Drugs for Epilepsy

Overview:

Approximately 10% of the population has at least one seizure in their lifetime.
Approximately 1% of the world's population has epilepsy, which is the fourth most common neurologic disorder after migraine, stroke, and Alzheimer's disease.
Epilepsy: is a chronic disorder of brain function characterized by the recurrent and unpredictable occurrence of seizures. **A seizure:** is a sudden surge of electrical activity in the brain that can result in uncontrollable muscle movements, loss of consciousness and loss of autonomic function like bowel or bladder control.

Excitatory neurons: result in a response (such as when muscle contracts).

Inhibitory neurons: result in the inhibition of responses (such as when a muscle is inhibited or relaxes).
GABA is inhibitory.
GABA opens chloride channels.
Opening chloride channels cancels the excitatory effect of opening sodium channels.

CLASSIFICATION OF SEIZURES:

- ❑ Focal (partial): involve only a portion of one hemisphere of the brain.
1) Simple: no loss of consciousness.
2) Complex: loss of consciousness.
- ❑ Generalized: involve both brain hemispheres
1) Tonic- clonic (Grand mal).
2) Absence (Petit mal).
3) Atonic seizures (drop attacks).

Tonic- clonic (Grand mal):

These seizures result in loss of consciousness, followed by tonic (continuous contraction) and clonic (rapid contraction and relaxation) phases. The seizure may be followed by a period of confusion and exhaustion due to depletion of glucose and energy stores.

Absence (Petit mal) seizure:

These seizures involve a brief, abrupt, and self-limiting loss of consciousness. The onset generally occurs in patients at 3 to 5 years of age and lasts until puberty or beyond. The patient stares and exhibits rapid eye blinking, which lasts for 3 to 5 seconds.

Atonic seizures (drop attacks):

These are characterized by a sudden loss of muscle tone.

Anticonvulsants: are medications used to prevent or stop seizures.
In general, seizures can be controlled with one medication in approximately 75% of patients. Patients may require more than one medication in order to optimize seizure control. Some patients may never obtain total seizure control.

Mechanism of Action of Antiseizure Medications:
Drugs reduce seizures through mechanisms such as:

1. blocking voltage-gated channels (Na+ or Ca2+).
2. enhancing inhibitory γ-aminobutyric acid (GABA)ergic impulses .
3. interfering with excitatory glutamate transmission.

Some antiseizure medications appear to have multiple targets within the central nervous system (CNS), whereas the mechanism of action for some agents is poorly defined.
Antiseizure medications suppress seizures but do not "cure"or "prevent" epilepsy.

Many features are common to most antiepileptics:
1. None of these drugs are curative.
2. They tend to be highly bound to plasma proteins.
3. They are usually cleared by hepatic metabolism.
   a. They may inhibit the metabolism of other drugs (valproic acid).
   b. They may induce the metabolism of other drugs (e.g., the effectiveness of oral contraceptives can be reduced [phenobarbital, phenytoin, carbamazepine]).
   c. For older agents, it is important to measure the serum anticonvulsant concentration.

Side effects that usually occur include:
a. CNS depression (Even phenytoin induces lethargy.)
b. Skin rashes (Lamotrigine and carbamazepine can cause Stevens–Johnson syndrome, a life-threatening skin condition that is thought to be immune complex mediated.)
c. Nystagmus.
d. Teratogenicity.
e. GI effects (nausea, vomiting).

1.Phenobarbital (Luminal): it is a barbiturate that has a half-life of 4 days. Patients develop some tolerance to the sedative–hypnotic effect, but not to the antiepileptic effect. Phenobarbital is used primarily in the treatment of status epilepticus when other agents fail. Repeated administration causes enzyme induction and reduces the effectiveness of co-administered drugs.

2. Primidone (Mysoline): is an active drug and is also partially metabolized to phenobarbital; thus, it has properties that are very similar to phenobarbital.

3. Phenytoin (Dilantin): is an effective antiepileptic with less sedative activity.
a.Elimination follows zero-order kinetics. After saturation of hepatic enzymes, small increases in dose can lead to large increases in blood concentration, resulting in drug induced toxicity.

b. Phenytoin induces CYP2C and CYP3A families and the UGT enzyme system.
d. It is often used in the treatment of focal and generalized tonic–clonic seizures & new-onset status epilepticus.
f. Phenytoin should not be administered in dextrose or glucose solution as it gets precipitated.
g. Although phenytoin is advantageous due to its low cost, the actual cost of therapy may be higher, considering the potential for serious toxicity and adverse effects.
Adverse effects (Note the 'H's)
Phenytoin has dose-dependent toxicity. The adverse effects are:

1. Hypertrophy and Hyperplasia of gums:
   Seen on chronic therapy and can be minimized by proper oral hygiene.
2. Hypersensitivity reactions include skin rashes, neutropaenia and rarely Hepatic necrosis.
3. Hirsutism: Due to increased androgen secretion.
4. Hyperglycaemia: Due to decreased insulin release.
5. Megaloblastic anaemia: Due to folate deficiency.
6. Osteomalacia: Due to increased metabolism of vitamin D.
7. Hypocalcaemia: Due to decreased absorption of Ca2+ from the gut.
8. Foetal Hydantoin syndrome: Cleft lip, cleft palate, digital Hypoplasia, etc. due to the use of phenytoin during pregnancy.

4.Fosphenytoin: is a prodrug that is rapidly converted to phenytoin in the blood within minutes. Whereas fosphenytoin may be administered intramuscularly (IM), phenytoin sodium should never be given IM, as it causes tissue damage and necrosis. Fosphenytoin is the drug of choice and standard of care for IV and IM administration of phenytoin. It is used in status epilepticus. Fosphenytoin can be administered in normal saline or glucose.

5. Carbamazepine (Tegretol): is a tricyclic anticonvulsant that has mood stabilization activity. Carbamazepine is effective for treatment of focal seizures, generalized tonic–clonic seizures, trigeminal neuralgia, and bipolar disorder. It is also used to treat Restless leg syndrome and shingles.
a. It induces mixed function oxidases in the liver. It induces its own metabolism, resulting in lower total carbamazepine blood concentrations at higher doses.
b. Carbamazepine is an inducer of the CYP1A2, CYP2C, CYP3A, and UDP glucuronosyltransferase (UGT) enzymes, which increases the clearance of other drugs.
c. Hyponatremia may be noted in some patients, especially the elderly, and may necessitate a change in medication.
d. Liver toxicity, syndrome of inappropriate antidiuretic hormone (SIADH), and aplastic anemia are potential side effects.
e. Carbamazepine should not be prescribed for patients with absence seizures because it may cause an increase in seizures.

6. Oxcarbazepine (Trileptal): is an analog of carbamazepine. It has less toxicity. It is approved for use in adults and children with focal seizures. Oxcarbazepine is a less potent inducer of CYP3A4 and UGT than is carbamazepine. The adverse effect of hyponatremia limits its use in the elderly.

7. Valproic acid (Depakene) and divalproex :

Valproic acid is effective for the treatment of focal and primary generalized epilepsies. It can be hepatotoxic, but it does not induce cytochrome P450 enzymes.

Divalproex sodium is a combination of sodium valproate and valproic acid that is converted to valproate ion in the gastrointestinal tract.

It was developed to improve gastrointestinal tolerance of valproic acid. All of the available salt forms are equivalent in efficacy (valproic acid and sodium valproate). Valproate inhibits metabolism of the CYP2C9, UGT, and epoxide hydrolase systems.

Rare hepatotoxicity may cause a rise in liver enzymes, which should be monitored frequently. Use in children under age 2 and women should be avoided if possible.

It is teratogenic, orofacial and digital abnormalities; neural tube defects with increased incidence of spina bifida, so it should not be given during pregnancy.

8. Ethosuximide (Zarontin): is the drug of choice for absence seizures. It also does not induce cytochrome P450 enzymes.

9. Clonazepam (Klonopin) : is a benzodiazepine, which produces considerable sedation. Tolerance can occur with long-term use.

10. Tiagabine (Gabitril): is effective as adjunctive treatment in focal seizures. Tiagabine should not be used for indications other than epilepsy.

11. Levetiracetam (Keppra): is approved for adjunct therapy of focal-onset, and primary generalized tonic-clonic seizures in adults and children. The drug is well absorbed after oral administration and is excreted in urine mostly unchanged, resulting in few to no drug interactions. Levetiracetam can cause mood alterations that may require a dose reduction or a change of medication.

12. Gabapentin (Neurontin): It is an analogue of GABA. It freely crosses BBB and acts by releasing GABA. It is orally effective, not metabolized in the body and excreted unchanged in urine. There is no enzyme-inducing property, so drug interactions are rare. useful as adjunct therapy for partial seizures. Gabapentin and levetiracetam are also used to treat neuropathic pain.

13. Topiramate (Topomax): is useful as an adjunct in treating refractory seizures. Topiramate is effective for use in focal and primary generalized epilepsy. It is also approved for prevention of migraine. It mildly inhibits CYP2C19 and coadministration with phenytoin and carbamazepine may reduce serum concentrations of topiramate. Adverse effects include somnolence, weight loss, and paresthesias. Renal stones, glaucoma, oligohidrosis (decreased sweating), and hyperthermia have also been reported. It reduces the effectiveness of oral contraceptives.

14. Felbamate (Felbatol): Felbamate has a broad spectrum of anticonvulsant action with multiple proposed mechanisms. It is an inhibitor of drugs metabolized by CYP2C19 and induces drugs metabolized by CYP3A4. It is reserved for use in refractory epilepsies because of the risk of aplastic anemia (about 1:4000) and hepatic failure.

15. Lamotrigine (Lamictal): Lamotrigine is effective in a wide variety of seizure types, including focal, generalized & absence seizures. It can also be used to treat refractory seizures, but they are not first-line therapy due to severe side effects. It is also used to treat bipolar disorder.

Women's Health and Epilepsy:

Women of childbearing potential with epilepsy require assessment of their antiseizure medications in regard to contraception and pregnancy planning.

Several antiseizure medications increase the metabolism of hormonal contraceptives, potentially rendering them ineffective. These include phenytoin, phenobarbital, carbamazepine, topiramate, oxcarbazepine, rufinamide, and clobazam. These medications increase the metabolism of contraceptives regardless of the delivery system used (for example, patch, ring, implants, and oral tablets).

Pregnancy planning is vital, as many antiseizure medications have the potential to affect fetal development and cause birth defects. All women considering pregnancy should be on high doses (1 to 5 mg) of folic acid prior to conception.

Divalproex and barbiturates should be avoided. If possible, women already taking divalproex should be placed on other therapies before pregnancy and counseled about the potential for birth defects, including cognitive and behavioral abnormalities and neural tube defects.

The pharmacokinetics of antiseizure medications and the frequency and severity of seizures may change during pregnancy. Regular monitoring by both an obstetrician and a neurologist is important.

Phenytoin, carbamazepine, valproate, lamotrigine, and phenobarbital all have been associated with teratogenic effects which include congenital heart defects, neural tube defects, cleft lip, cleft palate, and others.

The antiseizure drugs that induce CYPs have been associated with vitamin K deficiency in the newborn, which can result in a coagulopathy and intracerebral hemorrhage. Treatment with vitamin K1, 10 mg/d during the last month of gestation, has been recommended for prophylaxis.

Status Epilepticus: In status epilepticus, two or more seizures occur without recovery of full consciousness in between episodes. These may be focal or generalized, convulsive or nonconvulsive. Status epilepticus is life threatening and requires emergency treatment usually consisting of parenteral administration of a fast-acting medication such as a benzodiazepine, followed by a slower- acting medication such as phenytoin, fosphenytoin, divalproex, or levetiracetam.

Other Treatment:

- Surgery to remove an area of brain that is causing the seizure.
- Ketogenic diet is used in pediatric patients whose epilepsy is not controlled by medications (high fats and low carbohydrates).
- Vagus nerve stimulation (an electrical device that sends electrical signals to the vagus nerve).