pharmacology
Team 438

MED438

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Neuropsychiatry Block

Pharmacology Team 438

Drugs Used in Epilepsy

Objectives

By the end of the lecture , you should know:

- Describe types of epilepsy
- List the antiepileptic drugs.
- Describe briefly the mechanism of action of antiepileptic drugs.
- Enumerate the clinical uses of each drug.
- Describe the adverse effects of each antiepileptic drug & treatment of status epilepticus.
- Classify antiepileptic drugs according to the type of epilepsy treated and generation introduced
- Expand on pharmacokinetic and dynamic patterns of first and second generation antiepileptic drugs.

Color index:

Black : Main content
Red : Important
Blue: Males' slides only
Pink : Females' slides only
Grey: Extra info or explanation
Green : Dr. notes

Editing File

Epilepsy

Epilepsy is a chronic medical condition characterized by 2 or more unprovoked seizures (within 6-12 months). **It is a syndrome.**

The Difference Between:

1) Epilepsy & Seizures

Epilepsy

A group of related sign and symptoms characterized by a tendency for **recurrent** seizures

Seizures

Brief, sudden, uncontrolled abnormal electrical activity in the brain, are a symptom of epilepsy.

2) Syndrome & Disease

Syndrome

A set of medical signs and symptoms that occur together and suggest the presence of a certain disease (**idiopathic & combination of symptoms**).

Disease

The actual diagnosed impairment of health or a condition of abnormal functioning (**non- idiopathic & it's a combination of symptoms)**

Etiology & Triggers of Epilepsy

Etiology:

- Congenital defects, head injuries, trauma, hypoxia
- A poison, like lead
- Infection (bacteria or virus) e.g. meningitis, brain abscess, viral encephalitis.
- Fever in children (febrile convulsion).
- Concussion, depressed skull, fractures.
- Hypoglycemia
- Brain tumors (including tuberculoma), vascular occlusion, stroke
- PKU = Phenylketonuria
- Drug withdrawal, e.g. CNS depressants, alcohol or drug abuse or drug overdose, e.g. penicillin.
- Photo epilepsy[1]

Triggers:

- Fatigue
- Stress
- Sleep deprivation
- Poor nutrition
- Alcohol

1- epileptic seizures induced by flashes of light.

Classifications of Epilepsy

1 Primary Generalized

Both hemispheres + loss of consciousness.

A) Tonic-clonic: Stiffness followed by violent contractions & relaxation (1-2 minute)

B) Tonic: Muscle stiffness

C) Clonic: Spasms of contraction & relaxation

D) Atonic (loss of tone): Patients legs give under him & drop down

E) Myoclonic: Jerking movement of the body

F) Absence(Petit mal): Brief loss of consciousness with minor muscle twitches. Eye blinking

G) Status epilepticus: Recurring tonic-clonic seizure (30 min or more)

2 Partial (focal)

Arise in one cerebral hemisphere

A) Simple:
consciousness is retained

B) Complex:
Altered consciousness

C) Partial with secondary generalization:

Begins as partial
(simple or complex) and progress into Generalized seizure
(tonic clonic)

General rules for treatment of Epilepsy

- Epilepsy is usually controlled but not cured with medication.
- Up to 80% of patients can expect partial or complete control of seizures with appropriate treatment.
- Antiepileptic drugs are indicated when there is two or more seizures occurred in short interval (6 m -1y)
- An initial therapeutic aim is to use only one drug (monotherapy).
- Drugs are usually administered orally
- Monitoring plasma drug level is useful[1]
- Triggering factors can affect seizure control by drugs.
- Sudden withdrawal of drugs should be avoided.[2]

Withdrawal considered:

Seizure–free period of 2-5 years or longer → Normal IQ → Normal EEG prior to withdrawal → No juvenile myoclonic epilepsy

- Relapse rate when antiepileptics are withdrawn is 20-40%.

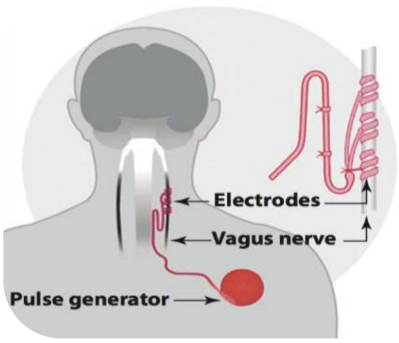
1- to avoid reaching toxic levels.
2- withdrawal of the drugs can only be by a doctor after meeting a certain criteria. Which is described in the following segment.

Treatment of Epilepsy

1. Drugs
2. Vagal Nerve Stimulation
3. Surgery
4. Ketogenic diet[1]

Vagal Nerve Stimulation

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



Anti-epileptic Drugs

1st Generation

- Phenytoin
- Carbamazepine
- Valproate
- Ethosuximide
- Phenobarbital & Primidone[2]
- Benzodiazepines (e.g.Clonazepam, lorazepam and diazepam)

2nd Generation

- Lamotrigine
- Topiramate
- Levetiracetam
- Gabapentin
- Pregabalin
- Felbamate
- Zonisamide

1- ketone bodies increase inhibitory neurotransmitters so balance the effect of glutamate ,and fuel are fuel cells for the brain.
2- they are not an anti epileptic drugs, but they have anti convulsant effect

MOA of Anti-epileptic drugs

They inhibit depolarization of neuron by:

- Inhibition of excitatory NTs **(glutamate)**
- enhancement of inhibitory NTs **(GABA)**
- Blockage of voltage-gated positive current **(Na^+,Ca^{2+})**
- Increase outward positive current **(K^+)**

1st Generation

Drug	Fosphenytoin	Phenytoin
MOA	• Blockade of Na+ & Ca2+ influx into neuronal axon. • Inhibit the release of excitatory transmitters • Potentiate the action of GABA	
P.K	• **Parenteral form of phenytoin** (IV & IM) • A Prodrug • rapidly converted to **phenytoin** in the body. **Advantage over phenytoin:** • Lower local tissue and cardiac toxicity • Less pain and phlebitis at injection site.	• Given **orally**, well absorbed from GIT • Also available I.V and I.M **(fosphenytoin)** • **Enzyme inducer.** • Metabolized by the liver to inactive metabolites • T½ approx. 20 hr. • Excreted in urine.
uses	• **Partial** and **generalized** tonic-clonic seizures • **Not** in absence seizure. • In **status epilepticus**, given IV.	
ADRs	• Nausea or vomiting • headache, vertigo, ataxia, diplopia , nystagmus • Sedation • **Gum(gingival) hyperplasia** →  • Hirsutism • Acne • **Folic acid deficiency (Megaloblastic anemia)**[1] • **Vit D deficiency (Osteomalcia)**[2] • Teratogenic effect (Contraindicated in pregnancy)	

1- Phenytoin blocks the absorption of folate at intestinal mucosa resulting in folic acid deficiency which is important for the process of erythropoiesis. Resulting in megaloblastic anemia.
2- Phenytoin blocks absorption of calcium which results in vitamin d deficiency resulting in osteomalacia.

1st Generation (cont...)

Drug	Carbamazepine
MOA	• Blockade of Na+ & Ca2+ influx into neuronal axon • Inhibit the release of excitatory transmitters • Potentiate the action of GABA
P.K	• Available as capsule & syrup **only orally**[1] • Well absorbed. • T½=18-35 hr • **Strong enzyme inducer including its own metabolism** • Metabolized by the liver to active & inactive metabolites • Excreted in urine
uses	• **Drug of choice in partial seizures** • Tonic-clonic seizures. (1ry & 2ry generalized) • **Not** in absence seizures • **Other uses:** ○ Bipolar depression[2], Trigeminal neuralgia
ADRs	• GIT upset. • Hypersensitivity reactions • Drowsiness , ataxia, headache & diplopia. • **Hyponatremia & Water intoxication**[3] • **Teratogenicity**

Drug	Ethosuximide
MOA	• **Inhibits T-type Ca2+ channels in thalamocortical neurons.**
P.K	• Syrup & capsule forms • Absorption is complete • T½ = 52-56 hr • Not bound to plasma proteins or tissues • Metabolized in liver • 10-20% of a dose is excreted unchanged the urine
uses	• **Drug of choice in absence seizures**
ADRs	• Gastric distress: Nausea & vomiting • **Drowsiness**, fatigue, **hiccups**, headaches.

1- isn't given i.v ⟶ so it's never used in status epilepticus.
2- given as a mood stabilizer in manic episodes.
3- known to potentiate the action of ADH " antidiuretic hormone". Which reduces diuresis, causing water to remain within the blood. Sodium gets reduced(hyponatremia) and water moves into the cells causing (water intoxication).

1st Generation (cont...)

Drug	Sodium Valproate (Broad spectrum antiepileptic)
MOA	• Blocks activated Na+ channels • **Enhances GABA synthesis & reduces degradation** • Suppress glutamate action • **Blocks T-type Ca2+ channels**[1]
P.K	• **Available as capsules, Syrup, I.V** • T½=12-16 hr. • Metabolized by the liver (inactive) • **Enzyme inhibitor** • Excreted in urine

uses	**It is effective for all forms of epilepsy**
	• Generalized tonic-clonic seizures. (1ry & 2ry)
	• **Absence seizures**
	• Complex partial seizures
	• Myoclonic
	• Atonic
	• photosensitive epilepsy
	• **Other uses:**
	  ○ Bipolar disorder and mania
	  ○ Prophylaxis of migraine
	  ○ **Lennox-Gastaut syndrome**[2]

ADRs	• GIT (nausea, vomiting, heart burn) • Weight gain (↑ appetite) • Transient hair loss, with re-growth of curly hair • **Thrombocytopenia** (not used with aspirin or coumadin)[3] • **Hepatotoxicity** & Transient increase in liver enzymes • **Teratogenicity (**neural tube defect**)**

1- channels specific to the etiology of absence seizures, hence its effectiveness in those cases.
2- hereditary syndrome common in children resulting in severe repeated convulsions.
3- concurrent use of valproic acid with these drugs might lead to hemorrhage. Also, coumadin is the trade name of warfarin.

2nd Generation

Drug	Topiramate
MOA	• Blocks **Na+** channels (membrane stabilization) • Potentiates the inhibitory effect of GABA.
P.K	• Well absorbed **orally** (80 %) • Food has no effect on absorption • T½= 18-24 hrs • Has **no effect** on microsomal enzymes • 9-17 % protein bound (minimal) • Mostly excreted unchanged in urine
uses	• Can be used alone for partial,generalized tonic-clonic, and absence seizures[1]. • Lennox- Gastaut syndrome (or **lamotrigine**, or **valproate**)
ADRs	• **Psychological or cognitive dysfunction** • Weight loss (can be a desirable effect) • Sedation, Dizziness, Fatigue • Urolithiasis • Paresthesias (abnormal sensation) • Teratogenicity (in animal but not in human)

Drug	Lamotrigine
MOA	• Blockade of **Na+**channels • Inhibits excitatory amino acid release (glutamate & aspartate)
P.K	• Available as **oral** tablets • Well absorbed from GIT • T½ approx. 24 hr • Metabolized primarily by glucuronidation. • **Does not induce or inhibit C.P-450 isozymes** [2]
uses	• As **add-on** therapy or as **monotherapy** in partial seizures. • **Lennox-Gastaut syndrome**
ADRs	• Influenza-like symptoms • Skin rashes (may progress to **Steven – Johnson Syndrome**[3]) →  • Somnolence • Blurred vision • Diplopia • Ataxia

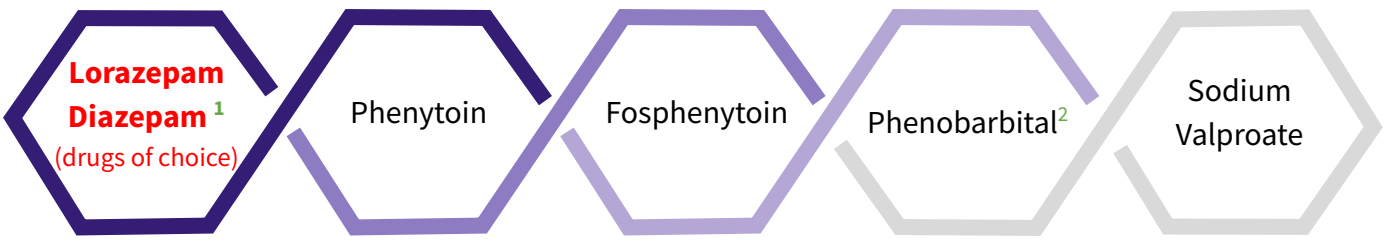
1- First choice of absence seizures 1- Ethosuximide 2- Sodium valproate due to their effect on T-type Ca Channel
2- doesn't affect cytochrome p-450 so less drug-drug interaction
3- it is a life threatening condition, it is a severe form of skin reaction , start as flu like symptoms then will involve skin causing rash and blisters and peel forming raw areas which can cause infection lead to septicemia " very important "

Type of seizure	Choice among drugs
Partial seizures	Carbamazepine \ phenytoin \ valproate \ lamotrigine.
Generalized seizures:	
Tonic-clonic (grand mal)	Valproate \ carbamazepine \ phenytoin \ 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 through IV injection of:



Pregnancy & Anti-epileptic

1. Seizure is very **harmful** for pregnant woman
2. **No** antiepileptic drug is **safe** in pregnancy. **The safest drug is Lamotrigine**
3. Monotherapy usually **better** than drug combination
4. Patient has to **continue** therapy
5. **Valproate** , **phenytoin** & **Carbamazepine** are **contraindicated** during pregnancy. [3]

1- MOA : Potentiate the action of GABA 1- lorazepam specific anticonvulsant. 2- diazepam: long acting benzodiazepine
2- MOA : Potentiate the action of GABA but Lorazepam and Diazepam preferred due to less toxicity because they don't affect cytochrome of the liver
3- What is safe during pregnancy? Lamotrigine and levetiracetam.

Some Questions Were Given By the Doctors

Q1: What 2 drugs don't inhibit or induce enzymes?
A:Topiramate, Lamotrigine

Q2: what drugs induce enzymes ?
A: Carbamazepine , phenytoin

Q3: What drugs inhibit enzymes ?
A: sodium valproate.

Q4: What drugs blocks both Na and glutamate ?
A:Lamotrigine

Q5: What drug is specific for absence seizure? And what's the MOA?
A: Ethosuximide
It inhibits T- type Ca2+ channels in the thalamocortical neurons.

Q6: What drug blocks Na and potentiate GABA?
A: Topiramate

Q7: What are used for Lennox - Gastaut syndrome?
A: Sodium Valproate, Topiramate, Lamotrigine

Q8: Elderly hypertensive patient came in complaining of a convulsions occurring several times throughout last week. He is already on lisinopril and aspirin. What antiepileptic drug would you avoid using with this patient?
A: sodium valproate

Q9: Patient was diagnosed with epilepsy and was given an anti-epileptic drug. After awhile he visited a dentist complaining of swollen gums that bleed on touch and while eating. What's the drug?
A: Phenytoin

Q10: Kid was noticed on him that he blanks out\zones into space for a while multiple times throughout the day. Which anti epileptic drugs would you not prescribe?
A:Carbamazepine , Phenytoin

Quiz

MCQ

1- A child is experiencing absence seizures that interrupt his ability to pay attention during school and activities. Which of the following therapies would be most appropriate for this patient?

A- Ethosuximide B- Carbamazepine C- Diazepam D- Carbamazepine plus primidone

2- A 25-year-old woman with myoclonic seizures is well controlled on valproate. She indicates that she is interested in becoming pregnant in the next year. With respect to her antiepilepsy medication, which of the following should be considered?

A- Leave her on her current therapy B- Consider switching to lamotrigine
Consider adding a second antiepilepsy medication D- Decrease her valproate dose

3- Which of the following drugs may cause psychological effect ?

A- Topiramate B- Sodium Valproate C- Ethosuximide D- Fosphenytoin

4- Which of the following drugs is an enzyme inhibitor?

A- Phenytoin B- Carbamazepine C- Sodium Valproate D- Ethosuximide

SAQ

-A 9 years old boy was playing and suddenly he stopped and started staring and blinking and then he got back to normal.
1-What is the type of seizure that he had?
2-Which drug would be most appropriate for this patient?

-A 32 years old man came to the ER with a flank pain a CT scan done for him and showed presence of a stone in the right kidney, when taking history he mentioned that he takes an entiepileptic drug for a long time.
3-What is the most likely drug that the patient takes?
4-What is the M.O.A of this drug?

-A 55 years old man brought to the ER unconscious by his sons after investigations it turns out that he has status epilepticus episode.
5-What is the drug of choice in this case?and what is the route of the administration of this drug?

Answers:

MCQ

Q1	A
Q2	B
Q3	A
Q4	C

SAQ

Q1	Absence seizure
Q2	Ethosuximide
Q3	Topiramate
Q4	Blocks Na+ channels (membrane stabilization) & Potentiates the inhibitory effect of GABA.
Q5	Lorazepam - intravenously

pharmacology

Team 438

Good Luck , Future Doctors!

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Share with us your ideas !