Advanced Pediatric Emergency Medicine Assembly

March 11 – 14, 2013
Lake Buena Vista, FL

Status Epilepticus Management Strategies: The Latest on the Use of Levetiracetam

This hot topic will focus on the use of new therapies for status epilepticus with a concentration on the use of levetiracetam (Keppra). What evidence exists for its use in the treatment of pediatric status epilepticus? What is the best route and dose of administration? What are the potential side effects? The speaker will use the evidence to incorporate levetiracetam in your treatment algorithm for pediatric status epilepticus.

- Discuss the evidence and experience for use of levetiracetam in pediatric status epilepticus.
- Outline the appropriate dose and route of administration for levetiracetam in pediatric status epilepticus.
- Describe potential side effects from administration of levetiracetam for pediatric status epilepticus.
- Incorporate, using evidence or published guidelines, the use of Keppra in the treatment algorithm for status epilepticus.

3/13/2013
1:15pm – 2:00pm

(+) No significant financial relationships to disclose
Status Epilepticus Management Strategies: The Latest on the Use of Levetiracetam

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Goals

• Pediatric status epilepticus (SE):
  – Epidemiology
  – Physiology and pharmacology

• Levetiracetam:
  – Evidence for use in SE
  – Dose and administration
  – Adverse effects

• Suggested treatment protocol
Status Epilepticus

• No universal definition
  – >30 minutes continuous seizure activity, or
  – ≥2 seizures without regaining consciousness

• Pediatric Epidemiology
  – 17-23/100,000 per year
  – 56% previously neurologically healthy
  – 10-25% with previous epilepsy
  – Risk of recurrent SE: 13%

Etiology

• “Common”
  – Anoxia
  – Malignancy
  – Head trauma
  – Metabolic disturbance
  – Medication noncompliance
  – Cerebral palsy
  – Infections
  – CNS malformation

• Uncommon
  – Autoimmune
  – Mitochondrial
  – Genetic disorders
  – Neurocutaneous
Complications

- Mortality: 3-5%
- Morbidity: 6-10%
  - Cerebral injury
    - Hypoxic, metabolic, excitotoxic, cerebral edema, venous thrombosis, CVA
  - Cardiorespiratory
  - Autonomic
  - Metabolic

Normal Seizure Termination
Local Neuronal Mechanisms

- $\downarrow$Na⁺/K⁺ gradient
- $\downarrow$ATP/glutamate
- $\uparrow$adenosine
Normal Seizure Termination
Remote Mechanisms

Other Brain Areas
• Superior Colliculus
• Reticular Activating System

Mechanism
• \( \uparrow \) GABA/inhibitory tone?
• \( \downarrow \) excitatory circuits?

Pathophysiology

• Two phases: activation and maintenance
• Impaired endogenous seizure termination mechanisms
• Ongoing seizure activity \( \Rightarrow \)
  – \( \downarrow \) GABA\(_A\) receptors
  – \( \uparrow \) NMDA receptor
• \( \uparrow \) seizure duration \( \Rightarrow \) \( \uparrow \) treatment resistance
Pathophysiology

Table 1. Initiation and maintenance of SE

<table>
<thead>
<tr>
<th>Initiators</th>
<th>Blockers of initiation phase</th>
<th>Blockers of maintenance phase</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low Na⁺, High K⁺</td>
<td>Na⁺ channel blockers</td>
<td>NMDA antagonists</td>
</tr>
<tr>
<td>GABAB antagonists</td>
<td>GABA₂ agonists</td>
<td>Tachykinin antagonists</td>
</tr>
<tr>
<td>Glutamate agonists: NMDA, AMPA, kainate, low Mg²⁺, low Ca²⁺, stimulation of glutamatergic pathways</td>
<td>NMDA antagonists, high Mg²⁺</td>
<td>Galanin</td>
</tr>
<tr>
<td>Cholinergic muscarinic agonists, stimulation of muscarinic pathways</td>
<td>AMPA/kainate antagonists</td>
<td>Dynorphin</td>
</tr>
<tr>
<td>Tachykinins (SP, NKB)</td>
<td>Cholinergic muscarinic antagonists</td>
<td>SP, Neurokinin B antagonists</td>
</tr>
<tr>
<td>Galanin antagonists</td>
<td>Galanin</td>
<td>Somatostatin</td>
</tr>
<tr>
<td>Opiate δ agonists</td>
<td>Opiate δ antagonists</td>
<td>NPY</td>
</tr>
<tr>
<td>Opiate κ agonists</td>
<td>Opiate κ antagonists</td>
<td>NPY, neuropeptide Y, SP, substance P</td>
</tr>
</tbody>
</table>

AMPA, As-amino-3-hydroxy-5-methylisoxazole-4-propionic acid; GABA, γ-aminobutyric acid; NKB, neurokinin B; NMDA, N-methyl-D-aspartate; NPY, neuropeptide Y; SP, substance P.

Wasterlain et al, Epilepsia, 2008
Initial Management

Significance of Early Treatment

- ↑ seizure duration ➔ ↑ treatment resistance
- Earlier treatment ➔ ↑ treatment success
- q1 minute seizure ➔ ↑ SE risk 5%

FIGURE 1. Continuum of seizures to status epilepticus.
Abend et al, Ped Emerg Care, 2008
First Line Agents

- Benzodiazepines: **0.1 mg/kg**
  - IV lorazepam
  - IM midazolam

Benzodiazepines

- Bioavailability
  - Intranasal: ~50%
  - Oral/Buccal/Rectal: ~20%
- Alternative Routes
  - Intranasal lorazepam/midazolam (0.2 mg/kg)
  - Rectal diazepam (0.5 mg/kg)
  - Buccal midazolam (0.5 mg/kg)
GABA Receptor

Second Line Agents

- Fosphenytoin
- Valproic Acid
- Levetiracetam
- Phenytoin
- Phenobarbital
Second Line Agents

- Continuous cardiopulmonary monitoring
- Dose: 20 mg/kg
  - Fosphenytoin: 15-20 mg/kg
  - Valproic Acid: 20-30 mg/kg
  - Phenytoin: 20 mg/kg
  - Phenobarbital: 15-20 mg/kg
Levetiracetam and Status Epilepticus

• Evidence:
  – 22 open-label case series since 2007
  – 707 total patients
  – ~70% success
  – ~10% adverse events (all mild)
• Dose: 20 mg/kg?
“Malignant”/Refractory SE

• Incidence: ~20%
• Treatment
  – General anesthesia
  – Sedative drip
    • Propofol: 2 mg/kg bolus, 5-10 mg/kg/hour
    • Midazolam: 0.1-0.3 mg/kg bolus, 0.05-0.4 mg/kg/hour
    • Thiopental: 2-4 mg/kg bolus, 3-5 mg/kg/hour
• Midazolam 0.1 mg/kg IM
• Diazepam 0.5 mg/kg PR

10-20 min. (ED)
• Lorazepam 0.1 mg/kg IV
• Midazolam 0.2 mg/kg IN?

20-60 min. (ED/ICU)
• Levetiracetam/fos-phenytoin/valproic acid -- 20 mg/kg IV

60-90 min. (ED-ICU)
• Levetiracetam/fos-phenytoin/valproic acid -- 20 mg/kg IV

90-120 min. (ED-ICU)
• Midazolam/propofol/bariturate drip
• General anesthesia
Thank you!
Please complete your evaluation forms!