



A REVIEW ON INTRANASAL TREATMENT FOR EPILEPSY

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Abstract: One of the most prevalent neurological conditions affecting the brain, epilepsy affects around 50 million people globally, with 90% of cases occurring in poorer nations. It is a general condition that impacts people of all ages. Infections in the brain, stroke, tumors, and elevated temperature are among the genetic variables that can be reasons for epilepsy. About 125,000 new instances of epilepsy are reported year; of these, 30% involve people under the age of 18 years old at diagnosis. In India, 3-11/1000 and 0.2-0.6/1000 are the observed prevalence and incidence, respectively. The antiepileptic medications that are currently on the market are usually taken orally, and as a result, they frequently show a high systemic distribution into tissues that are not their intended target, resulting in peripheral effects and restricted brain absorption. To enhance the effectiveness and tolerance of antiepileptic medication therapy, substitute Research has been done on administration tactics. The olfactory epithelium is located on the nasal cavity's roof. It is said to directly transport drugs breathed into the nose to the brain. One antiepileptic medication should typically be used to begin treatment. Typically, first-line medications include valproate, oxcarbazepine, carbamazepine, phenytoin, and phenobarbitone. The epidemiology, aetiology, pathophysiology, epilepsy categorization, symptoms, and epilepsy diagnosis and treatment.

Keywords: Epilepsy, Seizures , Intranasal route ,antiepileptic drug.

Introduction

Epilepsy is a disorder of the central nervous system and is characterized by periodic loss consciousness with or without convulsions related to and with abnormal electrical activity in brain[1,2]. Epilepsy is considered clinical manifestation of the abnormal and excessive discharging a set of neurons in the brain. A seizure is the result of a sudden excess of nerve cells discharges in the brain leading to abnormal body functions, often causing loss consciousness, excessive muscle activity or an abnormal sensation[3,4].

Chronic epilepsy is a neurological condition marked by repeated seizures, periods of aberrant behavior, and even unconsciousness. Despite being the most convenient method of administration for treating epilepsy, oral medication has little effect in treating acute epileptic attacks because of delayed absorption. Furthermore, because parenteral administration necessitates medical attention, it cannot be performed in an emergency.

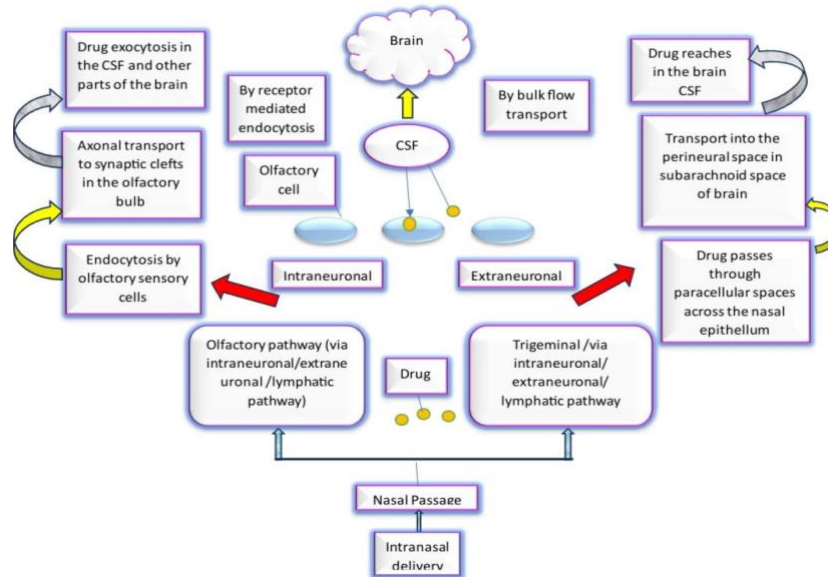


Fig 1. Intranasal administration to the brain.

3. Etiology

While some causes of seizures can affect children of any age, others have a predilection for certain age groups. For example, in newborns it is mostly about symptoms identifiable etiology such as neonatal encephalopathy, metabolic disorder or systemic infections of the central nervous system. In older infants and young children, febrile convulsions are the most common age-related cause. Structural etiology is determined when an abnormality is seen on neuroimaging and when symptoms are a seizure symptoms combined with electroencephalogram (EEG) data suggest this the abnormality is the likely cause of the seizures.

Epidemiology

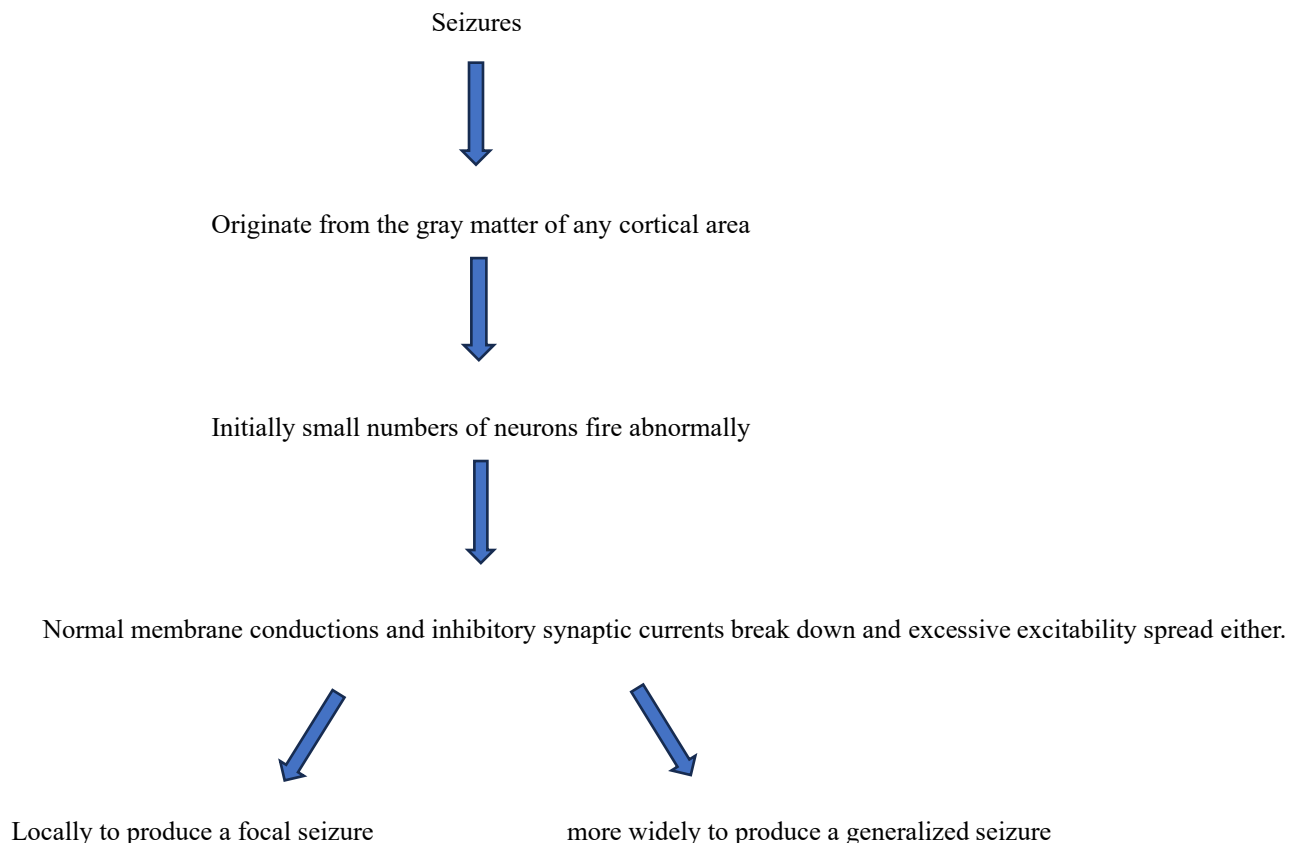
Epidemiology in the world:

One of the most prevalent neurological conditions is epilepsy. The annual incidence of newly diagnosed seizures in the United States is 120 per 100,000 individuals. At least 8% of the general population experiences at least one seizure. Within a 5-year period, recurrence rates of the initial unprovoked seizure might range from 23 percent to 80 percent. Every year, over 125,000 new cases of epilepsy are identified; thirty percent of those cases involve people under the age of eighteen [15]. In the US, neurological illnesses cost the economy over 800 billion dollars a year. In the US, epilepsy alone generates over 37 billion dollars in revenue yearly[5].

Epidemiology in India:

It is estimated that India will account for over 12 million cases of epilepsy worldwide, or nearly one-sixth of the total cases. India has a prevalence of 3-11/1000 and an incidence of 0.2-0.6/1000, according to data from recent studies. Epilepsy was more common in developing countries' rural areas than in their cities[6]

Pathophysiology of epilepsy [7]



Classification of epilepsy

Based on whether motor function is involved and if consciousness is maintained or diminished, seizures are categorized. "Simple partial" seizures are defined as focal seizures with intact awareness, whereas "complex partial" seizures are defined as focal seizures with impaired awareness. Tonic-clonic seizures are defined as having a stiffening (tonic) phase and a muscular jerking (clonic) phase that results in bilateral motor involvement [8].

Treatment

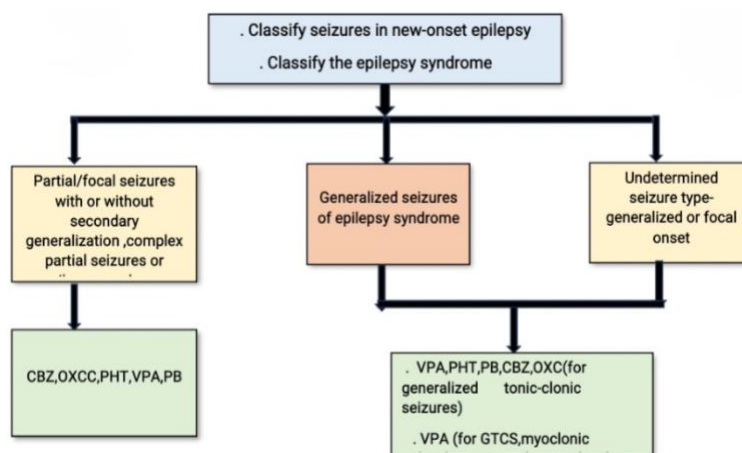


Fig 2.Treatment of seizure

Treatment should be started with a single conventional Anti-Epileptic Drug (AED). The dose should be gradually increased until seizure control is achieved. If the initial treatment is ineffective then second AED can be tried. The dose of the second drug is increased slowly until maximum tolerated dose is achieved. The first drug is then gradually tapered of If the treatment is ineffective, then combination therapy can be considered. Phenytoin, phenobarbitone, carbamazepine, oxcarbazepine and valproate are usually called “conventional” or “first-line drugs”. The other AEDs such as vigabatrin, topiramate, zonisamide, are called “new” or “second-line drugs”. It is preferable to use a conventional AED as the initial drug as they are less expensive and with lesser side effects. Newer AEDs can also be used when there are contraindications to the first line drugs Often referred to as "conventional" or "first-line drugs,". phenytoin, phenobarbitone, carbamazepine, oxcarbazepine, and valproate are among them .The other AEDs, like topiramate, vigabatrin, Zonisamide is referred to as "new" or "second-line" drugs. It is better to utilize a traditional AED. as the original medication because they cost less and with fewer adverse effects. More recent AEDs may also utilized when first-line medications aren't appropriate [9].

Methods of Diagnosis

Children with epilepsy continue to receive inadequate diagnosis, which leads to poor qua of life, mental impairment, and school dropout. The traditional EEG recording is primarily used in the current diagnostic pattern. Only around 60% of epileptic patients have acceptable control from antiepileptic medications; the remainder patients remain refractory. Surgery to remove the lesions is still a potential treatment for effective seizure control in these refractory epileptic cases.

Epilepsy diagnosis:-

1.Electroencephalogram (EEG) The dynamics of the brainwaves or anomalies in the electrical activity of the brain are measured by EEG. The frontal, temporal, parietal, and occipital lobes are found in each of the two hemispheres that make up the cerebral cortex of the human brain. Nineteen electrodes (plus system reference and ground) are typically utilized in clinical EEG applications to identify and capture electrical discharge activity in the brain. Surface electrodes and deep electrodes are the two varieties[10]

Advantages:

Because the aberrant paroxysmal discharges associated with epilepsy are clearly visible with a high temporal resolution, this is a very accurate, relatively inexpensive, and non-invasive means of diagnosing epilepsy (in the case of scalp EEG). This approach can be used to analyze a wide range of neurological conditions, making it possible to determine the kind of epilepsy, the seizure circuitry, and the best course of treatment.

Disadvantage :

As previously noted, there are a number of indicators, however an epilepsy diagnosis based solely on the EEG reading may not be possible. But when the discharge pattern is poorly understood, misdiagnosis can happen.

2. CT Scan, or computed tomography

One kind of radiological imaging method that creates a detailed two-dimensional image is a CT scan. Tomography, which means sectional radiology, comes from the Greek term "tomo," which means segment. A unique kind of radiological imaging method known as computer tomography involves mathematically reconstructing a tomographic plane or slice using a computer. Another name for it is CT (computerized axial tomography) [11]

Advantages: Accurate, painless, and non-invasive technique. 15–20 minutes of study time and a good visual quality. It is possible to see blood vessels, soft tissues, and bones all at once.

Disadvantages: Radiation exposure is a risk and may have deleterious effects on the developing fetus. In certain people, contrast materials might result in allergic responses and renal impairment. Moreover, MRI is necessary for a thorough examination although CT scanning is the best option for a prompt diagnosis.

3. Imaging with Magnetic Resonance (MRI)

A neuroimaging technique called MRI is utilized in radiology to show the intricate structure of various body parts. It creates high-resolution images by utilizing radio waves, magnetic field gradients, and powerful magnetic fields. CT and PET scans, two types of X-rays, are not used in this procedure. In order to create a three-dimensional image during the test, the patient is placed within an MRI scanner with a huge magnet and radio waves applied from all directions[12,13,14,15]

Advantages: This approach is precise and cutting edge. Because of the extremely high quality of the images acquired, the cause of epilepsy can be correctly identified and diagnosed. Along with determining the distribution of white and gray matter in the brain, MRI also aids in determining blood flow rate. In cases of refractory or drug-resistant epilepsy, it facilitates decision-making on the surgical excision of the afflicted part of the cortex while posing no risk of radiation exposure.

Disadvantage: It is a costly treatment that calls for highly advanced equipment and a skilled operator. It is not an intrusive or painful process, but it might be uncomfortable for the patients to have to stay motionless in a small area. MRI is not always able to differentiate between benign and malignant tumors. Patients who have pacemakers or who are carrying a metallic object inside of them are not eligible to use it.

4. PET, or Positron Emission Tomography

An imaging method called position emission tomography (PET) scans can help to show how tissues and organs operate. It works well for analyzing the chemical activity of the brain. A radioactive tracer element, which manifests as a bright spot reflecting chemical activity, is used in PET scans. The tracer element can be ingested, injected, or inhaled, and radiological imaging can then be used to map its internal anatomy[17].

Advantages: This extremely accurate technique has a wide range of applications in the fields of receptor pharmacology, gene expression, gene mapping, and receptor interaction. It can detect pico- and femtomolar concentrations of ligands and provide detailed images of the function of various brain regions in a very quick and dynamic manner.

Disadvantage: The use of radiolabeled probes to identify brain activities carries a risk of radiation exposure. Following metabolism, some probes become stuck inside the cell. Integration of MRI is necessary since PET pictures frequently capture inadequate analytical details. Due to the wide range of individual variances, it may result in erroneous diagnoses in cases of metabolic diseases and dubious outcomes.

5.Single Photon Emission Tomography (SPECT) (SPECT) is a unique kind of PET examination in which blood flow and metabolic uptake in a particular region of the brain are tracked. SPECT is a well-established technique that measures regional cerebral blood flow to assess neural activity in epilepsy. When structural neuroimaging studies do not reveal neurological symptoms, the SPECT is employed to assess the pathology [18].

Advantages: This is an extremely accurate and advanced procedure. It offers finely detailed, sharp pictures. It is feasible to make a decision.

disadvantage :The treatment is highly costly, there is a chance of radiation exposure, and maintaining a healthy diet is necessary to get good quality pictures.

Diagnosis of epilepsy

Electroencephalograph (EEG), Complete blood count (CBC), Blood Glucose, Kidney function testing, Liver Function tests, testing for infectious disorders.

Management of Epilepsy

The phrases “anticonvulsant” and “antiepileptic” are interchangeable. A drug known as an anticonvulsant keeps lab animals from having seizures brought on by research and Medicinal usage of an antiepileptic drug is intended to control the Convulsions[19].

Principles of management

1. Treatment is required for any circumstances that contribute to epilepsy, such as cerebral tumors.
2. Patients ought to be informed about the nature of the illness, how long it therapy and the requirement for adherence.
3. Avoiding precipitating variables including alcohol and sleep deprivation, emotional stress.
4. One should expect natural variance; for example, fits may happen. mainly or exclusively around periods in women.
5. Antiepileptic medication should only be administered in cases when the type and frequency calls for it, i.e., several fittings every six to twelve months[20].

Introduction to Nasal Delivery [21,22,23].

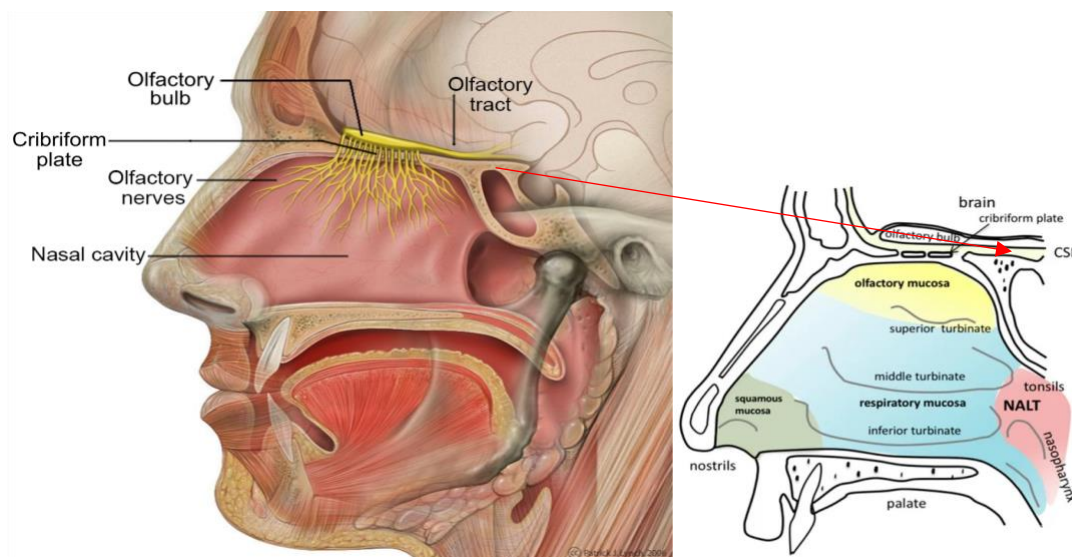


Fig 4. Representation of Olfactory Bulb

The nasal cavity is easily accessible, rich in blood vessels at the same time allows locally administered drugs to rapidly achieve effective blood levels while avoiding intravenous catheters and avoids immense pain. The human nasal cavity has a total volume of about 16 to 19 ml and a total surface of about 180 cm² and is divided by a septum into two nasal cavities. The volume of each cavity is approximately 7.5 ml, with a area approx. 75 cm². Nasal secretions mostly come from the submucosal environment glands, but goblet cells also contribute to them and transudate from plasma. Mucus is composed of water (95% glycoproteins (2%), albumin, immunoglobulins, lysozyme, lactoferrin and other proteins (1%), inorganic salts (1%) and lipids (<1%) Post drug administration into the nasal cavity, a solute can be deposited at one or more of anatomically distinct regions, the vestibular, respiratory and olfactory regions showing in above fig4.

Anatomy and histology of human nasal cavity

The respiratory region

The olfactory region

The vestibular region

Advantages and disadvantages of Nasal dosage form

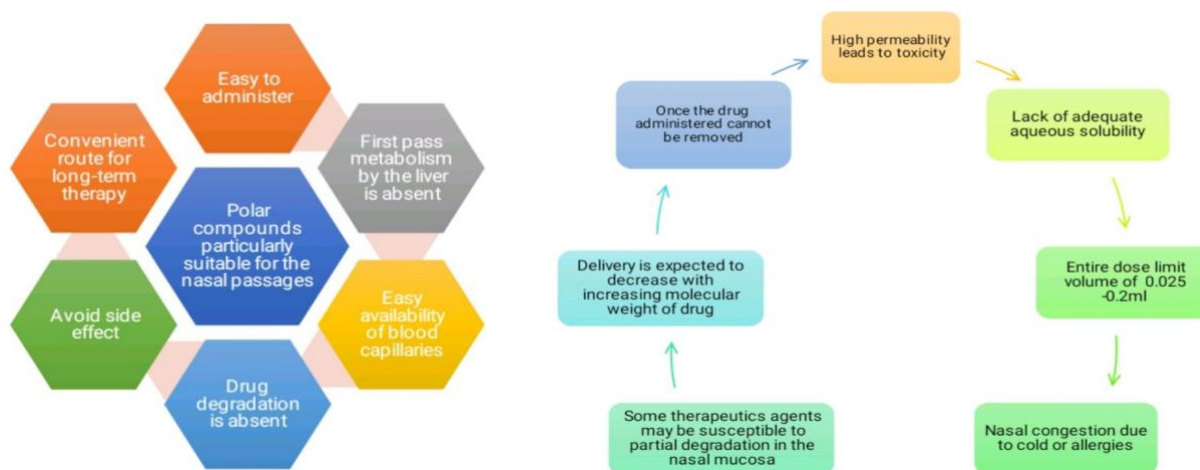


Fig4. Advantages and disadvantages of Nasal dosage form

Physiological factors affecting nasal absorption [24]

- Effect of deposition on absorption Deposition of the formulation in the anterior portion of the nose provides a longer nasal residence time. The anterior portion of the nose is an area of low permeability, while posterior portion of the nose where drug permeability is generally higher, and provides a shorter stay.
- Nasal blood flow Nasal mucosal membrane is very rich in vasculature and plays a vital role in the thermal regulation and humidification of the inhaled air. The blood flow and therefore the drug absorption will depend upon the vasoconstriction and vasodilatation of the blood vessels.
- Effect of enzymatic activity Several enzymes that are present in the nasal mucosa may affect the stability of drugs. For example,
 - proteases and aminopeptidases on the mucosa membrane. The level of aminopeptidase present is much lower than in the gastrointestinal tract. Peptides can also form complexes with immunoglobulin in the nasal cavity leading to an increase in molecular weight and decrease throughput.

Complications

Rarely does epilepsy occur in isolation; almost 50% of those who have it have one or more extra health issues. Mental health ailments (such as anxiety disorders, sadness, Autism spectrum disorder and psychosis) have been linked to epilepsy for a while, but more recent physical ailments (such as type 1 diabetes, digestive tract ulcers, arthritis, and persistent pulmonary illness) have additionally been correlated with epilepsy [25].

Prevention

It is estimated that 25% of occurrences of epilepsy are avoidable. The best defense against post-traumatic epilepsy is preventing head injuries. Sufficient Prenatal care can lower the number of new cases of birth injury-related epilepsy. The Usage of medications and other treatments to bring down a feverish person's body temperature Youngster can lessen the likelihood of having febrile seizures.

The avoidance of epilepsy Lowering of cardiovascular risk factors is the main focus of research linked to stroke. For example, steps to prevent or manage diabetes, high blood pressure, and Obesity, abstaining from smoke and excessive alcohol consumption.

Conclusion

A common neurological condition called epilepsy is characterized by abnormally high synchronous Brain activity related to neurons. It appears alongside or without unconsciousness. Epilepsy is more common in rural areas and is estimated to affect 5-8 people per 1000 people in high-income countries and 10 people per 1000 people in low-income countries. regions. Everyone is affected by epilepsy, which is a common illness. aging and more susceptible to sleep deprivation, infection of the system, possible external sensory triggers. The hallmark of epilepsy is increased excitatory neurotransmitter firing and reduction in the way that inhibitory neurotransmitters operate. Barbiturates, benzodiazepines, and ion channel It is preferred to use modulators to treat epilepsy. If seizures are not managed using polytherapy is advised after monotherapy.

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