Drug Treatment of Status Epilepticus in the Intensive Care Unit

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Faculty Disclosure

• None

Outline

De novo SE in the ICU
Refractory SE – management in the ICU

Current standards of care
Emerging therapies
Why Should SE Be Treated Aggressively in the ICU?

Attenuation of:

- Excitotoxic brain injury with prolonged SE
- Hyperthermia
- Hypotension
- Rhabdomyolysis
- Cardiac arrhythmias

Sophisticated support measures to manage many treatment-related complications

Current Practice

**First Line Therapy**

- Lorazepam: 81 (76%)
- Diazepam: 18 (17%)
- Other: 7 (7%)


**Second Line Therapy**

- PHT / FosPHT: 101 (95%)
- Other: 5 (5%)


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**Pharmacokinetic and Pharmacodynamic Properties of Benzodiazepines after IV Administration to Cats**

<table>
<thead>
<tr>
<th></th>
<th>Diazepam</th>
<th>Midazolam</th>
<th>Lorazepam</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octanol buffer partition coefficient</td>
<td>309</td>
<td>34 (pH 3)</td>
<td>475 (pH 7.5)</td>
</tr>
<tr>
<td>Unbound Vd (L/kg)</td>
<td>17</td>
<td>34</td>
<td>12</td>
</tr>
<tr>
<td>Time to peak CSF conc (min)</td>
<td>3.7</td>
<td>3.7</td>
<td>7.0</td>
</tr>
<tr>
<td>Onset of slow-wave EEG activity (min)</td>
<td>0.9</td>
<td>0.3</td>
<td>3.8</td>
</tr>
<tr>
<td>Duration of slow-wave EEG activity (min)</td>
<td>7.5</td>
<td>6.3</td>
<td>28.3</td>
</tr>
</tbody>
</table>

Adapted from Arendt et al. J Pharmacol Exp Ther 1983;227:98.
**Unbound Phenytoin Concentrations Following IV Administration of Phenytoin and Fosphenytoin**

- 1200 mg Fos-PHT @ 100 mg PE/min (triangles)
- 1200 mg Fos-PHT @ 150 mg PE/min (squares)
- 1200 mg PHT @ 50 mg/min (diamonds)

**Purple Glove Syndrome**

2 days following non-extravasated infusion of 1500 mg phenytoin through right hand vein

2 weeks later

**Refractory Status Epilepticus**

Definition: Ongoing SE despite treatment with either 2 or 3 “front-line” AEDs, ± persistent seizure activity for 0-2 hr

Frequency: 10 to 40% of SE episodes
15,000 to 60,000 cases per yr

**Current Practice**

- **Third Line Therapy**
  - Phenobarbital: 46 (43%)
  - IV-AED: 20 (19%)
  - Valproate: 17 (16%)
  - Inc. Dose of AEDs: 13 (12%)
  - Other: 10 (9%)

Response of Status Epilepticus to Sequential Treatments in VA Cooperative Trial

<table>
<thead>
<tr>
<th>% Responding</th>
<th>Overt SE n=384</th>
<th>Subtle SE n=134</th>
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</thead>
<tbody>
<tr>
<td>1st agent</td>
<td>12%</td>
<td>23%</td>
</tr>
<tr>
<td>2nd agent</td>
<td>23%</td>
<td>3%</td>
</tr>
<tr>
<td>3rd agent</td>
<td>3%</td>
<td>5%</td>
</tr>
<tr>
<td>Any other agent</td>
<td>55%</td>
<td>28%</td>
</tr>
<tr>
<td>Rx failure</td>
<td>15%</td>
<td>15%</td>
</tr>
</tbody>
</table>

Treiman DM, et al. unpublished data

Current Practice

Fourth Line Therapy


Meta-analysis of Treatment Response and Outcome in Refractory SE

<table>
<thead>
<tr>
<th>Midazolam (n=54)</th>
<th>Propofol (n=33)</th>
<th>Pentobarb (n=106)</th>
<th>Total (n=193)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute treatment failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>20</td>
<td>27</td>
<td>8</td>
</tr>
<tr>
<td>Breakthrough seizures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>51</td>
<td>15</td>
<td>12</td>
</tr>
<tr>
<td>Withdrawal seizures</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>63</td>
<td>46</td>
<td>43</td>
</tr>
<tr>
<td>Ultimate Rx failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>21</td>
<td>20</td>
<td>10</td>
</tr>
</tbody>
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Meta-analysis of Treatment Response and Outcome in Refractory SE

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</tr>
</thead>
<tbody>
<tr>
<td>Hypotension Requiring Pressors</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>30</td>
<td>42</td>
</tr>
<tr>
<td>Mortality</td>
<td></td>
<td></td>
</tr>
<tr>
<td>%</td>
<td>46</td>
<td>52</td>
</tr>
</tbody>
</table>

* statistically significant difference

Emerging Therapies for Status Epilepticus

IV Valproate

- Patients who are allergic to PHT or PBR
- Patients in absence or myoclonic SE
- As an alternative to PHT after a benzodiazepine
- After failure of benzodiazepine + PHT

25-45 mg/kg (undiluted or in 100 mL NS) at 500 mg/min or less in adults and at 3 mg/kg/min in children

In two recent randomized trials (total n=168), IV VPA terminated SE in 66-88% of patients (either as 1st-line treatment or after failure of a benzodiazepine)

Emerging Therapies for Status Epilepticus

NG Topiramate

- Rationale: diversity of mechanisms of action including blockade of glutamate receptors
- 300-1600 mg/d via NGT (adults)
- 10 mg/kg/d x 2 days, then 5 mg/kg/d (children)

13/13 patients reported in the literature with convulsive or nonconvulsive SE terminated following NG TPM – including 5 patients unresponsive to anesthetic agents. Time to response has varied from “several” to 48 hours

Emerging Therapies for Status Epilepticus

IV Levetiracetam

- Focal and “nonconvulsive” SE in adults and children
- Patients with liver failure or potential drug interactions
- 2000-4000 mg (adults) diluted 1:1 with NS administered over 5-15 mins; 30 mg/kg (children)

Most patients reported in the literature with focal, generalized convulsive, or nonconvulsive had SE terminated within 20-40 minutes after treatment with IV-LEV

Drug Treatment of Status Epilepticus - circa 2009...

Seizures continuing

Additional emergent drug therapy may not be required if seizures stop and the etiology of status epilepticus is rapidly corrected

Seizures continuing

Seizures continuing

Seizures continuing

Seizures continuing

Seizures continuing

Seizures continuing

Seizures continuing

Admit to ICU

Modified from Lowenstein DH. Epilepsia 2006;47(suppl 1):35.