



A CRITICAL REVIEW ON FACTORS AFFECTING THE ABSORPTION OF DRUG IN 'NASYA KARMA'

Dr. Lata Melkani*¹, Dr. Mitra Shuchi², Dr. Sharma Usha³, Dr. Rawat Sushma⁴ and Dr. Sharma Khemchand⁵

P.G Deptt. of Rasa Shastra and Bhaishajya Kalpana Uttarakhand Ayurved University, Dehradun.

*Corresponding Author: Dr. Lata Melkani

P.G Deptt. of Rasa Shastra and Bhaishajya Kalpana Uttarakhand Ayurved University, Dehradun.

Article Received on 10/04/2019

Article Revised on 01/05/2019

Article Accepted on 22/05/2019

ABSTRACT

INTRODUCTION- *Ayurveda* have always abide by the theory of 'Nasa' or Nose being the gateway to brain 'Sira'. With the amazingly accurate studies in anatomy one can now infer nose as one of the important route for medicine administration in diseases of head & neck. Nasal cavity is covered by a thin mucosa which is well vascularised. Hence, a drug molecule can be transferred quickly & directly to the systemic blood circulation. **METHODOLOGY-** This review article compiled many articles and reserach papers collected from different websites along with materials from *ayurvedic* texts. **DISCUSSION-** This article aims at proposing probable nasal routes through which drugs of nasya karma get absorbed. **CONCLUSION-** From review of various studies it can be concluded that there three probable pathways for nasal drug administration *Nasya Karma*.

KEYWORDS: *Nasya, Shira, Nasa, Vascularised mucosa.*

INTRODUCTION

As said by *Acharya vagbhatta*, "*Nasa hi shirso dwaram*"^[1] Nose is the pathway to the brain, nasya karma also known as intranasal drug delivery has been recognized as an important form of treatment in the *ayurvedic* system of medicine from the ancient times. *Acharya Vagbhatta* classified *Nasya* into three categories by means of their mode of action: *Virechan, Brimhan & Saman*. On the other hand *Acharya Caraka* said, "*Dwaram Hi Shirso Nasa*"^[2] & divided *Nasya* in three sections *Rechana, Tarpana, Saman*. *Acharya* also classified *Nasya* into five categories *Navana, Avapidha, Dhampan, Dhuma, Partimarsh*. *Navana Nasya* is considered to be the best among all.^[3] *Acharya Susruta* said "*Ausadhamsidho va sneho nasikabhayam diyate ety nasyam*"^[4] the medicated drug which is administrated through nasal route is known as nasya & he divided *Nasya* in two categories *Shirovirechana & Snehna* by means of their mode of action. *Nasya* drug enters the brain through *Shringataka Marma* & nourishes other sensory organs like eye, ear & oral cavity.^[5] In this paper an attempt has been made to critically review the factors affecting the absorption of drug in *nasya karma*. Even in the modern era, it has been found that several drugs have equivalent bioavailability through nasal route as parallel to oral administration. This drug delivery method is best suited when low doses of drugs have to be administrated or when the patient is in unconscious state.

MATERIAL AND METHODS

The material for this study have been collected from different sources

Nasya

Nasyakarma is one of the therapies among the *Panchakarma* therapies in which the medicated drugs are administered through the nasal route and is meant for *Shirogataroga*. *Urdhvanga chikitsa* one of the important branches of *Ashtanga Ayurveda* and for which *Nasyakarma* is the main therapeutic measure. All sense organs, which are above the clavicle, are considered under *Urdhvanga* e.g. *Nasa, Mukha, Netra and Shrotra*.

Classification of Nasya

Classification of *Nasya* is done in various manners depending upon various factors like form of drug, mode of action etc. as shown in the table.

SI. No.	Athours	Types	Names
1.	Charaka	3 types	<i>Mode of action: Rechana, Tarpana, Shamana.</i> ^[6]
		5 types	<i>Method of administration: Navana, Avapidana, Dhmapana, Dhuma, pratimarsha.</i> ^[7]
		7 types	<i>According to various parts of drugs utilized: Phala, patra, mula, kanda, pushpa, niryasa, twaka.</i> ^[8]
2.	Sushruta	5 types	<i>Shirovirechana, Pradhamana, Avapida, Nasya, Pratimarsha.</i> ^[9]
3.	Vagbhatta	3 types	<i>Virechana, Brimhana, Shamana.</i> ^[10]
4.	Kashyapa	2 types	<i>Shodhana, Poorana.</i> ^[11]
5.	Sharangadhara	2 types	<i>Rechana, Snehana.</i> ^[12]

Acharya Charaka classification of all the above mentioned types of *Nasya* can be interpreted as follows.

1. Navana Nasya

Method

Transnasal administration of *Sneha dravya* is considered as *Navana Nasya*.

Classification

- *Snehana Nasya*
- *Shodhana Nasya*.

Snehana Nasya

The *Nasya* which gives strength to all the *Dhatu*s and is used as *Dhatuposhaka*

Dose

- Hina Matra* 8 drops in each nostril.
- Madhyamamatra -Shukti Pramana-* 16 drops in each nostril.
- Uttama Matra- Panishukti Pramana-* 32 drops in each nostril

Indications

Vatika Shirahshula, Keshapata, Dantapata, Shmashrupata, Tivra karnashula, Timira, Nasaroga, Mukhashosha, Avabahuka, Akalaja Palitya.

Shodhana Nasya

Sushruta's Shirovirechana type is included in *Shodhana* type of *Navana nasya*. It eliminates the vitiated *Doshas*.

Drugs

In this type of *Nasya*, oil prepared by *Shirovirechana Dravyas* like *Pippali, Shigru* etc. can be selected.

Dose

It can be given in following dosage schedule

- *Uttama-* 8 drops
- *Madhyama-* 6 drops
- *Hina-* 4 drops.

Indications

Kaphapurna Talu & Shira, Aruchi, Shirogaurava, Shula, Pinasa, Ardhavabhedaka, Krimi, Pratishyaya, Apasmara and *Urdhvajatrugata Kapharogas*

In healthy persons *Navana nasya* given according to the following seasonal schedule.

According to Season *nasya kala*

- *Shita Kala*-Noon
- *Sharada and Vasanta*-Morning
- *Grishma Ritu*-Evening
- *Varsha Ritu*-Only when the sun is visible.

Time Schedule for *nasya*

- In *Kaphaja Roga* -Fore noon
- In *Pittaja Roga* -Noon
- In *Vataja Roga* -After Noon.^[13]

Indication of *Nasya*

Patient who regularly undergoes *Nasyakarma* does not become victim of diseases of eyes, ears and nose. Hair and beard does not turn gray. Hair doesn't fall but instead grows faster. There will be no sudden attack of diseases in the region above the clavicle (*Urdhvajatrugata*) of the body.

Anatomy of Nasal Cavity

"*Nasa*" (nose) is the pathway for *Shira* (or brain),^[14] contemporary modern science is now also of the view that nose is the only place where the brain meets the outside world? Nerve filaments, or axons of the 1st cranial nerve (the olfactory nerve) extend directly from the olfactory bulb in the limbic region of the brain to the upper posterior segments of the nose, penetrate the mucosal lining & allow direct contact with the environment without a peripheral sensory receptor relay. Millions of these neurons are present, acting as a chemical sensor, detecting scents from food & playing a role in social behaviour. Recent studies published in this decade suggest the potential existence of a functional pathway for medications to pass into the CNS from structures deep in the nose innervated by cranial nerves, a pathway sometimes called as nose to brain transport nose to brain pathway (N2B).^[15] Also on other hand the central region of the root of the nose is formed by cribriform plate of the ethmoid bone, which separates the nasal cavity from the floor of the anterior cranial fossae. It contains numerous small perforations that transmit the olfactory nerves & their sheathing meningeal layer.^[16] Mainly *Piamater* is now proved to be continuous with nasal mucosal layer and substances transmits through these from nose to

brain via nasal mucosa to piamater. Nasal cavity is also connected to all other cavities of sensory organs like.

- To orbital cavity by nasolacrimal duct.^[17]
- To oral cavity by incisive canal.^[18]
- To ear through Eustachian tube which opens in the nasopharynx.^[19]

“Imani siramarmani chaturangulapramanani” (Dalhan)^[20]

The Shringatak Marma is a Sira Marma (i.e. venous plexuses may be present in the area), with Chaturangul Praman (i.e. circumference of 4 Angul—approx. 7.8 cm). 1 Angula = 1.95cm.^[21]

Probable Mode of Action

“Nasayaam praniyamanamoushadham nasyam, Navanam nastah karmeti cha sangya labhate, Nasa hi shirso dwaram tatra avasechitamoushadha strotah srigatakam prapya vyapya murdhanam netraksotra kantadisiramukhani cha munjadishikamivasaktaam urdhvajatrugataam vaikarikumsheshamaashu doshasamhatimuttamangadapkarshati”.^[22]

The drug which is administrated by nasal route reaches Shringataka Marma by Nasasrotas and spreads in the brain & reaches at the junction place of Netra, Shrotra, Kantha Siramukhas (opening of the vessels).^[22] According to Acharya Susruta Shringatak marma is sadyapranahar marma, he classified it as a sira marma^[23] & as per Acharya Vagbhatta it is a dhamini marma.^[24] According to dr. Ghanekar's view shringataka marma can be concluded as cavernous sinuses on the basis of ideas

given by Rasyogasagar.^[25] This is the only venous structure in between which artery passes; and veins of eye directly drains into it, also the veins of nose & ear indirectly joins it. Henceforth, Cavernous sinus may be referred as Shringataka Marma.

Cavernous Sinus

The cavernous sinus is present in lateral sellae compartment of sphenoid bone. It receives blood via the superior & inferior ophthalmic veins, superficial cortical veins and is connected to the basilar plexus of veins posteriorly. It drains by 2 layer channels, the superior & inferior petrosal sinuses, ultimately into the internal jugular vein via the sigmoid sinus, also draining the emissary vein to pterygoid plexus. The internal carotid artery (carotid siphon) & CN III, IV, V (branches V₁ & V₂) and VI all pass through this fluid filled space.^[26]

Mechanism of Nasal Absorption

The absorbed drugs from the nasal cavity must pass through the mucus layer; it is the first step in absorption. Small uncharged drugs easily pass through this layer but large charged drugs are difficult to cross it. The principle protein of the mucus is mucin, it has the tendency to bind to the solutes, hindering diffusion. Two mechanisms have been predominantly used for drug absorption

- It involves an aqueous route of transport, also known as the paracellular route but it is slow and passive route.
- It involves transport through a lipoidal route & known as transcellular process.^[27]

Factors affecting the permeability of drugs through the nasal mucosa	Physiological factors	Pathological condition	Physiochemical properties of drug
Structural features	Blood supply and neuronal regulation	Environmental factors	Molecular weight
Biochemical changes	Nasal secretion		Lipophilicity
	Nasal cycle		Buffer capacity
	P ^H of the nasal cavity		Drug concentration
	Moucociliary clearance & ciliary beat frequency		Osmolarity
			Viscosity

Factors Affecting the Permeability of Drugs through the Nasal Mucosa

Structural Features

Nasal epithelium consist of different types cells so by this it shows variation in nasal absorption and other factors such as the presence of microvilli, cell density, surface area and the number of cells. The respiratory region is richly supplied with blood, has a large surface area and receives the maximum amount of nasal secretions.^[28]

Biochemical Changes

Nasal mucus acts as one of the enzymatic barrier to the delivery of drugs because of the presence of a large number of enzymes, which include oxidative and conjugative enzymes. These enzymes are responsible for

the degradation of drugs in the nasal mucosa and result in creation of a pseudo-first-pass effect, which hampers the absorption of drugs.^[29]

Physiological Factors

Blood Supply and Neuronal Regulation

Nasal mucosa is richly supplied with blood and presents a large surface area making it an optimal location for drug absorption. The blood flow rate influences significantly the systemic nasal absorption of drugs, so that as it enhances more drug passes through the membrane, reaching the general circulation.^[30]

Nasal Secretions

Anterior serous and seromucus glands produce nasal secretions approximately 1.5–2.1ml per day. The

permeability of drug through the nasal mucosa is affected by viscosity of nasal secretion.^[31]

Nasal Cycle

Nasal cycles of congestion (increased blood supply resulting from parasympathetic stimulation) and relaxation (decreased supply resulting from sympathetic stimulation) regulate the rise and fall in the amounts of drug permeated.^[32]

pH of The Nasal Cavity

It varies between 5.5–6.5 in adults and 5.0–7.0 in infants. Greater drug permeation is usually achieved at a nasal pH that is lower than the drug's pKa because under such conditions the penetrate molecules exist as unionized species. The ideal pH of a formulation should be within 4.5–6.5.^[33]

Mucociliary Clearance and Ciliary Beat Frequency

The main function of the mucociliary clearance system is to remove foreign substances (bacteria, allergens and so on) and particles from the nasal cavity, thus preventing them from reaching the lower airways. Reduced Mucociliary Clearance (MCC) and ciliary beating increases the time of contact between a drug and the mucus membrane and subsequently enhances drug permeation. Whereas, increased MCC decreases drug permeation.^[34]

Pathological Conditions

Diseases such as the common cold, rhinitis, atrophic rhinitis and nasal polyp are usually associated with mucociliary dysfunctioning, hypo or hyper secretions, and irritation of the nasal mucosa which influence drug permeation.^[35]

Environmental Factors

Temperatures in the range of 24°C cause a moderate reduction in the rate of Mucociliary clearance (MCC).^[36]

Physicochemical Properties of Drug

Molecular Weight

It is one of the important factors in nasal drug delivery system. Low molecular weight drugs are rapidly absorbed through nasal mucosa. The main reasons for this are the high permeability, fairly wide absorption area, porous and thin endothelial basement membrane of the nasal epithelium. Nasal delivery is expected to decrease with increasing molecular weight of the drug. A linear inverse correlation has been reported between the absorption of drugs and molecular weight up to 300 Da. Absorption decreases significantly if the molecular weight is greater than 1000 Dalton.^[37]

Lipophilicity

On increasing in lipophilicity, the permeation of the compound normally increases through nasal mucosa. Although the nasal mucosa was found to have some hydrophilic character, it appears that this mucosa is primarily lipophilic in nature and the lipid domain plays

an important role in the barrier function of these membranes.^[38]

Buffer Capacity

Nasal formulations are generally administered in small volumes ranging from 25 to 200µL. Hence, nasal secretions may alter the pH of the administrate dose. This can affect the concentration of unionized drug available for absorption.^[39]

Drug Concentration

Concentration gradient plays very important role in the absorption as well as the permeation process of drug through the nasal membrane due to nasal mucosal damage.^[40]

Osmolarity

Drug absorption can be affected by tonicity of formulation. Shrinkage of epithelial cells has been observed in the presence of hypertonic solutions. Hypertonic saline solutions also inhibit or cease ciliary activity. Low pH has a similar effect as that of a hypertonic solution.^[41]

Viscosity

A higher viscosity of the formulation increases contact time between the drug and the nasal mucosa thereby increasing the time for permeation. At the same time, highly viscous formulations interfere with the normal functions like ciliary beating or mucociliary clearance and thus alter the permeability of drugs.^[42]

Area of Nasal Membrane Exposed

One of the study conducted using 40 mg progesterone ointment, absorption was compared between applications to one nostril with application to both nostrils. Increased bioavailability was observed when ointment was applied in both the nostrils concluding that as the area of mucus membrane exposed increases, it should result in increased permeation.^[43]

Dosage Form

Acharya charaka mentioned five types of nasya on the basis of method of administration i.e. *Navana*, *Avapidana*, *Dhamapana*, *Dhuma*, *Pratimarsha*, & he classified *Navana* as *Snehna* or *Shodhana*.^[44]

DISCUSSION

Drug absorption in 'Nasya karma' is a complex process and depends upon drug properties, anatomical-physiological conditions of nasal cavity and intranasal pathways. The probable mode of action of drugs of Nasya karma can be.

1. Neurological Pathway

It may be through stimulation of Olfactory nerve & Trigeminal nerve (Ophthalmic & Maxillary branches). The peripheral olfactory nerves are chemoreceptor in nature. These nerves differ from other cranial nerves in its close relation with the brain. These are connected

with the higher centres of brain i.e limbic system, consisting mainly of amygdaloidal complex, hypothalamus, epithalamus, anterior thalamic nuclei parts of basal ganglia etc. So the drugs administration here stimulates the higher centres of brain which shows action on regulation of endocrine & nervous system functions.^[45]

2. Diffusion Of The Drug

Lipid soluble substances have greater affinity for passive absorption through the cell walls of nasal mucosa. Non-polar hydrophobic molecules diffuse through the lipid bilayer of the plasma membrane, into & out of cells.^[46]

3. Vascular Pathway

It is possible through the pooling of nasal venous blood into inferior ophthalmic vein (which in turn pools into facial vein) & deep facial vein. The facial vein has no valves. It communicates freely with the intracranial circulation, not only at its commencements and by the supra orbital veins which are connected with the ophthalmic vein, a tributary of the deep facial vein, which communicates through the pterygoid plexus with the cavernous venous sinus.^[47] Such a pooling of blood from nasal veins to venous sinuses of the brain is more likely to occur in head lowering position due to gravity, the absorption of drug into meninges and related intracranial organ is a point of consideration.

CONCLUSION

The mode of action & bioavailability of drugs in nasya karma is a complex process and it needs further elucidation through extensive clinical studies and their co-relation with pharmacodynamical & analytical studies done in animal models. The three probable mode of absorption are discussed above which may pave way for further studies in this regard.

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