Neuropharmacology III

Seizure Medications

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Objectives

- Pathophysiology of seizures
- Seizure classification
- Seizure treatment options
- Principles of therapy
- Special cases:
 - Pregnancy
 - Status epilepticus

Case 1: Febrile Seizure

- 2 y.o. child with URI and fever. Treated with acetaminophen.
- Suddenly eyes rolled back, lost response to voice or touch
- Limbs shook vigorously for 30-40 sec
- Awakened in ER gradually, without treatment
- Three hours later felt well, asked for her toys



Case 2: Daydreaming

- Mother brings her 5 y.o. son to the doctor, worried about his excessive "daydreaming"
- The episodes are frequent, and they start suddenly. He stops speaking and stares into the distance, frequently blinking his eyes and sometimes moving his fingers.
- Just as suddenly he returns to normal
- He has entered first grade, and the teacher says this is disrupting his learning.

Definitions

- Seizure: transient alteration of behavior due to abnormal synchronous electrical activity in the brain
- Epilepsy: condition with recurring, unprovoked seizures

Classification of Seizures

• Focal (Unilateral Onset)

-With or Without cognitive impairment

- Secondary Generalization (usually tonic-clonic)
- Generalized (Bilateral Onset)
 - -Absence or "Petit Mal"
 - -Tonic-Clonic
 - -Other

EEG During an **Absence Seizure**





10:20:19 D.BANANA, 10 secs/screen, 200 µV/cm, 70,0 Hz, 0,500

mont

www.www

Normal Mechanisms Preventing Seizure Activity (1)

Na Channel Inactivation

- Inactivated state establishes absolute & relative refractory periods
- Use-dependent block prevents sustained repetitive firing



Normal Mechanisms Preventing Seizure Activity (2)

Surround Inhibition

- Excitatory projections also activate GABA (inhibitory) interneurons
- Prevent spread of depolarization to adjacent neurons.



Seizure Etiologies

- Genes
- Acquired
 - Infections (e.g. meningitis) or fever
 - Mass effect: tumor or bleeding
 - Stroke, ischemia, concussion
 - Medications or drug withdrawal (alcohol)
 - Metabolic (low sodium, calcium, glucose)
 - Photic stimuli: flashing lights, visual patterns
 - Hyperventilation
 - Sleep deprivation, stress, emotion, startle

Pathways of Seizure Propagation



Tonic-Clonic Seizure

Tonic Phase

- Sudden ${\downarrow}\text{GABA}$ input ${\rightarrow} {\downarrow}\text{surround}$ inhibition
- Burst of activity in
 - Voltage-gated Na⁺ channels,
 - T-type and high-voltage-activated Ca⁺⁺ channels
 - Glutamate (NMDA) neurons

Clonic Phase

- Return of GABA inhibition
- Oscillation between inhibitory GABA and excitatory glutamate (AMPA) neurons

Abnormal Channel Activity in Tonic-Clonic Seizure



Absence Seizure

- Abnormal synchronization of thalamocortical and cortical cells
- Activation of dendritic T-type Ca⁺⁺ channel
 - Puts relay neurons into "sleep" mode rather than "transmit" mode
 - EEG similar to slow-wave sleep (spike and wave)
- Responds well to treatment with a drug that blocks T-type calcium channel (Ethosuximdie)

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Discovery of Antiepileptic Drugs (AEDs)

- Traditional: Random screening of compounds in animal models
- "Rational": Based on presumed biochemical or molecular mechanisms

Anticonvulsant Mechanisms

- Inhibit repetitive activity of neurons

 Slow recovery of inactivated voltage-gated sodium channels
 Inhibition of calcium channels
- Increase inhibitory inputs –GABA enhancers
- Reduce excitatory input –glutamate antagonists

Pharmacotherapy for Focal Seizure With Generalization



Commonly Used AEDs

- Phenytoin / Fosphenytoin
- Carbamazepine / Oxcarbazepine
- Phenobarbital
- Valproic acid
- Lamotrigine
- Topiramate
- Levetiracetam
- Diazepam

Phenytoin

- Slows recovery of inactivated Na⁺ channels
- Understanding pharmacokinetics is crucial:
 <u>hepatic metabolism with saturation kinetics</u>
 induces metabolism of other drugs
- Acute toxicity: nystagmus, ataxia, diplopia
- Chronic toxicity: hirsutism, gum hyperplasia, neuropathy, cerebellar dysfunction
- IV preparation not water soluble; propylene glycol vehicle can cause phlebitis, arrhythmias

Dose-Dependent Kinetics*



Simulation: Not patient data

Fosphenytoin (Cerebyx)



- Prodrug rapidly metabolized to phenytoin
- Water soluble
 - Allows IM administration
 - Eliminates propylene glycol vehicle
- 1200 mg Phenytoin = \$1.50; Fosphenytoin = \$119.00

General Principles for Choosing AEDs

- Most work well for both focal and generalized seizures
- Consider the side-effect profile for the individual patient
 - Importance of sedation
 - Potential for drug interactions
 - Cosmetic effects (phenytoin)

Management of Epilepsy

- Classify, localize and define etiology
- Focus on prevention
- Rx of an isolated seizure may not be necessary.
- Monotherapy preferred, add a second drug only if needed.
 - Drugs have complex interactions
 - Toxicities tend to be similar
- Serum concentration useful, but <u>treat the</u> <u>patient, not the numbers</u>

Management of Epilepsy: Surgical Interventions

- 20-30% of patients with epilepsy do NOT achieve successful treatment with AEDs
- Adding a third AED is rarely helpful
- Surgical consideration when
 - Seizure focus is defined
 - Surgical resection can be performed safely with a low probability of causing a functional impairment worse than the seizure

Temporal Lobectomy



Vagus Nerve Stimulation (VNS)

- VNS can help reduce frequency of seizures in patients with refractory epilepsy
- Works like a pacemaker, sends pulses of stimulation on a regular basis
- Exact mechanism of action is not known, can be activating rhythmic activity of brain stem neurosn

https://www.epilepsy.com/learn/treating-seizures-and-epilepsy/devices/vagus-nerve-stimulation-vns



https://www.researchgate.net/figure/Vagus-nerve-stimulation-VNSDownload-Power-Point-slide-264-KB_fig1_51696122

VNS

- Patients can place a magnet over the pulse generator if they feel the beginning of a seizure.
- In 80% of patients, heart rate increases right before a seizure; newer models of VNS can automatically detect this change in HR and give extra stimulations to abort seizures
- About 50% of patients experience >50% reduction in their seizures in one year



http://emmea.cyberonics.com/en/vns-therapy-for-epilepsy/patients-and-families/testimonials/noel-rome

Deep Brain Stimulation

- DBS of thalamus can reduce the frequency of seizures by 40% in one year, and 75% over 7 years;
- With responsive neurostimulation, the exact location of the seizure is automatically activated.
- Patients can place a magnet over the pulse generator if they feel an aura



https://www.ninds.nih.gov/About-NINDS/Impact/NINDS-Contributions-Approved-Therapies/Brain-stimulation-therapies-epilepsy

Management of Epilepsy

- Patient education regarding driving, swimming, and other activities
- Can taper AEDs gradually and stop if no seizures for two years
- Need to consider possibility of pseudo-seizures, with or without epilptiform seizures

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Pregnancy and anticonvulsants

- All presently available anticonvulsants may have teratogenic effects (~6-8% risk)
- Uncontrolled seizures also have an adverse effect on the fetus and the mother
- First 12 weeks is critical
- Fewest drugs and lowest doses are best
- Avoid valproic acid if possible and give folate supplementation (prevent neural tube defects)
- Abrupt discontinuation of any anticonvulsant is not a good idea

Management of Status Epilepticus

- Continuous seizures for > 5 minutes
- Goal is to stop seizures ASAP (time is brain)
- ABC's: Airway, Breathing, Circulation
- IV access, labs, history and exam
- Thiamin (100mg IV), glucose (50g IV)
- Lorazepam, 1-2 mg IV Q3-5 min to 10 mg total
- Fosphenytoin, 15-20 mg/kg IV or IM
- Phenobarbital, initial dose 5-10 mg/kg IV
- Refractory status requires expert consultation (may need anesthesia in extreme cases).

Case I: Recurrent Febrile Seizures

- Seizures treated with rectal diazepam
- Frequency 3-4/mo. in winter
- No seizures without fevers
- Normal development
- Tonsillectomy ended recurrent fevers - and seizures



Case 2: Daydreaming

- The EEG of the 5 year old boy showed typical spkie and wave pattern seen in patients with absence epilepsy
- Responded well to treatment with Ethosuximide
- At age 7, this drug was tapered and he remained free of seizures
- Normal development, no neurological deficits

Summary

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