Antiepileptic Drug Clinical Pearls: Clobazam and Ezogabine

2012 OSHP Annual Meeting
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Conflicts of interest
The presenter for this continuing pharmacy education activity reports no relevant financial relationships or other conflicts of interest.

Learning objectives
Identify the clinical utility of clobazam and ezogabine in the treatment of epilepsy

Clobazam (Onfi™)
- FDA approval October 2011
- Adjunctive therapy for seizures associated with Lennox-Gastaut syndrome (≥2 years of age)
- Schedule IV controlled substance
- REMS: Medication guide for suicidal ideation

Clobazam structure
Nitrogen substitutions at 1,5

Clobazam dosing

<table>
<thead>
<tr>
<th></th>
<th>Weight ≤30 kg</th>
<th>Weight &gt;30 kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Starting dose</td>
<td>5 mg/day</td>
<td>10 mg/day</td>
</tr>
<tr>
<td>Day 7</td>
<td>10 mg/day</td>
<td>20 mg/day</td>
</tr>
<tr>
<td>Day 14</td>
<td>20 mg/day</td>
<td>40 mg/day</td>
</tr>
</tbody>
</table>

Doses >5 mg/day should be divided BID

Clobazam dosing

- Populations with decreased clearance
  - Geriatric patients
  - CYP2C19 poor metabolizers
  - Child-Pugh score 5-9
- Alternative dosing recommendation
  - Start at 5 mg/day for two weeks
  - Titrate weekly to maximum dose of 20 mg/day

Clobazam adverse events

Dose-related
- Somnolence
- Constipation
- Drooling
- Insomnia
- Ataxia
- Aggression

Idiopathic
- Cough
- Pyrexia
- Upper respiratory tract infections

Long-term
- Behavior changes
- Dependence

Clobazam drug interactions

- Effects on other drugs
  - CYP2D6 inhibition
  - Induction of oral contraceptive metabolism
- Effect of other drugs on clobazam
  - No clinically-significant interactions with other antiepileptic drugs
  - Alcohol increases serum levels by 50%

Clobazam summary

- Clinical advantages
  - Lower risk of adverse effects compared to other benzodiazepines
  - Less tolerance over time
- Clinical concerns
  - Physical and psychological dependence
  - Withdrawal

Ezogabine (Potiga™)

- Approved June 2011
- Adjunctive treatment of focal seizures
- Schedule V controlled substance
- REMS: Medication guide for suicidal ideation and urinary retention

Ezogabine mechanism of action

- Novel mechanism
- Stabilizes KCNQ2-5 voltage-gated potassium channels in the open position

- KCNQ2-5 potassium channel stabilization
- Enhancement of neuronal M-current
- Hyperpolarization of neurons

#### Ezogabine dosing

<table>
<thead>
<tr>
<th></th>
<th>Starting dose</th>
<th>Weekly titration</th>
<th>Maximum daily dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal adult</td>
<td>100 mg/dose</td>
<td>150 mg/day</td>
<td>1,200 mg/day</td>
</tr>
<tr>
<td>Geriatric</td>
<td>50 mg/dose</td>
<td>150 mg/day</td>
<td>750 mg/day</td>
</tr>
<tr>
<td>GFR &lt;50 mL/min</td>
<td>50 mg/dose</td>
<td>150 mg/day</td>
<td>600 mg/day</td>
</tr>
<tr>
<td>Child-Pugh 7-9</td>
<td>50 mg/dose</td>
<td>150 mg/day</td>
<td>750 mg/day</td>
</tr>
<tr>
<td>Child-Pugh &gt;9</td>
<td>50 mg/dose</td>
<td>150 mg/day</td>
<td>600 mg/day</td>
</tr>
</tbody>
</table>

Doses >900 mg/day increased the risk of adverse events without added efficacy


#### Ezogabine adverse events

<table>
<thead>
<tr>
<th></th>
<th>Dose-related</th>
<th>Idiopathic</th>
<th>Long-term</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Dizziness</td>
<td>Nausea</td>
<td>Unknown</td>
</tr>
<tr>
<td></td>
<td>Somnolence</td>
<td>Diplopia</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
<td>Headache</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Asthenia</td>
<td>Fatigue</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Confusion</td>
<td>Constipation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Impaired memory</td>
<td>Urinary retention</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Impaired memory</td>
<td>QT prolongation</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Weight gain</td>
<td>Weight gain</td>
<td></td>
</tr>
</tbody>
</table>

#### Ezogabine drug interactions

- **Pharmacokinetic**
  - Metabolized primarily through UGT enzymes
  - Few clinically-relevant interactions identified

- **Pharmacodynamic**
  - Other drugs that prolong the QTc interval

#### Ezogabine summary

- **Clinical advantages**
  - New mechanism of action
  - Possible option for refractory epilepsy

- **Clinical concerns**
  - Dose-related adverse effects
  - Use with caution when used with other drug that prolong the QTc interval

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