Antiepileptic Drugs In Neurosurgery

Presenter:  Dr. Siddhartha Sahoo
Moderator:  Dr. Manmohan Singh
Dr. G.D Satyarthee
DEFINITIONS

♦ **Seizure**: the clinical manifestation of an *abnormal synchronization* and *excessive excitation* of a population of cortical neurons.

♦ **Epilepsy**: a tendency toward recurrent seizures unprovoked by acute systemic or neurologic insults.

*American Epilepsy Society*
Antiepileptic drugs

• A drug which 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

American Epilepsy Society
History

- Modern Treatment Of Seizures Started In 1850 With Bromides
- 1910: Phenobarbital
- 1940: Phenytoin (PHT)
- 1978: Valproate
- 1999: Levetiracetam
Cellular Mechanisms of Seizure Generation

♦ Excitation (too much)
  – Ionic-inward Na⁺, Ca²⁺ currents
  – Neurotransmitter: glutamate, aspartate

♦ Inhibition (too little)
  – Ionic-inward Cl⁻, outward K⁺ currents
  – Neurotransmitter: GABA
The neuronal excitation

- **Depolarization**
  - Gate threshold
  - Sodium gates close
  - Potassium gates open
- **Repolarization**
  - Active sodium and potassium pumps
- **Hyperpolarization**

<table>
<thead>
<tr>
<th>Potential</th>
<th>State</th>
</tr>
</thead>
<tbody>
<tr>
<td>+30 mV</td>
<td>2</td>
</tr>
<tr>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>-55 mV</td>
<td>4</td>
</tr>
<tr>
<td>-70 mV</td>
<td>5</td>
</tr>
<tr>
<td>-90 mV</td>
<td>6</td>
</tr>
</tbody>
</table>
Glutamate

- Brain’s major excitatory neurotransmitter
- Two groups of glutamate receptors
  - Ionotropic - fast synaptic transmission
    - NMDA, AMPA, kainate
    - Gated Ca\(^{++}\) and gated Na\(^{+}\) channels
  - Metabotropic - slow synaptic transmission
    - Regulation of second messengers (cAMP and Inositol)
    - Modulation of synaptic activity
GABA

♦ Major inhibitory neurotransmitter in the CNS
♦ Two types of receptors
  – GABA_A
    • Post-synaptic
    • Specific recognition sites
    • Linked to Cl⁻ channel
  – GABA_B
    • Pre-synaptic reduction in calcium influx
    • Mediated by K⁺ currents
Diagram of the GABA$_A$ receptor
Classification

<table>
<thead>
<tr>
<th>Sodium Channel</th>
<th>Calcium Channel</th>
<th>GABAergic</th>
<th>Glutamate</th>
<th>CA Inhibitor</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytin</td>
<td>Ethosuximide</td>
<td>GABAa Agonist</td>
<td>NMDA receptor</td>
<td>Acetazolamide</td>
<td>Unknown</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td></td>
<td>Benzodiazepines</td>
<td>Felbamate</td>
<td></td>
<td>Levetiracetam</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td></td>
<td>Barbiturates</td>
<td>AMPA/Kainate r.</td>
<td></td>
<td>Hormonal</td>
</tr>
<tr>
<td>Zonisamide</td>
<td></td>
<td>Uptake inhibitor</td>
<td>Topiramate</td>
<td></td>
<td>Progesterone</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td></td>
<td>Tiagabine</td>
<td>Metabotropic</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>GABA-transaminase</td>
<td>Experimental</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Vigabatrine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>GAD modulation</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Gabapentin</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Valproate (?)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Pharmacokinetic Principles

Absorption: entry of drug into the blood

– Essentially complete for all AEDs
  (except gabapentin)
– Timing varies widely by drug, formulation, patient characteristics
– Generally slowed by food in stomach
  (CBZ may be exception)
– Usually takes several hours
  (importance for interpreting blood levels)
Pharmacokinetic Principles

♦ Elimination: removal of active drug from the blood by metabolism and excretion
  – Metabolism/biotransformation — generally hepatic; usually rate-limiting step
  – Excretion — mostly renal
  – Active and inactive metabolites
  – Changes in metabolism over time
    *(Auto-induction with carbamazepine)* or
    with *polytherapy* *(enzyme induction or inhibition)*
  – Differences in metabolism by age, systemic disease
AED Serum Concentrations

- Optimizing AED therapy
- Assessing compliance
- To monitor pharmacodynamic and pharmacokinetic interactions.
- Most often individual patients define their own “therapeutic range” for AEDs.
- For the new AEDs there is no clearly defined “therapeutic range”.

2/28/11
AEDs in Neurosurgery 13
## PHARMACO KINETICS

<table>
<thead>
<tr>
<th>DRUG</th>
<th>Protein binding</th>
<th>Clearance</th>
<th>T1/2 (hrs)</th>
<th>Therapeutic level Mcg/ml</th>
<th>PK Interaction</th>
<th>Withdrawl over</th>
</tr>
</thead>
<tbody>
<tr>
<td>PHT</td>
<td>90</td>
<td>100% H</td>
<td>12-60</td>
<td>10 - 20</td>
<td>YES</td>
<td>4 wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Dose</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>dependent</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBZ</td>
<td>75-85</td>
<td>100% H</td>
<td>SD 20-55</td>
<td>6 - 12</td>
<td>YES</td>
<td>4wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Chr Rx</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>10-30</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>VPA</td>
<td>75-95</td>
<td>100% H</td>
<td>6-18</td>
<td>50 - 100</td>
<td>YES</td>
<td>4wks</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LEV</td>
<td>&lt;10%</td>
<td>66% renal</td>
<td>4-8</td>
<td>20 -60</td>
<td>No</td>
<td></td>
</tr>
</tbody>
</table>
# Antiepileptic Drug Interactions

<table>
<thead>
<tr>
<th>Induce metabolism of other drugs:</th>
<th>Inhibit metabolism of other drugs:</th>
<th>AEDs that are highly protein bound:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>Valproate</td>
<td>Valproate</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>Felbamate</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Topiramate</td>
<td>Tiagabine</td>
</tr>
<tr>
<td>Primidone</td>
<td></td>
<td>Carbamazepine</td>
</tr>
<tr>
<td></td>
<td>Neither inducer/inhibitor</td>
<td>Oxcarbazepine</td>
</tr>
<tr>
<td></td>
<td>Gabapentin</td>
<td>Topiramate</td>
</tr>
<tr>
<td></td>
<td>Lamotrigine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pregabalin</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tiagabine</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Levetiracetam</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Zonisamide</td>
<td></td>
</tr>
</tbody>
</table>
Adverse Effects

♦ Acute dose-related—reversible

♦ Idiosyncratic
  – uncommon
  – potentially serious or life threatening

♦ Chronic—reversibility and seriousness vary
Adverse effects (dose-related)

- Dizziness, Fatigue, Ataxia, Diplopia: all AEDs
- Irritability: levetiracetam
- Weight loss/anorexia: topiramate, zonisamide, felbamate
- Weight gain: valproate
  (also associated with polycystic ovarian syndrome)
  carbamazepine, gabapentin, pregabalin
Adverse Effects of AEDs: Serious

- **Typically Idiosyncratic:**
  - Renal stones
topiramate, zonisamide
  - Anhydrosis, heat stroke
topiramate
  - Acute closed-angle glaucoma
topiramate
  - Hyponatremia
carbamazepine, oxcarbazepine
  
  Used in DI
Adverse Effects of AEDs: Serious

- Typically Idiosyncratic:
  - Aplastic anemia
    Valproate, Carbamazepine, Felbamate, Zonisamide,
  - Hepatic Failure
    Valproate, Felbamate, Lamotrigine, Phenobarbital
  - Peripheral vision loss
    Vigabatrin
  - Rash
    Phenytoin, Lamotrigine, Zonisamide, Carbamazepine

Risk of “dangerous or even fatal skin reactions” such as Steven-Johnson Syndrome and Toxic epidermal necrolysis is increased in patients with HLA-B*1502 allele
Estimated absolute risk for those with the allele: 5%

American epilepsy society 2010
LONGTERM ADVERSE EFFECTS

♦ Endocrine/Metabolic Effects
  • Osteomalacia, osteoporosis
    • Carbamazepine
    • Phenobarbital
    • Phenytoin
    • Oxcarbazepine
  
  • Folate deficiency (anemia, teratogenesis)
    • Phenobarbital
    • Phenytoin
    • Carbamazepine
    • Valproate

• Altered connective tissue metabolism or growth
  (facial coarsening, hirsutism, gingival hyperplasia or contractures)
  • Phenytoin
  • Phenobarbital

Neurologic
  • Neuropathy
  • Cerebellar Syndrome
  phenytoin
Starting AEDs

• Discuss likely adverse effects

• Discuss unlikely but important adverse effects

• Discuss likelihood of success

• Discuss recording/reporting seizures, adverse effects, potential precipitants
Choosing Antiepileptic Drugs

• Limited placebo-controlled trials available, particularly of newer AEDs

• Several drugs are commonly used for indications other than those for which they are officially approved/recommended

• For **partial epilepsy** depends on
  
  *drug side-effect profile & patient’s preference/concerns*

• For **generalized epilepsy** depends on

  *predominant seizure type(s), drug side-effect & patient’s preference/concerns*

*ILAE Summary Guidelines and Summary of AAN evidence-based guidelines*
# CHOOSING ANTIEPILEPTIC DRUGS

<table>
<thead>
<tr>
<th>PARTIAL SEIZURES</th>
<th>GTCS</th>
<th>ABSENCE SEIZURES</th>
<th>MYOCLONIC SEIZURES</th>
</tr>
</thead>
<tbody>
<tr>
<td>BEST EVIDENCE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>Valproate</td>
<td>Ethosuximide</td>
<td>Valproate</td>
</tr>
<tr>
<td>Oxcarbamazepine</td>
<td>Topiramate</td>
<td>Valproate</td>
<td>Levetiracetam</td>
</tr>
<tr>
<td>Phenytoin</td>
<td></td>
<td></td>
<td>Clonazepam</td>
</tr>
<tr>
<td>Topiramate</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

alternatives

| Lamotrigine      | Phenytoin | Lamotrigine | Zonisamide |
| Gabapentine      | Carbamazepine | Levetiracetam | Topiramate |
| Levetiracetam    | Lamotrigine   | Clonazepam   | Felbamate  |
| Valproate        | Phenobarbital | Lamotrigine  | Zonisamide |
| Phenobarbital    |            |              |           |
| Pregabalin       |            |              |           |
| Zonisamide       |            |              |           |

2/28/11 AEDs in Neurosurgery

American Epilepsy Society 2010
Antiepileptic Drug: Monotherapy

- Simplifies treatment
- Reduces adverse effects
- Eighty percent of seizures can be controlled with monotherapy
- Monotherapy with different drug should be tried before 2 drugs together
- Conversion to single drug from multiple drugs
  - Eliminate sedative drugs first (barbiturate/benzodiazepine)
  - Withdraw antiepileptic drugs slowly over several months
Discontinuing AEDs

- **Seizure freedom for ≥2 years**
  
  implies overall >60% chance of success

- **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

  Consider relative risks/benefits (e.g., driving, pregnancy)

Pregnancy and AEDs:

- **EPTOIN**: Fetal Hydantoin Syndrome
- **VALPROATE**: Neural tube defects
- **OTHER CONGENITAL MALFORMATIONS**
  - Cardiac defects
  - Genitourinary defects
  - Oral clefts

- Risk with AED monotherapy 4.5% (OR 2.6)
- Risk with Polytherapy 8.6% (OR 5.1)

Lactation and AEDs

- **Breastfeeding should be encouraged unless clear risk posed**

- **Probably safe:**
  - Carbamazepine
  - Phenytoin
  - Valproate
  - Lamotrigine

- **“Use with caution” in lactating women:**
  - Primidone
  - Phenobarbital
  - Ethosuximide

*Pennell et al. Epilepsy and Behavior. 2007. 11: 263-9*
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose/ dosing frequency</th>
<th>Remarks</th>
<th>Therapeutic level Mcg/ml</th>
<th>Adverse effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>300–400 mg/d (3–6 mg/kg, adult; 4–8 mg/kg, child); od-bid</td>
<td>Loading dose: 20 mg/kg @ &lt;50 mg/min infusion Cardiac monitoring check BP</td>
<td>10 - 20</td>
<td>Gum hyperplasia Lymphadenopathy Hirsutism Osteomalacia Hyperglycemia Dizziness Diplopia Ataxia Incoordination</td>
</tr>
<tr>
<td>Carbamazepine</td>
<td>600–1800 mg/d (15–35 mg/kg, child); bid-qid</td>
<td>Start low and increase slowly Oral form only</td>
<td>6- 12</td>
<td>Aplastic anemia Leukopenia Hyponatremia</td>
</tr>
<tr>
<td>Valproate</td>
<td>750–2000 mg/d (20–60 mg/kg); bid-qid</td>
<td>Start 15 mg/kg/day Increment wkly 5-10mg/kg/day</td>
<td>50 - 100</td>
<td>Hepatotoxicity Thrombocytopenia Hyperammononemia Pancreatitis</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1000–3000 mg/d; bid</td>
<td></td>
<td>20 - 60</td>
<td>Sedation Fatigue Incoordination Psychosis</td>
</tr>
</tbody>
</table>
Thank you