



# Drugs Used in Epilepsy-II

# Carbamazepine

- Pharmacokinetics :

- Available as capsules & Syrup only orally
- Well absorbed
- **Strong enzyme inducer including its own metabolism**
- Metabolized by the liver to active & inactive metabolites
- Half life 18-35 hr
- Excreted in urine

# Carbamazepine

## Mechanism of action

- Blockade of Na<sup>+</sup> & Ca<sup>++</sup> influx into neuronal axon
- Inhibit the release of excitatory transmitters
- Potentiate the action of GABA

## Therapeutic uses:

- Drug of choice in partial seizures.
- Tonic-clonic seizures (1ry & 2ry generalized) but **Not** in absence seizures.

## **Other uses:**

- **Bipolar depression.**
- **Trigeminal neuralgia**

# Side effects

- **GIT upset**
- **Hypersensitivity reactions**
- **Drowsiness , ataxia, headache & diplopia**
- **Hyponatremia & water intoxication**
- **Teratogenicity**

# Sodium Valproate

- **Broad spectrum antiepileptic**
- **Pharmacokinetics:**
  - Available as capsules, Syrup , I.V
  - Metabolized by the liver ( inactive )
  - **Enzyme inhibitor**
  - Half life 12-16 hr
  - Excreted in urine

# Sodium valproate

## Mechanism of action

- Blocks activated Na<sup>+</sup> channels.
- **Enhances GABA synthesis & reduces degradation**
- Suppress glutamate action.
- **Blocks T-type Ca<sup>2+</sup> channels**

## **[II] Other uses:**

- **Bipolar disorder and mania**
- **Prophylaxis of migraine**
- **Lennox-Gastaut syndrome**

## Therapeutic Uses

### **[I] Epilepsy:**

**It is effective for all forms of epilepsy**

- Generalized tonic-clonic seizures (1<sup>ry</sup> or 2<sup>ry</sup>).
- Absence seizures
- Complex partial seizures
- Myoclonic
- Atonic
- photosensitive epilepsy

# **Sodium valproate, Side effects:**

- **GI (nausea, vomiting , heart burn)**
- **Weight gain (↑appetite )**
- **Transient hair loss, with re-growth of curly hair**
- **Thrombocytopenia (not used with aspirin or coumadin)**
- **Transient increase in liver enzymes & hepatotoxicity**
- **Teratogenicity (neural tube defect)**

# Ethosuximide

- Pharmacokinetics:

- Absorption is complete
- Syrup & capsule forms
- Not bound to plasma proteins or tissues
- Metabolized in liver
- Half life 52-56 hr
- 10-20% of a dose is excreted unchanged the urine



# Ethosuximide

- Mechanism of action

**Inhibits T- type  $\text{Ca}^{2+}$  channels in thalamo-cortical neurons**

# Ethosuximide

## Therapeutic uses

- **Absence seizures**

## Adverse effects

- **Gastric distress**  
nausea  
vomiting
- **Drowsiness, fatigue ,  
hiccups, headaches**

# Lamotrigine

- Pharmacokinetics

- Available as oral tablets
- Well absorbed from GIT
- Metabolized primarily by glucuronidation
- Does not induce or inhibit C. P-450 isozymes
- Half life approx. 24 hr

# Lamotrigine

<u>Mechanism of action</u>	<u>Therapeutic Use</u>
<ul style="list-style-type: none"><li>● Blockade of Na<sup>+</sup> channels</li><li>● Inhibits excitatory amino acid release ( glutamate &amp; aspartate )</li></ul>	<ul style="list-style-type: none"><li>● As <u>add-on</u> therapy or as <u>monotherapy</u> in partial seizures</li><li>● Lennox-Gastaut syndrome</li></ul>

# Lamotrigine, Side effects:

- Influenza-like symptoms
- Skin rashes (may progress to Steven –Johnson syndrome)
- Somnolence
- Blurred vision
- Diplopia
- Ataxia



# Topiramate

- Pharmacokinetics:

- Well absorbed orally ( 80 % )
- Food has no effect on absorption
- Has no effect on microsomal enzymes
- 9-17 % protein bound ( minimal )
- Mostly excreted unchanged in urine
- Plasma  $t_{1/2}$  18-24 hrs

# Topiramate

- **Mechanism of Action:**
- Blocks sodium channels (membrane stabilization) and also potentiates the inhibitory effect of GABA.
  
- **Clinical Uses:**
- Can be used alone for partial, generalized tonic-clonic, and absence seizures.
- Lennox-Gastaut syndrome ( or lamotrigine, or valproate ).



# Topiramate, Side effects:

- **Psychological or cognitive dysfunction**
- **Weight loss** ( can be desirable side effect)
- Sedation
- Dizziness
- Fatigue
- Urolithiasis
- Paresthesias (abnormal sensation )
- Teratogenecity (in animal but not in human)

# Summary

<b>Type of seizure</b>	<b>Choice among drugs</b>
<b><u>Partial seizures:</u></b> Carbamazepine or phenytoin or valproate or lamotrigine.	
<b><u>Generalized seizures:</u></b>	
<b>Tonic-clonic (grand mal)</b>	<b>Valproate or carbamazepine or phenytoin or Lamotrigine</b>
<b>Myoclonic</b>	<b>Valproate, clonazepam</b>
<b>Absence</b>	<b>Valproate, ethosuximide</b>
<b>Atonic</b>	<b>Valproate</b>

# Drugs used for treatment of Status Epilepticus

- Most seizures last from few seconds to few minutes. When seizures follow one another without recovery of consciousness, it is called “status epilepticus”
- It has a high mortality rate
- Death is from cardiorespiratory failure.

# Antiepileptics used in status epilepticus

## ❖ Intravenous injection of :

- Lorazepam, Diazepam (drugs of choice)
- Phenytoin
- Fosphenytoin
- Phenobarbital
- Valproate

# Vagal nerve stimulation

- It is an alternative for patients who have been refractory to multiple drugs
- Who are sensitive to the many adverse effects of anti epileptic drugs
- It is an expensive procedure

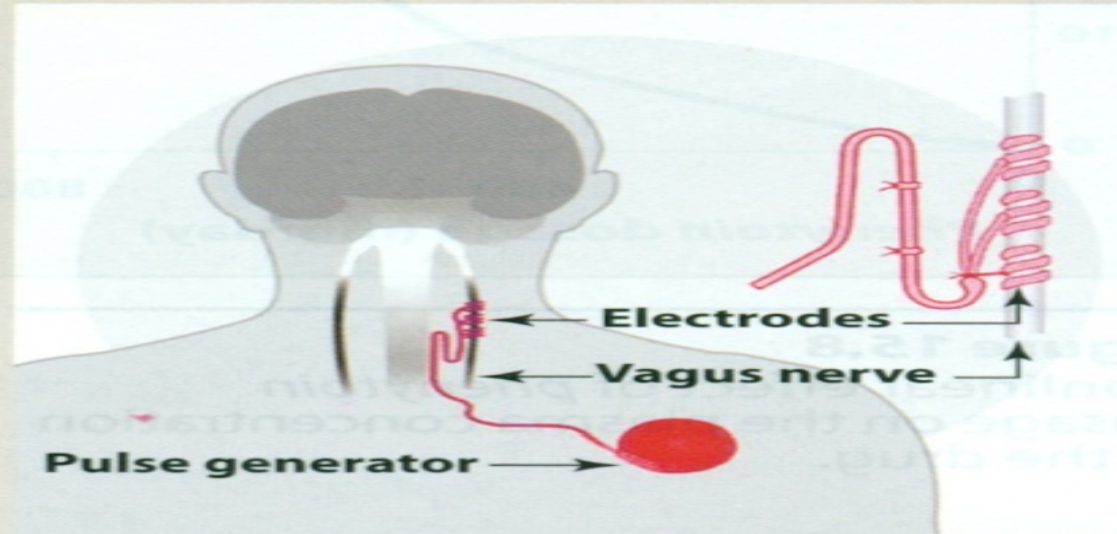
**A**

**1**

An implanted pulse generator connects to electrodes that coil around the vagus nerve.

**2**

The vagal nerve stimulator generates an electrical pulse that stimulates the vagus nerve.



**3**

This electrical stimulation prevents the abnormal electrical activity that can cause a seizure.

**4**

The patient activates the stimulator when they anticipate a seizure.

# Pregnancy & antiepileptics

- Seizure is very harmful for pregnant woman
- NO antiepileptic drug is safe in pregnancy
- Monotherapy usually better than drug combination
- Valproate & phenytoin are contraindicated during pregnancy
- Patient has to continue therapy

# Summary

- Epilepsy is classified into partial or generalized according to the site of lesion
- The exact mechanism of action of antiepileptics is not known
- Phenytoin is mainly used for treatment of generalized tonic-clonic seizures
- Carbamazepine is mainly used for treatment of partial seizures



# Summary

- Sodium valproate is a broad spectrum antiepileptic drug
- Lamotrigine & levetiracetam are used as monotherapy or adjunctive therapy in refractory cases
- Lorazepam , diazepam , phenytoin are used intravenously for treatment of status epilepticus



# Questions ???

10/27/20