Adverse Drug Reactions of Anti-Epileptic Drugs
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Learning Outcomes

• Describe the more common adverse drug reactions (ADRs) caused by standard anti-epileptic drugs (AEDs)
• Recognize the dangerous ADRs seen with AEDs
• Compare the different behavioral effects reported with the AEDs
• Predict those patients at highest risk of behavioral effects from AEDs

Goals of AED Therapy

• Improve seizure control
• Minimize side effects of the drugs
  – Risk vs. benefit

Available Anticonvulsants

• Carbamazepine
• Clobazam
• Eslicarbazepine
• Ethosuximide
• Ethotoin
• Gabapentin
• Felbamate
• Lacosamide
• Lamotrigine
• Levetiracetam
• Methsuximide
• Oxcarbazepine
• Perampanel
• Phenobarbital
• Phenytoin/Fosphenytoin
• Primidone
• Rufinamide
• Tiagabine
• Valproic Acid
• Vigabatrin
• Zonisamide
Adverse Drug Reactions

• Dose-related (Type A)
  − Generic and predictable
  − Explainable
  − Early in therapy or with a dose adjustment
  − Rarely require stopping the drug
  − Most ADRs seen in clinical trials
  − Patient-specific

• Idiosyncratic (Type B)
  − Unpredictable
  − Most likely in susceptible patients
  − Pathogenesis is unrelated to known mechanism of drug
  − Results from abnormal immunological reaction
  − May be more than one mechanism

Dose-Related ADRs
Risk Factors

• Starting dose and titration rate
  − Tolerance development
  − Early detection of toxicities
  − Side effects may occur within the standard range
    • Statistical estimate
    • Inter-individual differences
    • Effects associated with peak levels (timing of doses)

Dose-Related ADRs
Risk Factors

• Associated drugs
  − Co-administration of two (or more) AEDs
  − Additive or sometimes supra-additive ADRs

• Other diseases
  − Hepatic disease
    − Avoid those primarily metabolized in the liver
      − Lamotrigine and tiagabine
  − Renal disease
    − Avoid those with predominant renal excretion
      − Gabapentin and topiramate
Dose-Related ADRs
Most frequent

• Central Nervous System

• Gastrointestinal


Dose-Related ADRs
Most frequent

• CNS
  – Somnolence, sedation, dizziness and headache are the most often reported
  – Tolerance usually develops with slow dose titration
  – Relation to peak level
  – Cognitive effects
  – Psychiatric/behavioral effects


Dose-Related ADRs
Most frequent

• CNS – Cognitive Effects
  – Diminished attention, executive function, intelligence, language skills, memory and processing speed
    • Phenobarbital
      – Lower IQ scores
    • Topiramate

Dose-Related ADRs

Most frequent

• CNS – Psychiatric/Behavioral Effects
  – Depression and anxiety are common with epilepsy
    • Forced normalization
  – Patients are often unaware of cognitive and mood changes (but the family will be)
    • Behavioral effects (irritability and hostility) are the main concerns with levetiracetam, often seen at the start of therapy (occurring in up to 40% or more)


Psychiatric/Behavioral Effects

Risk Factors

• Poorer seizure control
• Mental retardation
• Previous behavioral problems/psychiatric history
  – ADHD
• Learning disabilities


CNS – Psychiatric/Behavioral Effects

<table>
<thead>
<tr>
<th>Drug</th>
<th>Aggression %</th>
<th>Psychosis %</th>
<th>Hyperactivity %</th>
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</thead>
<tbody>
<tr>
<td>Topiramate</td>
<td>1.9 – 81.8</td>
<td>1.3 – 18.9</td>
<td>2.7 – 4.4</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>2.3 – 27</td>
<td>0.3 – 1.6</td>
<td>2.5 – 3.8</td>
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<tr>
<td>Tiagabine</td>
<td>1 – 36.4</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>3.4 – 23</td>
<td>0.7 – 6.7</td>
<td>6.1 – 25.7</td>
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<tr>
<td>Clonazepam</td>
<td>1.3 – 21.9</td>
<td>NR</td>
<td>4 – 27</td>
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<td>Perampanel</td>
<td>&lt; 1 – 20</td>
<td>&lt; 1</td>
<td>NR</td>
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<td>Gabapentin</td>
<td>9.4 – 13</td>
<td>&lt; 1</td>
<td>0 – 11</td>
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<tr>
<td>Primidone</td>
<td>3 – 18.2</td>
<td>1.4</td>
<td>4.5</td>
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<td>Valproate</td>
<td>0 – 12</td>
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<td>0 – 10</td>
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<td>Rufinamide</td>
<td>3 – 11.6</td>
<td>0.6 – 4</td>
<td>3 – 4.7</td>
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<tr>
<td>Zonisamide</td>
<td>1.6 – 9</td>
<td>2.2 – 18.9</td>
<td>NR</td>
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</tbody>
</table>

Dose-Related ADRs

Most frequent

- Gastrointestinal
  - Nausea and vomiting are the most common
  - Occurs in virtually every AED
  - Tolerance usually develops
  - Dividing doses may be helpful


Idiosyncratic Adverse Effects

Risk Factors

- Genetics
  - Siblings of patients with a h/o idiosyncratic reactions to an aromatic AED (DPH, CBZ, PB)
  - HLA-B*1502 allele (Han Chinese)
    - CBZ-induced Stevens-Johnson syndrome (SJS)
- Age
  - Children are at a greater risk than adults
    - Greater risk of SJS with Lamotrigine vs adults
    - Much greater risk of valproic acid toxic hepatitis


Idiosyncratic Adverse Effects

Risk Factors

- Other diseases associated with epilepsy
  - Metabolic disorders, rheumatoid arthritis, SLE, multiple carboxylase deficiency, mitochondrial dysfunction, and others predispose to VPA toxicity
- Associated drugs
  - Drug interactions leading to increased levels of VPA or lamotrigine may increase risk of hypersensitivity

Idiosyncratic Adverse Effects

Risk Factors

• Previous history of allergic drug reactions
  – Cross-sensitivity occurs in about 50%
    • Especially when using lamotrigine or oxcarbazepine
• Starting dose and titration rate
  – Slow titration may allow desensitization to occur
    • Especially important with lamotrigine (rash)


Idiosyncratic ADRs

Most frequent

• Skin
  – Cutaneous manifestations are the most common idiosyncratic reactions caused by AEDs
    • Range from benign mild rashes to potentially life-threatening
      • DRESS, SJS and TEN


Drugs causing Stevens-Johnson Syndrome mnemonic:

PCP LAPSE
• Phenytoin
• Carbamazepine
• Phenobarbital
• Lamotrigine
• Allopurinol
• Penicillln
• Sulfat drugs
• Erythromycin

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Idiosyncratic ADRs
Most frequent

• Skin
  - DRESS (Dermatological Diseases, Rash with Eosinophilia and Systemic Symptoms)
    • Fever, skin eruption, eosinophilia, atypical lymphocytosis, arthralgia, lymphadenopathy and multi-organ involvement
  - Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis
    • Greatest in the first 8 weeks of therapy


Miscellaneous ADRs

• Weight gain
  - Valproate, Vigabatrin, Pregabalin
• Hypohidrosis
  - Topiramate
• Kidney stones
  - Topiramate, Zonisamide
• Hyponatremia
  - Carbamazepine, oxcarbazepine
• Concentric visual field defect
  - Vigabatrin (30-50% incidence)

Take Home Points

• All AEDs cause ADRs, most often CNS-related
• Early ADRs (dose related), Late (idiosyncratic)
• Go low, go slow for best tolerability
• Idiosyncratic effects require discontinuation
• CNS effects include cognitive and psychiatric effects