Status Epilepticus: Why, What, & How

Jae-Moon Kim, MD, PhD.

Department of Neurology, Chungnam National University Hospital
What is SE: Classic Definition

- Status epilepticus (SE):
  “more or less incessant Seizures” (Bourneville, 1876)
  “… a continuing epileptic state…” (Gastaut, 1970)

- ILAE commission report (1997)
  a single epileptic Sz > 30 min or
  a series of epileptic Sz during which
  function is not regained between
  ictal events in a > 30-min period"
SE: Operational Definition
(Lowenstein & Alldrige, 1998)

- Operational: Enduring epileptic condition that lasts more than 5 minutes/more than two discrete seizures w/o regaining of consciousness (5 Y–O>)
- Getting shorter…
SE: Conceptual Definition

- A failure of inhibitory mechanism that ordinarily terminate a seizure

  - This is consistent with epidemiologic data that identify a subgroup of patients with predisposition to prolonged seizure
Mechanisms of SE

- Failure of normal inhibitory pathway via GABA$_A$ receptor
- Loss of inhibitory drive causes activation of excitatory feedback loops
- Leading to repetitive, synchronous firing of large groups of neurons
- Decreased effectiveness of Zn$^{++}$
- Further decline in GABAergic function
- Enhanced glutamate excitation & cell death by glutamate
What is SE?
Intracellular distribution of GABA(A) subunits in hippocampal neurons from SE and control rats. Top row: Double-label immunocytochemistry in dentate and CA3c of control and SE animals using antibodies to GABA(A) b2/b3 subunits (red) and synaptophysin (green). Note the co-localization (yellow) of receptor subunits with presynaptic sites in controls (left) and greater internalization of receptor subunits during SE (right). Second row: Similar confocal image of granule cells using antibodies to GABA(A) c2 subunits (red) and synaptophysin (green). Internalization is seen in soma and proximal dendrites of animal in SE. Third row: EEGs recorded from dorsal hippocampus 1 h after PPS or sham stimulation. Fourth row: mIPSCs mean traces from a typical granule cell from a control and an SE animal, demonstrating smaller amplitude and prolonged decay in the latter.
Model of the role of receptor trafficking in the transition from single seizures to SE. After repeated seizures, the synaptic membrane of GABAA receptors forms clathrin-coated pits (Cl), which internalize. This inactivates the receptors, which are no longer within the reach of the neurotransmitter. These vesicles evolve into endosomes (E), and reach a phosphorylation-dependent decision point where they are transported toward the soma to lysosomes (L) where the receptors are destroyed, or to the Golgi apparatus (G) from where they are recycled to the membrane. By contrast, in NMDA synapses, subunits are mobilized to the synaptic membrane and assemble into additional receptors. As a result of this trafficking, the number of functional NMDA receptors per synapse increases while the number of functional GABAA receptors decreases.
Glutamate Receptors & SE

% of control mRNA levels

<table>
<thead>
<tr>
<th></th>
<th>CA1</th>
<th>CA3</th>
<th>DG</th>
<th>CTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>mGluR1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mGluR2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mGluR3</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mGluR4</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>mGluR5</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

24 hrs

Control vs. Status Epilepticus
What happens in the brain during SE?

- Calcium ion influx, Changes of NTs/receptors
- Gene activation and expression,
- Receptor moves
- Kinase activation, enzyme systems
- Cell loss
- Synaptic remodelling
- Neurogenesis, Network reorganization

Sec/min  Min/hours  Hours  Days  Days/weeks/months
Metabolic Changes during Seizure

- CBF is increased: mismatch?
- Lipids are actively metabolized in synaptic membranes: FFA & arachidonic acids ↑, PG & leucotriene → Memb. destruction & free radical formation
- Protein & nucleic acid synthesis is inhibited
- Second messenger system is activated: c-AMP, c-GMP ↑: phosphorylase kinase ↑
- Calcium influx is increased
Neurotoxicity in SE

- Role of energy metabolism & blood flow
- EAAs
- Intracellular Ca\(^{++}\): influx, intracellular calcium sequestration, dysfunction of Na\(^{+}\) channel, failure of Ca\(^{++}\)-ATPase pump
- Free radicals: Peroxidation of phospholipids produce leukotriene and free radical
- Certain neuronal populations: somatostatin-containing interneuron vs. GABAergic interneuron in the hilus
Why SE?
Epidemiology of SE
SE and Epilepsy

- 10–12% of first unprovoked seizure or newly diagnosed patient presented with SE
- 25–40% of SE occurred in the patients with epilepsy
- 15–27% of epilepsy patient will experience at least one or more SE

Dodson et al, JAMA 1993
Shinnar et al, Pediatric 1996
Berg et al, Ann Neurol 1999
SE: Incidence

Incidence per 100,000

Age

Males
Females
## SE: Incidence

<table>
<thead>
<tr>
<th></th>
<th>Actual</th>
<th>Estimated*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Richmond</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incidence of SE/100,000</td>
<td>41</td>
<td>61</td>
</tr>
<tr>
<td>Episodes of SE/100,000</td>
<td>50</td>
<td>78</td>
</tr>
<tr>
<td>Mortality/100,000</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td>United States</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases of SE/year</td>
<td>102,000</td>
<td>152,000</td>
</tr>
<tr>
<td>SE events/year</td>
<td>126,000</td>
<td>195,000</td>
</tr>
<tr>
<td>Deaths/year</td>
<td>22,200</td>
<td>42,000</td>
</tr>
</tbody>
</table>
SE: Mortality

- Richmond study 22%
- Rochester study 21%
- Bologna study 33%
- Two European study: 10% (Anoxic encephalopathy was excluded)
- 23% in RSE vs. 8% without RSE
- Use of different AEDs, achievement of burst-suppression, clinical variables, demographic data did not affect prognosis. Underlying cause is an only determinant of prognosis

Logroscino G. et al., Epilepsia, 2005
Rosetti AO. et al., Arch Neurol, 2005
SE & Mortality: GCSE In-Hospital Study

USA, 2000–2004, National Inpatient Sample
Age: 39 ± 25.6 years, male sex (53.4%)
Overall in-hospital mortality was 399 in 11,580 (3.45%)
Age was a significant predictor of death
Mortality tripled with mechanical ventilation
(7.43% vs 2.22%, OR 2.79)
Predictors of mortality: hypoxic–ischemic brain injury (OR 9.85), CVD (OR 2.08), female (OR 1.34), and higher comorbidity index (OR 6.79)

Factors Increasing Mortality

1) Underlying disease
2) Slow, inappropriate Tx.
3) Duration of SE
4) Types of SE (GCSE)
5) Older age
Risk Factors of SE
Who is at risk for SE?

1. Acute symptomatic seizures
2. Prior history of prolonged seizure or seizure clustering
3. Preexisting neurologic abnormalities
4. Very young/old
5. Genetic preponderance
Acute Symptomatic Seizures

- Tend to last longer than unprovoked seizures
  - 193 patients with SE (>30 minutes)
  - 50 patients (26%) with SE lasting > 1 hour

<table>
<thead>
<tr>
<th>Time</th>
<th>Acute Symptomatic (%)</th>
<th>Unprovoked (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1 hour</td>
<td>22/45 (49%)</td>
<td>74/91 (81%)</td>
</tr>
<tr>
<td>&gt;1 hour</td>
<td>23/45 (51%)</td>
<td>17/91 (19%)</td>
</tr>
</tbody>
</table>
Who is at risk for SE?

1. Acute symptomatic seizures
2. Prior history of prolonged seizure or seizure clustering
3. Preexisting neurologic abnormalities
4. Very young/old
5. Delayed treatment
6. Genetic preponderance
Occurrence of SE and Recurrent SE

Placebo-term trial of tiagabine: 9/769 (1.2%)
Long-term open-label trials of tiagabine: 107/2248 (5%)
  Prior SE: 39/118 (33%)
  No prior SE: 68/2130 (3%)

External comparison of prior studies

<table>
<thead>
<tr>
<th></th>
<th>Prior SE</th>
<th>No prior SE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rochester study</td>
<td>27%</td>
<td>5%</td>
</tr>
<tr>
<td>Finland cohort</td>
<td>33%</td>
<td>5%</td>
</tr>
<tr>
<td>Bronx cohort</td>
<td>38%</td>
<td>6%</td>
</tr>
<tr>
<td>New Haven cohort</td>
<td>20%</td>
<td>5%</td>
</tr>
</tbody>
</table>

Shinnar et al., 2001
SE recurrence

11–25% of SE recurs

Risk factor of recurrence

- Young (35%) & old (10%)
- Existing neurologic deficit
- Remote symptomatic/progressive encephalopathy
- Diffuse brain lesion

Shinnar et al., 1992
SE in Finnish Child Cohort

- SE occurred in 27% (41/150) of epileptic children
- F/U > 30 years
- Recurrent SE in 56% (22/41)
- First episode occurs early:
  - 30 (73%) patients before or at onset of epilepsy
  - 36 (88%) patients within 2 years of onset
  - All within 6 years of diagnosis

Sillanpaa et al, Epilepsia 1998
## Duration of FC

<table>
<thead>
<tr>
<th>First FC</th>
<th>Second FC</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>simple</td>
<td>complex</td>
<td></td>
</tr>
<tr>
<td>Simple &lt;10 min</td>
<td>70</td>
<td>11</td>
<td>8</td>
<td>(9%)</td>
</tr>
<tr>
<td>Complex &lt;10 min</td>
<td>20</td>
<td>5</td>
<td>5</td>
<td>(17%)</td>
</tr>
<tr>
<td>Complex &gt;10 min</td>
<td>8</td>
<td>2</td>
<td>7</td>
<td>(41%)</td>
</tr>
</tbody>
</table>

\[p = 0.03\]

Berg AT & Shinnar S. 1996
SE and Clustered Seizures

- 76 patients with refractory complex partial epilepsy admitted for the video-EEG monitoring
  - 21(28%) had at least 1 SE
  - 36(47%) had clustered seizures

- SE occurred in 44% of those with seizure clusters but only 13 in those without (p<0.002)

- 75% of SE occurred in the patients with history of seizure cluster
SE and Clustered Seizures

- Using questionnaire
- 3> seizures within 24 hours
- 29% showed seizure clustering, most common in ETLE
- Higher convulsive SE rate (OR: 3.0) and hospitalization (OR: 5.3)

Haut SR et al., Epilepsia, 2005
Who is at risk for SE?

1. Acute symptomatic seizures
2. Prior history of prolonged seizure or seizure clustering
3. Preexisting neurologic abnormalities
4. Very young/old
5. Genetic preponderance
<table>
<thead>
<tr>
<th>Precipitant</th>
<th>Children (≤16 y), %</th>
<th>Adults (&gt;16 y), %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cerebrovascular</td>
<td>3.3</td>
<td>25.2</td>
</tr>
<tr>
<td>Medication change</td>
<td>19.8</td>
<td>18.9</td>
</tr>
<tr>
<td>Anoxia</td>
<td>5.3</td>
<td>10.7</td>
</tr>
<tr>
<td>Ethanol-/drug-related</td>
<td>2.4</td>
<td>12.2</td>
</tr>
<tr>
<td>Metabolic</td>
<td>8.2</td>
<td>8.8</td>
</tr>
<tr>
<td>Unknown</td>
<td>9.3</td>
<td>8.1</td>
</tr>
<tr>
<td>Fever/infection</td>
<td>35.7</td>
<td>4.6</td>
</tr>
<tr>
<td>Trauma</td>
<td>3.5</td>
<td>4.6</td>
</tr>
<tr>
<td>Tumor</td>
<td>0.7</td>
<td>4.3</td>
</tr>
<tr>
<td>CNS infection</td>
<td>4.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Congenital</td>
<td>7.0</td>
<td>0.8</td>
</tr>
</tbody>
</table>
Who is at risk for SE?

1. Acute symptomatic seizures
2. Prior history of prolonged seizure or seizure clustering
3. Preexisting neurologic abnormalities
4. Very young/old
5. Genetic preponderance
Age as a Risk Factor of SE

- In northern Italy, 2-year prospective study
- Under 60 y-o, incidence of SE was 2.9/100,000 whereas in the elderly 38.6/100,000
- Acute symptomatic patients were 30% and 60% of them were CVD

Vignatelli L., et al., Eur Neurol, 2005
SE in Old: In the VA coop. study

- 226 (43.6%) out of 516 SE were age > 65
- Overt GCSE were 157 patients (69%)
  PB (71.4%) > LZP (53.3%) > PHT alone (41.5%)
- Subtle GCSE were 69 patients (31%)
  PB (30.8%) > LZP (14.3%) > PHT alone (11.8%)
  > DZP + PHT (7.7%)

- Aggressive Tx of NCSE in the elderly???

Treiman DM & Walker MC, Epilepsy Res, 2006
Who is at risk for SE?

1. Acute symptomatic seizures
2. Prior history of prolonged seizure or seizure clustering
3. Preexisting neurologic abnormalities
4. Very young/old
5. Genetic preponderance
Twin studies of SE

- Frequency of SE among monozygotes of affected individuals > 90 times more frequent
- Concordance rate is much higher in monozygote than dizygote (p<0.001)
Duration Issues of SE
How long do Seizure Lasts?

- Most seizures (>90%) last less than 2 minutes – Data from video-EEG monitoring of refractory complex partial seizures undergoing epilepsy surgery

Theodore et al, Neurology 1983
How Long Do SE Lasts?

30 min. – 2 hrs: 38%
  (FSE & idiopathic)
2 hrs. – 24 hrs.: 38%
Over 24 hrs: 25%
  (acute/remote symptomatic)
SE: Duration Issues

- 88% responded to first-line drugs and 12% required second-line drugs.
- The mean duration of SE was significantly long in nonresponders (Mean ±: 32.6 vs. 15.2 ± 18.32, p < 0.006).
- Duration (p < 0.01) and acute symptomatic etiology (p < 0.038) were the independent predictors of no-response to first-line drugs.
- Significantly better response in patients of SE <2h (p<0.05).

Murthy et al. Epilepsia. 2007
Time Delay in the Treatment of SE
## Time to Tx: From Seizure To ER

<table>
<thead>
<tr>
<th>ER location</th>
<th>Sz to 911</th>
<th>911 to ER</th>
<th>Tx at ER</th>
</tr>
</thead>
<tbody>
<tr>
<td>Urban</td>
<td>23</td>
<td>7</td>
<td>15</td>
</tr>
<tr>
<td>Rural</td>
<td>27</td>
<td>9</td>
<td>20</td>
</tr>
<tr>
<td>Overall</td>
<td>25</td>
<td>8</td>
<td>18</td>
</tr>
</tbody>
</table>

Goldberg A, 1998
Time from onset of SE to initiation of Tx

<table>
<thead>
<tr>
<th>Tx Access Interval</th>
<th>Time</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Average</td>
<td>Range</td>
</tr>
<tr>
<td>Onset of Szs</td>
<td>30</td>
<td>15-140</td>
</tr>
<tr>
<td>Arrival of EMT to ER</td>
<td>20</td>
<td>10-40</td>
</tr>
<tr>
<td>Arrival at ER to Tx</td>
<td>35</td>
<td>15-83</td>
</tr>
<tr>
<td>Total</td>
<td>85</td>
<td></td>
</tr>
</tbody>
</table>

N=30 at San Bernadino, CA

Jordan KG et al., Neurosurg Clin N Am, 1994
Prehospital Treatment Study

- From 1994–1997
- Total seizure call: 1623 (Not SE: 1066, SE: 567)
- Exclusion: 307 (Cardiac dysrhythmia, hypotension, chronic BDZ use, pulmonary disease)
- Total 258 patients with SE

Alldredge BK, et. al., NEJM, 2001
### Prehospital Treatment Study

<table>
<thead>
<tr>
<th></th>
<th>Pbo</th>
<th>DZP</th>
<th>LZP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Randomization</strong></td>
<td>71</td>
<td>68</td>
<td>66</td>
</tr>
<tr>
<td><strong>Demographics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>52</td>
<td>50</td>
<td>50</td>
</tr>
<tr>
<td><strong>Sex(M/F)</strong></td>
<td>42/29</td>
<td>41/27</td>
<td>46/20</td>
</tr>
<tr>
<td><strong>Baseline assess(%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>55</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>Impaired/independent</td>
<td>22</td>
<td>21</td>
<td>24</td>
</tr>
<tr>
<td>Impaired/dependent</td>
<td>20</td>
<td>21</td>
<td>20</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>9</td>
<td>0</td>
</tr>
</tbody>
</table>

Alldredge BK, et. al., NEJM, 2001
**Primary Outcome: SE upon arrival at ER**

<table>
<thead>
<tr>
<th>SE</th>
<th>Placebo(71)</th>
<th>DZP(68)</th>
<th>LZP(66)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>15(21)</td>
<td>29(43)</td>
<td>39(59)</td>
</tr>
<tr>
<td>Yes</td>
<td>56(79)</td>
<td>39(57)</td>
<td>27(41)</td>
</tr>
</tbody>
</table>

\[ P < 0.01 \]

Alldredge BK, et. al., NEJM, 2001
Primary Outcome: SE upon arrival at ER

<table>
<thead>
<tr>
<th>Termination of SE</th>
<th>LZP vs. PBO</th>
<th>LZP vs. DZP</th>
<th>DZP vs. PBO</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadj. OR*</td>
<td>5.4(2.3–13.2)</td>
<td>1.9(0.9–4.3)</td>
<td>2.8(1.2–6.7)</td>
</tr>
<tr>
<td>Adj. OR †</td>
<td>4.8(1.9–13.0)</td>
<td>1.9(0.8–4.4)</td>
<td>2.3(1.0–5.9)</td>
</tr>
</tbody>
</table>

* 95% CI
† Race, pretreatment interval, interval from treatment to ER, etiology

Alldredge BK, et. al., NEJM, 2001
Secondary Outcome: Pre-hospital Complications at ER

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>DZP</th>
<th>LZP</th>
</tr>
</thead>
<tbody>
<tr>
<td>No</td>
<td>55(77%)</td>
<td>61(90%)</td>
<td>59(89%)</td>
</tr>
<tr>
<td>Yes</td>
<td>16(23%)</td>
<td>7(10%)</td>
<td>7(11%)</td>
</tr>
<tr>
<td>Ventilation assisted</td>
<td>11/60</td>
<td>6/62</td>
<td>7/59</td>
</tr>
</tbody>
</table>

P=0.02
Complications: Hypotension, dysrhythmia, respiration assisted

Alldredge BK, et. al., NEJM, 2001
EEG Issues
Role of EEG in SE: Dx.

- Patients with altered consciousness by uncertain cause: NCSE, subtle SE
- DDx. of true- vs. non-epileptic events.
- Types of SE including focality of the SE.
- PEDs, electrographic SE
- E-EEG diagnose 37% of the SE patients with altered consciousness
- 10% of e-EEG are SE

Galdames-Contreas D et al., Rev Neurol, 2004; Privitera M, 1994; Valeras PN, 2003
Criteria for NCSE (from Chong & Hirsch, 2005 modified the criteria of Young et al., 1996)

Any pattern lasting at least 10 s satisfying any one of the following three primary criteria

**Primary criteria**
1. generalized SWC at 3 Hz
2. Repetitive generalized or focal spikes, sharp-waves, spike-and-wave complexes at >4/s
3. Unequivocal evolution in frequency (gradually increasing or decreasing by at least 1/s, e.g. 2–3/s), morphology, or location (gradual spread into or out of a region involving at least two electrodes). Evolution in amplitude alone is not sufficient. Change in sharpness without other change in morphology is not enough to satisfy evolution in morphology

**Secondary criterion**
Sequential rhythmic, periodic, or quasi-periodic waves at 1/s and unequivocal evolution in frequency (gradually increasing or decreasing by at least 1/s, e.g. 2–3/s), morphology, or location (gradual spread into or out of a region involving at least two electrodes). Evolution in amplitude alone is not sufficient. Change in sharpness without other change in morphology is not enough to satisfy evolution in morphology
Role of EEG in SE: Tx.

- SE is responsive to treatment?
- Confirm burst-suppression (Depth of anesthesia and making rapid decision of dose increase)
- Residual electrographic seizure
- PEDs
- SE stops/recurs

Erikson K & Kalvianinen R., 2005
Persistent NCSE after the control of GCSE

- 52% had no after-SE discharges
  - gen, slowing, attenuation, PLEDs, focal slowing, burst suppression
- The remaining 48% demonstrated persistent EEG seizures
  - Over 14% manifested NCSE, predominantly CPSE

DeLorenzo RJ et al., Epilepsia, 1998
Residual EEG SE after control of visible SE in VA Coop Study

- 130 overt GCSE with EEG monitoring begun within 30 minutes of Tx.
- 26/130 (20%) remained in EEG SE after motor movement stopped.

Faught E., Epilepsia, 1995
How: Treatment Issues
Standard Treatment of SE

0 Min. Make the Dx by observing one additional seizure in patient with history of recent seizures or impaired consciousness or by observing continuous seizure activity for more than 10 minutes. Start EEG as soon as possible, but do not delay Tx while waiting for the EEG unless unnecessary to verify diagnosis.

5 Min. Establish iv catheter with normal saline
Draw blood for serum chemistry, hematology, AED concentrations. If hypoglycemia is suspected, confirm by finger stick. Then administer 100 mg of thiamine followed by 50 ml of 50% glucose by direct push into the IV line. In children, 2 ml/Kg of 25% glucose IV push.
Standard Treatment of SE

10 Min. Administer lorazepam (0.1 m/Kg) by IV push (<2 mg/min)

If status does not stop, start phenytoin (20 mg/Kg) by slow IV push (<50 mg/min) directly into IV port closest to the patient. Monitor BP and ECG closely during infusion.

If status does not stop after 20 mg/Kg of phenytoin, add 5 mg/Kg, to a maximum dose of 30 mg/Kg.

=> Success in 70% of SE
Standard Treatment of SE

60 Min. If status persists, consider intubation before giving PB (20 mg/Kg) by IV push (<100 mg/min). MDZ/propofol can be used as tertiary anti-SE drugs. If status persists, start barbiturate coma. Either administer more PB or give pentobarbital (5-15 mg/Kg) slowly as initial IV dose to suppress all epileptiform activity. Continue 0.5-5 mg/Kg/hr to maintain EEG suppression. Slow rate of infusion periodically to see if seizure have stopped. Monitor BP, EKG, and respiratory function closely.
Advances in Therapy for SE

- San Francisco Prehospital study
- VA coop trial
- Role of excitatory a.as. in RSE
- Clinical study for RSE: mida vs. propofol
  Columbia study
- What is the goals of RSE & future Tx
Prehospital Care

- Secure the airway
- Administer supplemental 100% oxygen
- Infuse isotonic IV fluids and glucose
- Immobilize the cervical spine in patients with possible trauma.
- Consider PR diazepam (0.5 mg/kg/dose) or IM midazolam (0.1–0.2 mg/kg)
Prehospital Care

- Infuse isotonic IV fluids 20 mL/kg with glucose (eg, 200 mL [D5NS] IV over 1 h for a 10-kg child).
- Glucose – 0.25–0.50 g/kg for hypoglycemia
- Naloxone – 0.1 mg/kg for narcotic overdose
- Thiamine – 100 mg for possible deficiency
- Pyridoxine – 50–100 mg for possible deficiency
- Antibiotics – If meningitis is strongly suspected, initiate treatment with antibiotics prior to cerebrospinal fluid (CSF) analysis or CNS imaging.
### VA SE Coop Study
(Pharmacokinetics)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Dose (mg/Kg)</th>
<th>Conc. Achieved (µg/ml)</th>
<th>Duration of infusion (min)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>0.1</td>
<td>0.23</td>
<td>4.7</td>
</tr>
<tr>
<td>PB</td>
<td>15</td>
<td>31.2</td>
<td>16.6</td>
</tr>
<tr>
<td>DZP/PHT</td>
<td>0.15/15</td>
<td>0.25/31.8</td>
<td>42</td>
</tr>
<tr>
<td>PHT</td>
<td>16</td>
<td>30.0</td>
<td>33</td>
</tr>
</tbody>
</table>

Treiman DM, NEJM, 1998
### VA SE Coop Study (Tx Success)

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Overt</th>
<th>Subtle</th>
</tr>
</thead>
<tbody>
<tr>
<td>LZP</td>
<td>64.9</td>
<td>17.9</td>
</tr>
<tr>
<td>PB</td>
<td>58.2</td>
<td>24.2</td>
</tr>
<tr>
<td>DZP+PHT</td>
<td>55.8</td>
<td>8.3</td>
</tr>
<tr>
<td>PHT</td>
<td>43.6</td>
<td>7.7</td>
</tr>
<tr>
<td>Mean</td>
<td>55.5</td>
<td>14.9</td>
</tr>
</tbody>
</table>

Same result in Cochrane database review, 2006

Treiman DM, NEJM, 1998
VA SE Coop Study (Tx Success by EEG pattern)

<table>
<thead>
<tr>
<th>Pattern</th>
<th>Successfully Treated(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discrete</td>
<td>75</td>
</tr>
<tr>
<td>Wax &amp; Wane</td>
<td>30</td>
</tr>
<tr>
<td>Continuous</td>
<td>24</td>
</tr>
<tr>
<td>Punctuated</td>
<td>8</td>
</tr>
<tr>
<td>PEDs</td>
<td>7</td>
</tr>
</tbody>
</table>

Treiman DM, NEJM, 1998
VA SE Coop Study (Adverse Effects)

<table>
<thead>
<tr>
<th></th>
<th>LZP</th>
<th>PB</th>
<th>DZP+PHT</th>
<th>PHT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated (N)</td>
<td>97</td>
<td>91</td>
<td>95</td>
<td>101</td>
</tr>
<tr>
<td>Hypoventilation</td>
<td>14.4</td>
<td>13.3</td>
<td>18.9</td>
<td>10.9</td>
</tr>
<tr>
<td>Hypotension</td>
<td>27.8</td>
<td>34.1</td>
<td>32.6</td>
<td>28.7</td>
</tr>
<tr>
<td>Arrhythmia</td>
<td>12.4</td>
<td>3.3</td>
<td>2.1</td>
<td>8.9</td>
</tr>
<tr>
<td>Sedation</td>
<td>11.3</td>
<td>20.9</td>
<td>12.6</td>
<td>13.9</td>
</tr>
</tbody>
</table>

Treiman DM, NEJM, 1998
VA SE Coop Study: Response to treatment

<table>
<thead>
<tr>
<th>Resp. rate(%)</th>
<th>Overt SE (n=384)</th>
<th>Subtle SE (n=134)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First drug</td>
<td>55.5</td>
<td>14.9</td>
</tr>
<tr>
<td>Second drug</td>
<td>7.0</td>
<td>3.0</td>
</tr>
<tr>
<td>Third drug</td>
<td>2.3</td>
<td>4.5</td>
</tr>
<tr>
<td>Any other drug</td>
<td>23.2</td>
<td>27.8</td>
</tr>
<tr>
<td>No response</td>
<td>11.7</td>
<td>50.0</td>
</tr>
</tbody>
</table>
Clinical Response to IV BDZ

![Graph showing survival and recovery of consciousness for responders and nonresponders.]

- **Survival**: Responders have a higher survival rate compared to nonresponders.
- **Recovery of Consciousness**: Responders show a significant improvement in recovery compared to nonresponders.
EEG Response to IV BDZ

![Graph showing survival and recovery of consciousness for responders and nonresponders.]

- **Survival**: The y-axis represents the percentage of responders and nonresponders, with responders achieving a higher survival rate compared to nonresponders.
- **Recovery of Consciousness**: For recovery of consciousness, responders show a significant improvement over nonresponders.

Legend:
- Yellow: Responder
- Blue: Nonresponder
Success Rate of AEDs in Childhood SE (177 SE)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Success rate(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopental</td>
<td>90.4 (19/21)</td>
</tr>
<tr>
<td>MDZ</td>
<td>57.6 (57/99)</td>
</tr>
<tr>
<td>Lidocane</td>
<td>41.7 (25/60)</td>
</tr>
<tr>
<td>PHT</td>
<td>39.9 (16/41)</td>
</tr>
<tr>
<td>DZP</td>
<td>36.0 (59/164)</td>
</tr>
</tbody>
</table>

Hamano S., et al., No To Hattatsu, 2005
Anticonvulsant Treatment of SE

- Prehospital treatment: DZP PR, MDZ IM is preferred
- The optimal protocol for management of SE begins with a benzodiazepine (lorazepam)
- If the seizures cease, no further drugs are immediately necessary, and the etiology of SE should be investigated.
- If seizures continue, administer IV phenytoin.
Anticonvulsant Treatment of SE

- If these are not effective, administer IV PB to induce barbiturate coma.
- Finally, consider general anesthesia with pentobarbital or midazolam.
- Midazolam (0.1–0.2 mg/kg IM) is most effective when IV access is not immediately available. Midazolam is the only benzodiazepine that can be administered safely IM with equivalent rapid onset and moderate duration of action.
### FIRST LINE THERAPY

<table>
<thead>
<tr>
<th>Medication</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>81</td>
<td>78%</td>
</tr>
<tr>
<td>Diazepam</td>
<td>18</td>
<td>17%</td>
</tr>
<tr>
<td>Other*</td>
<td>7</td>
<td>7%</td>
</tr>
</tbody>
</table>

### SECOND LINE THERAPY

<table>
<thead>
<tr>
<th>Medication</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin/Fosphenytoin</td>
<td>101</td>
<td>95%</td>
</tr>
<tr>
<td>Other**</td>
<td>5</td>
<td>5%</td>
</tr>
</tbody>
</table>

### THIRD LINE THERAPY

<table>
<thead>
<tr>
<th>Medication</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenobarbital</td>
<td>46</td>
<td>43%</td>
</tr>
<tr>
<td>dILV-AED†</td>
<td>20</td>
<td>19%</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>17</td>
<td>16%</td>
</tr>
<tr>
<td>Increase doses of AEDs</td>
<td>13</td>
<td>12%</td>
</tr>
<tr>
<td>Other †</td>
<td>10</td>
<td>9%</td>
</tr>
</tbody>
</table>

### FOURTH LINE THERAPY

<table>
<thead>
<tr>
<th>Medication</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>dILV Pentobarbital</td>
<td>38</td>
<td>35%</td>
</tr>
<tr>
<td>dILV Propofol</td>
<td>18</td>
<td>17%</td>
</tr>
<tr>
<td>dILV Midazolam</td>
<td>17</td>
<td>16%</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>16</td>
<td>15%</td>
</tr>
<tr>
<td>Valproic acid</td>
<td>9</td>
<td>9%</td>
</tr>
<tr>
<td>Other †</td>
<td>7</td>
<td>7%</td>
</tr>
</tbody>
</table>
When does SE become refractory?

- No standard definition
- Most authors have considered when adequate doses of a BDZ and PHT fail to terminate SE
  - Some authors have required PB as well
- Duration of SE prior to Tx
Practical Guideline in Reducing RSE

- EEG should be available at any time for the patient with unexplained altered consciousness
- Treating in the ICU: ventilation and hemodynamic support
- EEG monitoring
- Abolish all clinical and EEG epileptic activity often until burst-suppression
- Pento(USA), Thiopental sodium(EU) or MDZ(adult/children), and propofol(adult)

Kalviainen R et al., CNS Drugs, 2005
Anticonvulsant Treatment of SE

- The optimal protocol for management of SE begins with a benzodiazepine (lorazepam)
- For patients without parenteral access, IM midazolam is best.
- If the seizures cease, no further drugs are immediately necessary, and the etiology of SE should be investigated.
Anticonvulsant Treatment of SE

- If seizures continue, administer IV phenytoin.
- If these are not effective, administer IV phenobarbital to induce barbiturate coma.
- Finally, consider general anesthesia with pentobarbital or midazolam.
- Midazolam (0.1–0.2 mg/kg IM) is most effective when IV access is not immediately available. Midazolam is the only benzodiazepine that can be administered safely IM with equivalent rapid onset and moderate duration of action.
Practical Guideline in Treating RSE

- Once seizure has been controlled for 12–24 hours, gradual taper-out is needed in MDZ/propofol. (Pentobarbital and thiopental sodium do not need tapering)
- Continuous EEG monitoring is needed in gradual tapering
- Previous PHT/VPA iv. should be continued during the SE to prevent further recurrence of SE.
- If additional medication is needed, LEV/TPM is preferred: High dose with minimal idiosyncracy

Kalviainen R et al., CNS Drugs, 2005
Commonly Recommended Drugs for Refractory SE

- High dose barbiturate
  - Pentobarbital
  - Thiopental
  - PB
- High dose BDZ
  - MDZ
  - LZP
  - DZP
- Propofol
High-Dose BDZ

- **Midazolam**
  - Loading dose 0.2 mg/Kg
  - Maintenance dose 0.1 – 3 mg/Kg/h
  - Goal: Seizure suppression
  - IM injection may be helpful

- **Lorazepam**
  - Up to 9 mg/h
Propofol

- GABA$_A$ agonist with several other mechanisms
- Conflicting reports on the effect of low dose on interictal spike
- Early reports of convulsions probably represents myoclonus
- Withdrawal seizures
Propofol

- Consider an initial dose of 3–5 mg/kg
- Maintenance dose of 1 mg/kg/h; Increased to achieve seizure control
  - Onset of action in 3–5 min
  - Duration of action is only 5–10 minutes after drug is stopped
  - Up to 15 mg/kg/h has been used
Ketamine

- Protracted SE are refractory...
- NMDA antagonists become more important
- Anecdotal use for refractory CPSE
  - Dose: Uncertain
  - General anesthetic dose: 1–4.5 mg/Kg following 0.5–2.5 mg/Kg q 30–45 minutes or 50–100 mg followed by 50–100 mg/hr
VPA

- No respiratory depression
- 20–30 mg/Kg loading dose was safe (rate of 3–6 mg/kg/min) -> 64–204.1 μg/ml (mean 132.6)
- One report described hypotension
- Less efficacy with less A/E
Research report

Topiramate reduces neuronal injury after experimental status epilepticus

Marivi Niebauer a, Michael Gruenthal a,b, *

a Department of Anatomical Sciences and Neurobiology, University of Louisville School of Medicine, Louisville, KY, USA
b Department of Neurology, University of Louisville School of Medicine, Louisville, KY, USA

Accepted 11 May 1999

Abstract

Prolonged seizures are associated with injury to vulnerable neurons, particularly in the hippocampus. Identification of compounds that attenuate injury after prolonged seizures could be of value in the management of refractory status epilepticus. We hypothesized that topiramate, an anticonvulsant with multiple mechanisms of action, would attenuate hippocampal neuronal injury when given after experimental status epilepticus. Limbic status epilepticus was induced in adult male Wistar rats for 140 min by unilateral hippocampal electrical stimulation. Rats then received intraperitoneal injections of either vehicle (n = 6) or topiramate at 20 mg/kg (n = 6), 40 mg/kg (n = 7) or 80 mg/kg (n = 7). Three days later, hippocampal sections were processed for neuronal degeneration using a silver impregnation stain. Seizure-induced damage was assessed by measuring the density of silver staining in hippocampal regions CA1, CA3 and dentate hilus. Administration of topiramate at each dose was associated with a significant reduction in staining density bilaterally in area CA1 and the dentate hilus. Reduction in staining density in area CA3 was seen contralateral to the side of stimulation at the two higher topiramate doses only. The results indicate that administration of topiramate after experimental status epilepticus can attenuate seizure-induced hippocampal neuronal injury. © 1999 Elsevier Science B.V. All rights reserved.
TPM in SE

- Towne et al. Neurology 2003;60:332–4
- Kahriman M et al., Epilepsia 2003;44:1353–6
- Bensalem & Fakhoury, Epilepsy Behav, 2003;7:57–60
- After consecutive treatment following regimen for SE: Lorazepam, PHT, PB, midazolam and pentobarbital in some cases
TPM in SE

- 300–1600 mg/d, mostly 500 mg bid via NG tube, initially, and then, tapering to maintenance dose
- Every patients (9 adults 3 children) reported to be improved
- WE tried low dose TPM(100–400 mg/d) as an adjunctive treatment of SE in 13 patients with success. (11/13 without serious A/E)
- 2 patients were given high dose treatment, because of persistent ictal discharges during tapering of midazolam continuous infusion.
TPM in SE

- TPM in SE was a good adjunctive therapy in most patients.
- Short term high dose regimen will be more successful in treating SE.
- TPM just after the PHT loading without seizure control may be considered. Far more useful during reducing IV anesthetics with EEG monitoring (ictal discharges).
Keppra in SE

- Reduce mitochondrial dysfunction after SE (Gibbs et al., Epilepsia, 2006)
- 2000 mg/d (750–9000 mg) resolved SE in 10/23 (43%) of SE
- May be alternative Tx of SE (Rosetti & Bromfield, Epilepsy & Behavior, 2006)
Other approaches to refractory SE

- Lidocaine
- PB
- Thiopental Sodium
- Paraldehyde
- Chlormethiazol

- CZP
- Isoflurane
- Mg
- Surgery
  - Resection
  - Subpial resection
  - VNS