

Nasal Drug Delivery-A Pre Hospital Therapy in Status Epilepsy- Review

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Abstract: Status epileptics is a brain disorder. It is an important neurological emergency with high mortality and morbidity. it causes loss of cerebral autoregulation and neuronal damage. Prompt and immediate prehospital treatment is required to shorten the duration of seizures. So Parents and care givers need simple, safe, efficacious prehospital therapy. As per parents and care givers needs and consideration of severity of status epileptics and complexity of brain this review has been focused on intra nasal route as a prehospital therapy. It is a potential route and alternative route for the administration of anticonvulsant drugs. It prevents the enzymatic or acidic degradation and first-pass hepatic metabolism. The nasal mucosa is one of the most permeable and highly vascularized site for drug administration ensuring rapid absorption and onset of therapeutic action. The objective of the review is to provide information of status epileptics and its dangerous effects, need of rapid prehospital treatment, factors to be considered in nasal drug delivery, new strategies of delivery of antiepileptic drugs by intra nasal route.

Keywords: Status epileptics, Intranasal drug delivery, Brain targeting, anticonvulsant drug, Absorption enhancer, Blood Brain Barrier

Abbreviation: Status Epileptics(SE), AntiEpileptic Drug(AED)

I. Introduction

Epilepsy is characterized by abnormal electrical activity within the brain, which can result in either generalized or partial seizures. Generalized seizures are widespread, affecting both hemispheres of the brain. Partial seizures originate at a focus and are isolated to specific areas of the brain. The presence of a focal lesion can be detected by electroencephalographic readings and functional molecular resonance imaging¹.

Status epileptics is a brain disorder. It is defined as seizure lasting more than 30 min during which the patient does not regain consciousness. It is an important neurological emergency with high mortality and morbidity². Status epileptics causes cell damage in the hippocampus, amygdala, cerebellum, thalamus, middle cerebral cortical layers after 60 min of convulsive status epileptics. The cerebral neurons in the epileptic focus are continually firing and have increased metabolic demands. Status epileptics is harder to control, so prompt treatment is required to control seizure otherwise it causes loss of cerebral autoregulation and neuronal damage^{3,4}.

Prolonged seizures (more than 5 min) can cause increased metabolic rate, neuronal injury, cerebral oxygen extraction, massive sympathetic and parasympathetic over activity like tachycardia, hypertension, hyperglycemia, hyperthermia, excessive sweating in generalized or partial seizures.⁵ These dangerous seizures commonly occur in outside the hospital. Immediate and prehospital treatment is required to shorten the duration of seizures. So parents and care givers need simple, safe, efficacious prehospital therapy⁵.

Brain is a complex organ and it is protected by blood brain barrier and cerebrospinal fluid barrier⁶. Brain is tightly segregated from circulating blood by BBB. It consists of tight junctions called zonula occludens produced by interaction of several transmembrane proteins such as occludin and claudin. Most of CNS drugs cannot reach the brain in sufficient concentration due to this complexity. Based on parents and care givers needs and severity of status epileptics and complexity of blood brain barrier potential prehospital therapy is needed. Intra nasal route is a non-injective special route to target brain by olfactory nervous system. It has less side effect and no first pass metabolism. So this review has been focused on nasal drug delivery.

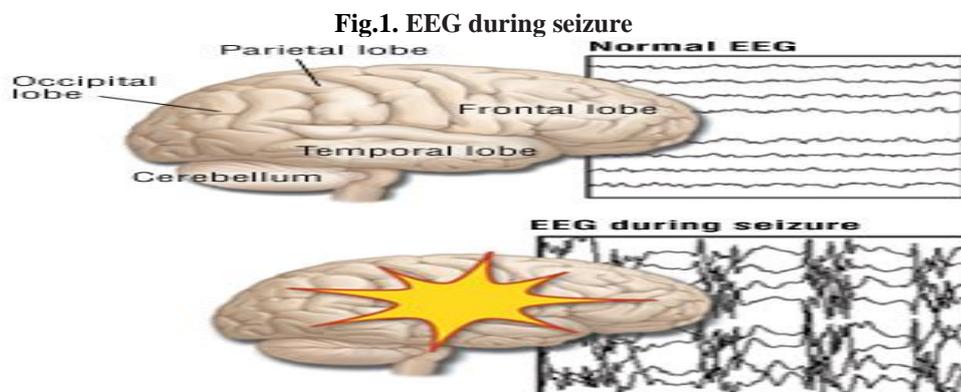
The goal of review is study of delivering antiepileptic drugs (AEDs) to the brain by intra nasal route to reduce the frequency and severity of seizures without causing side effects. This transvascular route seems reasonable due to the high vascularity of the brain.

II. Status Epileptics

SE is differentiated from other seizures by duration. SE presents as a prolonged seizure, a seizure that lasts longer than expected. Definition of SE or 'established' SE requires that seizures last for a minimum of 30 min^[6]. Studies of SE have shown that more prolonged seizures are associated with a worse outcome.

During seizure changes in the subunit composition of AMPA, NMDA and GABA receptors promote self-sustaining seizures^[7]. When the brain is exposed to prolonged seizures, there is a rapid decrease in the

number of functional postsynaptic GABAA receptors^[8,9] and an increase in the number of functional postsynaptic NMDA receptors^[10]. It leads to loss of inhibition and increase in excitation in the brain synapses promote self-sustaining prolonged seizures (**Figure 1**)



NEED OF RAPID PREHOSPITAL TREATMENT

Convulsivestatus epilepticus (SE) is a life-threatening emergency which requires rapid treatment .prolonged seizures cause brain damage. Several clinical studies have shown that more prolonged seizures are associated with a worse outcome.Parameters affect the prognosisof SE is age, etiology and SE duration^[11,12,13,14]. Age is a nonmodifiable factor and etiology may or may be modifiable or treatable .One of study have shown that *the* duration of SE was shorter (32 vs 60 min) and the risk of recurrent seizures was lower (58 vs 85%) in pre-hospital diazepam^[15].Regarding this to shorten the SE duration appropriate rapid prehospital treatment is needed.

NASAL ROUTE AND ITS IMPORTANCE

Nasal route is the preferred and noninvasive route for brain targeting . Because brain and nose compartments are connected with each other via olfactory ,trigeminalnerves,the vasculatures, the cerebrospinal fluid,and lymphatic system⁽¹⁶⁾.Nasal cavity consist of vascularised epithelium ,large surface area and lower enzymatic activity when compare to GIT⁽¹⁷⁾. This pathway of nose to brain deliver the drugs directly to CNS without first pass metabolism⁽¹⁸⁾and provide faster and maximum therapeutic effect. Generally intravenous route is given for immediate relief from status epilepsy.due to good bioavailability. But it produces pain ,irritation,local systemic adverse effect,and produces precipitation and tissue necrosis⁽¹⁹⁾. For status epilepsy Nasal route is alternative route to parentalsince it has good bioavailability and less side effect.Absorbtion mechanisms of nasal route are

- a) **Paracellular Transport-** It involves an aqueous route of transport. Polar compounds pass through this route. but this route is slow and passive
- b) **(b)Transcellular Transport** - It is responsible for the transport of lipophilic drugs. Drug also crosses the cell membranes by an active transport route via carrier-mediated transport⁽²⁰⁾.

III. Advantages Of Nasal Drug Delivery^(21,22,23)

- 1) No drug degradation in GIT .
- 2) Hepatic first pass metabolism is avoided.
- 3) Bioavailability is good.
- 4) Nasal route is an alternative route toparental.
- 5)Patient compliance
- 6) Polar compounds also provide good bioavailability by nasal route by addition of surfactants
- 7)large nasal mucosa surface area for dose absorption.
- 8) Ease of administration, non-invasive.
- 9) Lower dose reduced side effects.
- 10) Self-administration.

IV. Limitations^(24,25)

- 1)When molecular weight of drug is increased,drug Delivery is decreased.
- 2 Frequent use of intra nasal routecausesmucosal damages .
- 3) Very specific amount i.e. 25-200µ can be delivered throw intra nasal route.
- 4) Drug administration is difficultduring cold or allergic reaction.

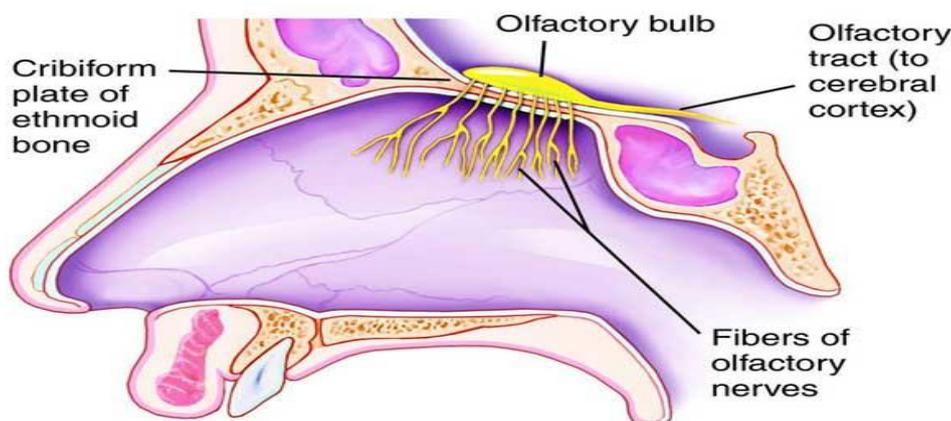
- 5) Some drugs causes nasal irritation.
- 6) Improper administration causes loss of doses.

V. Nasal Anatomy And Physiologas Related To Intranasal Drug Delivery

Intranasal sprays of medication intended for systemic drug absorption are generally designed to target the turbinates on the medial wall of the nasal cavity. The nasal cavity is located above the oral cavity & hard palate and below the skull base. The left & right nasal cavity becomes continuous in the back of nose via the opening to the nasopharynx. Nose is divided by middle septum into two symmetrical halves, each one opening at the face through nostrils & extending to the nasopharynx. Nasal cavity is lined with mucus layer and hair²⁶, composed of 95% water, 2% mucin, 1% salt, 1% other proteins such as albumin, immunoglobulin, lysozymes & lactoferrin, & 1% lipid²⁷. The main role of nose are olfaction, regulation of humidity & temp of inhaled air and removal of microorganism or particulate matter from inhaled air²⁸.

Mucus present over epithelial cell causes mucociliary clearance. Drug transported from nasal cavity for absorption through mucus only⁽²⁹⁾. Mucus moves only in one direction from the anterior to posterior part of nasal cavity to the nasopharynx^{30,31,32,33}. Mucous secretion gives immune protection against inhaled bacteria or virus. Mucous has water holding capacity, it exhibit surface electrical activity, it also act as transport & adhesive for particulate matter towards nasopharynx³⁴.

Fig.2. Nasal anatomy & physiology



OLFACTORY REGION:

Olfactory region is located on the roof of the nasal cavities which separates the nasal cavities from the cranial cavity and contains olfactory receptor cells for smell perception⁽³⁵⁾. It consist of three cell types:

1. Olfactory neural cells,
2. Sustenticular (supporting) cells,
3. The basal cells

Olfactory neuron are interspaced between supporting cell³⁶. The cilia contain chemical detector, it will get activated by odour and cause depolarisation by ion gated channel or C-GMP pathway³⁷. beneath the epithelium layer lamina propria is present. Which contain blood supply, mucous secretion acinarglands, nasal lymphatic, & neuronal supply that consist of olfactory axon bundles, autonomic nerve fibre and maxillary branch of trigeminal nerve³⁸. Filia olfactory are unique feature that act as ionic reservoir for action potential propagation. Mesaxons are pores in Filia olfactory that allow passage of extracellular fluid into neuronal bundle structure. The transport of drug in nasal membrane to bloodstream is passive diffusion³⁹.

VI. Factors To Be Considered In Nasal Drug Delivery

Eventhough Nasal Route is the good attempt to deliver the drug to brain ,otaher factors also important to attain better bioavailability. The factors are

1. Physicochemical Factors of Drug
2. Formulation Factors
3. Nasal Cavity Factors

6.1 PHYSIOCHEMICAL PROPERTIES OF DRUGS ⁴⁰:

MOLECULAR WEIGHT:

Drugs molecular weight up to 300 Daltons have more absorption. When the molecular weight is greater than 1000 Daltons Absorption can be decreased. It should be enhanced with the use of absorption enhancers. Shape is also an important factor that affects the absorption of drugs. Linear molecules have lower absorption whereas the cyclic – shaped molecules showed higher absorption.

PARTICLE SIZE:

Particle sizes greater than 10µm are easily absorbed in the nasal cavity. Too fine particles i.e, below 5 µm should be avoided for nasal administration because chances of inhalation directly into the lungs⁴¹.

SOLUBILITY AND DISSOLUTION RATE:

Drug solubility and dissolution rates directly influence nasal absorption from powders and suspensions⁴². The absorption profile is not only influenced by drug solubility but also by the nature of pharmaceutical preparations. Therefore, drugs poorly soluble in water or requiring high doses may affect the dissolution rate. The particles deposited in the nasal cavity should get dissolved prior to absorption.

POLYMORPHISM:

Drug molecule exists in different polymorphs. Each polymorph has different dissolution rate. Polymorphic nature has affected the solubility of drugs and their absorption through biological membranes⁴³.

CHEMICAL FORMS:

The chemical form of a drug is an important factor in determining absorption. For example structural modification of carboxylic acid esters of L-Tyrosine was significantly greater absorption than of L-Tyrosine⁴⁴.

LIPOPHILICITY:

Lipophilic drug can easily get through intranasal route. Pharmacokinetic profile of lipophilic drug administered through intravenous route is similar as intranasal route. For example Bioavailability of fexofenadine was 100% from the microemulsion applied intranasal route and absolute bioavailability was about 68% compared to intravenous administration⁴⁵. Bioavailability of polar drug is generally low. Polar drug having molecular weight less than 1000Da will generally pass through membrane⁴⁶.

Permeability of such polar drug can be improved by adding absorption enhancers like surfactants (laureth-9, sodium lauryl sulphate) bile salt, bile salt derivatives, fatty acid, phospholipid, cationic compound like chitosan & its derivatives, poly-L-arginine⁴⁷.

6.2 FORMULATION FACTORS:

PH OF THE FORMULATION:

The pH of the nasal cavity and pKa of a particular drug can be considered to optimize systemic absorption. When pH range is 4.5 to 6.5, Nasal irritation can be minimized. pH influences the drug ionization. Unionized form of drug reaches the systemic absorption⁴⁷.

BUFFER CAPACITY:

Nasal formulations are generally in small volumes ranging from 25 to 200µL. Hence, nasal secretions may alter the pH of the administered dose. This can affect the concentration of unionized drug available for absorption. Therefore, during formulation buffer capacity may be adjusted to maintain the pH⁴².

VISCOSITY:

Higher the viscosity of the formulation greater contact with nasal mucosa thereby increases the time for permeation. At the same time, highly viscous formulations may alter the normal functions like ciliary beating, mucociliary clearance and thus alter the permeability of drugs⁴⁸.

DRUG CONCENTRATION, DOSE AND DOSE VOLUME:

These are three interrelated parameters that affect the performance of the nasal delivery performance. Nasal absorption of L-Tyrosine was shown to increase with drug concentration in nasal perfusion experiments.

6.3 NASAL CAVITY FACTORS:

ENZYMES BARRIER:

Nasal mucosa contain various enzymes such as cytochrome P450- dependent monooxygenase, carboxyl esterase and amino peptidase. These enzymes degrade the drug molecule in nasal cavity and affect the bioavailability. It provides a pseudo-first-pass effect⁴⁹..

MUCOCILIARY CLEARANCE:

The fast clearance of formulation through nasal cavity is due to the mucociliary clearance. Particles entrapped in nasal mucosa get transport & cleared from body. This both combined action at mucous & cilia is called as mucociliary clearance⁵⁰. Mucociliary clearance is directly proportional to residence (contact) time between drug and epithelial cells⁵¹. The clearance may be improved by adding bioadhesive material in formulation in the less ciliary part i.e. anterior part of nose^{52,53}.

PROTECTIVE BARRIERS: the nasal membrane is a physical barrier & the mucociliary clearance is a temporal barrier to drug absorption across nasal epithelium⁵⁴.

Table 1: Absorption enhancers and mechanisms of action⁵⁵⁻⁶³

Classification	Mechanism
Surfactants	Perturbation of intercellular lipids, Protein domain integrity, Disrupts membrane,
Bile salts	Disrupts membrane, Open tight junctions, Mucolytic activity
Cyclodextrins	Inclusion of membrane Compounds, Open Tight junctions
Fatty acids	Increase fluidity of phospholipid domains, Disrupts membrane
Cationic compounds	Ionic interaction with negative charge on the mucosal surface
Chelators	Interfere with CaPolyacrylates
+Ve Charged polymers	Ionic interaction with negative charge on the mucosal surface
Bioadhesive Materials	Reduce nasal clearance, Open tight junctions

VII. Enhancement Of Bioavailability Of Intranasal Formulation

Physicochemical factors, formulation factors, nasal cavity factors are the barriers to good bioavailability. To improve the bioavailability of intranasal formulation researchers have concentrated on novel drug formulation and addition of absorption enhancers in intranasal formulation.

7.1 ABSORPTION ENHANCERS OR MUCOSAL PENETRATION ENHANCERS⁽⁵⁵⁻⁶³⁾

When a drug has large molecular weight, lack of lipophilicity, enzymatic degradation and poor permeability, to improve the bioavailability absorption enhancers are incorporated in intranasal formulation. (table:1)

7.2 NOVEL DRUG FORMULATION NANOPARTICLES

Nanoparticles are drugs are enclosed or incorporated within carriers and particles ranging from 1 to 1000nm in size. It is made by biodegradable and biocompatible polymers. Nanoparticles have several advantages due to their small size. Smallest nanoparticles easily penetrate the mucus membrane by paracellular route⁽⁶⁴⁾ For example Margaret F prepared intranasal nanoemulsion of risperidone. This study demonstrated rapid and larger extent of transport of risperidone to brain by intranasal route⁽⁶⁵⁾.

TABLE 2 : Current strategies of delivery of antiepileptic drugs by intra nasal route

Drug	Formulation	References
Risperidone	Mucoadhesive nanoemulsion	Mukeshkumar et al(65)
Clonazepam	Mucoadhesive microemulsion	Vyas TK et al (66)
Zolmitriptan/sumatriptan	Mucoadhesive microemulsion	Vyas TK et al (67)
Clonazepam	Mucoadhesive microemulsion	Tushar.K et al(68)
Lorazepam	Microemulsion	Hou, L.; Zhou, J. P (69)
Midazolam	Microemulsion	ShafirBotner, Amnon C. (70)
Diazepam	Microemulsion	ShafirBotner, Amnon C. (70)
Mirtazapine	Nanoparticle loaded nasal gel	Rakhi Choudhary et al(71)
Sumatriptan	Mucoadhesive microemulsion	Vyas TK et al (72)

Valporic acid	Nanostructured lipid carrier	Shararehskandarietal (73)
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MICROEMULSION

Intra nasal microemulsion is one of the non invasive drug delivery to systemic circulation .Vyas has formulated and reported that clonazepam microemulsion has faster onset of action and prolonged duration of action in status epileptics. Mucoadhesivemicroemulsion of Zolmitriptan and Sumatriptan studies also reported that rapid and larger extend of drug transport into rat brain⁽⁶⁶⁾. Mucoadhesivemicroemulsion of clonazepam study revealed that clonazepam reached the brain rapidly and effectively⁽⁶⁷⁾.

VIII. Conclusion

Acute isolated seizure, repetitive or recurrent seizures, and status epilepticus are all deemed medical emergencies. Mortality and worse neurologic outcome are directly associated with the duration of seizure activity. To shorten the seizure speed of drug delivery is needed particularly in out side the hospital. Nasal drug delivery is considered as a promising alternative formulation to intravenous for rapid delivery of anti convulsant drugs to brain via the olfactory system . It is simple ,safe ,efficacious and gifted one to status epileptic patients.

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