Anticonvulsants

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What are Seizures?

- A seizure is a transient alteration of behavior due to abnormal synchronous electrical activity in the brain.
What is Epilepsy?

- Epilepsy is a condition where there are recurring, unprovoked seizures.
EEG during a seizure

Focal onset with secondary generalization

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<th>Baseline</th>
<th>10 sec</th>
<th>1 minute</th>
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<td>CZ-C3</td>
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<td>C3-T3</td>
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<td>T3-SP1</td>
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A Classification of Seizures

- **Partial Seizures (Focal Onset)**
  - Simple Partial
  - Complex Partial
  - with secondary generalization

- **Generalized (Bilateral Onset)**
  - absence
  - myoclonic
  - tonic-clonic
  - other types
Antiepileptics- drug discovery

- Traditional: random screening of compounds in animal models
- “Rational” - based on presumed biochemical or molecular mechanisms.
Target Mechanisms for anticonvulsants

- Inhibit repetitive activity of neurons -
  - blockade of voltage-gated sodium channels
- Increase inhibitory inputs -
  - GABA enhancers
- Reduce excitatory input
  - glutamate antagonists
Drugs for partial and secondarily generalized seizures

- Phenytoin / fosphenytoin
- Carbamazepine
- Barbiturates
- Valproic acid
- New and investigational agents
Phenytoin

- Mechanism: Blocks voltage-dependent Na\(^+\) channels
- Understanding pharmacokinetics is crucial to safe and effective use:
  - hepatic metabolism with saturation kinetics
  - induces metabolism of other drugs
- Acute toxicity: nystagmus, ataxia, diplopia
- Chronic toxicity: hirsuitism, gums, neuropathy, cerebellar dysfunction
- Not water soluble - for IV must be dissolved in propylene glycol
Fosphenytoin (Cerebyx) a “prodrug”

- Fosphenytoin is rapidly metabolized to phenytoin
- Fosphenytoin is water soluble; allows IM administration, and eliminates toxicity of propylene glycol vehicle required for phenytoin
- 1200 mg phenytoin = $1.50; fosphenytoin = $119.00
Carbamazepine

- Blocks voltage-dependent Na$^+$ channels
- Metabolism:
  - hepatic metabolism
  - induces metabolism of itself
  - Induces metabolism of other drugs (other anticonvulsants, OCP’s, warfarin)
  - toxic metabolites

- Toxicity
  - Common: ataxia, diplopia, sedation
  - Rare (but potentially fatal): aplastic anemia (1 in 6 million)
Barbiturates

- Enhances GABA-mediated chloride conductance
- Two commonly used as anticonvulsants:
  - Phenobarbital:
    » PO, IV, or IM
    » Long half-life (100 hours)
    » hepatic metabolism, strong inducer
    » sedating
  - Primidone
    » metabolized to phenobarbital and PEMA
Valproic Acid

- Carboxylic acid
- Effective in both partial and primary generalized seizures
- Oral or IV formulations
- Hepatic metabolism, induces metabolism of other anticonvulsants

Toxicity:
- Common: tremor, weight gain, nausea
- Rare, but potentially fatal: hepatotoxicity. Most common under 2 years and with multiple anticonvulsants.
New and investigational anticonvulsants

- Felbamate
- Gabapentin
- Lamotrigine
- Topiramate

- Tiagabin
- Levliracetam
- Zonisamide

- All of these released since 1994
- None are currently FDA approved for monotherapy
Principles for the management of epilepsy

- Classify, localize and define etiology
- Not every seizure needs to be treated
- Monotherapy preferred
- Treat the patient, not the numbers
- 80% of patients can achieve control with 1 agent, 90% with multiple agents
- Consider surgical approaches
Pregnancy and anticonvulsants

- All presently available anticonvulsants may have teratogenic effects
- Uncontrolled seizures also have an adverse effect on the fetus
- First 12 weeks is critical
- Fewest drugs and lowest doses are best
- Avoid valproic acid if possible (neural tube defects)
- Abrupt discontinuation of any anticonvulsant is not a good idea
Management of Status Epilepticus

- Definition and identification
- Goal is control of seizures with 60 minutes
- ABC’s: Airway, Breathing, Circulation
- IV access, initial 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