

Drugs Used in Epilepsy-II

2nd Lecture

By

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Slides adopted from Dr. Yieldez Bassiouni

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⁺ & Ca⁺⁺ 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⁺ channels.
- **Enhances GABA synthesis & reduces degradation**
- Suppress glutamate action.
- **Blocks T-type Ca²⁺ 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^{ry} or 2^{ry}).
- 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 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">● Blockade of Na⁺ channels● Inhibits excitatory amino acid release (glutamate & aspartate)	<ul style="list-style-type: none">● As <u>add-on</u> therapy or as <u>monotherapy</u> in partial seizures● Lennox-Gastaut syndrome

Lamotrigine, Side effects:

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



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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

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

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**

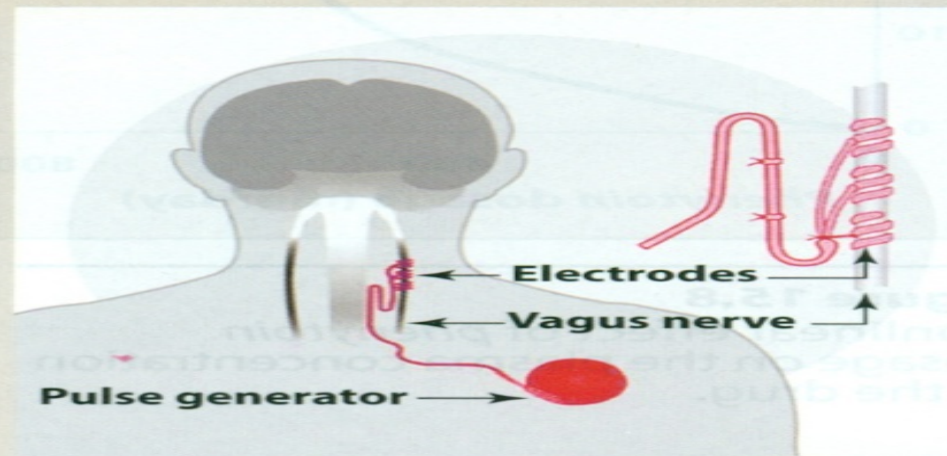
Vagal nerve stimulation

- 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

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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 ???

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