Neuropharmacology of Antiepileptic Drugs

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Outline

• Antiepileptic Drugs (AEDs): Structure and function
• Selection of AEDs: Older, Newer, and Newest AEDs
• Pharmacokinetic issues and drug interactions
• Laboratory monitoring
• Adverse effects
• Special Populations
• Special Formulations
Antiepileptic Drug

♦ A drug that decreases the frequency and/or severity of seizures in people with epilepsy

♦ Treats the symptom of seizures, not the underlying epileptic condition

♦ Goal—maximize quality of life by minimizing seizures and adverse drug effects
History of Early AED therapy and Epilepsy Surgery

• “Some have freed themselves from such a disease by drinking the hot blood from the cut throat of a gladiator: a miserable aid made tolerable by a malady still more miserable” Celsus c.30AD

• “To drive an iron nail into the place first struck by the head of an epileptic in his fall is said to be deliverance from that malady” Pliny the Elder 23-79 AD
Early antiepileptic agents

• Brain of a vulture
• Blood of a turtle
• Heart of a raw cormorant
• Excrement of a crocodile
• Testes of a boar
• Bile of a weasel
• Bones of a chameleon
History of Antiepileptic Drug Therapy in the U.S.

- 1857 - Bromides
- 1912 - Phenobarbital
- 1937 - Phenytoin
- 1954 - Primidone
- 1960 - Ethosuximide
History of Antiepileptic Drug Therapy in the U.S.

- 1974 - Carbamazepine
- 1975 - Clonazepam
- 1978 - Valproate
- 1993 - Felbamate, Gabapentin
- 1995 - Lamotrigine
- 1997 - Topiramate, Tiagabine
- 1999 - Levetiracetam
- 2000 - Oxcarbazepine, Zonisamide
- 2005 - Pregabalin
Major AEDs marketed in the US

- Zonisamide
- Oxcarbazepine
- Levetiracetam
- Tiagabine
- Topiramate
- Fosphenytoin
- Lamotrigine
- Gabapentin
- Felbamate
- Valproate
- Carbamazepine
- Primidone
- Ethosuximide
- Phenytoin
- Phenobarbital

Period since introduction
Antiepileptic Drug Therapy
Structures of Commonly Used AEDs

Chemical formulas of commonly used old and new antiepileptic drugs

*Adapted from Rogawski and Porter, 1993, and Engel, 1989*
Antiepileptic Drug Therapy
Structures of Commonly Used AEDs

Valproic Acid
Felbamate
Gabapentin

Lamotrigine
Tiagabine
Topiramate
Antiepileptic Drug Therapy
Structures of Commonly Used AEDs

Levetiracetam

Oxcarbazepine

Zonisamide
Abnormal Excitation

Excitation:
- Ionic: inward Na\(^+\), Ca\(^{++}\) currents
- Neurotransmitter: Glutamate, Aspartate

Inhibition:
- Ionic: inward Cl\(^-\), outward K\(^+\) currents
- Neurotransmitter: GABA
Targets for Controlling Seizures

• **Na\(^+\) Channel**  Action potential frequency
• **Ca\(^+\) Channel**
  – T-type  Thalamocortical reverberations
  – L-type  Cortical excitation
  – N-type  Neurotransmitter release
• **GABA transmission**  Inhibition
  – GABA receptor activity
  – GABA synthesis/release
  – GABA uptake
• **Glutamate transmission**  Excitation
AEDs: Molecular and Cellular Mechanisms

- **Phenytoin, Carbamazepine**
  - Block voltage-dependent sodium channels at high firing frequencies

- **Barbiturates**
  - Prolong GABA-mediated chloride channel openings
  - Some blockade of voltage-dependent sodium channels

- **Benzodiazepines**
  - Increase frequency of GABA-mediated chloride channel openings
AEDs: Molecular and Cellular Mechanisms

♦ Felbamate
  – May block voltage-dependent sodium channels at high firing frequencies
  – May modulate NMDA receptor via strychnine-insensitive glycine receptor

♦ Gabapentin
  – GABA analogue but does NOT bind GABA receptor
  – Binds calcium channel ? Reduces release of excitatory neurotransmitters

♦ Lamotrigine
  – Blocks voltage-dependent sodium channels at high firing frequencies
  – May interfere with pathologic glutamate release
AEDs: Molecular and Cellular Mechanisms

♦ Ethosuximide
  – Blocks low threshold, “transient” (T-type) calcium channels in thalamic neurons

♦ Valproate
  – May enhance GABA transmission in specific circuits
  – Blocks voltage-dependent sodium channels

♦ Vigabatrin
  – Irreversibly inhibits GABA-transaminase
AEDs: Molecular and Cellular Mechanisms

♦ Topiramate
  – Blocks voltage-dependent sodium channels at high firing frequencies
  – Increases frequency at which GABA opens Cl-channels (different site than benzodiazepines)
  – Antagonizes glutamate action at AMPA/kainate receptor subtype
  – Inhibition of carbonic anhydrase

♦ Tiagabine
  – Interferes with GABA re-uptake
AEDs: Molecular and Cellular Mechanisms

- Levetiracetam
  - Mechanisms of action unknown
  - Has specific binding site to synaptic membranes

- Oxcarbazepine
  - Blocks voltage-dependent sodium channels at high firing frequencies
  - Exerts effect on K+ channels

- Zonisamide
  - Blocks voltage-dependent sodium channels and T-type calcium channels

- Pregabalin
  - Binds alpha-2-delta subunit of voltage sensitive calcium channels
  - Reduces calcium influx to nerve terminals and decreases release of excitatory neurotransmitters
## Commonly Used AEDs and proposed mechanisms of action

<table>
<thead>
<tr>
<th>AED</th>
<th>Block Sodium Currents</th>
<th>Enhance GABA Mediated Chloride Currents</th>
<th>Block T-Calcium Currents</th>
<th>Block Glutamate Mediated Currents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>++</td>
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<tr>
<td>Clonazepam</td>
<td>+</td>
<td>++</td>
<td>-</td>
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<tr>
<td>Ethosuximide</td>
<td>-</td>
<td>-</td>
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<tr>
<td>Felbamate</td>
<td>+/-</td>
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<tr>
<td>Gabapentin</td>
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<tr>
<td>Lamotrigine</td>
<td>++</td>
<td>+/-</td>
<td>+/-</td>
<td>+?</td>
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<tr>
<td>Levetiracetam</td>
<td>+/-</td>
<td>+/-</td>
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<td>Oxcarbazepine</td>
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<tr>
<td>Phenobarbital</td>
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<tr>
<td>Phenytoin</td>
<td>++</td>
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<tr>
<td>Tiagabine</td>
<td>-</td>
<td>++</td>
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<tr>
<td>Topiramate</td>
<td>++</td>
<td>+/-</td>
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<tr>
<td>Valproate</td>
<td>++</td>
<td>+/-</td>
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<td>+?</td>
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<tr>
<td>Zonisamide</td>
<td>++</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
<td>+/-</td>
</tr>
</tbody>
</table>

++major action; + definite action, moderate; +/-possible action; -/? Unknown, probably no action; - no action
Mechanisms of AEDs: Conclusions

- AEDs have multiple sites of action
- They can interact with
  - Ion channels
  - Neurotransmitter-gated channels
  - Enzymes involved with neurotransmitter synthesis and release
- Each AED has a unique profile of actions
“Loved Jamaica!”
GOALS OF PHARMACOTHERAPY

Complete seizure control
No side effects
Improved quality of life
Maintenance of normal lifestyle
Maximized development in children
Avoidance of chronic intractable epilepsy
Antiepileptic Drug Choice

Adverse effects  Individual circumstances

Effectiveness for epilepsy syndrome

Pharmacokinetics  Cost  Drug Interactions
Monotherapy vs Polytherapy

• Monotherapy is preferable whenever possible
• Potential disadvantages of polytherapy
  – Increased adverse effects
  – Chronic toxicity
  – Difficult to manage pharmacokinetic and pharmacodynamic interactions
  – Reduced compliance
  – Higher cost
  – Increased teratogenicity
• Monotherapy is sufficient for most patients
• Investigate monotherapy fully before adding 2\textsuperscript{nd} drug
Success in AED regimens

- Seizure free 47% Monotherapy first AED
- Not seizure free 36% All regimens attempted
- Seizure free 13% Monotherapy 2nd AED
- Seizure free 1% Monotherapy 3rd AED
- Seizure free 3% Polytherapy

Starting AEDs

• “Start low and go slow”
• Some AEDs can be successfully loaded intravenously or orally
  – Phenytoin, phenobarbital, valproate, levetiracetam
• Some can follow moderately rapid titration schedule
  – Gabapentin, oxcarbazepine
• Some require prolonged titration schedules
  – Carbamazepine, lamotrigine, topiramate, tiagabine, zonisamide
Monotherapy: Reasons for Failure

- Drug resistant condition
- Incorrect diagnosis
- Underlying progressive neurological disorder
- Inappropriate AED
- Suboptimal dosing
- Toxicity limits dose
- Intolerable adverse effects
- Unmanagable drug interactions
- Noncompliance
- ‘Lifestyle’
Partial Onset Seizures: Traditional First Line Antiepileptic Drugs

- Phenytoin (Dilantin)
- Carbamazepine (Tegretol, Tegretol XR, Carbatrol)
VA Cooperative Study

Mattson et al Comparison of carbamazepine, phenobarbital, phenytoin, and primidone in partial and secondarily Generalized tonic clonic seizures NEJM 1985;313:145-151
Partial Onset Seizures: Alternative AEDs (Older)

- Phenobarbital
- Primidone
- Valproic acid (Depakote)
Partial Onset Seizures: Alternative AEDs (Newer)

- Lamotrigine (Lamictal)$^{1,2,3}$
- Topiramate (Topamax)$^{1,2,3}$
- Oxcarbazepine (Trileptal)$^{1,2,3}$
- Gabapentin (Neurontin)$^{2,3}$
- Tiagabine (Gabatril)$^{3}$
- Zonisamide (Zonegran)$^{3}$
- Levetiracetam (Keppra)$^{3}$
- Pregabalin (Lyrica)$^{3}$

1 = FDA indication monotherapy  2 = AAN guidelines  3 = FDA indication add-on
Generalized Seizures: AED Choice

Generalized (broad spectrum)

Valproate (Depakote)
Lamotrigine (Lamictal)
Ethosuximide (Zarontin)
Topiramate (Topamax)
Levetiracetam (Keppra)
Zonisamide (Zonegran)
When to switch and how to do it!

- Lack of efficacy
- Intolerable side effects
- Overlap medications
- Consider pharmacokinetic interactions carefully!!
- Complex schedules
Pharmacokinetic Principles: Absorption

- Essentially complete for all AEDs (except gabapentin)
- Timing varies widely by drug, formulation, patient characteristics
- Generally slowed by food in stomach
- Usually takes several hours (importance for interpreting blood levels)
- Only clinically significant interaction is phenytoin and enteric feeding
Antiepileptic Drug Interactions

• Pharmacokinetic
  – Displacement from plasma proteins
  – Metabolic drug interactions
    • Cytochrome P450 isoenzymes
    • Glucuronidation
  – Renal excretion

• Pharmacodynamic
Displacement from Plasma Proteins

• Clinically important only for drugs >90% protein bound
  – Phenytoin, Valproic Acid, Diazepam, Tiagabine

• Small proportion of total drug displaced
  – Total drug concentration falls
  – Free drug concentration often does not change

• Therapeutic effects seen at lower total drug level
Drug Metabolism

Glucuronidation

Conjugation

Cytochrome P-450

Gut

Liver

Oxidation

Sulfation

CYP 1A, 2C, 2D, 3A
Dose-dependent accumulation of phenytoin
Plasma levels of carbamazepine (200 mg TID) change over time

Toxic

“Therapeutic”
Metabolism: The Cytochrome P450 Isoenzyme System

- The enzymes most involved with drug metabolism
- Enzymes have broad substrate specificity, and individual drugs may be substrates for several enzymes
- The principal enzymes involved with AED metabolism include CYP2C9, CYP2C19, CYP3A4
Enzyme Inducers/Inhibitors: General Considerations

- Inducers: Increase clearance and decrease steady-state concentrations of other substrates

- Inhibitors: Decrease clearance and increase steady-state concentrations of other substrates
Pharmacokinetic Interactions: Possible Clinical Scenarios

Be aware that drug interactions may occur with

- Addition of inducer/inhibitor to existing medication regimen
- Addition of a new medication when inducer/inhibitor is present
- Removal of an inducer/inhibitor from chronic medication regimen
# The Cytochrome P-450 Enzyme System

<table>
<thead>
<tr>
<th>Inducers</th>
<th>Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenobarbital</td>
<td>erythromycin</td>
</tr>
<tr>
<td>primidone</td>
<td>nifedipine/verapamil</td>
</tr>
<tr>
<td>phenytoin</td>
<td>trimethoprim/sulfa</td>
</tr>
<tr>
<td>carbamazepine</td>
<td>propoxyphene</td>
</tr>
<tr>
<td>tobacco/cigarettes</td>
<td>cimetidine</td>
</tr>
<tr>
<td></td>
<td>valproate</td>
</tr>
</tbody>
</table>
AED Inducers: General Considerations

- Results from synthesis of new enzyme
- Tends to be slower in onset/offset than inhibition interactions
- Broad Spectrum Inducers:
  - Carbamazepine
  - Phenytoin
  - Phenobarbital/primidone
- Selective CYP3A Inducers:
  - Felbamate, Topiramate, Oxcarbazepine
The Cytochrome P-450 Enzyme System

- Substrates (metabolism enhanced by inducers):
  - steroid hormones
  - HIV drugs
  - cancer chemotherapy
  - vitamins
  - warfarin
  - AEDs
  - (many more)
Example: Carbamazepine

• Knowledge that carbamazepine is an inducer of and substrate for CYP3A4 predicts:
  – It will reduce plasma concentrations of CYP substrates such as oral contraceptives (!), tiagabine, and itself (!) (autoinduction)
  – Rise in plasma carbamazepine concentrations with addition of erythromycin (CYP3A4 inhibitor)
Drug Metabolizing Enzymes: UDP- Glucuronyltransferase (UGT)

- Important pathway for drug metabolism/inactivation
- Currently less well described than the cytochrome P450 system
- 2 distinct families UGT1 and UGT2 (each with 8 isoenzymes)
- Several isoenzymes that are involved in AED metabolism include: UGT1A9 (VPA), UGT2B7 (valproate, lorazepam), UGT1A4 (lamotrigine)
Inhibition

- Competition at specific hepatic enzyme site

- Onset typically rapid and concentration (inhibitor) dependent

- Possible to predict potential interactions by knowledge of specific hepatic enzymes and major pathways of AED metabolism
AED Inhibitors

♦ Valproate
  - UDP glucuronosyltransferase (UGT)
    ↑ plasma concentrations of Lamotrigine, Lorazepam
  - CYP2C19
    ↑ plasma concentrations of Phenytoin, Phenobarbital

♦ Topiramate & Oxcarbazepine
  - CYP2C19
    ↑ plasma concentrations of Phenytoin

♦ Felbamate
  - CYP2C19
    ↑ plasma concentrations of Phenytoin, Phenobarbital
Pharmacodynamic Interactions

- Occur at site of action-modify pharmacological effect without changing plasma drug concentrations
  - Additive (sum of individual drugs)
  - Synergistic (combined effects greater than sum)
  - Antagonistic (less than additive)
- May be adverse or beneficial
- Few recognized examples of therapeutic synergy: Valproate + Lamotrigine
Steady State and Half Life

From Engel, 1989
Compliance

• Few studies specific to AEDs
• Estimated non-compliance up to 60% in adults and 75% in children
• Factors associated with non-compliance
  – Long duration of epilepsy
  – Complicated dosing or monitoring regimen
  – Poor tolerability
  – Frequent changes in medication
  – Poor understanding of condition and med directions
  – Fear of addiction to AEDs
  – Low frequency of seizures
AED Serum Concentrations

- Most AED dosing decisions made on a clinical basis
- AED serum concentrations are a rough guide
  - Evaluating the efficacy of medication therapy for epilepsy-establishing benchmark
  - Optimizing AED therapy
  - Assessing compliance
  - Teasing out drug-drug interactions
  - Monitoring during pregnancy
AED serum concentrations

“You may believe you’ve been overcharged, but, remember, you’re overmedicated.”
# Potential Target Range of AED Serum Concentrations

<table>
<thead>
<tr>
<th>AED</th>
<th>Serum Concentration (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>4-12</td>
</tr>
<tr>
<td>Ethosuximide</td>
<td>40-100</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>10-40</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>10-20</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>50-100</td>
</tr>
</tbody>
</table>
## Potential Target Range of AED Serum Concentrations

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<thead>
<tr>
<th>AED</th>
<th>Serum Concentration (mg/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gabapentin</td>
<td>6-21</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>5-18</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>10-40</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td>12-24 (MHD)</td>
</tr>
<tr>
<td>Tiagabine</td>
<td>?</td>
</tr>
<tr>
<td>Topiramate</td>
<td>4.0-25</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>7-40</td>
</tr>
<tr>
<td>Pregabalin</td>
<td>?</td>
</tr>
</tbody>
</table>
Adverse Effects

♦ Acute: dose-related & reversible

♦ Idiosyncratic:
  – uncommon
  – potentially serious or life threatening

♦ Chronic—reversibility and seriousness vary

• SEE HANDOUT FOR DETAILS
Acute, Dose-Related Adverse Effects of AEDs

- Neurologic/Psychiatric – most common
  - Sedation, fatigue
  - Unsteadiness, uncoordination, dizziness
  - Tremor
  - Paresthesia
  - Diplopia, blurred vision
  - Mental/motor slowing or impairment
  - Mood or behavioral changes
  - Changes in libido or sexual function
Acute, Dose-Related Adverse Effects of AEDs (cont.)

- Gastrointestinal (nausea, heartburn)
- Mild to moderate laboratory changes
  - Hyponatremia (may be asymptomatic)
  - Increases in ALT or AST
  - Leukopenia
  - Thrombocytopenia
  - Elevations of alkaline phosphatase
- Weight gain or loss
Idiosyncratic Adverse Effects of AEDs

- Rash, Exfoliation
- Signs of potential Stevens-Johnson syndrome
  - Skin changes- maculopapular rash
  - Fever and mucus membrane involvement
  - Laboratory monitoring probably not helpful in early detection
  - Patient education
Idiosyncratic Adverse Effects of AEDs

- Hematologic Damage
  (marrow aplasia, agranulocytosis)
  - Early symptoms: abnormal bleeding, acute onset of fever, symptoms of anemia
  - Laboratory monitoring probably not helpful in early detection
  - Patient education
- Hepatic Failure
Long-Term Adverse Effects of AEDs

♦ Neurologic:
  • Neuropathy
  • Cerebellar syndrome

♦ Endocrine/Metabolic Effects
  • Vitamin D – Osteomalacia, osteoporosis
  • Folate – Anemia, teratogenesis
  • Altered connective tissue metabolism or growth
    • Facial coarsening
    • Hirsutism
    • Gingival hyperplasia
Discontinuing AEDs

- Seizure freedom for \( \geq 2 \) years implies overall >60% chance of successful withdrawal in some epilepsy syndromes

- Favorable factors
  - Control achieved easily on one drug at low dose
  - No previous unsuccessful attempts at withdrawal
  - Normal neurologic exam and EEG
  - Primary generalized seizures except JME
  - “Benign” syndrome

- Consider relative risks/benefits (e.g., driving, pregnancy)
Antiepileptic Drugs in Special Populations
Treatment Recommendations: The Elderly

- Choose AEDs according to adverse effect profile and interactions with coexisting medical conditions
- AEDs with no drug-drug interactions are desirable
- Begin at low dosage and titrate to clinical effect
- Monitoring of serum AED levels may be useful
Pharmacokinetic Factors in the Elderly

- **Absorption** — little change
- **Distribution**
  - decrease in lean body mass important for highly lipid-soluble drugs
  - fall in albumin leading to higher free fraction
- **Metabolism** — decreased hepatic enzyme content and blood flow
- **Excretion** — decreased renal clearance
Antiepileptic Drug Choice in the Elderly: The VA Coop Study

- N=593 >60 y.o, new onset
- Randomized to CBZ, GBP, LTG
- Outcome measure: retention rate
  - Efficacy
  - Tolerability
AEDs in Pediatrics

- Extrapolation of efficacy data from adult studies
- Susceptibility to specific adverse effects (valproate hepatotoxicity, lamotrigine rash)
- Age-related pharmacokinetic factors
  - Neonate: low protein binding, low metabolic rate, possible decreased absorption if given with milk/formula
  - Children: faster metabolism
Pharmacokinetic Factors in Pediatrics

- Neonate—often lower per kg doses
  - Low protein binding
  - Low metabolic rate

- Children—higher, more frequent doses
  - Faster metabolism
Women and Antiepileptic Medications
Women with Epilepsy

• Oral Contraceptives
  – Phenobarbital, Phenytoin, Carbamazepine, Oxcarbazepine, Topiramate

• Teratogenicity
  – Maintain on Folate during childbearing years
  – Pregnancies usually healthy but ‘high risk’
  – Limit AED exposure but also avoid seizures
  – All Drugs Class C or D
  – Valproate and Phenobarbital particularly implicated
  – Developmental delay?

• Breastfeeding

• Bone Health
  – Older AEDs promote bone loss
Special Formulations of AEDs

• Extended release
  – Carbatrol, Tegretol XR Depakote ER

• Liquid formulations
  – Phenytoin, carbamazepine, phenobarbital, valproic acid, gabapentin, levetiracetam, oxcarbazepine

• Sprinkles or capsules

• Dispersible
  – Lamotrigine

• Rectal administration
  – Valium gel (Diastat)

• IV formulations
  – Phenobarbital, phenytoin (IV phenytoin, fosphenytoin), valproate, levetiracetam, benzodiazepine and anesthetic agents
Status Epilepticus

Main message:
Treat early and aggressively
Definition of Status Epilepticus

• No consensus definition
• Single or ecurrent seizures without an intervening of consciousness between seizures lasting more than 30 minutes.
• Operational definition: 5 minutes
• Generalized Convulsive Status Epilepticus (tonic-clonic)
• Non convulsive Status Epilepticus
Rectal Use Benzodiazepines

- Rectal diazepam gel commercially available
  - frequent seizures
  - reside far from medical care
  - comes in adjustable doses
Parenteral Benzodiazepines

• **Diazepam**
  - 0.2 mg/kg dosing
  - 5mg/min IV push
  - Highly lipophilic
  - Rapid BBB penetrance
  - Elimination T ½ = 48 hours
  - Redistribution T ½ = 60 minutes
  - Short effective CNS t 1/2

• **Lorazepam**
  - 0.1 mg/kg
  - 2 mg/min
  - Slightly less lipid soluble
  - Redistribution T ½ = 2-3 hours; strongly bound to bzd receptor
  - Longer effective CNS T 1/2
  - Little accumulation in lipid stores
IV Phenytoin

- Effective
- Lacks CNS depression
- Vehicle (propylene glycol) may cause hypotension
- pH = 13 - tissue necrosis if infiltrates
- Infuse 50mg/min
- Cardiac monitoring required.

Fosphenytoin

- Water soluble phosphate ester of phenytoin
- Must be cleaved to phenytoin prior to effect
- May be given up to 150 mg/min
- Rapidly converts after IV or IM to active form
- ECG, BP and resp monitoring
Refractory Status Epilepticus

- Failure of first line therapy followed by a second line therapy (benzodiazepine + phenytoin)
- Occurs in 10-40% of cases of status
- Treatment options
  - Barbiturates
  - Continuous benzodiazepine infusions (midazolam)
  - Propofol
  - Other
- EEG monitoring unless status ended and patient waking up
Barbiturates

- **Phenobarbital**
  - IM/IV
  - 20 mg/kg at ≤ 5 mg per minute (0.75 mg/kg per minute)
  - Moderately rapid penetration to CNS
  - $T\frac{1}{2} = 100$ hours
  - Hypotension, sedation, infection

- **Pentobarbital**
  - 3-5 mg/kg load, 1-10 mg/kg/hr infusion
  - $T\frac{1}{2} = 27$ hours
  - Similar side effect profile
What is the role of new AEDs or new formulations?

- **Depacon (15-30 mg/kg)**
  - Well tolerated
  - No CNS depression
  - Modest evidence for use in status epilepticus
- **Keppra (IV levetiracetam 500-5000 mg)**
  - Well tolerated
  - No CNS depression
  - Minimal evidence for efficacy in status epilepticus
- **Topiramate**
- **Inhalation anesthetics (isoflurane, desflurane)**
- **Ketamine**
Conclusions

• Selection of AEDs is challenging: Older, Newer, and Newest AEDs
• Complex pharmacokinetic issues and drug interactions
• Laboratory monitoring
• Adverse effects
• Special Populations
• Be prepared with a rapid response to status epilepticus
Abbreviations used in lecture

- AED: antiepileptic drug
- PHT: phenytoin
- PB: phenobarbital
- CBZ: carbamazepine
- VPA: valproic acid
- LTG: lamotrigine
- GBP: gabapentin
- TPX: topiramate
- TGB: tiagabine
- LEV: levetiracetam
- OXC: oxcarbazepine
- FBM: felbamate
- ZON: zonisamide
- PGB: pregabalin