Antiepileptic Drugs (AEDs): Using Patient Cases to Illustrate Contemporary Issues

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Objectives

• With a focus on the newer drugs, discuss AED characteristics
• Use mini-cases to illustrate contemporary issues

Long-Term Management Strategies for Epilepsy

Antiepileptic Drug (AED) Therapy

1st Generation
- PB - Phenobarbital
- PHT - Phenytoin
- CBZ - Carbamazepine
- VPA - Valproic Acid

2nd Generation
- FBM - Felbamate
- GBP - Gabapentin
- LTG - Lamotrigine
- FOS - Fosphenytoin
- TPM - Topiramate
- TGB - Tiagabine
- OCBZ - Oxcarbazepine
- LEV - Levetiracetam
- ZNS - Zonisamide
- PGB - Pregabalin

Vagus Nerve Stimulator
Surgery
Ketogenic Diet

Antiepileptic Drugs
KEY

1st Generation
- PB
- PHT
- CBZ
- VPA

2nd Generation
- FBM
- GBP
- LTG
- FOS
- TPM
- TGB
- OCBZ
- LEV
- ZNS
- PGB
Summary of 1st Generation AEDs

- Vast Clinical Experience
- Use in Both Partial and Primary Generalized Epilepsies
  - exception: CBZ - Absence
- Incomplete Efficacy
- Unfavorable Pharmacokinetics (metabolism)
- Narrow Therapeutic Range
  - Small window between efficacy & toxicity
- Adverse CNS Effects
- Drug-Interactions

Influence on Hepatic Metabolism

- 1st Generation AEDs
  - Enzyme Inducers
    - Phenobarbital
    - Phenytoin
    - Carbamazepine
  - Enzyme Inhibitor
    - Valproate

Pharmacokinetic Interactions

Serum Concentration

- Add an Inhibitor
- Remove an Inducer
- Add an Inducer
- Remove an Inhibitor

Graves 1995

AED Therapy

Template for all 7

“2nd Generation”
Gabapentin (GBP, Neurontin®)

- Mechanism
  - designed, yet unknown
- Dose (900 to 3600 mg/day [TID to QID])
- Side Effects
  - fatigue, dizziness, ataxia
- Drug Interactions
  - none with AEDs [only Antacids]
- Clinical Pearl
  - non-Epilepsy uses
  - adjust dose for renal function

Lamotrigine (LTG, Lamictal®)

- Mechanism
  - Na⁺ Channels, Glutamate
- Dose (100 to 400 mg/day [BID regimen])
- Side Effects
  - sedation, diplopia, ataxia, nausea - rash
- Drug Interactions
  - influenced by others – incl. OCs
- Clinical Pearls
  - Slow taper - (esp. VPA)
  - Cleft palate
  - Extended-release formulation in clinical trials
  - New generic form now available (Summer 2008)

Topiramate (TPM, Topamax®)

- Mechanisms - multiple
  - Na⁺ Channels, Glutamate, GABA, CAI
- Dose
  - 200 to 400 mg/day [BID - QD renal]
- Side Effects
  - difficulty concentrating (poly > mono), kidney stones, weight loss
- Drug Interactions
  - influenced by others
  - above 200 mg/day can ↓ OCs
- Clinical Pearls
  - visual changes / use outside of epilepsy / hydration

Oxcarbazepine (OCBZ, Trileptal®)

- Mechanism - Na⁺ Channels
- Dose
  - adjunctive (600 to 1,200 mg/day [BID])
  - monotherapy (up to 2,400 mg/day)
- Side Effects
  - dizziness, somnolence, diplopia, n/v, ataxia, hyponatremia
- Drug Interactions
  - weak inhibitor (PHT) / inducer (OCs)
- Clinical Pearl
  - dose-dependent enzyme inducer (>1,200 mg/day)
Levetiracetam (LEV, Keppra®)

- **Mechanism**
  - Unknown – distinct from other AEDs
- **Dose**:
  - 1,000 to 3,000 mg/day [BID]
- **Side Effects**
  - Somnolence, asthenia, dizziness, behavior changes
- **Drug Interactions**
  - None with AEDs
- **Clinical Pearl**
  - Adjust dose for renal function
  - IV formulation

Zonisamide (ZNS, Zonegran®)

- **Mechanism**
  - Na⁺ and T-calcium channels, CAI
- **Dose**: 100 to 600 mg/day (BID or QD)
- **Side Effects**:
  - Somnolence, dizziness, nausea, headache, agitation/irritation, kidney stones, weight loss
- **Drug Interactions**
  - No effect on others
- **Clinical Pearl**
  - Appr. Japan & Korea ’89
  - Sulfonamide
  - Use outside of epilepsy

Pregabalin (PGB, Lyrica®)

- **Mechanism**
  - Neuromodulator
    - In animal models – anticonvulsant, analgesic, & anxiolytic
    - No demonstrated effects on GABAergic mechanisms
- **Dose** - 150 to 600 mg/day (BID or TID)
- **Side Effects**
  - Dizziness, ataxia, weight gain, asthenia
- **Drug Interactions**
  - None
- **Clinical Pearl**
  - Adjust dose for renal function
  - Concomitant conditions

Summary of 2nd Generation AEDs

- **Safer**
- **More expensive**
  - Though generics here & more coming
- **May help with intractable partial seizures**
- **Not profoundly more potent**
- **Less drug interactions**
- **Use outside of Epilepsy**
  - Psychiatry, Headache, Pain, etc.
Which AED?

• What parameters use?
  – Efficacy
    • all FDA-approved
  – Toxicity
  – Drug Interactions
  – Dosing schedule
  – Clinical impression
  – Art > Science

Contemporary Topics

• Using patient scenarios, cover new information on the use of AEDs
  – Woman of childbearing potential
  – Switching AED formulations
  – Older adult

Woman of Childbearing Potential

• 29 YOF with partial epilepsy and cerebral palsy in outpatient clinic
  – Seizures = none recent
  – Current meds
    • extended-release carbamazepine 200 mg b.i.d.
    • oral contraceptives & folic acid daily
  – She & new husband desire start family
  – Key counseling issues

• Aspects of pre-pregnancy planning
  – Monotherapy
  – Folic acid supplementation
  – Seizure control
  – Education of patient on risks

Patient Concerns

• As of August 2008, what are we able to discuss with women regarding the risks of AEDs during pregnancy?
  – Latest Information
    • Pregnancy Registry
      – Description
      – Malformations
    • NEAD study
      – Malformations
      – Cognition
### When Woman Becomes Pregnant

- **Encourage enrollment into the AED pregnancy registry**
  - Allow more data to be accrued especially for newer AEDs
  - For pregnant women taking any AED
    - For epilepsy or non-epilepsy purpose
  - Patients call 1-888-AED-AED4
  - www.aedpregnancyregistry.org
- **Three telephone calls**
  - Initial (10 min), 7 months (5 min), Post-partum (5 min)

### AED Pregnancy Registry Enrollment Data (11/07)

<table>
<thead>
<tr>
<th>Enrollment:</th>
</tr>
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<tbody>
<tr>
<td>6,142 participants as of November 2007</td>
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</table>

<table>
<thead>
<tr>
<th>Participants:</th>
</tr>
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<tbody>
<tr>
<td>Gravidity:</td>
</tr>
<tr>
<td>1st Pregnancy: 38%</td>
</tr>
<tr>
<td>2nd Pregnancy: 30%</td>
</tr>
<tr>
<td>3rd Pregnancy: 17%</td>
</tr>
<tr>
<td>4th &amp; Pregnancy: 16%</td>
</tr>
<tr>
<td>Education:</td>
</tr>
<tr>
<td>Some high school or less: 21%</td>
</tr>
<tr>
<td>Some college: 25%</td>
</tr>
<tr>
<td>College: 34%</td>
</tr>
<tr>
<td>Post-graduate: 21%</td>
</tr>
<tr>
<td>Ethnicity:</td>
</tr>
<tr>
<td>White: 80%</td>
</tr>
<tr>
<td>Black: 4%</td>
</tr>
<tr>
<td>Hispanic: 6%</td>
</tr>
<tr>
<td>Other: 4%</td>
</tr>
<tr>
<td>Drug Taken:</td>
</tr>
<tr>
<td>23 different monotherapies and 197 different polytherapy combinations</td>
</tr>
</tbody>
</table>

### What do we know now?

- **Risk of Major Malformation from US Registry**
  - Polytherapy = ↑ risk
  - Specific AEDs
    - General population = 1.6%
    - Phenobarbital = 6.5%
    - Valproic Acid = 10.7%
    - Carbamazepine = 2.6%
    - Lamotrigine = 2.9% (GSK)
- **August 2006 Issue Neurology (Meador, et al.)**
  - Neurodevelopmental Effects of Antiepileptic Drugs (NEAD Study) - 333 pregnancies
    - Serious adverse outcomes (major malts, fetal death)
      - CBZ (8.2%), LTG (1.0%), PHT (10.7%), VPA (20.3%)

### Woman of Childbearing Potential

- **29 YOF with partial epilepsy and cerebral palsy in clinic**
  - After discussion, opted to transition from carbamazepine to lamotrigine
    - Suggested wait on pregnancy
  - Return to clinic 6 months later - No new seizure activity after transition
    - She and her husband are now actively trying to become pregnant.
- **Education of patient on risks**
  - Provide new information regarding lamotrigine’s risk in pregnancy
Lamotrigine (Lamictal®)
Recent Findings

- AED Pregnancy Registry Data
  - 564 infants LTG monotherapy 1st trimester
  - Between 1997 & 3/1/06
    - Major malformations 2.7%
      - vs. 1.6% unexposed
    - 5 infants cleft lip/palate = 1:113
      - vs. 1:6,160 unexposed
      - Relative risk LTG = 32.8
    - Other AED registries = 1:405


AEDs & Neurodevelopment

- “Although we’ve had a great deal of information in the past 2 years on anatomical teratogenicity from AED in utero exposure, we have had much less with regard to cognitive outcomes. Animal studies of AEDs clearly show behavioral teratogenesis at dosages less than those required to produce anatomical teratogenicity.”
  
  Meador KJ. 2006

- Adab 2001 (UK)
- Additional Educational Needs
  - VPA = 30%, CBZ = 3.2%
- Adab 2004 (UK)
  - Verbal IQ
    - Children exposed to VPA lower than other AEDs or no exposure
- Failer 2002 (FIN)
  - Mean Verbal IQ Scores
    - VPA 80, CBZ 96, Controls 92
- Eriksson 2005 (FIN)
  - Low intelligence
    - VPA 19% vs CBZ or no exposure 0%

- Limitations to retrospective analyses
- NEAD Study
  - Prospective evaluation of long-term cognitive and behavioral development
    - 1st set of results – 12/06

AEDs & Neurodevelopment

- NEAD Study (Meador et al. 2006)
  - Pregnant women on monotherapy
    - CBZ, LTG, PHT or VPA
  - Long-term goal = examine cognition at age 6
  - Data presented 12/06 – age 2
    - Mental Scale of the Bayley Scales of Infant Development (n=166)
      - CBZ (n=43), LTG (n=57), PHT (n=38), VPA (n=28)
      - Children’s Mental Development Index (MDI)
        - Controlled (Mom’s IQ, AED levels, Sz type, etc)
AEDs & Neurodevelopment

• NEAD Study (Meador et al. 2006)
  – Results
    • Strong correlation between mother & child’s IQ
    • VPA-exposed kids lower MDI scores ($p=0.028$)

<table>
<thead>
<tr>
<th>AED</th>
<th>MDI Score</th>
<th>Scores &lt;70</th>
</tr>
</thead>
<tbody>
<tr>
<td>VPA</td>
<td>85</td>
<td>25%</td>
</tr>
<tr>
<td>PHT</td>
<td>90</td>
<td>13%</td>
</tr>
<tr>
<td>CBZ</td>
<td>94</td>
<td>12%</td>
</tr>
<tr>
<td>LTG</td>
<td>97</td>
<td>11%</td>
</tr>
</tbody>
</table>

• Further studies needed
  – Effect permanent? Other AEDs?

Contemporary Topics

• Using patient scenarios, cover new information on the use of AEDs
  – Woman of childbearing potential
  – Switching AED formulations
  – Older adult

Formulation Switching

H.B. is a 70 YO female with a history of “blackouts” accompanied by urinary incontinence. These episodes were confirmed by EEG to be epileptic seizures. She is taking Lamictal® (lamotrigine) 100 mg BID and has been seizure free for over a year.

• She expresses concern over the cost of her Lamictal®. She has been receiving the brand name for many years but her friend told her there is now a generic available. She would like your opinion about switching formulations.

Formulation Switching

• Finding the right dose of the optimal treatment to prevent seizures is a complex and sometimes lengthy process.

• An increase in seizures or adverse effects can occur when AEDs are switched
  • Brand name → Generic
  • Generic → Generic
  • Generic → Brand

• 2nd generation AEDs → generic
  – Already or in near future
Recent Patient & Pharmacist Study

- Education of the epilepsy patient & healthcare professionals involved in their care is important
- Because AEDs plays a major role in treatment, pharmacists serve an important function in the health care of patients with this chronic disease
- Example of Pharmacist Care
  - Reporting adverse drug reactions with AED formulation switching through the FDA’s Safety Information and Adverse Event Reporting Program (MedWatch)
    - www.fda.gov/medwatch — In existence since 1996

Purpose

- To assess patient and pharmacist knowledge of & attitude toward AED formulation switching and reporting of adverse drug reactions in patients with epilepsy
### Incidence of Problems with AED Formulation Switching

<table>
<thead>
<tr>
<th>Population</th>
<th>Question</th>
<th>Yes</th>
<th>No</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n=82)</td>
<td>I have experienced problems when switching between the same forms of my antiepileptic drug(s).</td>
<td>43%</td>
<td>19%</td>
<td>38%</td>
</tr>
<tr>
<td>Pharmacists (n=112)</td>
<td>I know other patients that have experienced problems when switching between the same forms of their antiepileptic drugs.</td>
<td>48%</td>
<td>17%</td>
<td>35%</td>
</tr>
</tbody>
</table>

### AED Formulation Switching

- **Our clinic**
  - Factor in patient finances
    - DAW not always work
  - Desire our patients to keep on same formulation
    - Talk to Pharmacist about trying to keep same manufacturer available

### Patient Resources

- **Clinical Care**
  - Seizure calendar
  - Pillbox
    - Adherence
- **Patient Support**
  - Epilepsy Foundation of Central Ohio [614-261-1100]
    - Educational sessions
    - Social Workers
    - Support groups
    - Summer Camp for Kids

### Resources

- **Organizations**
  - Epilepsy Foundation of America (EFA)
    - www.efa.org
  - Local Affiliate
    - Epilepsy Foundation of Central Ohio
      - www.epilepsy-ohio.org
  - American Epilepsy Society (AES)
    - www.aesnet.org
  - AED Pregnancy registry
    - 1-888-233-2334
      - All patients taking AEDs
        - No matter the condition
  - AED Summary Table
Summary

• Epilepsy
  – A chronic condition with multiple drug therapies
  – Newer information available on
    • Impact of AEDs in women of child-bearing age
    • Issues related to AED formulation switching
    • Choice of AEDs in the older adults

Thank you for your attention!

Are there any questions?

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