

Harvard-MIT Division of Health Sciences and Technology

HST.151: Principles of Pharmacology

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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**

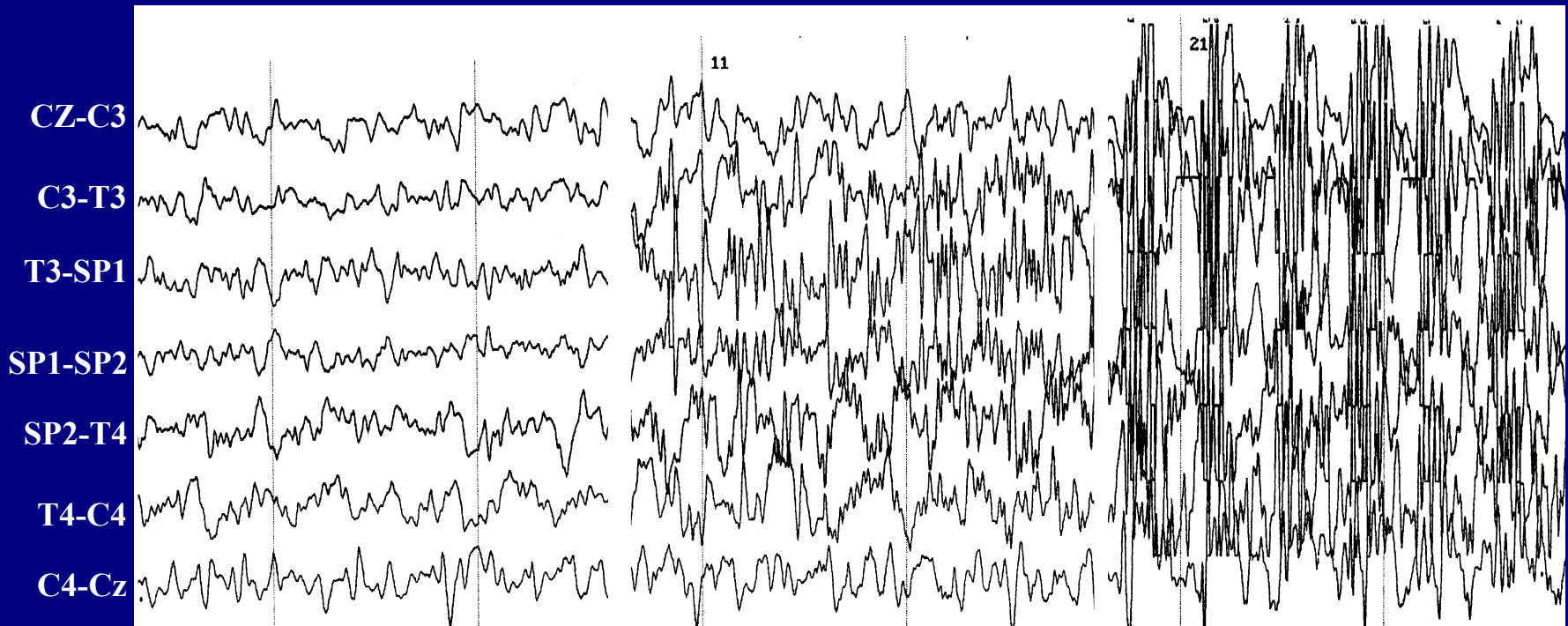
EEG during a seizure

Focal onset with secondary generalization

Baseline

10 sec

1 minute



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*

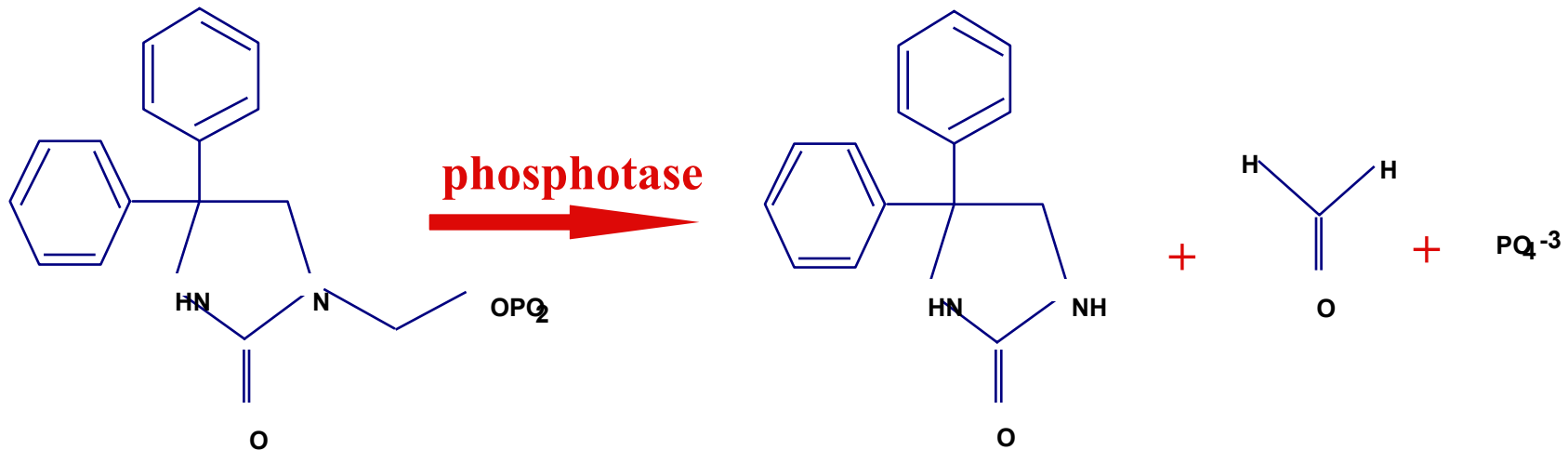
Phenytoin

- ◆ **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: hirsutism, gums, neuropathy, cerebellar dysfunction**
- ◆ **Not water soluble - for IV must be dissolved in propylene glycol**

Fosphenytoin (Cerebyx) a "prodrug"

Fosphenytoin

phenytoin



- ◆ 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

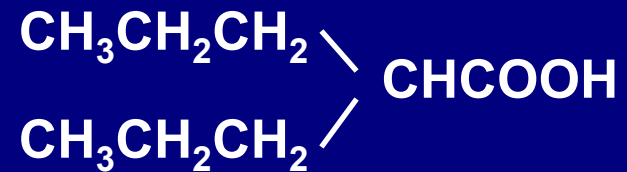
Carbamazepine

- ◆ **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
- ◆ Leviracetam
- ◆ 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