Epilepsy

- Approximately 1% of world population suffers from epilepsy
- Results from abnormal firing of cortical neurons resulting in a paroxysmal depolarizing shift
- Seizure classification:
  - Focal
  - Generalized
- Treatment modalities depend on type of disorder and presentation
Anticonvulsants

• Goal of treatment
  • prevent the initiation of abnormal electrical firing or prevent the generalization of abnormal firing
• 4 major mechanisms of anticonvulsant activity
  • Sodium channel blockade
  • GABA agonism
  • Calcium channel antagonism
  • Inhibition of excitatory amino acids

Anticonvulsants

• Phenobarbital

Phenobarbital

• One of oldest sedative hypnotics on market
• Rarely used with advent of benzodiazepines and propofol
• Often used in management of status epilepticus and alcohol withdrawal syndromes
Phenobarbital Mechanism

- Bind to GABA receptor and open Cl- channel resulting in hyperpolarizing of neuron

Phenobarbital Toxicity Clinical

- Patients present with slurred speech confusion coma
- Hyperpolarization of neurons in medulla leads to hypoventilation and respiratory failure
- Decreased vasomotor tone and ionotropy may lead to cardiovascular collapse
- Pts may progress from nystagmus to absent pupillary light reflex

Phenobarbital Toxicity – Treatment

- Aggressive supportive care
- Consider MDAC
Anticonvulsants

Phenytoin

Fosphenytoin

Anticonvulsants

Phenytoin

Fosphenytoin

• First line treatment for seizure disorders
• Not indicated in management of seizure related to toxins
• Cannot be administered IM

• Water soluble pro-drug
• Converted to phenytoin by phosphatases
• May be administered IM

Phenytoin Mechanism

• Binds to sodium channel in inactive state
• Results in time, usage and voltage dependent blockade of AP
• Promotes sodium efflux from neurons
• Reduces post-tetanic potentiation at synapses preventing propagation of seizure focus
Phenytoin Toxicity - Clinical

- Increasing neurologic dysfunction with predominately cerebellar signs
  - Ataxia, nystagmus, confusion
- No reports of cardiotoxicity from PO ingestion
- Cardiotoxicity and hemodynamic collapse occur with rapid IV infusion
  - Due to diluents (propylene glycol and ethanol)

Phenytoin Toxicity

- Narrow therapeutic window
  - Saturable kinetics
- Therapeutic concentration 10-20 mcg/mL
  - Above these concentrations converts to zero-order kinetics
  - t1/2 increases with increasing plasma levels

Phenytoin Toxicity - Treatment

- Primarily supportive
- May use multidose activated charcoal, however beware of precipitating seizure as concentrations decline
Phenytoin Adverse Effects

- Hematologic: Dyscrasias, aplastic anemia, pseudolymphoma
- GI: Hepatotoxicity
- Immunologic: Decreased IgA, lupus-like syndrome
- Neurologic: Peripheral Neuropathy, idiopathic intracranial hypertension

Anticonvulsants

<table>
<thead>
<tr>
<th>Carbamazepine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oxcarbazepine</td>
</tr>
</tbody>
</table>

- First line treatment in epilepsy
- Preferred agent for seizure control in pregnancy
- Unpredictable absorption
- Potent CYP3A4 inducer

- Keto-analog of carbamazepine
- Functions as a prodrug
- Less effect on CYP3A4
Carbamazepine Mechanism

• Mechanism of action is sodium channel blockade

• Therapeutic concentration 8-12 mg/L

Carbamazepine Toxicity - Clinical

• Chronic toxicity mimics cerebellar syndrome with ataxia, nystagmus and confusion

• Seizures are common even in patients with no previous seizure history

• Anticholinergic effects lead to tachycardia, mydriasis and confusion

• Acute OD may result in waxing and waning level of consciousness, prolonged coma

• Often due to bezoar formation and enterohepatic recirculation

Carbamazepine Toxicity

• Symptoms may be delayed due to erratic absorption

• Concentrations of >12 mg/L may produce drowsiness and neurologic findings

• Sodium channel blockade results in wide complex tachycardia

• Qtc prolongation may occur

• SIADH
Carbamazepine Treatment

- ABCs
- Treat seizures with benzodiazepines
- Consider Sodium Bicarbonate for QRS > 100 ms
- MDAC decreases enterohepatic recirculation.

Oxcarbazepine

- Generally thought to be less toxic
- No routine measurement of serum concentrations
- Supportive care

Carbamazepine – Adverse Effects

- Hematologic: Agranulocytosis, aplastic anemia, thrombocytopenia
- GI: Hepatotoxicity
- Cardiac: Myocarditis
- Dermatologic: Photosensitivity, morbilliform rash
Anticonvulsants

• Valproic acid

Valproate - Mechanism

• Anticonvulsant approved in 1995 for mania (mood stabilizer)
• Therapeutic Concentration 30-120 mg/L
• Increases GABA (inhibits degradation)
• Frequency dependent Na+ effects
  – Slows rate of recovery from inactivation

Valproate
Valproate Toxicity

- GI – nausea, vomiting
- CNS – sedation, respiratory depression, ataxia, seizure, coma
- Hyperammonemia, hypernatremia, hypocalcemia, metabolic acidosis
- Presentation can be delayed with sustained-release products

Valproate Treatment

- MDAC
- Naloxone (reverse sedation)
- Supportive care
- Carnitine
  - Hyperammonemia and altered mental status
  - PO 12.5 mg/kg q 8
  - Children max 2 g per day
  - IV 50 mg/kg bolus; 20 mg/kg q 4
  - Maximum 10 g/day

Valproate – Adverse Effects

- Hematologic: Thrombocytopenia
- GI: Pancreatitis, hepatotoxicity, hyperammonemia
- Neurologic: Encephalopathy
Anticonvulsants

- Levetiracetam

Levetiracetam - Mechanism

- Not well described
- Blocks N-type calcium channels on the presynaptic terminal of neurons
- Therapeutic concentration: 10-70 mg/L
- Not routinely monitored

Levetiracetam - Toxicity

- Generally benign
- Neuro: Ataxia, nystagmus, lethargy
Levetiracetam - Treatment

- Treatment is supportive
- Treat seizures with benzodiazepines

Anticonvulsants

- Lamotrigine

Lamotrigine - Mechanism

- Blocks pre and post synaptic sodium channels
Lamotrigine Toxicity Clinical

- Neuro: Lethargy, ataxia, nystagmus
- Cardiac: QRS widening 2/2 sodium channel blockade

Lamotrigine Toxicity Treatment

- Activated charcoal
- Supportive care
- Benzodiazepines for seizures

Lamotrigine Adverse Effects

- Hematologic: Agranulocytosis
- Dermatologic: Stevens-Johnson, TEN
- GI: hepatotoxicity
Anticonvulsants

- Gabapentin

Gabapentin Mechanism

- Mostly used for pain syndromes
- GABA modulator
- May affect post-synaptic calcium channels
- Therapeutic concentration 2-15 mg/L

Gabapentin Toxicity - Clinical

- Neurologic: Sedation, ataxia, lethargy
Gabapentin Toxicity - Treatment

- Supportive care
- Consider AC
- No role for flumazenil

Gabapentin Adverse Effects

- Dystonia, asterixis

Anticonvulsants

- Topiramate
### Topiramate Mechanism

- Unclear
- Some sodium channel blockade
- GABA effects
- Therapeutic range: 4-30 mg/dL

### Topiramate Toxicity Clinical

- Neurologic: Lethargy, ataxia, nystagmus, coma
- Echolalia

### Topiramate Toxicity - Lab

- Non-anion gap metabolic acidosis
- Elevated serum chloride
- Hypokalemia
- Acidosis may persist for days
Topiramate Toxicity - Management

- AC
- Supportive Care
- Metabolic acidosis may be treated with sodium bicarbonate 1-2 mEq/kg IV
- Consider dialysis

Anticonvulsants

- Tiagabine

Tiagabine Mechanism

- Inhibits reuptake of GABA in presynaptic terminal
- Therapeutic concentrations 5-70 ng/mL
Tiagabine Toxicity Clinical

• Neurologic: Lethargy, nystagmus, grimacing, seizure

Tiagabine Toxicity Treatment

• AC
• Phenobarbital for seizures

Miscellaneous Anticonvulsants

• Ethosuximide – May block t-type calcium channels.
  • Used in absence seizures
  • May cause pancytopenia, hepatotoxicity
• Vigabatrin – inhibits GABA-transaminase
  • Psychosis
• Felbamate – has weak inhibitory effects at the GABA receptor.
  • Reversible renal failure, crystalluria, hepatic failure, aplastic anemia
• Zonisamide – Inhibits sodium and T-type calcium channels
  • Coma
Proconvulsant Agents

• INH
• Gyrometria spp
• Theophylline
• Phenylbutazone
• Tramadol
• Buproprion

• Camphor
• Organochlorines
• Lidocaine
• Quinine
• Rhododendron
• Cicutoxin

Microbial Neurotoxins

Botulism
Several Types

- Infant Botulism – 72%
- Foodborne Botulism – 24%
- Wound Botulism
- Adult Infectious Botulism

http://neuromuscular.wustl.edu/neuromuscular/bot.htm#ref1

Botulism

- Toxin produced by a spore forming gram-positive bacillus, *Clostridium botulinum*
- Spores resilient
- Withstand boiling
- Produce toxin in anaerobic milieu
- Most toxic substance known
  - Human lethal dose is 1 ng/kg, heat labile toxin
- 7 types (A-G): A, B, E most common

Botulism

- Type A - West of Mississippi
- Type B - East of Mississippi
- Type E - Pacific NW, Alaska
- In the U.S. less than 200 cases annually.

Long, PPPID 2008
MUKTUK (MEAT INSIDE SKIN AND FAT OF A WHALE)

After taken from whale, leave 2 days hanging up to dry. Cut into 6” x 6” pieces. Cook until tender. After cooked, keep in a cool place in a 45-gallon drum of oil, in order to have muktuk all year.

Botulism

• Symptoms develop 1-3 days after inhalation or ingestion. Bulbar palsy (dysarthria, dysphagia, blurred vision, ptosis).
• Disease progresses to affect skeletal muscles, producing descending, symmetrical, flaccid paralysis.
• May lead to respiratory failure.

http://www2.cdc.gov/phtn/botulism/alaska/alaska.asp
Botulism

- Botulinum Toxin
  - Consists of 2 polypeptide chains of 100 kD (heavy chain) and 50 kD (light chain) linked by disulfide bond
  - After absorption, the toxin binds irreversibly to receptors on presynaptic cholinergic and adrenergic nerve endings and a portion is internalized
  - Light chain is a Zn$^{2+}$-containing protease that hydrolyzes the intracellular proteins needed for vesicle fusion.
  - Acetylcholine stored in vesicles is unable to be released.

Botulism

- Serotypes A and E cleave SNAP-25 (synaptosome-associated protein weighing 25K daltons) that is a protein that is membrane bound on the cytosol side.
- Serotype B cleaves a protein associated with acetylcholine storage vesicles in the cytoplasm (VAMP/ synaptobrevin).

Botulism - Exam

- Pts with botulism are alert, oriented, afebrile.
- Neurologic exam: Bulbar palsies, flaccid paralysis, sensation intact.
- Often several patients will simultaneously present with progressive descending flaccid paralysis.
- However may be difficult to diagnose if patients go to different hospitals
  - "Four Ds":
    - Diplopia
    - Dysarthria
    - Dysphonia
    - Dysphagia
Botulism Types

- Infant and Adult infectious botulism from ingestion of spores.
  - Predisposition in people with abnormal gut
  - Relative achlorhydria in infants
  - Spores elaborate toxin.
  - Occasionally found in honey

Botulism

- Foodborne Botulism
  - Ingestion of improperly canned or prepared food.
  - Toxin is elaborated in food.
  - Patients present with nausea, vomiting and diarrhea – sx develop early.
  - Occasionally present with odynophagia
  - Often delayed diagnosis as neurologic features lag behind.
  - Subtle neuro sx may include anticholinergic features

Botulism

- Wound Botulism
  - Acquired by IVDU, skin popping
  - Traumatic injuries with contamination
  - Bacteria replicate, elaborate toxin
  - Neuro sx predominate
Botulism Diagnosis

- Diagnosis is clinical.
- Classic EMG finding is brief, small, abundant motor unit action potentials to repetitive stimulation.

Botulism Testing

- Laboratory tests are not very useful
- Definitive testing: Mouse toxicity assay, immunoassay, available at CDC (and other governmental labs).

Botulism Treatment

- Toxin destroyed by
  - Heating food > 85°C (185°F) for 5 minutes
  - Direct sunlight for 1-3 hours
  - Chlorine
- Limited supply of antitoxin available through CDC –
  - Bivalent treats A & B
  - Trivalent: Treats A, B, E
- USAMRIID has investigational antitoxin and toxoid preparations – pentavalent: Treats A, B, C, D, E
Botulism

- Antitoxin is effective in animals if administered early after exposure, before development of serious symptoms. Will not reverse existing paralysis.
- Recombinant vaccines are under development.

Baby BIG

- Lyophilized powder of IgG.
- Purified immunoglobulin derived from pooled adult plasma from persons immunized with pentavalent botulinum toxoid.
- Donors selected for high titers of neutralizing antibody against botulinum neurotoxins type A and B.

Botulism

- Respiratory failure is most common cause of death.
- Monitor pts for respiratory muscle weakness:
  - Assess adequacy of gag and cough reflexes
  - Dangerous sign – drooling
- Monitor respiratory parameters: Oxygen sat., VC, NIF
- Mechanical ventilation is the most important treatment.
Tetanus

- *Clostridium tetani*
- Gram + obligate anaerobic rod
- Found in soil, manure

Tetanus

- At risk populations
- Unvaccinated, neonates, IVDU
Tetanus

- Spores enter through breach in the skin
- Tetanospsamin exotoxin spreads by retrograde axonal transport to CNS

Tetanus

- Toxin composed of 2 polypeptide chains
  - Heavy (100 kD) and light chain (50 kD)
  - β - chain binds to gangliosides on neurons
  - α - chain targets vesicle-associated membrane protein in presynaptic terminals
  - Cleaves synaptobrevin, preventing release of glycine and GABA

Tetanus - Exam

- Diffuse muscle spasms precipitated by light and noise.
- Often starts in mouth – risus sardonicus
- Spreads to rest of body
- Pt alert and oriented during episodes
- Autonomic instability
Tetanus

• Benzodiazepines for muscle spasms
• Metronidazole 1 g IV q 12 x 7-10 days
• Treat autonomic dysfunction with labetalol
• Surgical debridement of wound
• Give human tetanus immune globulin 5000 U IM to neutralize unbound toxin
• Keep pt in a dark quiet room as noise or light may precipitate spasms

Tetanus

• Immunization in ED has reduced incidence of tetanus in USA
• Consider immunization if patient has not been updated in > 5 years.
Neurotoxic Plants

- *Strychnos nux-vomica*
  - Strychnine – pesticide for rodents and coyotes
  - Binds to α subunit of glycine receptor in spinal cord and prevents Cl⁻ entry into cell
  - Results in tetanus-like syndrome

Neurotoxic Plants

- *Anamirta cocculus*
  - Picrotoxin – Fish poison
  - Blocks GABA₉ receptor
  - Results in seizures
Neurotoxic Plants

• *Lathyrus sativa*
  - Grass pea contains glutamate analog β-N-oxalyl-L-α,β-diaminopropionic acid
  - Activates NMDA receptor and excitotoxicity by increasing calcium in neuron
  - Neurodegeneration of anterior horn cells
  - Clinical findings include BLE cramping, muscle wasting, paralysis

Neurotoxic Plants

• *Cycadophyta spp*
  - Fix nitrogen in roots with species of cyanobacteria that produce β-methylamino-L-alanine (BMAA)
  - Excitotoxin that activates NMDA, AMPA and kainite receptors
  - Depletes glutathione in neuron
  - Causes ALS/Parkinsonian/Dementia syndrome in Chamorro tribe in Guam

Neurotoxic Plants

Glutamic acid

BMAA

ODAP
Neurotoxic Plants

• Bitter Cassava
• Skin contains cyanogenic glycosides linamarin
• Pts develop BLE paresis and spasticity, thought to be due to mitochondrial dysfunction in anterior horn cells
• Syndrome known as Konzo

Basal Ganglia Toxins

• MPTP
• CO
• Cyanide
• Hydrogen Sulfide
• Carbon disulfide
• Manganese
• 3-nitropropionic acid
• Annonaceae alkaloids
• Methanol
• Copper

Movement Disorders

• Chorea
  • Antiparkinsonians
  • Antipsychotics
  • Cocaine
• Dystonia
  • Antiemetics
  • Antipsychotics
  • Levodopa
Movement Disorders

• Dyskinesia
  • Antipsychotics
  • Calcium Channel Blockers
  • Fluvoxamine
• Akathesia
  • SSRIs
  • Antiemetics

Demyelinating Toxins

CNS
  • Hexachlorophene
  • “Chasing the dragon”
  • Arsenic

PNS
  • Nitrous Oxide
  • Tacrolimus
  • Suramin
  • Amiodarone
  • Diptheria

Axonopathies

• N-Hexane
• Vicristine
• Acrylamide
• Thallium
• Triorthocresyl phosphate
• INH
• Platinum
• Colchicine
• Taxol
• Methyl Bromide