PHARMACOTHERAPY OF THE EPILEPSIES

Seizure refers to a transient alteration of behavior due to the disordered, synchronous, and rhythmic firing of populations of brain neurons

Epilepsy refers to a disorder of brain function characterized by the periodic and unpredictable occurrence of seizures

The epilepsies are common and frequently devastating disorders, affecting approximately 2.5 million people in the United States alone.

Epileptic seizures often cause transient impairment of consciousness, leaving the individual at risk of bodily harm and often interfering with education and employment

Therapy is symptomatic, effective prophylaxis & cure are not available.

The mechanisms of action of antiseizure drugs fall into three major categories:

1- Limit the sustained, repetitive firing of neurons, an effect mediated by promoting the inactivated state of voltage-activated Na+ channels

2- involve enhanced γ-aminobutyric acid (GABA)- mediated synaptic inhibition, an effect mediated either by a presynaptic or postsynaptic action

3- limit activation of a particular voltage-activated Ca2+ channel known as the T current.

Seizures are thought to arise from the cerebral cortex.

Partial seizures (beginning focally in a cortical site):

- Simple partial seizure is associated with preservation of consciousness
- Complex partial seizure is associated with impairment of consciousness

Generalized seizures (involve both hemispheres widely from the outset):

- Absence
- Myoclonic
- Tonic-clonic

The type of epileptic seizure is one determinant of the drug selected for therapy

Mechanism of seizure:

Partial seizure:

A reduction of inhibitory synaptic activity (GABA) or enhancement of excitatory synaptic activity (Glutamate) might be expected to trigger a seizure.

Enhancing GABA-mediated synaptic inhibition would reduce neuronal excitability and raise the seizure threshold. Several drugs are thought to inhibit seizures by regulating GABA-mediated synaptic inhibition through an action at distinct sites of the synapse. The principal postsynaptic receptor of synaptically released GABA is termed the GABAA receptor

Activation of the GABAA receptor inhibits the postsynaptic cell by increasing the inflow of Cl- ions into the cell, which tends to hyperpolarize the neuron.

Generalized seizures:

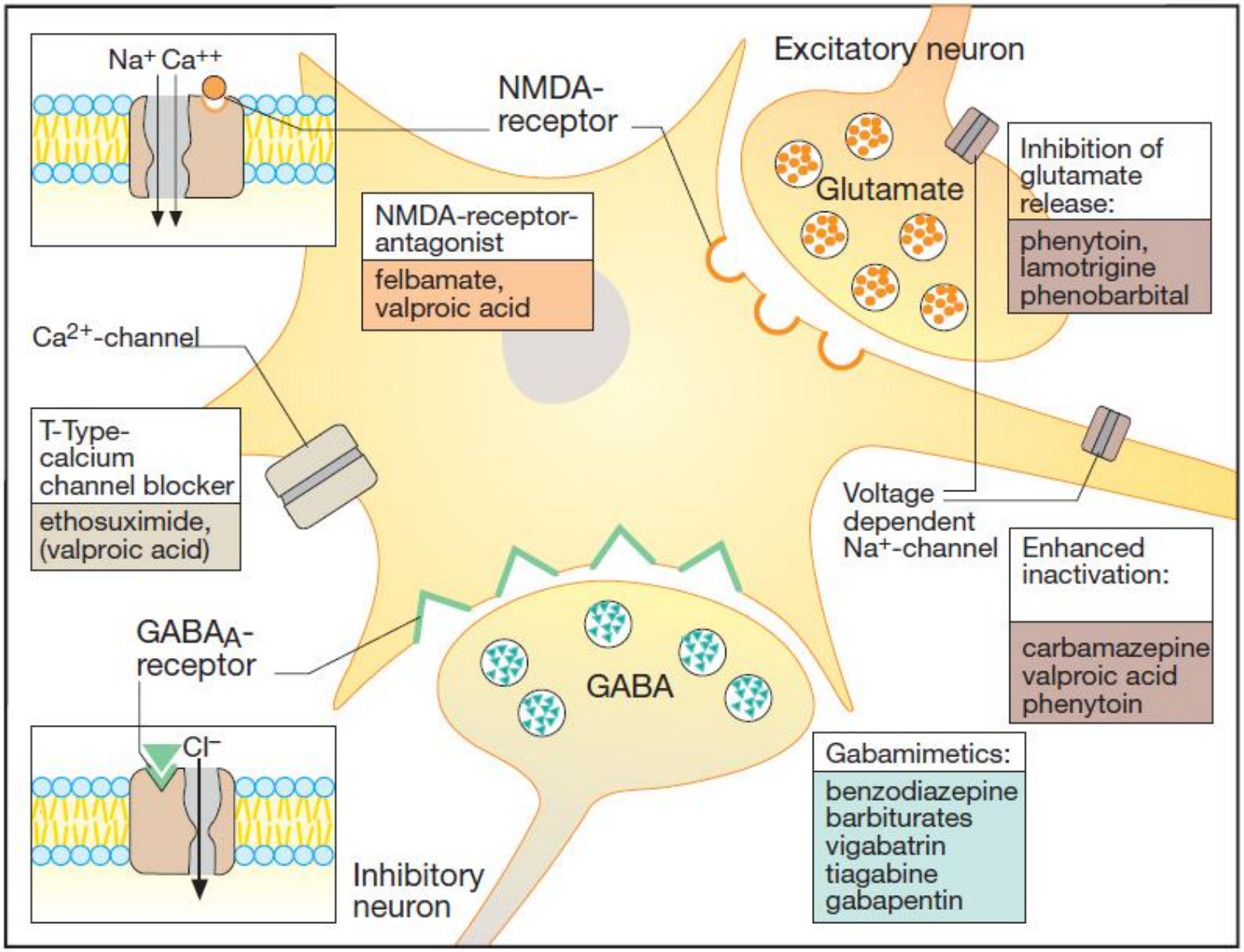
Absence Seizures:

In contrast to partial seizures, which arise from localized regions of the cerebral cortex, generalized-onset seizures arise from the reciprocal firing of the thalamus and cerebral cortex.

The EEG hallmark of an absence seizure is generalized spikeand-wave discharges at a frequency of 3 per second (3 Hz).

One intrinsic property of thalamic neurons that is pivotally involved in the generation of the 3-Hz spike-and-wave discharges is a particular form of voltage regulated Ca^{2+} current, the low threshold ("T") current.

Importantly, the principal mechanism by which antiabsence-seizure drugs (*ethosuximide, valproic acid*) are thought to act is by inhibition of the T current.



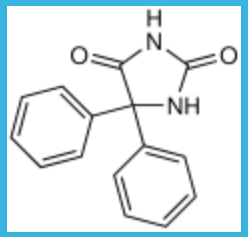
A. Neuronal sites of action of antiepileptics

Antiseizure drugs:

The first antiepileptic drug was *bromide*, in the late nineteenth century.
Phenobarbital was the first synthetic organic agent recognized as having antiseizure activity.
Phenytoin suppressed seizures in the absence of sedative effects.

The chemical structures of most of the drugs introduced before 1965 were closely related to phenobarbital:
hydantoins and the succinimides
Between 1965 and 1990:
iminostilbene (carbamazepine)
branched-chain carboxylic acid (valproic acid)
in the 1990s :
phenyltriazine (lamotrigine)
cyclic analog of GABA(*gabapentin*)
sulfamate-substituted monosaccharide (topiramate)
nipecotic acid derivative (tiagabine)
pyrrolidine derivative (*levetiracetam*)

Phenytoin:



Is effective against all types of partial and tonic-clonic seizures but not absence seizures.
Phenytoin exerts antiseizure activity without causing general depression of the CNS. In toxic doses, it may produce excitatory signs and at lethal levels a type of decerebrate rigidity.

In the range of therapeutic drug levels the effects on Na+ channels are selective.

At concentrations five- to tenfold higher, reduction of spontaneous activity and enhancement of responses to GABA; these effects may underlie some of the unwanted toxicity associated with high levels of phenytoin.

Pharmacokinetic Properties:

The pharmacokinetic characteristics of phenytoin are influenced markedly:

by its binding to serum proteins(90%)
by the nonlinearity of its elimination kinetics
by its metabolism by CYPs (interaction with warfarin & Contraceptives).

Fosphenytoin:

The low aqueous solubility of phenytoin hindered its intravenous use and led to production of *fosphenytoin,* a watersoluble prodrug. Fosphenytoin is converted into phenytoin by phosphatases in liver and red blood cells with a half-life of 8 to 15 minutes.

Toxicity:

The toxic effects of phenytoin depend on:
The route of administration
The duration of exposure
The dosage

Intravenous administration causes Cardiac arrhythmias & CNS depression

Acute oral overdosage results primarily in signs referable to the cerebellum and vestibular

Toxic effects associated with chronic treatment include: Dose-related)

cerebellar-vestibular effects

other CNS effects

Behavioral changes

Increased frequency of seizures

Gastrointestinal symptoms

Gingival hyperplasia

Osteomalacia(Due to altered Vit D & Vit K metabolism)

Megaloblastic anemia

Hirsutism

Inhibition of release of antidiuretic hormone

Inhibition of insulin secretion

Serious adverse effects, including those on the skin, bone marrow, and liver, probably are manifestations of drug allergy. Although rare, they necessitate withdrawal of the drug

Therapeutic Uses:

- Partial and tonic-clonic but not absence seizures
- Trigeminal and related neuralgias (carbamazepine may be Preferable)
- Cardiac arrhythmias

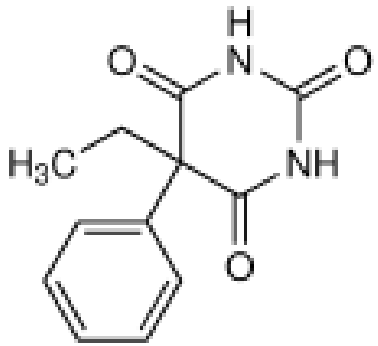
Phenytoin preparations differ significantly in bioavailability and rate of absorption. In general, patients should consistently be treated with the same drug from a single manufacturer. However, if it becomes necessary to temporarily switch between products, care should be taken to select a therapeutically equivalent product and patients should be monitored for loss of seizure control or onset of new toxicities.

Phenobarbital:

The first effective organic antiseizure agent

Exert maximal antiseizure action at doses below those required for hypnosis

Potentiating of synaptic inhibition through an action on the $GABA_A$ receptor



Pharmacokinetic Properties:

Oral absorption of phenobarbital is complete but somewhat slow; peak concentrations in plasma occur several hours after a single dose.

It is 40% to 60% bound to plasma proteins and bound to a similar extent in tissues, including brain.
Up to 25% of a dose is eliminated by pH-dependent renal excretion of the unchanged drug

the remainder is inactivated by hepatic microsomal enzymes, principally CYP2C9, with minor metabolism by CYP2C19 and CYP2E1. Phenobarbital induces CYP2C and CYP3A subfamilies. Drugs metabolized by these enzymes can be more rapidly degraded when coadministered with phenobarbital; importantly, oral contraceptives are metabolized by CYP3A4.

Toxicity:

- Sedation is the most frequent undesired effect , but tolerance develops during chronic medication

- Nystagmus and ataxia occur at excessive dosage

- Phenobarbital sometimes produces irritability and hyperactivity in children, and agitation and confusion in the elderly

- Scarlatiniform or morbilliform rash possibly with other manifestations of drug allergy, occurs in 1% to 2% of patients

- Megaloblastic anemia that responds to folate and osteomalacia that responds to high doses of vitamin D occur during chronic phenobarbital therapy of epilepsy

- plasma concentrations of 10 to 35 μg/ml are usually recommended for control of seizures

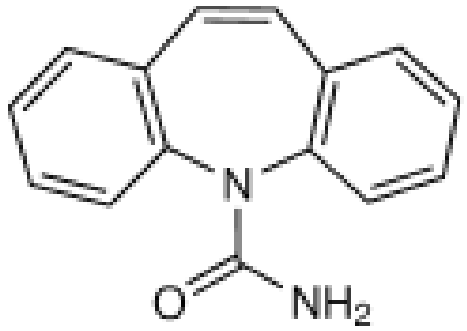
- The relationship between plasma concentration of phenobarbital and adverse effects varies with the development of tolerance.

- Sedation, nystagmus, and ataxia usually are absent at concentrations below 30 μg/ml during long-term therapy, but adverse effects may be apparent for several days at lower concentrations when therapy is initiated or whenever the dosage is increased.

Mephobarbital (MEBARAL) is *N*-methylphenobarbital. It is *N*-demethylated in the hepatic endoplasmic reticulum, and most of its activity during long-term therapy can be attributed to the accumulation of phenobarbital

Carbamazepine:

- Carbamazepine was initially approved in the United States for use as an antiseizure agent in 1974.
- It has been employed since the 1960s for the treatment of trigeminal neuralgia.
- It is now considered to be a primary drug for the treatment of partial and tonic-clonic seizures.



Diffrences with Phenytoin:

Carbamazepine has been found to produce therapeutic responses in manic-depressive patients, including some in whom lithium carbonate is not effective.

Carbamazepine has antidiuretic effects that are sometimes associated with reduced concentrations of antidiuretic hormone (ADH) in plasma.???

Pharmacokinetic Properties:

• The pharmacokinetics of carbamazepine are complex. They are influenced by its limited aqueous solubility and by the ability of many antiseizure drugs, including carbamazepine itself, to increase their conversion to active metabolites by hepatic oxidative enzymes.

• The predominant pathway of metabolism in humans involves conversion to the 10,11-epoxide.

• Hepatic CYP3A4 is primarily responsible for biotransformation of carbamazepine.

• Carbamazepine induces CYP2C, CYP3A, thus enhancing the metabolism of drugs degraded by these enzymes. Of particular importance in this regard are oral contraceptives, which are also metabolized by CYP3A4.

Toxicity:

Acute intoxication with carbamazepine can result in:

- stupor or coma
- hyperirritability
- convulsions
- respiratory depression

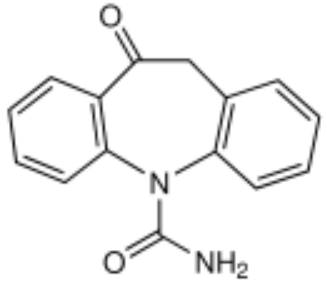
Chronic adverse efects:

- drowsiness
- vertigo
- ataxia
- diplopia
- blurred vision
- increase the frequency of seizures, especially with overdosage
- retention of water, with decreased osmolality and concentration of Na+ in plasma
- Hematologic & hepatic adverse effects
- hepatic or pancreatic abnormalities

Therapeutic Uses:

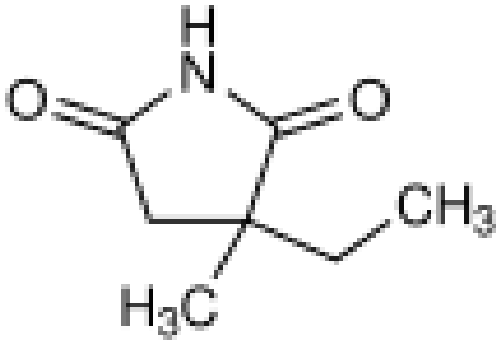
- Generalized tonic-clonic seizures
- Simple and complex partial seizures
- The primary agent for treatment of trigeminal and glossopharyngeal neuralgias
- Use in the treatment of bipolar affective disorders

Oxcarbazepine:



- A keto analog of carbamazepine.
- A prodrug immediately converted to its main active metabolite, a 10-monohydroxy derivative.
- Its mechanism of action is similar to that of carbamazepine
- A less potent enzyme inducer than carbamazepine
- Substitution of oxcarbazepine for carbamazepine is associated with increased levels of phenytoin and valproic acid, because of reduced induction of hepatic enzymes
- Not induce the hepatic enzymes involved in its own degradation
- Not appear to reduce the anticoagulant effect of warfarin
- Induce CYP3A and thus reduces plasma levels of steroid oral contraceptives.
- It has been approved for monotherapy or adjunct therapy for partial seizures in adults and as adjunctive therapy for partial seizures in children ages 4 to 16.

Ethosuximide:



Pharmacokinetic Properties:

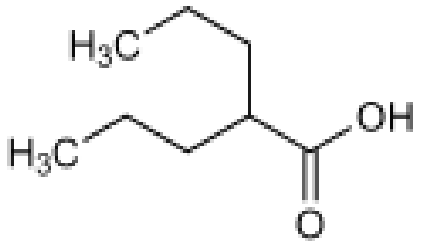
- Absorption of ethosuximide appears to be complete
- Peak concentrations in plasma within about 3 hours
- Not significantly bound to plasma proteins
- During long-term therapy, its concentration in the CSF is similar to that in plasma.
- The apparent volume of distribution averages 0.7 L/kg
- Approximately 25% of the drug is excreted unchanged in the urine.
- The remainder is metabolized by hepatic microsomal enzymes, but whether CYPs are responsible is unknown..
- The plasma half- life of ethosuximide averages between 40 and 50 hours in adults and approximately 30 hours in children.

Toxicity:

The most common dose-related side effects are gastrointestinal complaints (nausea, vomiting, and anorexia) and CNS effects (drowsiness, lethargy, euphoria, dizziness, headache, and hiccough)

Parkinsonlike symptoms and photophobia also have been reported. Restlessness, agitation, anxiety, aggressiveness, inability to concentrate, and other behavioral effects have occurred primarily in patients with a prior history of psychiatric disturbance.

Valproic acid:



The antiseizure properties of valproic acid were discovered serendipitously when it was employed as a vehicle for other compounds that were being screened for antiseizure activity.

a simple branched-chain carboxylic acid

Valproic acid produces effects on isolated neurons similar to those of phenytoin and ethosuximide

It involves metabolism of GABA

Pharmacokinetic properties:

- Its hepatic metabolism occurs mainly by UGT enzymes and β-oxidation

- Its extent of binding to plasma proteins is usually about 90%

•A high proportion of valproate is bound to albumin, and the high molar concentrations of valproate in the clinical setting result in valproate's displacing phenytoin and other drugs from albumin

- Valproate primarily inhibits the metabolism of drugs that are substrates for CYP2C9, including phenytoin and phenobarbital

- Valproate also inhibits UGT and thus inhibits the metabolism of lamotrigine and lorazepam.

- The concurrent administration of valproate and *clonazepam has been associated with the development of absence status epilepticus*

Therapeutic Uses.

Valproate is effective in the treatment of absence, myoclonic, partial, and tonic-clonic seizures

Benzodiazepines:

A large number of benzodiazepines have broad antiseizure properties, but only *clonazepam* and *clorazepate* have been approved in the United States for the long-term treatment of certain types of seizures

Diazepam and lorazepam have well-defined roles in the management of status epilepticus

Benzodiazepines act at subsets of $GABA_A$ receptors and increase the frequency, but not duration, of openings at GABA-activated Cl channeles.

At higher concentrations, diazepam and many other benzodiazepines can reduce sustained high-frequency firing of neurons, similar to the effects of phenytoin, carbamazepine, and valproate

Pharmacokinetic Properties:

- well absorbed after oral administration
- redistributed in a manner typical of that for highly lipid-soluble agents
- Central effects develop promptly, but wane rapidly as the drugs move to other tissues.
- Diazepam is redistributed especially rapidly, with a half-life of redistribution of about 1 hour
- plasma protein binding 99% for diazepam & 85% for clonazepam
- Diazepam & Colorazepat → N-desmethyldiazepam (a less active metabolyte) → Oxazepam
- Clonazepam is metabolized principally by reduction of the nitro group to produce inactive 7-amino derivatives
- Lorazepam is metabolized chiefly by conjugation with glucuronic acid
- Half-life: Diazepam>Clonazepam>lorazepam

Toxicity:

- drowsiness and lethargy(50% of patients)

- Muscular incoordination and ataxia are less frequent

- Behavioral disturbances, especially in children, can be very troublesome; these include aggression, hyperactivity, irritability, and difficulty in concentration

- Cardiovascular and respiratory depression may occur after the intravenous administration of diazepam, clonazepam, or lorazepam, particularly if other antiseizure agents or central depressants have

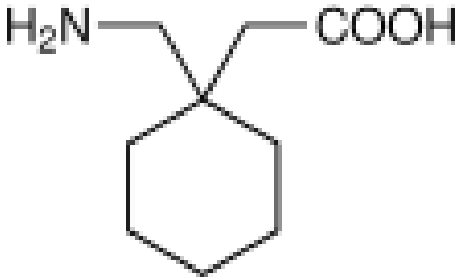
Therapeutic Uses

Clonazepam is useful in the therapy of absence seizures as well as myoclonic seizures in children. However, tolerance to its antiseizure effects usually develops after 1 to 6 months of administration, after which some patients will no longer respond to clonazepam at any dosage

While diazepam is an effective agent for treatment of status epilepticus, its short duration of action is a disadvantage, leading to the more frequent use of lorazepam

clorazepate is effective in combination with certain other drugs in the treatment of partial seizures & is not recommended for children under the age of 9.

Gabapentin:



The anticonvulsant mechanism of action of gabapentin is unknown. Despite its design as a GABA agonist, gabapentin does not mimic GABA when iontophoretically applied to neurons in primary culture. Gabapentin may promote nonvesicular release of GABA through a poorly understood mechanism.

High affinity gabapentin binding sites have been located throughout the brain; these sites correspond to the presence of voltage-gated calcium channels specifically possessing the alpha-2-delta-1 subunit. This channel appears to be located presynaptically, and may modulate the release of excitatory neurotransmitters which participate in epileptogenesis and nociception.

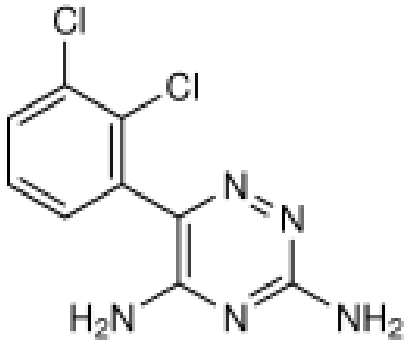
Pharmacokinetics:

- Gabapentin is absorbed after oral administration and is not metabolized in humans.
- It is not bound to plasma protein.
- It is excreted unchanged, mainly in the urine
- It has no known interactions with other antiseizure drugs.

Therapeutic Uses

- Gabapentin is effective for partial seizures, with and without secondary generalization, when used in addition to other antiseizure drugs.
- Gabapentin also is being used for the treatment of migraine, chronic pain, and bipolar disorder.

Lamotrigine:



Lamotrigine is a phenyltriazine derivative initially developed as an antifolate agent based on the incorrect idea that reducing folate would effectively combat seizures

Lamotrigine blocks sustained repetitive firing & delays the recovery from inactivation of Na channels, mechanisms similar to those of phenytoin

Pharmacokinetics:

- Lamotrigine is completely absorbed and metabolized primarily by glucuronidation.
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- The plasma half-life of a single dose is 15 to 30 hours. phenytoin, carbamazepine, or phenobarbital reduces the half-life and plasma concentrations of lamotrigine.
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- Conversely, valproate markedly increases plasma concentrations of lamotrigine, likely by inhibiting glucuronidation.
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- Addition of lamotrigine to valproic acid produces a reduction of valproate concentrations by approximately 25% over a few weeks

- Concurrent use of lamotrigine and carbamazepine is associated with increases of the 10,11-epoxide of carbamazepine and clinical toxicity in some patients.

Therapeutic Use:

monotherapy and add-on therapy of partial and secondarily generalized tonic- clonic seizures in adults and Lennox-Gastaut syndrome in both children and adults.

Lennox-Gastaut syndrome is a disorder of childhood characterized by multiple seizure types, mental retardation, and refractoriness to antiseizure medication.

Toxicity:

- Dizziness, ataxia, blurred or double vision, nausea, vomiting
- Rash when lamotrigine was added to another antiseizure drug.
- A few cases of Stevens-Johnson syndrome and disseminated intravascular coagulation have been reported.

Levetiracetam:

The mechanism of action is unknown.

No evidence for an action on voltage-gated Na^+ channels or either GABA- or glutamate-mediated synaptic transmission has emerged

Pharmacokinetics:

It is rapidly and almost completely absorbed after oral administration & not bound to plasma proteins.

Ninety-five percent of the drug and its inactive metabolite are excreted in the urine, 65% of which is unchanged drug; 24% of the drug is metabolized by hydrolysis of the acetamide group.

It neither induces nor is a high- affinity substrate for CYP isoforms or glucuronidation enzymes and thus is devoid of known interactions with other antiseizure drugs, oral contraceptives, or anticoagulants.

Tiagabine:

- Tiagabine inhibits the GABA transporter, GAT-1, and thereby reduces GABA uptake into neurons and glia
- It has clinical efficacy against partial and tonic-clonic seizures.

Pharmacokinetics:

Tiagabine is rapidly absorbed after oral administration, extensively bound to serum or plasma proteins, and metabolized mainly in the liver, predominantly by CYP3A.
Its half-life of about 8 hours is shortened by 2 to 3 hours when coadministered with hepatic enzyme-inducing drugs such as phenobarbital, phenytoin, or carbamazepine

The fact that tiagabine and other drugs thought to enhance effects of synaptically released GABA can facilitate spike-and-wave discharges in animal models of absence seizures raises the possibility that tiagabine may be contraindicated in patients with generalized absence epilepsy.

Topiramate:

Topiramate reduces voltage-gated Na currents similar to that of phenytoin.
It activates a hyperpolarizing K current, enhances postsynaptic GABA -receptor currents, and also limits activation of the AMPA-kainate-subtype(s) of glutamate receptor.
It also is a weak carbonic anhydrase inhibitor(renal calculi)

Reduced estradiol plasma concentrations occur with concurrent topiramate, suggesting the need for higher doses of oral contraceptives when coadministered with topiramate.

The most common adverse effects are somnolence, fatigue, weight loss, and nervousness.

Zonisamide:

- It inhibits the T-type Ca^{2+} currents

- It inhibits the sustained, repetitive firing of spinal cord neurons by prolonging the inactivated state of voltage-gate Na^{+} channels

- Phenobarbital, phenytoin, and carbamazepine decrease the plasma concentration/dose ratio of zonisamide, whereas lamotrigine increases this ratio

- Addition of zonisamide to other drugs in refractory partial seizures is effective

- Approximately 1% of individuals develop renal calculi during treatment with zonisamide, which may relate to its ability to inhibit carbonic anhydrase.

GENERAL PRINCIPLES AND CHOICE OF DRUGS FOR THE THERAPY OF THE EPILEPSIES

Unless extenuating circumstances such as status epilepticus exist, only monotherapy should be initiated.

To minimize dose-related adverse effects, therapy with many drugs is initiated at reduced dosage

If a seizure occurs despite optimal drug levels & confirmed compliance , another drug should be substituted

In the event that therapy with a second single drug also is inadequate, many physicians resort to treatment with two drugs simultaneously

It

It seems wise to select two drugs that act by distinct mechanisms

Additional issues that warrant careful consideration are the unwanted effects of each drug and the potential drug interactions.

Once initiated, antiseizure drugs are typically continued for at least 2 years.

Carbamazepine and phenytoin were the most effective overall for single-drug therapy of partial or generalized tonic-clonic seizures.

Control of secondarily generalized tonic-clonic seizures did not differ significantly with carbamazepine, phenobarbital, or phenytoin.

The best data indicate that ethosuximide and valproate are equally effective in the treatment of absence seizures.

Thank you