Managing Drug Interactions with Antiepileptic Drugs

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Newer Generation AEDs

- Felbamate (Felbatol®)
- Gabapentin (Neurontin®)
- Lamotrigine (Lamictal®)
- Levetiracetam (Keppra®)
- Oxcarbazepine (Trileptal®)
- Pregabalin (Lyrica®)
- Rufinamide (Banzer®)
- Tiagabine (Gabitril®)
- Topiramate (Topamax®)
- Vigabatrin (Sabril®)
- Zonisamide (Zonegran®)
- Lacosamide (Vimpat®)
- Ezogabine (Potiga®)

See attached

Case Reports: “Newer” Generation AED-Induced Stevens-Johnson Syndrome (SJS)

- Oxcarbazepine (Trileptal®)
- Levetiracetam (Keppra®)
What is SJS?

- Life-threatening skin disease that usually results from a drug reaction
  - Onset: 7 to 60 days after initiating new drug regimen
  - Mortality rate of 5 – 12%

- Erythematous rash across face and trunk, may continue to spread to other body areas
  - Rash can form into blisters
  - "Sloughing-off" of skin
  - All mucous membranes have the potential to become inflamed
    - Eyes, mouth, vaginal and anal areas

- Non-specific symptoms
  - Cough
  - General aching
  - Headaches
  - Fevers


What is SJS?


What is SJS?


Treatment of SJS

- Stop offending medication
- Supportive care
  - Fluid replacement and nutrition
  - Wound and eye care
- Adjunctive medications
  - Pain
  - Antihistamines
  - Antibiotics
  - Topical and oral steroids
  - Immunoglobulins

Oxcarbazepine-Induced SJS

- 38 year old female presents with fever, sore throat, and fatigue
- History of “drug allergy”
- Developed right partial bronchial seizure, secondary to parasagittal mass lesion
  - Oxcarbazepine was administered
  - 600 mg/day x 3 days
  - Then increased to 900 mg/day


Oxcarbazepine-Induced SJS

- Patient developed papular rash all over body
- Diagnosed with Stevens-Johnson Syndrome
  - Erythematous rash with mucosa involvement 2 weeks after oxcarbazepine initiation
  - Patient was only taking oxcarbazepine during those 2 weeks


Oxcarbazepine-Induced SJS

- Package insert warning
  - 3 to 10 fold increase in reporting rates of SJS
- Antiepileptic drugs with aromatic rings:
  - Phenytoin, Lamotrigine, Carbamazepine, and Oxcarbazepine
  - Common risk allele in Asian patients carrying HLA-B*1502
  - FDA recommends genetic testing before use in Asian patients
  - Epoxide Hydrolase Deficiency
  - Most commonly seen in African Americans


Which of the following patient populations commonly carry the HLA-B*1502 allele?

A. African American
B. Asian
C. Eastern European
D. Indian

Levetiracetam-Induced SJS

- 27 month old female underwent hypothermic open heart surgery
- Operation was successful
  - Cardiorespiratory arrest occurred on day 7 after surgery
  - Patient intubated
- Seizures occurred on day 8
  - Patient received phenobarbital 5 mg/kg/day
  - Oxcarbazepine added on day 32 at 10 mg/kg/day


Levetiracetam-Induced SJS

- Patient develops rash on day 34
  - Rash worsened on day 35
- Patient switched to levetiracetam 20 mg/kg/day
  - Presumed oxcarbazepine allergy
  - No new rashes appear
  - Primary rash begins to disappear
- Patient extubated on day 39

Levetiracetam-Induced SJS

- Levetiracetam dose increased to 30 mg/kg/day on day 41
- More rashes begin to appear after being on levetiracetam x 9 days (day 43)
  - Body temperature reached 40°C
  - Fevers persisted
  - Rashes extended from face and torso to:
    - All 4 limbs
    - Mucous membranes (mouth, lips, vulva, anus)
    - Exudate formed on mouth and lips


Diagnosed with Stevens-Johnson Syndrome


Case Reports: “Newer” Generation AED-Induced Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)

- Lamotrigine (Lamictal®)
- Levetiracetam (Keppra®)
What is Drug Rash with Eosinophilia and Systemic Symptoms (DRESS)?

- Severe drug-induced reaction presenting with varying degrees of:
  - Cutaneous eruption (rash)
  - Fever
  - Lymphadenopathy (at least TWO sites)
  - Cervical, axillary, inguinal
  - Internal organ involvement
- Difficult to diagnose
- Mortality rate of 10 - 20%
- Delayed onset of 2 - 6 weeks after new drug initiation


SJS vs. DRESS

<table>
<thead>
<tr>
<th>DRESS Syndrome</th>
<th>SJS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous features</td>
<td>Generally begins on face and extremities. Facial edema, morbilliform eruption, exfoliative dermatitis, tight blisters.</td>
</tr>
<tr>
<td>Hematological abnormalities</td>
<td>Eosinophilia +, +/-. Presence of atypical lymphocytes, leukocytes +.</td>
</tr>
<tr>
<td>Systemic involvement</td>
<td>Adenopathy +, +/-. Hepatitis +, +/-. Intestinal, renal nephritis, tubular nephritis, interstitial nephritis, pterional encephalitis, mesenteric involvement.</td>
</tr>
</tbody>
</table>

What is DRESS?

![Image of skin layers: Dermis and Epidermis]


Treatment of DRESS

- Stop offending medication
- Supportive care
  - Fluid replacement and nutrition
  - Skin care
- Systemic corticosteroids
- Adjunctive medications
  - Pain
  - Antihistamines
  - Antibiotics
  - Topical steroids


Lamotrigine-Induced DRESS

- 75 year old male with generalized tonic-clonic seizures
- Clinical examination and neurologic investigations unremarkable
- Lamotrigine initiated and patient discharged
- Day 40 after initiation, patient developed:
  - Exanthematous rash
  - Fever
  - Peripheral lymphadenopathies
  - Hypereosinophilia

Lamotrigine-Induced DRESS

- Lamotrigine hypersensitivity suspected, and drug stopped on day 45
- On day 47 patient presented with acute abdominal pain, elevated lipase
  - Acute pancreatitis confirmed on CT scan
- Patients condition worsened → transferred to ICU with multiorgan failure
- DRESS Syndrome confirmed
  - Compatible skin histology
  - Concomitant HHV-6 infection

Levetiracetam-Induced DRESS

- 31 year old male with a low-grade astrocytoma
- Presented with tonic-clonic seizures, treated with:
  - Levetiracetam 1 gram BID
  - Dexamethasone 12 mg/day → 2 mg/day
- On day 45 (after levetiracetam initiation), dexamethasone was discontinued

Levetiracetam-Induced DRESS

- Patient developed fever and dyspnea on day 46
- Admitted on day 49:
  - CXR: bilateral interstitial infiltrates
  - LDH 222 U/L (<204)
  - Ferritin 223 mg/mL (13-178)
  - CRP 3.1 mg/dL (<0.5)
- Neurologic fever suspected
  - Dexamethasone 6 mg/day reinitiated
Levetiracetam-Induced DRESS

- Patient discharged on day 55 with dexamethasone 4 mg x two more days
- On day 59, patient presented again with:
  - Erythematous maculopapular rash
  - Recurrent fever, dyspnea, and (+) CXR
  - LDH 516 (<204)
  - Ferritin 419 ng/mL (13-178)
  - CRP 2.6 mg/dL (<0.5)
  - ALT 60 U/L (<56), AST 58 U/L (<30)
- Diagnosed with DRESS Syndrome


Rate of DRESS Syndrome With AEDs

<table>
<thead>
<tr>
<th>AED</th>
<th>No Case</th>
<th>Possible</th>
<th>Probable</th>
<th>Definite</th>
<th>Cases (%) (n=172)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbamazepine</td>
<td>3</td>
<td>10</td>
<td>20</td>
<td>14</td>
<td>47 (27)</td>
</tr>
<tr>
<td>Lamotrigine</td>
<td>3</td>
<td>3</td>
<td>2</td>
<td>2</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Oxcarbazepine</td>
<td></td>
<td></td>
<td></td>
<td>1</td>
<td>2 (1)</td>
</tr>
<tr>
<td>Phenytoin</td>
<td>-</td>
<td>3</td>
<td>4</td>
<td>3</td>
<td>10 (6)</td>
</tr>
<tr>
<td>Valproate</td>
<td>1</td>
<td>3</td>
<td></td>
<td></td>
<td>7 (4)</td>
</tr>
<tr>
<td>Zonisamide</td>
<td>-</td>
<td>1</td>
<td>2</td>
<td>1</td>
<td>4 (2)</td>
</tr>
</tbody>
</table>


Which of the following AEDs have been associated with DRESS?

A. Carbamazepine
B. Lamotrigine
C. Levetiracetam
D. All of the above
In Conclusion

- Stevens-Johnson Syndrome
  - Commonly presents with:
    - Rash
    - Skin sloughing
    - Inflamed mucous membranes
    - Fever
  - Associated with the initiation of oxcarbazepine and levetiracetam therapy

- Asian patients carrying the HLA-B*1502 allele are 10x more likely to develop SJS
  - Genetic testing prior to carbamazepine therapy


In Conclusion

- Drug Rash with Eosinophilia and Systemic Symptoms Syndrome
  - Commonly presents with:
    - Rash
    - Fever
    - Lymphadenopathies
    - Systemic organ involvement
  - Associated with the initiation of lamotrigine, levetiracetam, and carbamazepine therapy

Thank you