Antiepileptic Drugs

Epilepsy is a central nervous system disorder (neurological disorder) in which nerve cell activity in the brain becomes disrupted, causing seizures or periods of unusual behavior, sensations and sometimes loss of consciousness.

Table 24–1. Classification of seizure types.

Partial seizures
Simple partial seizures
Complex partial seizures
Partial seizures secondarily generalized
Generalized seizures
Generalized tonic-clonic (grand mal) seizures
Absence (petit mal) seizures
Tonic seizures
Atonic seizures
Clonic and myoclonic seizures
Infantile spasms[1]

[1]An epileptic syndrome rather than a specific seizure type; drugs useful in infantile spasms will be reviewed separately.

Partial seizure

- A partial seizure means the epileptic activity took place in just part of the patient's brain.
- There are two types of partial seizure:
  - ✓ Simple partial seizure - the patient is conscious during the seizure. In most cases, the patient is also aware of their surroundings, even though the seizure is in progress.
  - ✓ Complex partial seizure - the patient's consciousness is impaired. The patient will generally not remember the seizure, and if they do, their memory will be vague.

Secondary generalized seizure

- occurs when the epileptic activity starts as a partial seizure, but then spreads to both halves of the brain. As this development happens, the patient loses consciousness.

Generalized seizure

- A generalized seizure occurs when both halves of the brain have epileptic activity. The patient's consciousness is lost while the seizure is in progress.

1. Tonic-clonic seizures (previously known as grand mal seizures) - these are perhaps the best known type of generalized seizure. They cause a loss of consciousness, body stiffness, and shaking.
2. Tonic seizures - muscles become stiff. They may cause a fall.
3. Clonic seizures - associated with rhythmic, jerking movements.

Generalized seizure

5. Atonic seizures - loss of muscle control, causing the individual to drop suddenly.
6. Myoclonic seizures- usually appears as sudden jerks of arm or legs
7. Absence seizures (previously called petit mal seizures) - doesnot involve falling down or experiencing involuntary jerk movements.

Manifestation includes-

✓ Brief loss of consciousness or awareness

✓ Slight loss of muscle tone cause child to drop objects

✓ Lip smacking, eyelid twitching, slight movement of hands

Status Epilepticus

- **Status epilepticus** (**SE**) is a single epileptic seizure lasting more than five minutes or two or more seizures within a five-minute period without the person returning to normal between them.
- is a life-threatening medical emergency particularly if treatment is delayed.

Classification

1. barbiturates – phenobarbitone
2. Deoxybarbiturates – primidone
3. Hydantoins – phenytoin
4. Iminostilbene – carbamazepine
5. Succinimide – ethosuximide
6. Aliphatic carboxylic acid – valproic acid
7. Benzodiazepines – diazepam, clobazam, clonazepam
8. Newer drugs – lamotrigine, gabapentin
9. Miscellaneous drugs – acetazolamide, trimethadione.

The Major Antiepileptic Drugs

- The main drugs in current use are: phenytoin, carbamazepine, valproate and ethosuximide.
- Secondary drugs include:
  - Phenobarbitone: highly sedative
  - Various benzodiazepines (e.g. clonazepam);

  Diazepam used in treating status epilepticus.

MOA of antiepileptic drugs

- Drugs that are effective in seizure reduction accomplish this by a variety of mechanisms, including-

1. blockade of voltage-gated channels (Na+ or Ca2+),
2. enhancement of inhibitory GABAergic impulses, or
3. interference with excitatory glutamate transmission.

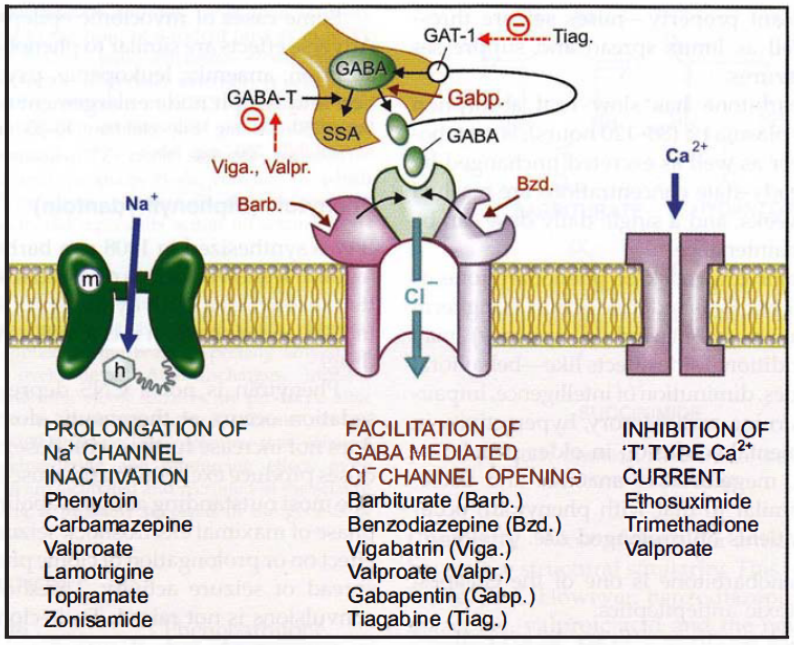

Fig. 30.2: Major mechanisms of anticonvulsant action
m: Activation gate; h: Inactivation gate; GABA-T: GABA transaminase; SSA: Succinic semialdehyde; GAT-1: GABA transporter

Phenobarbitone

- act primarily at the GABA : BZD receptor-Cl^- channel complex and potentiate GABAergic inhibition by increasing the lifetime of Cl- channel opening induced by GABA.
- Adverse effect: major sedation
- Long term use: behavioral abnormalities, impairement of learning and memory, rashes, megaloblastic anaemia.

Phenytoin

Mechanism of Action:

- Phenytoin blocks voltage-gated sodium channels by selectively binding to the channel in the inactive state and slowing its rate of recovery.
- At very high concentrations, phenytoin can block voltage-dependent calcium channels and interfere with the release of mono aminergic neurotransmitters.

Adverse Effect (Narrow therapeutic index)

- Gastrointestinal irritation- nausea loss of appetite, stomach pain
- Ataxia and diplopia
- Gingival hyperplasia, hirsutism, increased collagen proliferation.

Phenytoin

Use

- First line antiepileptic drug for generalized tonic clonic, partial seizures but Ineffective in absence seizure.
- Status epilepticus that doesnot improve with BZD
- Trigeminal neuralgia- second choice of drug alternate to carbamazepine

- Dose: 100mg BD; Maximum 400mg/d

Carbamazepine

MOA: blocks sodium channel

Adverse effect: produces dose-related neurotoxicity-sedation, dizziness, vertigo, diplopia and ataxia. Vomiting, diarrhoea, worsening of seizures are also seen with higher doses.

Use

- Generalized tonic clonic seizure, partial seizure
- Trigeminal and related neuralgias

Dose: 200-800 mg/day BID

Valproic acid (Sodium valproate)

- Valproate is very effective against absence seizure.
- Mechanism: it acts by potentiating inhibitory neurotransmitter GABA. It prevents degradation and uptake of GABA.
- Relatively few unwanted effects: anorexia, nausea, drowsiness, ataxia, tremor teratogenicity, liver damage (rare, but serious)
- Dose: 200 mg TDS
- Indication: most of myoclonic seizures and tonic clonic seizure.

Ethosuximide

- The main drug used to treat absence seizures, may exacerbate other forms
- Acts by blocking T-type Ca^{2+}-channels and suppress generation of absence seizure.
- Relatively few unwanted effects, mainly nausea and anorexia. (mental disturbances)
- Dose: 20-30 mg/kg/day

Benzodiazepine

- Diazepam: preferred drugs for Status epilepticus.
- Nitrazepam: petit mal ,especially myoclonic seizures and infantile spasms.
- Clonazepam: is one of the most effective in some cases of myoclonic seizures. Used in petit mal and status epilepticus

Gabapentin (GABA)

- It is an amino acid which is structurally related to GABA. However it does not bind to GABA receptor directly. It enhance the GABA release and inhibit the neuronal firing.
- First line drug for pain due to diabetic neuropathy, and post herpetic neuralgia and has some prophylactic effect in migraine too
- Dose: 300mg HS followed by 600mg BID next day
- Adverse effect: diziness, fatigue, nausea, vomiting, rash, pruritus, diplopia(avoid driving while taking this medication),