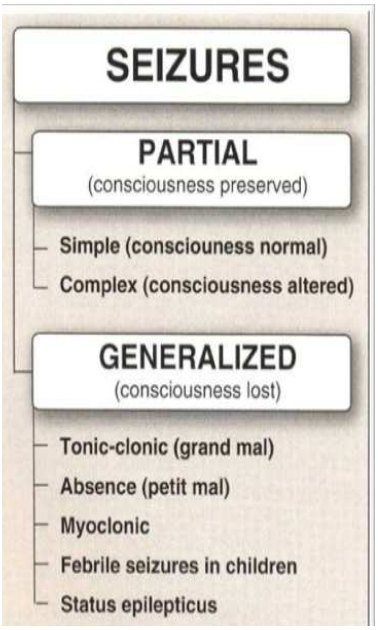
Dr: 3azza
Week :16

Anti-Epileptic

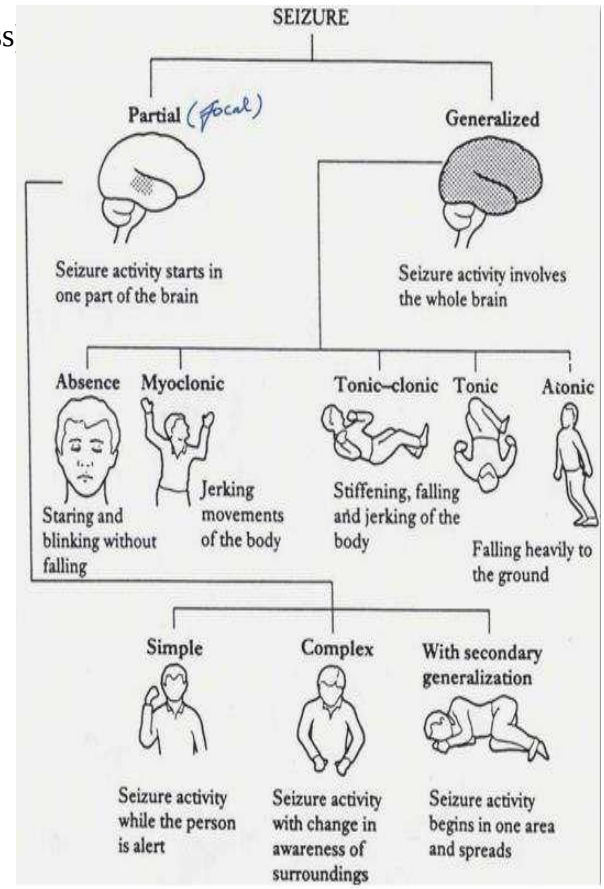
Etiology:

- Congenital defect (familial)
- Head injuries (following car accidents or trauma)
- Trauma
- Hypoxia (mainly in infancy)
- Infection on the brain (either bacterial or viral)
- Brain tumors
- Drug withdrawal
- Fever in children (febrile convulsions at 40 ^{o}C)
- Hypoglycemia



Classification of epileptic seizures:

1. **Partial seizures:**
   Simple (Jacksonian) (no loss of counsiousness)
   Complex(Psychomotor) (with loss of counsiousness
2. **Generalized seizures**:
   - **Tonic-clonic** (Grand mal) (characterized by tonic rigidity of all extremities, followed by clonic jerky movement and urinary incontinence is common.)
   - **Absence** (Petit mal) (occure suddenly, in children, the focus mainly in thalamic neurons which is Ca^{++} dependent → treated by blocking of Ca^{++} channels or by enhancing GABA)
   - Tonic
   - Clonic
   - Atonic (loss of tone →collapse)
   - Myoclonic
   - Status epilepticus (repeated attacks without rest)
     It is an emergency so → I.V or I.M
   - Febrile (in children caused by fever)



! most imp 2types :
1. Tonic-clonic
2. Absence

➲For further reading about epilepsy go to medicine lecture

Phenytoin

✹Enzyme inducer

Pharmacokinetics :

- Well absorbed orally, can be given as I.V or I.M (main route of antiepileptic drugs coz it's a chronic dis. Except in status epilepticus)
- Highly bound to plasma proteins
- Enzyme inducer
- Plasma half-life 20 hr (increases as the dose increased) .
- Metabolized in liver to inactive metabolites
- Excreted mainly in urine as inactive metabolite, (some is excreted unchanged)

Mechanism of action:

1. Block Na+ channels & inhibit the generation of repetitive action potential. (main action of antiepileptic drugs)
2. Potentiate the GABA system & reduce the glutamic system
3. At higher concentration it can block voltage-dependent Ca^{++} channel

➲ (L-type which is found in cardiac & smooth m. that's why it's ineffective for treating absence epilepsy in which the problem in the T-type & the significance of this action is unclear.)

Clinical uses:

- Effective in generalized tonic-clonic (drug of choice) & partial seizures.
- Not effective in absence seizures.
- Used in status epilepticus (fosphenytoin is a solution in which phosphate mixed with phenytoin to make it soluble so that it can be given IV or IM)
- Digitalis induced arrhythmia (anti-arrhythmic)

☒ Drug interaction:

- Drugs that affect phenytoin metabolism
- Increase metabolism of other drugs (inducer) e.g. oral contraceptive causing unplanned pregnancy →give high dose of estrogen to prevent pregnancy or use IUCD (intra-uterine contraceptive device)
- With warfrine causing bleeding

Adverse effects:

➲CNS adverse effects :

(early &dose related):

- Diplopia & ataxia are dose related,
  Nystagmus (CNS side effects, the first side effects to appear)
- Peripheral neuropathy (decrease in deep tendon reflex)
- Sedation with high dose only

➲Others :

- Gingival hyperplasia
- Hirsutism, coarsening of facial features(irreversible, due to hormonal changes).
- Osteomalacia (disturbance in vit.D mainly in females)
- Hypersensitivity reaction
- Lymphadenopathy (confusing with Hodgken's lymphoma)
- Heamatological side effect (rare as agranulocytosis)
- Hepatitis (rare)
- Teratogenic effect (cleft lip, cleft palat) → so # in pregnancy
- Megaloblastic anemia (decrease folate level) → give folic acid

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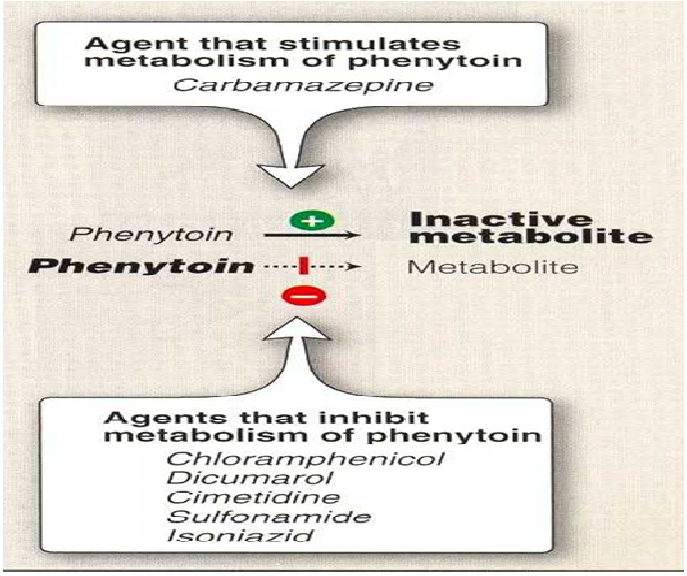
➲Used in :

- Generalized tonic-clonic
- Partial
- Status
- digitalis induced arrhythmia

➲Not used in :

- Absence seizure



Carbamazepine

✹Enzyme inducer

Pharmacokinetics :

- Related to antidepressant drugs (TCA).
- Given only orally. (so → not given in status epilepticus)
- Highly bound to plasma proteins.
- Potent enzyme inducer,(including its own metabolism - علي وعلى اعدائي-)
  (it's plasma Half-life decreases with chronic use).

- Completely metabolized, one of metabolities has anticonvulsant activity.
- Slow release preparations can be used. (commonly used)
- Excreted in urine.

Mechanism of action:

1) Blocks sodium channels.(main action)
2) Inhibits uptake & release of norepinephrine from brain synapse.
3) Potentiates the action of GABA.

Clinical uses:

- Drug of choice in partial seizures (either simple or complex) mainly complex type.
- Not used in absence seizures,febrile,status epilepticus.
- In trigeminal neuralgia.
- bipolar disorders. (in depressant phase)
- mood stabilizer.

➲Used in :	➲Not used in :
- Partial (simple & complex) - Trigeminal neuralgia - Bipolar disorder. - Mood stabilizing	- Absence - Febrile - Status

Adverse effects:

1st : CNS adverse effects :

- Drowsiness,
- dizziness,
- ataxia,
- mental confusion,
- blurred vision,
- dry mouth (of central origin).

2nd :

- Hepatotoxicity (commone)
- Blood dyscrasis (leucopenia , aplastic anemia) (commone)
- Hyponatremia
- water intoxication.
- GIT upset (nausea,heart burn).

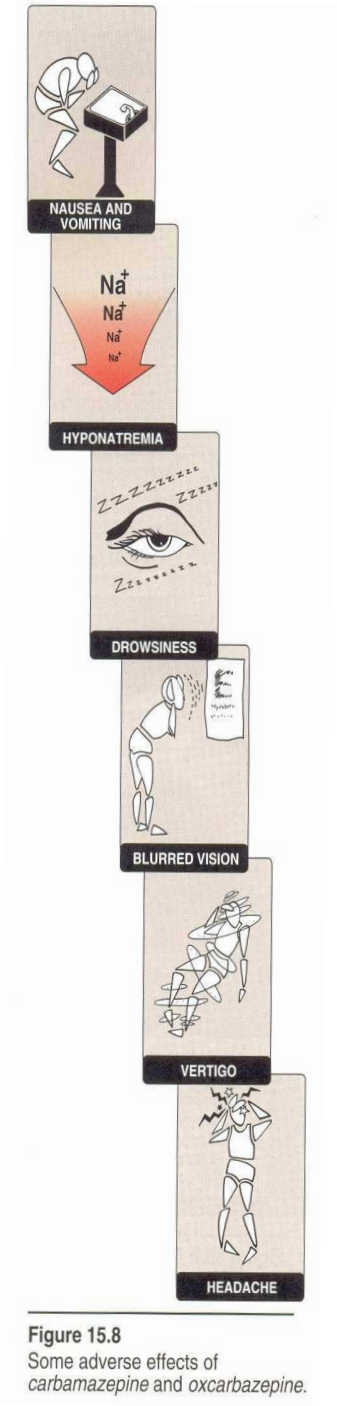


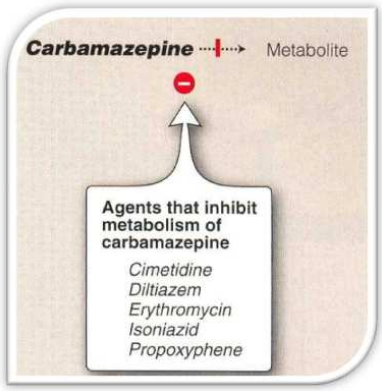
Figure 15.8
Some adverse effects of *carbamazepine* and *oxcarbazepine*.

Adverse effects & precautions:

- Frequent blood & liver function tests are recommended.
- Teratogenic effects (less than other antiepileptic drugs).
- Avoid drinking grape fruit juice (enz. Inhibitor) while on carbamazepine as it can affect the level of the drug.
- Avoid mix the drug with other medications. (drug drug interaction)
- Avoid driving a car or operating machinery. (one of the AE of anti-depressants are sedation)

☒Drug interaction:

- Enzyme inducer.



Sodium Valproate

✹Enzyme inhibitor

- It is the sodium salt of valproic acid
- Broad spectrum anti epileptic drug

Pharmacokinetics :

- Well absorbed orally.
- Highly bound to plasma proteins.
- Metabolized in liver to inactive metabolites.
- Plasma Half-life (15-hrs).
- Excreted in urine.
- Enzyme inhibitor.

Mechanism of action: (has multi mechanisms → so broad spectrum)

1. Blocking sodium channels.
2. Increase GABA content of the brain(**mainly).**

(differ than potentiates the action):

- As it facilitate(stimulates)(GAD)-glutamic acid decarboxylase- enzyme responsible for GABA synthesis.
- Also has inhibitory effect on GABA-T(transferase)(degradation of GABA).

Clinical uses:

- Effective in all types of epilepsy.
- It's preferred if the patient has concomitant generalized tonic-clonic & absence seizures.
- Bipolar disorders.
- Mood stabilizer.
- Migraine prophylaxis.

- **Better in** : absence , generalized tonic-clonic &mycolic
- **Less effective in** :partial &atonic

Adverse effects:

1st :

GIT upset as :

- Heartburn
- Nausea
- Vomiting
- Abdominal pain

➲(drug should be started graduall). (common complaints)

2nd :

Sedation&Fine tremor

➲More than other antiepileptic drugs

3rd :

Weight gain (increase appetite). (as AE of anti-depressant).

4th :

Hair-loss.(common in children)

5th :

Hepatotoxicity (idiosyncratic toxicity). (we should perform LFT)

6th :

Congenital malformation (spina pifida) when taken by pregnant women .

7th :

- Enzyme inhibitor
- Thrombocytopenia.

Adverse effects & Drug interactions:

- Teratogenic (spina bifida).
- Enzyme inhbitor.

➲Used in :

- All types of epilepsy
- concomitant generalized tonic-clonic & absence seizures.

Ethosuximide:

✹no effect on liver enzyme

Pharmacokinetics:

- Completely absorbed orally
- Not bound to plasma protein
- Completely metabolized
- Has v low total body clearance
- T1/2= 40 hours

Mechanism of action:

1. block Ca channel (T-Type) mainly thalamic neurons which provide a pacemaker that generate the rhythmic cortical discharge of an absence attack. (main action) (it competes with valproic a. in Rx. Of absence seizure & the latter preferred in combination type.)
2. Na /K ATPase (depress the cerebral metabolic rate).
3. inhibits GABA aminotransferase.

Clinical uses:

- Absence seizure is the only clinical use (D.O.C)

👽Adverse effects:

1st:

Gastric Upset (nausea ,ANOREXIA so→ weight loss), must be taken after meal

2nd :

Skin rashes (stevens jhonson syndrome) not commonly 1-2%

3rd :

- Fatigue
- Dizziness
- Euphoria
- Headache
- Eosinophilia
- Thrombocytopenia
- leukopenia

☒Drug interaction :

It interacts with valproic acid → decrease ! level of ethosuximide clearance

♠Not Enzyme inhibitor or inducer

➲Used in :

Absence

Lamotrigine

✹No effect on liver enzyme

Pharmacokinetics :

- Well absorbed orally.
- Metabolized in the liver.
- Protein binding (55%) –moderate-
- Excreted in urine.
- No effect on hepatic enzymes.
- Half life is 24 hours.

Mechanism of Action:

1. As phenytoin & carbamizipine (blocks Na- channels). -Mainly -
2. Inhibits release of excitatory neurotransmitters –glutamate-
3. Inhibitory action on voltage-activated calcium channels. (it explains its work in absence seizures).

Clinical Uses:

- As an add-on(adjunctive) therapy in generalized tonic-clonic seizures & in patients with resistant partial seizures .
- Monotherapy for partial seizures -2nd line-
- Effective in absence seizures & myoclonic seizures in children.

Adverse Effects:

1st:

- Life threatening dermatitis in 5% of the patients (stevens-johnsons syndrome).

2nd: Nausea & vomiting

3rd : Influenza-like syndrome.

4th :

- Dizziness & ataxia.
- Somnolence.
- Aggressive behavior

➲Used in :

Add-on therapy in :-

- Generalized tonic-clonic
- Resistant partial

Monotherapy in:

- Partial
- Absence
- Myclonic

Topiramate

✹No effect on liver enzyme

Pharmacokinetics :

- Rapidly absorbed orally .
- No food effect.
- Plasma protein binding is 15%.
- Metabolized (20-50%).
- Excreted mainly unchanged in urine .
- No effect on hepatic enzymes.
- Half life is 20-30 hours.

Mechanism of Action:

1. Blocks Na-channels .
2. Potentiates the inhibitory effects of GAD.
3. Depresses the excitatory amino acids.

Clinical Uses:

- Effective against partial & generalized tonic-clonic seizures .
- Absence seizures
- Myoclonic seizures.
- Refractory seizures.

Adverse Effects:

- ♣ Somnolence , fatigue, dizziness , parasthesias , confusion.
- ♣ Glaucoma (you must stop the drug if it develops in the patient)
- ♣ Renal stones (weak carbonic anhydrase inhibitor)
- ♣ Weight loss. (loss of H_2O)
- ♣ Cognitive impairment.
- ♣ Teratogenic in animals but not proved until now in humans .

◎(that does not mean that it is totally safe to be used)

❖ Oral contraceptive pills are less effective with topiramate & higher estrogen doses may be required. (of unknown cause!)

➲Used in :

- Partial
- Generalized tonic–clonic
- Absence
- Refractory

Vigabatrine

✹No effect on liver enzyme

Pharmacokinetics:

- Rapidally absorbed orally
- Minimally bind to plasma protein MCQ
- Plasma half life is short 6-8hrs
- Produces a long lasting effect
- Can be given by mouth once daily
- Excreted in the urine

- Has Slow clearance from ! body

Mechanism of action:

1- Increase GABA contents in the brain

✷ by irreversible inhibition of GABA metabolizing enzyme GABA – Aminotransferase (GABA T) (MCQ)

Clinical uses:

- Partial seizures (adjunctive therapy)
- Drug of choice in infantile spasm (west syndrome) mainly used in refractory cases

(Infantile spasm is congenital disorder characterized by epileptic attack associated with mental retardation, the drug improve epileptic attacks with no evidence that mental retardation is alleviated by therapy).

👽Adverse effects:

1st : Agatation , Confusion , psychosis (aggressive behavior)

2nd : Drowsiness , Dizziness

3rd: Visual field defects in one third of patients(long term therapy) (irreversible – not diplopia). MCQ

- Weight gain→↑ appetite
- It is contraindicated in Mental illness

➲Used in :

- Partial
- Infantile

Gabapentine

✹No effect on liver enzyme

Pharmacokinetics:

- Given orally
- Not metabolized
- No effect on hepatic enzymes
- Not bound to plasma protein
- Short T1/2 = 5-8 hrs
- Taken twice or three times daily
- Excreted via kidney

Mechanism of action:

1- Structurally related to GABA

2- but not add on GABA receptors

3- May affect GABA metabolism or release or uptake causing increase of GABA content of the brain.

Clinical uses:

- As adjuvant in partial or generalized tonic clonic seizures
- Neuropathic pain MCQ(nerve injury ,neuro injery ..etc).

Adverse effects: (mainly CNS)

- ♣ Somnolence
- ♣ Dizziness
- ♣ Ataxia
- ♣ Nystagmus
- ♣ Headache
- ♣ Tremors

➲Used in :

Partial .

Generalized tonic-clonic .

Neuropathic pain .

Phenobarbitol

✹Enzyme inducer

They are considered as ! drug of choice for seizures only in children .

Mechanism of action:

1- Block activated Na- channels.
2- Potentiate the action of GABA.
3- ↓the action of excitatory transmitters as glutamate.

Clinical uses:

- Effective in partial, generalized tonic-clonic seizures, status epileptics, but not effective in absence seizures or infantile spasm or atonic attacks
- Because of paradoxical hyperactivity in children it is not used in fibrile attack but effective (ya3ni effective in fibrile but not used .)
- Not effective in absence , infatile & atonic .(التكرار يعلم الشطار ض3)

Adverse effects:

- Main side effect is sedation (imp) coz it's one of the sedative& hypnotic drugs.
- Megaloblastic anemia.
- Osteomalacia.
- Hypersensitivity reactions.
- Respiratory & circulatory failure.
- Enzyme inducer (potent). (imp)

➲Used in :

- Partial .
- Generalized tonic-clonic
- Status

➲Effective in but not used :

- Fibrile attacks

➲Not Used in :

- Absence
- Infatile
- Atonic

Benzodiazepines:

✹No effect on liver enzyme

Clinical uses:

Diazepam is :

- effective in status epileptics & generalized seizures.
- Drug of choice in febrile seizure, given rectally. (MCQ)

Clonazepam is :

effective in status epileptics , absence seizures, myoclonic seizure& infentile spasm.

Adverse effects:

Main side effect of this group is sedation & tolerance.

➲Used in : **Clonazepam**
Status
Absence
Myclonic
Infentile

➲Used in : **Diazepam**
Status
Generalized
Febrile (D.O.C)

Zonisamide:

✹No effect on liver enzyme

♠Sulfonamide derivative.

Pharmacokinetics:

- Has good oral bioavailability ,
- low protein binding
- long T½ = 1-3 days.

Mechanism of action:

1- Block mainly Na+ channels &
2- may act also on Ca++ channels
3- as well as enhancement GABA action.

Clinical uses:

- Partial seizures.
- Generalized tonic- clonic.
- Infantile spasm.
- Myoclonic.

👽Adverse effects:

- ♣ Drowsiness.
- ♣ Cognitive impairment.
- ♣ Serious skin rash.
- ♣ No interaction with other anti seizures.
- ♣ Does not effect the drugs .

➲Used in :

Partial

Generalized tonic-clonic

infantile

myoclonic

Generral Rules for Treatment of Epilepsy:

- Accurate diagnosis.
- Antiepileptic drugs are given when 2 or more attacks in short time(6month).
- Antiepileptic drugs are given to suppress & reduce frequency of attack.(not radical cure , about 75% curable)
- Monotherapy is preferred.
- Drugs are usually given orally.
- Monitoring plasma level of drug is useful, but not a routine.
- Avoid sudden withdrawal (causing status epilepticus).
- Treatment must not be for life, most patients can be relieved within few years.
- Treatment must be continue for 1-2years at least after the last fit.

Epilepsy & Pregnancy:

- Physiological changes of pregnancy affect the pharmacokinetics of the drug.
- Monitor drug level is very useful.
- We can not stop drug therapy during pregnancy but:
  - Use the drug at their lower therapeutic doses.
  - Use drug with low incidence of teratogenicity (with gradual withdrawal to the previous teratogenic drug before pregnancy or in unplanned pregnancy& give the leaset teratogenic gradually at same time).

Status Epilepticus:

- Frequent attacks of severe forms of seizures.

Drugs:

1. Diazepam(I.V)
2. Clonazepam(I.V)
3. Phynytoin(I.V)
4. Phenobarbital(I.V)

Fibrile Seizures:

Drugs

1. Diazepam 1st(rectally, I.V)
2. Sodium valproate (I.V)
3. Phenobarbital(not commonly used now)

Infantile spasm:

- Used to control the seizures not other features as retardation.

Drugs:

1. Clonazepam
2. Nitrazepam
3. Vigabatrin
4. Zonisamide

❖تجميعات :

Block Ca^{++} channels

1. ethosuxamide
2. lamotrigine
3. zonisamide

treat absence

1. Ethosuxamide→DOC
2. lamotrigine
3. valproate
4. topiramate
5. BDZs :: clonazepam , chlorazepat

all cause sedation except

1. ethosuxamide
2. zinosamide

on hair

loss→ valproate
hairsutism → phenytoin

treat myoclonic

1- Valproate → DOC.
2- Lamotrigine
3- topiramate
4- zonisamide
5- BDZs :: clonazepam , chlorazepate

broad spectru

1. valproate
2. topiramate

D.O.C

1. partial (esp. complex)l
carbamazepin
2.generalized tonic-colonic
phenytoin
3. myoclonic
valproate
4. absence
ethosuxamide
valproate (2nd DOC)l
5. febrile
diazepam
6. all other types in children→
phenobarbitone
7. in pregnancy→topiramate
carbamazepin (less)l

Collected by : 424

Enzyme inducers :

- Phenytoin.
- Caramazepin
- Phenobarbitol

enzyme inhibitors :

- Sodium valproate

No effect on liver enzymes :

- Lamortrigine
- Topiramate
- Vigabatrine
- Gabapentine
- Benzodiazepines
- Zonisamide
- Ethosuxamide

حاولت أسهل المحاضرة قد ما أقدر :/ ...

دعواتي ، ولاتنسونا من دعوتاكم =)

Done by :

- نرمين العثيمين ،أشجان الحجي
- دانة العيسى ، بسمة الحسن
- حنان الشنقيطي،بدور الشلوي
- الدانة آل سعد

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