Antiseizure Drugs

Assistant Prof. Dr. Najlaa Saadi
PhD Pharmacology
Faculty of Pharmacy
University of Philadelphia

Seizures

Episodes of brain dysfunction resulting from abnormal discharge of cerebral neurons

Partial Seizures, Simple

Consciousness preserved; manifested as convulsive jerking, paresthesias, psychic symptoms (illusions, hallucinationsand autonomic dysfunction

Partial Seizures, Complex

Impaired consciousness that is preceded, accompanied, or followed by psychological symptoms

Tonic-clonic Seizures, Generalized

Tonic phase (less than 1 min) involves abrupt loss of consciousness, muscle rigidity, and respiration arrest; clonic phase (2–3 min) involves jerking of body muscles, with lip or tongue biting, and fecal and urinary incontinence; formerly called grand mal

Absence Seizures, Generalized

Impaired consciousness (often abrupt onset and brief), loss of postural tone, or enuresis; begin in childhood (formerly, petit mal) and usually cease by age 20 yrs

Myoclonic Seizures

Single or multiple myoclonic muscle jerks

Status Epilepticus

A series of seizures (usually tonic-clonic) without recovery of consciousness between attacks; it is a life-threatening emergency

Tonic-clonic & Partial Seizures

- Carbamazepine
- Lamotrigine
- Phenytoin
- Valproic acid

Absence Seizures

- Clonazepam
- Ethosuximide
- Valproic acid

Myoclonic Seizures

- Clonazepam
- Lamotrigine
- Valproic acid

Back-up & Adjunctive Drug

- Felbamate
- Gabapentin
- Lamotrigine
- Levetiracetam
- Phenobarbital
- Tiagabine
- Topiramate
- Vigabatrin
- Zonisamide

Pharmacokinetics

- Well absorbed orally and have good bioavailability.
- Most antiseizure drugs are metabolized by hepatic Enzymes (except gabapentin & vigabatrin)

- Enzyme inhibiter & drug that displace anticonvulsants from plasma protein binding sites,increase plasma concentrations of the antiseizure agents
- Enzymes inducer (rifampin) decrease the effect of antiseizure agents (inadequate seizure control).
- Carbamazepine and phenytoin are enzyme inducer ,increase metabolism of themselves .

Phenytoin

- The oral bioavailability of phenytoin is variable
- Rapid-onset and extended-release forms are available.
- Plasma proteins binding (97–98%),
- Carbamazepine, sulfonamides, valproic acid, compete for binding
- Enzyme inducers (phenobarbital, rifampin) decrease plasma concentration
- Enzyme inhibiter (cimetidine, isoniazid) increase plasma concentration
- Phenytoin is enzyme inducers , decreasing the effects carbamazepine, clonazepam& and lamotrigine
- Fosphenytoin is a water-soluble prodrug form of phenytoin that is used parenterally.

Carbamazepine

- It is enzyme inducer increase metabolism of the drug itself ,as well as increase metabolism of clonazepam, lamotrigine, and valproic acid
- Carbamazepine metabolism can be inhibited by valproic acid.

Valproic Acid

- Compete phenytoin for plasma protein binding
- Valproic acid inhibits the metabolism of carbamazepine, ethosuximide, phenytoin, phenobarbital, and lamotrigine.
- Hepatic biotransformation leads to formation of a toxic metabolite ,which is the cause of the hepatotoxicity of the drug.

Other Drugs

- Gabapentin, pregabalin, levetiracetam, and vigabatrin , are eliminated by the kidney, largely in unchanged form.
- Lamotrigine is eliminated via hepatic glucuronidation.
- Tiagabine, topiramate, and zonisamide undergo both hepatic metabolism and renal elimination of intact drug

Mechanisms of Action

- The general effect of antiseizure drugs is to suppress repetitive action potentials in epileptic foci in the brain.
- Many different mechanisms are involved in achieving this effect.

Sodium Channel Blockade

- At therapeutic concentrations, phenytoin, carbamazepine, lamotrigine, and zonisamide block voltage-gated sodium channels in neuronal membranes.
- Phenobarbital and valproic acid may exert similar effects at high doses

GABA-Related Targets

- Benzodiazepines facilitate the inhibitory effects of GABA (interact with GABA receptor &increase frequency of of chloride ion channel opening)
- Phenobarbital and other barbiturates facilitate the inhibitory effects of GABA (interact with GABA receptor &increase duration of chloride ion channel opening)

- Vigabatrin irreversibly inactivate GABA aminotransaminase (GABA-T) (enzyme that terminate the action of GABA . valproic acid at very high concentrations also inhibit this enzyme
- Tiagabine inhibits a GABA transporter (GAT-1) in neurons and prolonging the action of the neurotransmitter.
- Gabapentin is a structural analog of GABA, but it does not activate GABA receptors directly.
- Other drugs that may facilitate the inhibitory actions of GABA include felbamate, topiramate, and valproic acid.

Calcium Channel Blockade

- Ethosuximide inhibits (T type) Ca^{2+} currents, especially in thalamic neurons that act as pacemakers to generate rhythmic cortical discharge.
- Valproic acid have similar action
- Gabapentin and pregabalin (primary action)

Other Mechanisms

- In addition to its action on calcium channels, valproic acid causes neuronal membrane hyperpolarization, by enhancing K+ channel permeability.
- Phenobarbital acts on both sodium channels and GABA-chloride channels, it also acts as an antagonist at some glutamate receptors.
- Felbamate blocks glutamate receptors.
- Topiramate blocks sodium channels and potentiates the actions of GABA and may also block glutamate receptors.

Clinical Uses

Generalized Tonic-Clonic Seizures

- Valproic acid, carbamazepine, and phenytoin are the drugs of choice for generalized tonic-clonic (grand mal) seizures.
- Phenobarbital is now considered to be an alternative agent in adults but continues to be a primary drug in infants.
- Lamotrigine and topiramate and several others may be used in refractory cases.

Partial Seizures

- The drugs of first choice are carbamazepine or oxcarbazepine or lamotrigine or phenytoin.
- Alternatives include felbamate, Phenobarbital, topiramate, and valproic acid.
- gabapentin and pregabalin can be used

Absence Seizures

- Ethosuximide or valproic acid are the preferred drugs because they cause minimal sedation.
- Ethosuximide is often used in uncomplicated absence seizures if patients can tolerate its gastrointestinal side effects.
- Valproic acid is particularly useful in patients who have concomitant generalized tonic-clonic or myoclonic seizures
- Clonazepam is effective as an alternative has the disadvantages of causing sedation and tolerance.

Myoclonic and Atypical Absence Syndromes

- Myoclonic seizure syndromes are usually treated with valproic acid
- lamotrigine is approved for adjunctive use, but is commonly used as monotherapy.
- Clonazepam can be effective, but the high doses required cause drowsiness.
- Felbamate has been used with the primary drugs but has both hematotoxic and hepatotoxic potential

Status Epilepticus

- Intravenous diazepam or lorazepam is usually effective in terminating attacks and providing short-term control.
- For prolonged therapy, intravenous phenytoin , it is highly effective and less sedating than benzodiazepines or barbiturates.
- However, phenytoin may cause cardiotoxicity (perhaps because of its solvent propylene glycol), and fosphenytoin (water soluble) is a safer parenteral agent.
- Phenobarbital used in status epilepticus, especially in children.
- In very severe status epilepticus that does not respond to these measures, general anesthesia may be used.

Other Clinical Uses

- Bipolar disorders, (valproic acid) which is now often used as a first-line drug in the treatment of mania carbamazepine and lamotrigine also use in bipolar disorder.
- Trigeminal neuralgia (carbamazepine is the drug of choice)
- Pain of neuropathic origin gabapentin has efficacy in pain of neuropathic origin, including postherpetic neuralgia. Phenytoin is used in the treatment of migraine.

Adverse effects and complications of antiepileptic drugs

Antiepileptic Drug	Adverse Effects
Benzodiazepines	Sedation, tolerance, dependence
Carbamazepine	Diplopia, cognitive dysfunction, drowsiness, ataxia; rare occurrence of severe blood dyscrasias and Stevens-Johnson syndrome; teratogenic potential
Ethosuximide	Gastrointestinal distress, lethargy, headache, behavioral changes
Felbamate	Aplastic anemia, hepatic failure
Gabapentin	Dizziness, sedation, ataxia, nystagmus; does not affect drug metabolism (pregabalin is similar)
Lamotrigine	Dizziness, ataxia, nausea, rash, rare Stevens-Johnson syndrome
Levetiracetam	Dizziness, sedation, weakness, irritability, hallucinations, and psychosis have occurred
Oxcarbazepine	Similar to carbamazepine, but hyponatremia is more common; unlike carbamazepine, does not induce drug metabolism
Phenobarbital	Sedation, cognitive dysfunction, tolerance, dependence, induction of hepatic drug metabolism; primidone is similar
Phenytoin	Nystagmus, diplopia, sedation, gingival hyperplasia, hirsutism, anemias, peripheral neuropathy, osteoporosis, induction of hepatic drug metabolism
Tiagabine	Abdominal pain, nausea, dizziness, tremor, asthenia; drug metabolism is not induced
Topiramate	Drowsiness, dizziness, ataxia, psychomotor slowing and memory impairment; paresthesias, weight loss, acute myopia
Valproic acid	Drowsiness, nausea, tremor, hair loss, weight gain, hepatotoxicity (infants), inhibition of hepatic drug metabolism
Vigabatrin	Sedation, dizziness, weight gain; visual field defects with long-term use, which may not be reversible
Zonisamide	Dizziness, confusion, agitation, diarrhea, weight loss, rash, Stevens-Johnson syndrome

Toxicity

Teratogenicity (Congenital malformations)

- Neural tube defects (spina bifida) are associated with the use of valproic acid
- Carbamazepine has been implicated as a cause of craniofacial anomalies and spina bifida
- A fetal hydantoin syndrome has been described after phenytoin use by pregnant women.

Over Dosage Toxicity

CNS depression & respiratory depression may occur with over dosage.

Management

- Airway management (mechanical ventilation)
- Flumazenil may be used in benzodiazepine overdose

Life-Threatening Toxicity

- Fatal hepatotoxicity has occurred with valproic acid, with greatest risk to children younger than 2 years and patients taking multiple anticonvulsant drugs.
- Skin rashes and life-threatening Stevens-Johnson syndrome with Lamotrigine (Children are at higher risk)
- Aplastic anemia and acute hepatic failure have limited the use of felbamate

Withdrawal

Withdrawal should be gradually to avoid increased seizure frequency and severity