy of ONZETRA Xsail for the acute treatment of a migraine with or without aura was established in a multicenter, randomized, double-blind, placebo-controlled study (Study 1).[8]

In study 1, the percentage of patients who had a reduction in a mild or a moderate headache due to a migraine in 90 minutes of administration of ONZETRA Xsail 22 mg was significantly greater when compared to placebo. It can be seen from **Table 2**.

Table 2: Percentage of Patients with Headache Relief (Primary Efficacy Endpoint), with No Headache, No Nausea 2 hours Post Treatment with ONZETRA Xsail

2 hours post treatment	ONZETRA 22 mg (n=108)	Placebo (n=104)
Headache relief	68%	45%
No Headache	34%	17%
No Nausea	82%	79%

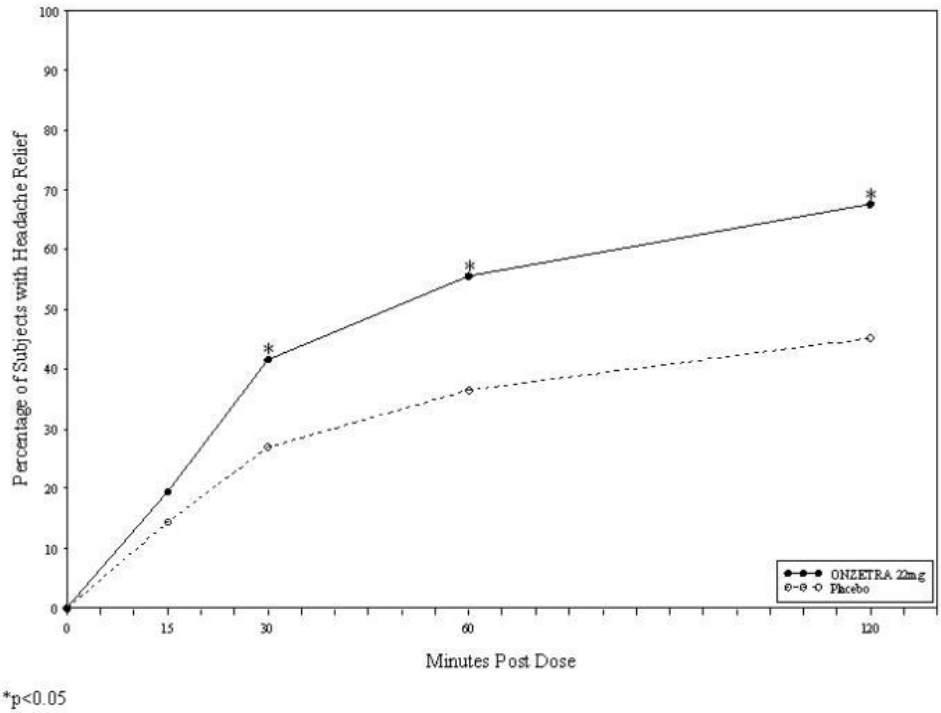

Fig. 6: Percentage of Patients with Headache Relief within 2 Hours with ONZETRA Xsail

A sumatriptan powder (7.5 or 15 mg delivered dose or placebo) is intranasally administered by the bi-directional nasal device and observed much significant pain relief when compared to the sumatriptan subcutaneous injection and also of less systemic exposure.

In the most recent study, Tc^{99m}-labeled lactose powder was delivered with the Breath Powered powder device**(Fig 7).** A capsule fill and particle size profile similar to sumatriptan powder were used. For measuring differences in a deposition, the nose was divided into 3

horizontal segments, and a vertical dividing line was positioned at the head of the inferior turbinate, and radiation counts within each segment were quantified after administration.[5]

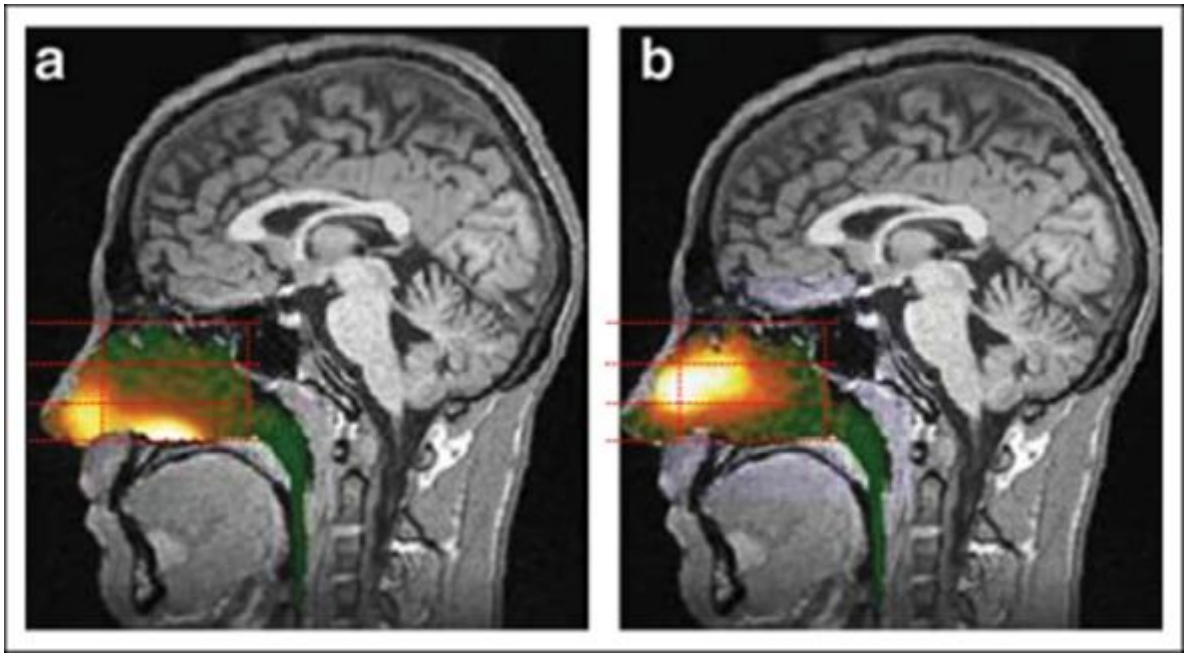

Fig. 7: Gamma Scintigraphy reports of the nose showing drug deposition

APPLICATIONS:

The main advantage of nasal delivery is, it is convenient to route when compared to parenteral route for long-term therapy and drugs which cannot be absorbed orally may be delivered to systemic circulation and quick onset of action avoiding the first pass metabolism.

Nose to brain:

Delivery of the drug to olfactory bulb offers a significant approach which avoids blood-brain-barrier and getting access to CNS. When comparing to traditional nasal sprays, Optinose's device has reached possibly more than 30-40% of the dose to targeted regions providing much scope for treating Parkinson's and Alzheimer's.

When a 3.4 mg of Midazolam delivered intravenously by traditional methods and intranasally using Optionose's bi-directional delivery device, it had shown the much faster onset of action and duration sedation was longer. However, the bioavailability of delivered formulation was only 68%, compared with 100% from iv.[10]

Therapeutic effects in a migraine:

The potential positive mediated by positive air pressure, rapid vibrations produced by rattling capsule, and removal of NO may all play a role in alleviating migraine headache. In addition, there are possibilities of delivery of drugs including triptans, DHE, lidocaine, NSAIDS etc. A very small daily dose of a triptan or other drugs in this manner may offer sufficient receptor blockage to reduce the number of acute attacks. Even topical steroids may prove valuable alone or as an adjuvant therapy in a cluster headache or in a sinus headache.[5]

CONCLUSION:

OptiNose had successfully converted bi-directional drug delivery from a concept into a functioning technology. However, in delivery to the CNS as well as the other applications. OptiNose is partnering its technology with pharmaceutical companies for indications where significant therapeutic benefits could arise from bidirectional delivery as well as progressing a number of in-house applications for indications such as rhinosinusitis, migraine, and Parkinson's disease.[10]

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