Indian J Otolaryngol Head Neck Surg
(April–June 2009) 61:90–94
DOI: 10.1007/s12070-009-0044-2

Review Article

# Intranasal drug delivery: a novel approach

**Yashpal Chugh · Pragati Kapoor · A. K. Kapoor**

## Introduction

Intranasal drug delivery occupies the prime place against newer drug delivery systems to transport drugs to CNS bypassing the blood brain barrier. Recent advances in molecular neurobiology have led to development of new classes of therapeutic agents that can interact with specific targets. The blood brain barrier (BBB) represents one of the strictest barrier in human beings. The BBB allows lipid-soluble molecules transport across the membrane and limits access of molecules which are too large or has polar functioning groups to the CNS [1]. Consequently, it prevents the use of many therapeutic agents because of the inability of the agents to reach and maintain effective concentration in the brain for an appropriate length of time. It is particularly true for drugs used for treating brain tumor, Alzheimer's disease, stroke, head injury, spinal cord injury, anxiety, depression, and other CNS disorders.

The BBB also impedes the use of many newer genetically engineered drugs such as human recombinant neurotrophic factors and other therapeutic agents that can protect brain cells from damage and promote nerve repair. The impediment created by BBB can be overcome in three ways:

1. By manipulation of the drug to make BBB permeable to it either through prodrug approach, or utilization of carriers or transporters, or altering the integrity of the barrier. However these methods are complex and do not work effectively for all therapeutic agents. Besides, even the lipophilic substances administered by a variety of routes of administration are subjected to metabolism by the liver and excretion by the kidney thereby reducing the amount of circulating drug available to the brain and consequently their therapeutic efficacy with regard to CNS.
2. Direct drug delivery to the brain by intracerebroventricular (icv) devices or surgical implantation of devices. It requires invasive neurosurgery. The method releases an active molecule near its pharmacological target for a variable period of time. But this method has its own limitations. It may be utilized for administration of water soluble anticancer drugs or treatment of intractable pain by direct central administration of morphine.
3. Bypassing the BBB by intranasal delivery: It is a novel approach and provides a non-invasive, simple and rapid method to deliver the therapeutic agents to the CNS. This method works because of the unique connection, which the olfactory and trigeminal nerves provide between the brain and external environments. Of late, the intranasal route is found suitable for the transport of drugs to the CNS [2].

Y. Chugh[1] · P. Kapoor[2] · A. K. Kapoor[1] (✉)
[1]Department of Pharmacology,
MLN Medical College, Allahabad, India
[2]RML Hospital, New Delhi, India

E-mail: drakkapoor@rediffmail.com

### Intranasal drug delivery

By intranasal route a wide variety of therapeutic agents including both small molecules and macromolecules can be successfully delivered to the CNS. Thus, it is feasible to deliver challenging drugs to the CNS efficiently such as small polar molecules, peptides and proteins, and even the large proteins and polysaccharides such as vaccines or DNA plasmids exploited for DNA vaccines. Besides, intranasal delivery neither require any modification of the therapeutic agents nor require that drugs be coupled with any carrier [2].

### Nasal physiology

The nose is divided into two nasal cavities via the nasal septum. The volume of each cavity is approximately 7.5 ml and the surface area is about 75 cms. The nasal epithelium

is covered by a mucus layer. The pH of mucosal secretion is slightly acidic (5.5–6.5). The mucus layer entraps particles which are cleared from nasal cavity by the cilia. The particle clearance within the nose is about every 20 min. Functionally, the nose is divided into three functional regions – vestibular, respiratory and olfactory. Of these, the respiratory region is the most important for systemic drug delivery [3].

Several enzymes are present in the nasal cavity such as cytochrome P-450 enzyme isoforms, carboxylesterases and glutathione S-transferases which may play a role in metabolism of drugs.

**Mechanism**

Two mechanisms are involved in the nasal delivery of drugs to the CNS. First, a fast rate that depends on lipophilicity. Second, a slower rate that depends on molecular weight.

The transport of drugs across the nasal membrane and into the blood stream may involve either the passive diffusion of drug molecules through the pores in the nasal mucosa or some form of non-passive transport. Thus, the transport mechanism of substances such as insulin, mannitol or propranolol across the nasal mucosa occurs by a passive transport mechanism. The addition of deoxycholate (0.1%) enhances the transport of insulin and mannitol. Regarding transport of tyrosine and phenylalanine across rat nasal mucosa it has been shown that both these amino acids are absorbed by an active transport process and requires energy.

**Neuronal pathways**

The neuronal connections between the nasal mucosa and brain provide a unique pathway for the non-invasive delivery of the therapeutic agents to the CNS, even to those drugs which do not cross BBB [3–5]. The olfactory epithelium is the major path for substances entering the CNS and the peripheral circulation. The olfactory neuronal pathway provides both an intraneuronal and extraneuronal pathway into the brain [6]. The intraneuronal pathway involves axonal transport and requires longer time for drugs to reach different brain regions. While the extraneuronal pathway involves bulk flow transport through perineural channels thus delivering drugs directly to the brain parenchymal tissues and/or CSF. The extraneuronal pathway allows therapeutic agents to reach CNS within minutes [7]. Besides, the trigeminal neural pathway may also be involved in rapid delivery of protein therapeutic agents, such as insulin-like growth factor-1 to the brain and spinal cord following intranasal administration [8].

**Drug distribution**

The mode of drug administration by affecting drug distribution can influence extent of absorption of the drug. Hence, the drug distribution in the nasal cavity is an important factor that affects the efficiency of nasal absorption. With nasal breathing, particles having an aerodynamic size of 10–20 μm are deposited on nasal mucosa. Any particle with aerodynamic diameter of 50 μm or greater does not enter nasal passage. In essence, particle size determines the deposition of particles in the respiratory tract. The prolonged residence of drug formulation in the nasal cavity is therefore of utmost importance for intranasal drug delivery.

It has been observed in animal studies that the use of mucoadhesive in situ gel enhances the bioavailability of metoclopramide HCl [9]. Thus, improvement of the delivery system, the technique used in the application as well as drug formulations are necessary to achieve better clinical effects. Drug delivery systems including liposomes, cyclodextrins, micro and nanoparticles are being investigated to increase the bioavailability of drugs delivered intranasally.

**Drug absorption**

The first step in the absorption of drugs from nasal cavity is passage through the mucus. Small uncharged particles easily pass through mucus layer. However, larger or charged particles may find it more difficult to cross.

There are several mechanisms for absorption through the mucosa e.g., transcellular or simple diffusion across the membrane, paracellular transport via movement between cells, and transcytosis by vesicle carriers. Drug absorption is restricted by potential metabolism before reaching the systemic circulation and limited residence time in nasal cavity.

Nasal absorption probably depends on aqueous channel diffusion. Water soluble substances such as sodium cromoglycate are well absorbed depending on aqueous channel diffusion (pores). The rate of absorption through aqueous channel depends on the molecular size of the compound. Besides nasal absorption also depends on molecular weight, size, shape, formulation, pH etc. The molecular weight is an important factor of absorption. Good bioavailability can be achieved for molecules upto 1000 Da (without enhancers) which can be extended to 6000 Da with enhancers. Linear shape molecules are less absorbed as compared to cyclic-shaped molecules. Hydrophilicity has been found to decrease a drug's bioavailability. pH of the drug formulation is also important for absorption since nasal irritation is minimized when products are delivered at pH 4.5–6.5.

Absorption enhancers are used to increase bioavailability by improving absorption. These include surfactants, phospholipids, glycosides, glycol, cyclodextrin etc. For example calcitonin which is a polypeptide containing 32 amino acids and molecular weight of 3500 Da has low nasal bioavailability but when calcitonin is used along with enhancers such as cyclodextrins its absorption is increased [10].

Indian J Otolaryngol Head Neck Surg
(April–June 2009) 61:90–94

## Applications of intranasal drug delivery

*(A) Delivery of small molecules to the CNS* Many small molecules are transported directly to the brain and/or CSF from the nasal cavity. For e.g., estrogen, progesterone, folic acid etc. The size and lipophilicity of small molecules affect delivery to CNS following intranasal delivery. Intranasal delivery of diazepam with nasal spray results in rapid onset and this approach may be helpful during emergency treatment of status epilepticus. In animal studies it has been observed that higher concentrations of dopamine, cephalexin are attained in the CNS with intranasal delivery.

Azelastine nasal spray provides a safe and effective therapy for allergic rhinitis and vasomotor rhinitis. Further, in patients with allergic rhinitis, the combination of azelastine and nasal corticosteroids increased treatment efficacy by more than 40% compared with either product used alone [11].

*(B) Delivery of DNA plasmids to the CNS* Nasal route is particularly attractive for immunization because of ease of administration and induction of potent immune responses in the respiratory tract. Intranasal administration leads to a higher distribution of DNA plasmids to the brain. It is observed that DNA plasmids reach the brain within

**Table 1** Small molecules and macro molecules being studied for nasal delivery [15]

**Small molecules**

1. **Autonomic nervous system drugs**
   a. Sympathomimetics: Dopamine, dobutamine, ephedrine, epinephrine, phenylephrine, tramazoline, xylometazoline
   b. Parasympathomimetics: Methacholine, nicotine
   c. Parasympatholytics: Atropine, ipratropium, scopolamine
2. **Central nervous system drugs**
   a. Stimulants: Cocaine, lidocaine
   b. Depressants: Diazepam, lorazepam, midazolam, ketamine, fentanyl, diamorphine
3. **Cardiovascular drugs:** Isosorbide dinitrate, propranolol, verapamil, hydralazine, nitroglycerin, clofilium tosylate
4. **Autocoids**
   i) **Histamine and antihistamines**
   a. Histamine:
   b. Antihistamines: Meclizine, azelastine
   c. Mast cell stabilizers: Disodium cromoglycate
   ii) **Prostaglandins**
5. **Narcotics and antagonists:** Buprenorphine, naloxone
6. **Adrenocorticosteroids**
7. **Sex hormones:** Estradiol, progesterone, norethindrone, testosterone
8. **Antibiotics:** Gentamicin, cephalosporin, penicillins, tyrothricin
9. **Antiviral drug:** Enviroxime
10. **Antimigraine drugs:** Dihydroergotamine, ergotamine tartrate
11. **Vitamins:** Folic acid, cyanocobalamin
12. **Inorganic compounds:** Colloidal carbon, colloidal gold, inorganic salts, lead
13. **Diagnostic drugs:** Dye T-1824, phenosulfonphthalein, potassium ferrocyanide, vital dyes

**Macro molecules**

1. **Amino acids**
2. **Peptides:** Calcitonin, secretin, thyrotropin-releasing hormone (TRH), cerulein, enkephalin analog-leucin enkephalin, mekephamid, pentagastrin, SS-6, substance P, kyrotrophin, cholecystokinin
3. **Polypeptides and proteins**
   a. Albumins
   b. Anterior pituitary hormones: Adrenocorticotropic hormone, gonadotropin-releasing hormone, growth hormone
   c. Posterior pituitary hormone: Oxytocin, vasopressin
   d. Pancreatic hormones: Insulin, glucagon
   e. Biological products: Interferon, vaccines
   f. Horseradish peroxidase

15 min following intranasal delivery. This indicates that nasal administration may be a potential route for the delivery of therapeutic genes to the brain with reduced side-effects in the other organs [12]. More recently nanoparticles are being used as carriers for nasal vaccine delivery.

*(C) Delivery of protein therapeutic agents or macromolecules to CNS* Bioavailability of protein molecules is fairly low owing to their large molecular size and rapid enzyme degradation. Peptide or protein drugs are mostly administered parenterally because oral administration results in poor bioavailability. Nasal administration of peptide and protein compounds provides an attractive and convenient delivery route for e.g., desmopressin, lypressin, oxytocin and nafarelin acetate. The intranasal administration of peptides and proteins is superior to oral route which is studded with shortcomings such as rapid enzymatic degradation, physiochemical instability and susceptibility to "first-pass metabolism." Human studies have shown that proteins such as insulin, adrenocorticotropic hormone (ACTH), arginine vasopressin (AVP) and cholecystokinin (CCK) analog are directly delivered to the brain from nasal cavity. Delivery of protein therapeutic agents to the CNS clearly involves extraneuronal transport.

Increased nasal absorption of protein therapeutic agents can be achieved by using bioadhesive agents and absorption enhancers. Common bioadhesive agents are cellulose, starch, dextran and chitosan. The usual absorption enhancers are surfactants, glycoside, glycols and cyclodextrins. Bioavailability and residence time of the drugs that are administered via the nasal route can be increased by bioadhesive drug delivery systems by utilizing microspheres, liposomes and gels. This is particularly true for the delivery of the macromolecules such as insulin and growth hormone. In animal studies intranasal insulin with mucoadhesive chitosan gel has shown a higher bioavailability as reflected by a greater fall in blood glucose level [13].

In rodents, neurotrophic factors such as NGF, IGF-1, FGF etc. have been delivered to CNS by intranasal route. In animal model, intranasal delivery of IGF-1 reduces infarct volume and improves neurologic functions in rats with middle cerebral artery occlusion (MCAO).

Research in human beings has demonstrated that CSF concentration of 17 β-estradiol following intranasal delivery of its prodrug was higher compared to an equivalent i.v. dose. This is of significant value in the treatment of Alzheimer's disease [14]. Direct delivery of macromolecules to the CNS by intranasal route has been demonstrated in human beings with corticotropin-releasing hormone (CRH) without altering plasma cortisol or CRH levels.

### Advantages of nasal drug delivery

1. Non-invasive, simple, rapid and convenient method of delivering drugs.
2. Bypasses the BBB and targets the CNS thus facilitates treatment many neurologic and psychiatric disorders.
3. Rich vasculature and highly permeable structure of the nasal mucosa greatly enhance drug absorption.
4. A wide range of drugs can be delivered.
5. Does not require any modification of the therapeutic agent being delivered.
6. Reduces systemic exposure and thus curtails systemic side-effects.
7. Problem of degradation of peptide drugs is minimized upto a certain extent.
8. Increases bioavailability of drugs by avoiding destruction in the GIT and hepatic first-pass metabolism.

### Limitations

1. Concentration achievable in different regions of brain and spinal cord varies with each agent.
2. Delivery of higher molecular weight drugs is restricted.
3. Nasal congestion due to cold or allergies may interfere with this method of delivery.
4. Some drugs are partially degraded in nasal mucosa.
5. Some drugs may cause irritation to the nasal mucosa.
6. Frequent use of this route may result in mucosal damage and may lead to infection and anosmia.

## Conclusion

In conclusion, the intranasal delivery has several advantages. It is both rapid non-invasive and bypasses the BBB. It targets the CNS thus reduces systemic side-effects. It facilitates delivery of genetically engineered and biotech drugs. Intranasal delivery may facilitate the treatment and prevention of many different neurologic and psychiatric disorders.

## References

1. Greig NH, Genka S, Rapoport SI (1990) Delivery of vital drugs to the brain for the treatment of brain tumours. J Control Release 11:61–78
2. Illum L (2003) Nasal drug delivery – possibilities, problems and solutions. J Control Release 87:187–198
3. Illum L (2000) Transport of drugs from the nasal cavity to the central nervous system. Eur J Pharm Sci 11:1–18
4. Mathison S, Nagilla R, Kompella UB ((1998)) Nasal route for direct delivery of solutes to the central nervous system: fact or fiction? J Drug Target 5:415–441
5. Thorne RG, Frey WH 2nd (2001) Delivery of neurotrophic factors to the central nervous system: Pharmacokinetic considerations. Clin Pharmacokinet 40:907–946
6. Thorne RG, Emory CR, Ala TA, Frey WH 2nd (1995) Quantitative analysis of the olfactory pathway for drug delivery to brain. Brain Res 692:278–282

7. Chen XQ, Fawcett JR, Rahman YE, Ala TA, Frey WH (1998) Delivery of nerve growth factor to the brain *via* the olfactory pathway. J Alzheimers Dis 1:35–44
8. Frey WH, Thorne RG, Pronk G (2000) Delivery of Insulin like growth factor-1 to the brain and spinal cord along olfactory and trigeminal pathways following intranasal administration: a noninvasive method for bypassing the blood brain barrier. Soc Neurosci Abstract 26:1365–1370
9. Zaki NM, Awad GA, Mortada ND, Abd Elhady SS (2007) Enhanced bioavailability of metoclopramide HCl by intranasal administration of a mucoadhesive in situ gel with modulated rheological and mucociliary transport properties. Eur J Pharm Sci. 32(4–5):296–307
10. Schipper NGM, Verhoef JC, Merkus FWHM (1995) Methylated beta-cyclodextrin is able to improve the nasal and intramuscular administration of salmon calcitonin. Calcif Tissue Int 56:280–282
11. Kaliner MA (2007) A novel and effective approach to treating rhinitis with nasal anthistamines. Ann Allergy Asthama Immunol 99(5):383–390
12. Oh YK, Kim JP, Hwang TS, Ko JJ, Kim JM, Yang JS, et al. (2001) Nasal absorption and biodistribution of plasmid DNA: an alternative route of DNA vaccine delivery. Vaccine 19:4519–4525
13. Varshosaz J, Sardai H, Heidari A (2006) Nasal delivery of insulin using bioadhesive chitosan gels. Drug Deliv 13(1): 31–38
14. Al-Ghananeem AM, Traboulsi AA, Dittert LW, Hussain AA (2002) Targeted brain delivery of 17 β-estradiol *via* nasally administered water soluble prodrugs. AAPS Pharm Sci Tech 3:1–8
15. Talegaonkar S, Mishra PR (2004) Intranasal delivery: An approach to bypass the blood brain barrier. Indian J Pharmacol 36:140–47