Anticonvulsants

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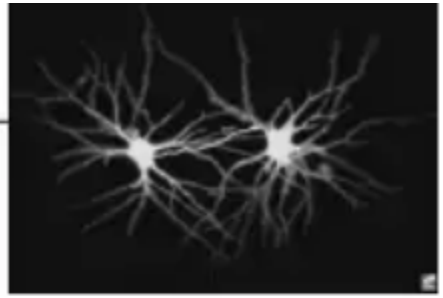
Anteplieptic drugs (AEDs)

- Definitions and Terminology
- Etiologies and risk factors
- Classifications of seizures
- Management of epilepsy
- Principles of treatment
- Classification of Antiepileptic
- Mechanism of Antiepileptic drug
- Special cases: pregnancy
- Comparison between new and traditional Antiepileptic drugs

Epilepsy:

- is a disorder of cerebral cortex
- characterized by recurrent (periodic and unpredictable) **seizures.**
- often accompanied by:
  - episodes of unconsciousness
  - and/or amnesia

Seizures



Seizures are

- sudden, transitory, and uncontrolled episodes of brain dysfunction
- resulting from abnormal electrical discharge in cerebral neuronal cells
- associated with prolonged depolarisation of cerebral neurons
- result in motor, sensory or behavioral changes.

Anti-epileptic drugs (AEDs)

AEDS act by:

- I. Block the initiation of the electrical discharge from the focal area
- II. Prevent the spread of abnormal electrical discharge to adjacent brain area

AEDs prevent depolarisation of neurones by:

- inhibition of excitatory neurotransmitters,
- direct membrane stabilisation
- stimulation of inhibitory.

Causes for Acute Seizures

- Idiopathic
- Trauma
- Encephalitis
- Drugs
- Withdrawal from depressants
- Tumor
- High fever
- Hypoglycemia
- Extreme acidosis
- Extreme alkalosis
- Hyponatremia
- Hypocalcemia

TRIGGERS:

Fatigue, stress, poor nutrition, alcohol and sleep deprivation.

I. Partial (Focal) Seizures

1. **Partial (focal) seizures (60%):** they start locally in a certain site, its divided into:

A. Simple partial:

- may occur at any age,
- without loss of consciousness,

1. Jacksonian motor epilepsy: convulsion in single group of muscles or limb.
2. Jacksonian sensory epilepsy or paresthesia in some localized region.

I. Partial (Focal) Seizures

B. Complex partial (psychomotor or temporal lobe): it is associated with

- loss of consciousness for about 30 seconds to 2 minutes.
- Disturbances of cognitive, affective, and psychomotor (chewing movement, diarrhoea, urination) or sensory hallucinations (smell or taste).

Generalized Seizures

- begin locally,
- rapidly spread,
- affect the whole brain,
- may be convulsive or non convulsive,
- immediate loss of consciousness.

Generalized Seizures

- 1) Tonic-clonic. Patient fall in convulsion & may bite his tongue & may lose control of his bladder or bowel.
- 2) Tonic. Some patients, after dropping unconscious experience only the tonic or clonic phase of seizure.
- 3) Atonic (akinetic). Starts between the ages 2-5 yrs. The pt's legs simply give under him & drops down.

Generalized Seizures

- 4) Myoclonic: Sudden, brief shock like contraction which may involve the entire body or be confined to the face, trunk or extremities.
- 5) Absence: Loss of consciousness without involving motor area. Most common in children (4-12 yrs).
- 6) Status epilepticus (reoccuring seizure): Continuous seizure without intervening return of consciousness.

First aid for seizures

Do

- Remove harmful objects nearby
- Cushion their head
- aid breathing by gently placing in recovery position

Don't

- Restrain the person movement
- Put anything in the person's mouth
- Give them anything to eat and drink

until they are fully recovered

Management of Epilepsy

- Therapy is symptomatic in that the majority of drugs prevent seizures, but neither effective prophylaxis or cure is available.

The goal of the therapy is to improve the patient's quality of life through:

1. maximize the seizure control
2. minimize drug side effects

Management of Epilepsy

Antiepileptics are indicated when there is two or more seizures occurred in short interval (6 m - 1year)

Drug choice is based on:

1. Classification of seizures.
2. Patient's age & health state
3. Data on efficacy, tolerability, safety and pharmacokinetics

Starting Treatment

- Rx should always be started with a single drug at a small dose
- All common side-effects must be discussed
  - teratogenicity and contraception if applicable
- Importance of compliance should be stressed
- Careful titration is a must
  - start low, go slow

Classification of Anticonvulsants

Classical

- **Phenytoin**
- **Phenobarbital**
- **Primidone**
- **Carbamazepine**
- **Ethosuximide**
- **Valproic Acid**
- **benzodiazepines**

Newer

Felbatol (felbamate)	1993
Neurontin (gabapentin)	1994
Lamictal (lamotrigine)	1995
Topamax (topiramate)	1996
Gabitril (tiagabine)	1998
Keppra (levetiracetam)	1999
Trileptal (oxcarbazepine)	2000
Zonegran (zonisamide)	2000
Lyrica (pregabalin)	2005
Ezogabine	
other	

Treatment Strategies:

- Modification of ion conductances.
- Increase inhibitory (GABAergic) transmission.
- Decrease excitatory (glutamatergic) activity.

They do their actions by:

↓ axonal conduction by preventing Na^+ influx through fast Na^+ channels

Example:

- Carbamazepine, oxcarbamazepine
- phenytoin,
- also at high doses barbiturates and valproate
- Lamotrigine, felbamate, topiramate

They do their actions by:

- ↓ presynaptic Ca^{+2} influx through type T channels in thalamic neurons
- ethosuximide
- valproic acids
- lamotrigine

TREATMENT OF SEIZURES

Seizure disorder	Drugs
Tonic-clonic(Grand mal) Drug of Choice	Carbamazepine or Valproate or Phenytoin or Phenobarbital
Alternatives:	Topiramte Lamotrigine (as adjunct or alone) Gabapentin (as adjunct)
Partial (simple or complex) Drug of choice	Carbamazepine or Topiramte or Phenytoin or Valproate
Alternatives:	Phenobarbital Lamotringine (as adjunct or alone) Gabapentin (as adjunct)

TREATMENT OF SEIZURES

Absence (petit mal) DOC*	**Valproate or Ethosuximide**
Alternatives:	**Clonazepam** **Lamotrigine**
Myoclonic, Atonic DOC	**Valproate**
Alternatives:	**Clonazepam**
Status Epilepticus DOC	**Diazepam, i.v.** **or Phenytoin, i.v. or Vaproate**
Alternatives:	**Phenobarbital, i.v**
Febrile Seizures *** DOC = Drug of choice** **** Preferred**	**Diazepam, rectal**** **Diazepam, i.v** **Valproate** Corticotropin (IM) or prednisolone

AEDs pharmacokinetics

Most classical antiepileptic drugs exhibit similar pharmacokinetic properties.

- Good absorption (although most are sparingly soluble).
- Low plasma protein binding (except for phenytoin, BDZs, valproate, and tiagabine).
- Conversion to active metabolites (carbamazepine, primidone, fosphenytoin).

PHENYTOIN Adverse effects

- Ataxia and nystagmus.
- Cognitive impairment.
- Hirsutism
- Gingival hyperplasia, Coarsening of facial features.
- folate dependent megaloblastic anaemia,
- osteomalacia
- Inhibition of ADH,
- inhibition of insulin secretion →hyperglycemia and glycosuria
- Hypoprothrominemia--coagulopathy
- **Exacerbates absence seizures.**

Phenytoin teratogenicity

Fetal hydantoin syndrome include

- cleft lip, cleft palate
- congenital heart disease
- slowed growth
- mental deficiency

CARBAMAZEPINE
Pharmacokinetics

- Absorbed slowly, enters brain rapidly
- Potent inducer of hepatic drug metabolising enzymes
  - own half life reduces over 2-3 weeks
  - increases metabolism of theophylline, warfarin and various hormones
  - complex drug interactions with other anticonvulsant agents

CARBAMAZEPINE
Adverse effects

- Stupor, coma, and resp. dep, along with drowsiness, dizziness, vertigo, ataxia, blurred vision, diplopia, bradycardia, skin rashes, GI upsets.
- The 10,11-epoxide metabolite →blood dyscrasias (leukopenia and aplastic anemia), and serious liver toxicity.
- Hyponatremia in elderly

OXCARBAZEPINE (Trileptal)

- Closely related to carbamazepine
  10-KETO DERIVATIVE OF CARBAMAZEPINE
- With improved toxicity profile.
- Less potent than carbamazepine.
- Active metabolite (MHD).
- Mechanism of action, similar to carbamazepine It alters Na^+ conductance and inhibits high frequency repetitive firing.

Toxicity:
•Hyponatremia
•Less hypersensitivity and induction of hepatic enzymes than with carbamazepine.

SODIUM VALPROATE

- **inhibits P450 system**

Adverse effects

- Elevated liver enzymes including own.
- Tremor, hair loss, changes in hair growth
- increased appetite Weight gain.
- coagulopathy (inhibition of platelet aggregation),
- Idiosyncratic **hepatotoxicity.**
- Negative interactions with other antiepileptics.
- Teratogen: spina bifida

FELBAMATE (Felbatrol)

- Effective against partial seizures but has severe side effects.
- Thus, used only for refractory cases.
- One of the metabolites; α,β-unsaturated aldehyde, 2-phenylpropenal is chemically reactive, like acrolein covalently linking proteins as well as DNA, it can cause liver and bone marrow toxicity

GABAPENTIN (Neurontin)

- Used as an adjunct in partial and generalized tonic-clonic seizures.
- Does not induce liver enzymes.
- not bound to plasma proteins.
- drug-drug interactions are negligible.
- Low potency.
- An a.a.. Analog of GABA that does not act on GABA receptors, it may however alter its metabolism, non-synaptic release and transport.
- Alleviate both diabetic neuropathies pain and post herpetic pain

Toxicity:

- Somnolence.
- Dizziness.
- Ataxia.
- Headache.
- Tremor.

VIGABATRIN

- Partial Seizures
- Inhibit GABA transaminase

ADVERSE EFFECTS:

- Depression,
- psychosis,
- visual dysfunction

LAMOTRIGINE (Lamictal)

- Presently use as add-on therapy with valproic acid.
- Almost completely absorbed
- $T_{1/2}$ = 24 hrs
- Low plasma protein binding
- Blocks sodium channels, & high voltage Ca^{+2} channel
- thus its effective in partial, generalized, myoclonic, absence seizures & Lennox-Gastaut syndrome (LGS).
- Approved for use in bipolar disorder

Toxicity:

- Dizziness
- Headache
- Diplopia
- Nausea
- Somnolence
- Rash

LEVETIRACETAM (Keppra)

- Adjunct Rx of refractory Partial Seizure
- Unknown mechanism of action but binds to presynaptic vesicle protein

ADVERSE EFFECT

Dizziness, sleep disturbances, headache, and asthenia (LACK OF ENERGY)

TIAGABINE (Gabatril)

- 100% bioavailable,
- highly protein bound.
- $T_{1/2}$ = 5 -8 hrs
- Effective against partial and generalized tonic-clonic seizures.
- GABA uptake inhibitor GAT-1

Toxicity:

- Dizziness
- Nervousness
- Tremor
- Difficulty concentrating
- Depression
- Asthenia
- Emotional
- Psychosis
- Skin rash

TOPIRAMATE (Topamax)

Broad spectrum antiseizure activity, also used in migraine

Toxicity:

- Somnolence
- Fatigue
- Dizziness
- Cognitive slowing
- Paresthesias
- Nervousness
- Confusion
- Urolithiasis
- Weight loss

- Rapidly absorbed, bioav. is > 80%, has no active metabolites, excreted in urine. $T_{1/2}$ = 20-30 hrs
- blocking of voltage-dependent sodium channels
- Additionally ↑ the frequency of Cl^- channel opening by binding to GABA receptor.
- High-voltage calcium currents (L-type) are reduced
- Depresses excitatory action of kainate on AMPA receptors.
- Carbonic anhydrase inhibiter effect
- Teratogenic in animal models

ZONISAMIDE

- Sulfonamide derivative
- Orally active half-life 50-60 hrs
- Both focal and generalized

MECHANISM OF ACTION

- Blocks voltage-gated Na^{+} channels and T-type Ca^{+2} current,
- enhancement of GABA-receptor function

ADVERSE EFFECTS

somnolence,
Ataxia,
hyperthermia (children)
Kidney stone

Special Cases: Pregnancy

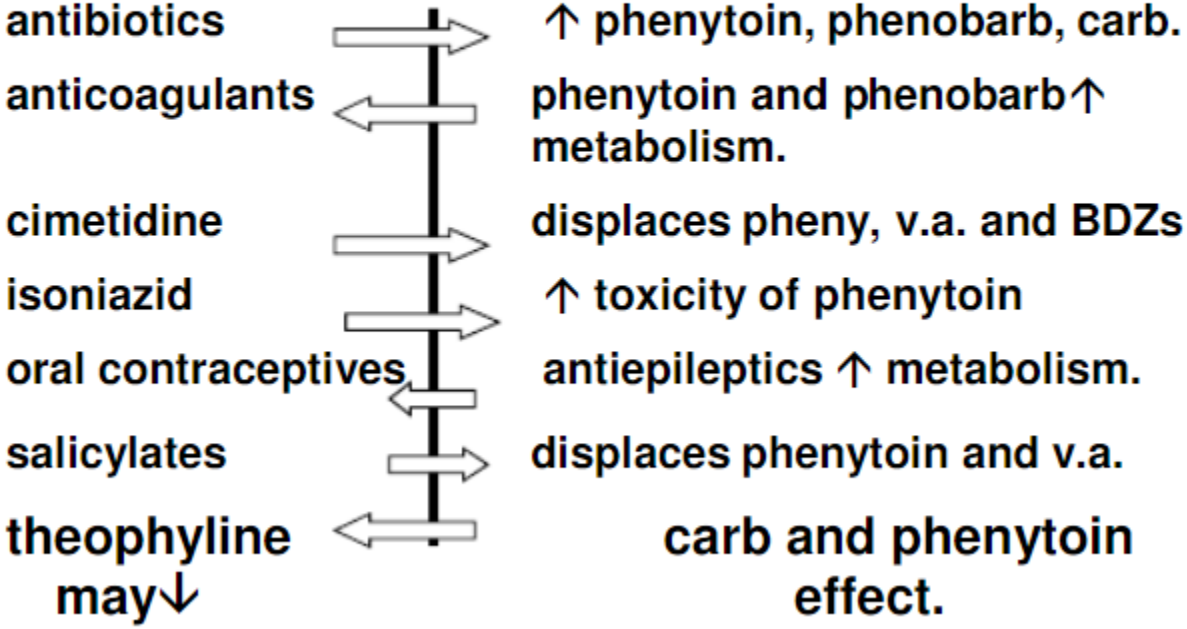
- Seizure very harmful for pregnant women.
- Antiepileptic drugs associated with increased (2-3 fold) incidence of birth defects (cleft lip/palate and cardiac defects)
- Significant risk of neural tube defects, folic acid is recommended to be given for every pregnant women with epilepsy
- Phenytoin, sodium valproate are absolutely contraindicated and oxcarbamazepine is better than carbamazepine.

Special Cases: Pregnancy

- Monotherapy usually better than drugs combination.
- Experience with new anticonvulsants still not reliable
- Newborns of mothers receiving phenobarbitone, or phenytoin may develop hypoprothrominemia, heamorrhage prevented by Vit. K
- Drugs are secreted in small quantities into breast milk but not usually sufficient to prevent breast feeding (phenobarbitone significantly)

ANTISEIZURE DRUG INTERACTIONS

With other drugs:



Are the New AEDs Superior to the traditional AEDs?

- Despite the lack of comprehensive clinical trials comparing the NEW and Traditional AEDs, there is evidence to suggest some advantages of the new agents;

- Better tolerability
- Same efficacy
- Broad spectrum activity
- Lack of hepatic enzyme induction
- Minimal Drug interactions

•New are significantly more expensive
•Felbamate & lamotrigine demonstrated serious toxicity, which have been documented with phenytoin, carbamazepine and VA

THANK YOU

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