SEIZURES
PHARMACOLOGY

University of Hawai‘i Hilo Pre-Nursing Program
NURS 203 – General Pharmacology
Danita Narciso Pharm D
LEARNING OBJECTIVES

- Understand the pharmacodynamics involved in the medications used to treat seizures
- Understand what a seizure is and the general principles behind treatment
- Understand the differences between the classes of medications to treat seizures
- Know the difference between seizure, convulsions, epilepsy, and status epilepticus
A seizure is an electrical disturbance in the brain that can affect consciousness, motor activity, and sensation.

Epilepsy is a condition associated with periodic unpredictable seizures.

Types of seizures:
- Partial (focal) – abnormal neuronal firing in one brain area in one hemisphere
- Generalized – abnormal neuronal firing that progresses to the involvement of many neurons in both hemispheres
- Special syndromes

WHAT IS A SEIZURE?
STATUS EPILEPTICUS (SE)

- A deadly seizure or seizures
  - 1 in 5 is deadly
- Greater than 30 minutes in length
  - Any seizure > than 5 minutes can progress to SE
- 1 continuous seizure or multiple seizures with no gain of consciousness between seizures
- Can cause neuronal damage
WHAT CAUSES SEIZURES?

- Infectious illness (meningitis/encephalitis)
- Trauma (brain/head)
- Metabolic disorders (changes in glucose, sodium, or water that can alter electrical impulses)
- Vascular diseases (affecting respiratory gases and changes in perfusion due to hypotension, stroke, shock, or arrhythmias)
- Pediatric disorders (fever)
- Cancer (Rapidly growing tumors occupying brain space and disrupting blood flow to areas of the brain)
Chloride ion hyperpolarizes the cell
Calcium anion polarizes the cell
Sodium anion polarizes the cell
HOW WE ATTEMPT TO TREAT SEIZURE

- Chloride ion hyperpolarizes the cell
- Calcium anion polarizes the cell
- Sodium anion polarizes the cell

NORMAL

SEIZURE
Treatment is based on
- Signs/symptoms
- Past medical history
- Comorbid disease states/pathologies

Drug therapy doses
- Start low & go slow
- Increase until symptoms resolve or ADRs become intolerable
- Additional medications
- Taper
MEDICATIONS WE USE TO TREAT SEIZURES

- Drugs that stimulate the actions of GABA
  - Benzodiazepines
  - Barbiturates
- Drugs that inhibit the influx of sodium
- Drugs that inhibit the influx of calcium
Uses
- Glaucoma, edema, **centrencephalic epilepsies** & symptoms of acute mountain sickness

Kinetics
- **Onset** – tables 1-2 hours (IR/ER), IV 2-10 minutes
- **Duration** – ER (18-24 hours), IR, (8-12 hours), IV (4-5 hours)
- **Protein bound** – 95%
- **Absorption** – dose dependent, erratic

Kinetics cont.
- **Distribution** - **Erythrocytes, kidneys, BBB**
- **Half life** – 2.4-5.8 hours
- **Excretion** – urine (70-100%), extended release capsule 47% as unchanged drug

ADRs
- Flushing, convulsions, depression, photosensitivity, decreased appetite, D/N/V, tinnitus, polyuria, renal failure

Interactions
- Use carefully with other CNS agents
- Pregnancy C
- Excreted in breast milk

**ACETAZOLAMIDE** – MOA FOR SEIZURES IS NOT KNOWN
• SV2A protein
  • Involved in the modulation of synaptic vesicle release

• Levetiracetam
  • Binds to SV2A
  • Exact mechanism and activity not known
LEVETIRACETAM – ALTERS NT RELEASE VIA SYNAPTIC VESICLE MODULATION

- **Uses**
  - Myoclonic, partial-onset, generalized tonic-clonic seizures

- **Kinetics**
  - **Absorption** – rapid/complete (oral), Tmax & Cmax increase when taken after a high fat/calorie meal (breakfast)
  - **Metabolism** – not extensive (liver)
  - **Half life** – 6-8 hours
  - **Excretion** – urine (66% unchanged)

- **ADRs**
  - Increase BP (children), behavioral issues, HA, drowsiness, vomiting, infection, weakness, nasopharyngitis

- **Interactions**
  - Minor – CNS depressants
  - Pregnancy C
  - Excreted in breast milk
- Decrease GABA metabolism
  - Enzymes involved
    - GABA transaminase
    - Succinic semialdehyde dehydrogenase

Valproic Acid

Involved in the breakdown of GABA
Under normal circumstances
- Sodium enters the cell
- Threshold is met
- Action potential takes place

Sodium channel inactivation gate
- Blocks the Na channel
- Inhibits the influx of sodium
- Delays actions potential
- Prolong refractory period
Blockade of the L & T type calcium channels

- **L-type Ca++ Gabapentin**
- **T-type Ca++ Valproic Acid**
DRUGS THAT MIMIC OR STIMULATE GABA
- Benzodiazepines (diazepam)
  - Others also used
  - Uses – convulsive disorders, adjunct to refractory epilepsy (rectal gel) for patients already on stable therapy
- Dosage forms
  - Oral (Solution, tablet)
  - Injection (IM & IV)
  - Rectal
- Pregnancy D
- Metabolite in breast milk

- Barbiturates (phenobarbital)
  - Uses – Generalized tonic-clonic, status epilepticus, partial seizures, sedation
- Dosage forms
  - Oral
  - Injection
- Kinetics
  - Protein binding – 20-45%
  - Metabolism – CYP2C19
  - Half life – 2-5 days
- ADRs
  - Sedation, bradycardia, hypotension, drowsiness, dizziness, HA, N/V, constipation
- Interactions
  - MAJOR!!!! CYP enzyme inducer (3A4, 1A2, 2C9, & more)
  - Pregnancy B/D
  - Found in breast milk
GABAPENTIN – BLOCKS L-TYPE CALCIUM CHANNELS

- **Uses** – Partial onset seizures
- **Kinetics**
  - Absorption – variable
  - Protein bound - < 3%
  - Half life – 5-7 hours
  - Excretion – urine (unchanged drug) amount proportional to renal function
- **ADRs**
  - Dizziness, drowsiness, fatigue, ataxia, infection
- **Interactions**
  - CNS depressants (safe with other anticonvulsants)
  - Pregnancy C
  - Excreted in breast milk
- **Dose adjusted per renal function (renaly dosed)**
LAMOTRIGINE – WORKS ON SODIUM CHANNELS

- **Uses** – **Epilepsy (monotherapy or adjunct)**
- **Kinetics**
  - Absorption – immediate & rapid
  - Metabolized – Liver & kidney
  - Half life – 25-33 hours (longer in the elderly, with co-administration, & liver damage)
  - Excretion – urine (90-94% - only 10% as unchanged drug), feces 2%
- **ADRs**
  - HA, dizziness, insomnia
  - BBW
    - Stevens-Johnsons syndrome (SJS)
    - Toxic epidermal necrosis (TEN)
- **Interactions**
  - Substrate for CYP3A4 (3A4 inducers)
  - Valproic acid (increase lamotrigine levels – UGT inhibition)
  - Pregnancy C
  - Excreted in breast milk
Phenytoin (fosphenytoin IV)
- **Uses** – Generalized tonic-clonic & complex partial
- **Kinetics**
  - Administration – oral
  - Absorption – slow but almost complete
  - Distribution – very lipophilic
  - Protein bound – 90%
  - Metabolized – Liver (CYP2C9 & 2C19)
  - Half life – 2-22 hours (higher concentrations = higher half lives – enzyme saturation)
- **ADRs**
  - Gingival hyperplasia (excessive growth of gum tissue), rash (measles-like), acne, hirsutism (hair growth), GI distress, vitamin D deficiency, osteomalacia, folic acid deficiency, lymph node hyperplasia, teratogenic (similar to fetal alcohol syndrome)
  - Nystagmus (oscillations of the eyes), diplopia (double vision), ataxia, drowsiness (signs of toxicity)
- **Interactions**
  - Warfarin, NSAIDS (increase risk of bleed)
  - **MAJOR!!!** CYP inducer (3A4, 2C9, 2C19, & more)
  - Pregnancy D
  - Excreted in breast milk

**HYDANTOINS – PHENYTOIN (INCREASED REFRACTORY PERIOD THROUGH PROLONGED CLOSURE OF THE INACTIVATION GATE ON NA CHANNEL)**
TOPIRAMATE – SODIUM CHANNELS

- **Uses**
  - Epilepsy & migraine

- **Kinetics**
  - Absorption – Good/rapid
  - Metabolism – liver, renal reabsorption (increased by inducers)
  - Half life – 21-56 hours (depending on product)
  - Excretion – urine (70% unchanged drug)

- **DRRs**
  - Drowsiness, fatigue, **weight loss**

- **Interactions**
  - CYP inducers, CNS depressants
  - Mostly minor
  - Pregnancy D
  - Excreted in breast milk
- **Carbamazepine**
  - Uses – Partial seizures & generalized tonic-clonic, bipolar disorder, alcohol withdrawal
  - Kinetics
    - Administration – oral
    - Distribution – very lipophilic
    - Metabolism – hepatic (CYP3A4) to active metabolite
    - Half life – 25-65 hours
  - ADRs
    - GI distress, nystagmus, diplopia, ataxia, SJS
    - BBW – aplastic anemia & agranulocytosis
  - Interactions
    - Valproic acid – inhibits one of the metabolic enzymes of carbamazepine
    - **MAJOR!!!! CYP enzyme inducer (3A4, 2C9, 2C19, 1A2, & more)**
      - **EVEN INDUCES ITSELF**
    - Pregnancy D
    - Active metabolites in breast milk

- **Oxcarbazepine**
  - Prodrug of carbamazepine
  - Uses – Partial seizures
  - Differences
    - No blood dyscrasias
    - Less CYP inducer activity

**CARBOXAMIDES** - **INCREASED REFRACTORY PERIOD THROUGH PROLONGED CLOSURE OF THE INACTIVATION GATE ON NA CHANNEL**
VALPROIC ACID – SODIUM CHANNEL, CALCIUM CHANNEL, GABA METABOLISM, & MORE EFFECTS

- **Uses**
  - Partial & simple & complex absence seizure

- **Kinetics**
  - Administration – oral & injection
  - Absorption – rapid
  - Metabolism – Liver
  - Half life - 9-16 hours
  - Excreted – urine (inactive metabolites)

- **ADRs**
  - N/V/anorexia, drowsiness, dizziness, lethargy, HA, tremor, hair loss, teratogenic (neural tube), increased blood nitrogen, thrombocytopenia

- **BBW**
  - Liver failure, pancreatitis, teratogenicity

- **Interactions**
  - Increases concentrations of carbamazepine, lamotrigine, lorazepam, rufinamide
  - Pregnancy X
  - Excreted in breast milk
LACOSAMIDE — ENHANCES SLOW ACTIVATION OF SODIUM CHANNELS

- **Uses** — Partial onset seizure (monotherapy or adjunct)
- **Kinetics**
  - Absorption — complete
  - **Metabolism** — CYP3A4, 2C9, 2C19 — inactive metabolite
  - Half-life — 13 hours
  - Excretion
    - Urine 95%
      - 40% unchanged drug
      - 30% inactive metabolite
      - 20% uncharacterized metabolite
    - Feces < 0.5%
- **ADRs**
  - Dizziness, fatigue, ataxia, HA, N/V, tremor, diplopia, blurred vision
- **Interactions**
  - Substrates & inhibitors of CYP enzymes
  - Otherwise minor
  - Pregnancy C
  - Unknown if excreted in breast milk
Pregnancy

- Drugs to treat seizures may decrease effectiveness of OCPs
- Additional protection recommended
- Many drugs are category D or worse
- Great care must be used

- Brand medically necessary
- High fat/low carb diet or fasting
  - Side effects

SEIZURES & PREGNANCY & OTHER CONSIDERATIONS