STATUS EPILEPTICUS
ALBERTO PINZON, MD, MSBE, PhD

November is National Epilepsy Awareness Month

DISCLOSURE
SPEAKER FOR SUNOVION AND UCB PHARMACEUTICALS
SEIZURE

“A transient occurrence of signs and/or symptoms due to abnormal excessive or synchronous neuronal activity in the brain. The term transient is used as demarcated in time, with a clear start and finish.”

Gastaut, 1973

SEIZURE
“Status epilepticus is a condition resulting either from the failure of the mechanisms responsible for seizure termination or from the initiation of mechanisms, which lead to abnormally prolonged seizures (after time point t1). It is a condition, which can have long-term consequences (after time point t2), including neuronal death, neuronal injury, and alteration of neuronal networks, depending on the type and duration of seizures.”

Operational dimensions:
- Length of the seizure and the time point t2 beyond which the seizure should be regarded as "continuous seizure activity."
- Time point t2 is the time of ongoing seizure activity after which there is a risk of long-term consequences.

Table 1. Operational dimensions with t1 indicating the time that emergency treatment of SE should be started and t2 indicating the time at which long-term consequences may be expected

<table>
<thead>
<tr>
<th>Type of SE</th>
<th>Operational dimension 1 (t1)</th>
<th>Operational dimension 2 (t2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time: status</td>
<td>1 min</td>
<td>360 min</td>
</tr>
<tr>
<td>Rapid S/L with any IC</td>
<td>10 min</td>
<td>180 min</td>
</tr>
<tr>
<td>Abnormalities: seizures</td>
<td>10-15 min</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

*Evidence for the time frame is uncertain and future data may lead to modification.*
**Forms SE**

Convulsive status epilepticus: Repeated generalized tonic-clonic seizures with persistent postictal depression of neurologic function between seizures.

Nonconvulsive status epilepticus: seizures produce a continuous or fluctuating “epileptic twilight” state (Complex)

Repeated partial seizures: focal motor signs, focal sensory symptoms, or focal impairment of function (e.g. aphasia) not associated with altered awareness (epilepsia partialis continua).
IM midazolam outperformed IV lorazepam, with 73% of seizures terminating prior to arrival in the ED compared to 63% (p < 0.001).
PHENYTOIN
Dose: 20 mg/kg in a nonglucose solution, with a second dose of 10 mg/kg given if needed
Target level: 15–20 mg/L.

Limitations
Rate limited to 50 mg/min (25 mg/min in the elderly and patients with cardiovascular disease)
Hypotension, due to the propylene glycol diluent.
QT prolongation, cardiac monitoring is recommended
Extravasation can produce necrosis

FOSPHENYTOIN
Water soluble with lower pH
Solution pH is 8.6–9.
decreases vascular irritation
decreases tissue toxicity
IM administration possible
Conversion half-life is 8 to 15 minutes, measured in phenytoin equivalents
and can be given at up to 150 mg PE/min.
No controlled studies of its use in SE.
Infusion faster than phenytoin
Hypotension may still happen

VALPROATE
Increases regional neuronal concentrations of GABA by both inhibiting its metabolism and increasing its synthesis
Safety profile
Loading dose of 15 to 20 mg/kg in dextrose-containing solutions at a rate of 3 to 6 mg/kg/min.
Target levels: 75–100 mg/L
Overall efficacy of 63.3% and favorable tolerance of rapid administration

Seizures were aborted in 66% in the valproate vs 42% in the phenytoin group.

Valproate was effective in 79% and phenytoin was effective in 25%.
No significant differences in side effects between the two groups

LEVETIRACETAM
Misra et al.
Levetiracetam infusion controlled status in 76.3% of patients with lorazepam achieving the same in 75.6%
Slightly better 24-h seizure freedom noted in patients in the levetiracetam group

PHENOBARBITAL
GABA<sub>A</sub> receptor agonist
Profound respiratory depression and hypotension from its vasodilatory and cardiodepressant effects.
Long half-life, which can make complications difficult to manage.

DIAGNOSTIC TESTING
Laboratory Studies
- Serum electrolytes
- Ca, Mg
- Glucose
- Renal and Liver function testing
- Antiepileptic drug levels
- Toxicology screen
- Thyroid panel
NEUROIMAGING
Initial Brain CT without contrast should be considered for all SE patients once they have been stabilized. Consider MR, PET in RSE.

LUMBAR PUNCTURE
If suspected CNS infection if LP contraindicated and infection still suspected, empiric antibiotic or antiviral therapy.

EEG MONITORING
SE
Comatose after generalized seizure
Intubation/Sedation/Paralytics
Anoxic Brain Injury

REFRACTORY STATUS EPILEPTICUS (RSE)
Refractory status epilepticus can be defined as status epilepticus that continues despite treatment with benzodiazepines and one antiepileptic drug.
RSE occurs in 23%–43% of patients with SE
EARLY REFRACTORY (<48 hrs)
LATE REFRACTORY (≥48 hrs)
SUPER-REFRACTORY (≥24 hrs)
REFRACTORY SE

Check
- Antiepileptic levels (Valproic, Phenytoin, Lamotrigine, Oxcarbazepine)
- Adequate anti-epileptic? i.e. Dravet’s may worsen with Na+ channel blockers (phenytoin, carbamazepine, rufinamide, lamotrigine, fosphenytoin, oxcarbazepine).
- Interactions with other medications (i.e. certain antibiotics-Valproic)
- Pro-epileptogenic medications (i.e. Bupropion)
- Auto-immune pathology?

IMMUNOLOGIC DISORDERS CAUSING STATUS EPILEPTICUS

- Paraneoplastic encephalitis
- Hashimoto encephalopathy
- Anti-NMDA-receptor encephalitis
- Anti-VGKC-receptor encephalitis
- Rasmussen encephalitis
- Cerebral lupus
- Adult-onset Still disease
- Anti-GAD antibody associated encephalitis
- Goodpasture syndrome
- Thrombotic thrombocytopenic purpura
- Antibody-negative limbic encephalitis
ANESTHETICS

Continuous IV infusion of
Benzodiazepine
Barbiturate
Propofol

MIDAZOLAM
Short acting, GABA<sub>A</sub> receptor agonist
Loading dose: 0.2 mg/kg
Infusion: 0.05 to 2.0 mg/kg/h

PROPOFOL
GABA<sub>A</sub> agonist
Immediate suppression of seizure activity after a bolus infusion
Rapid recovery
Loading dose: 3 to 5 mg/kg
Infusion: 1 to 15 mg/kg/h

ANESTHETIC BARBITURATES

Pentobarbital and thiopental shorter acting than phenobarbital.
Highly lipid soluble hence prolonged elimination.
Thiopental more lipid soluble and the metabolic pathway can become saturated, leading to an accumulation of thiopental and delays in recovery when stopped.

PENTOBARBITAL
Load: 5 to 15 mg/kg over 1 hour.
Infusion: 0.5 to 10.0 mg/kg/h.
**PHENOBARBITAL**

Loading: 20 mg per kg

Maintenance: 1 to 3 mg per kg per day

Respiratory suppression

---

**KETAMINE**

IV ketamine

60 episodes of refractory GSE in 46 adult and 12 pediatric patients

Loading dose: (median 1.5 mg/kg; maximum 5 mg/kg)

Continuous infusion: (median 2.75 mg/kg/hr; maximum 10 mg/kg/hr) Controlled seizures in 19 episodes (32%).

**Adverse events**

- Syndrome similar to PRIS (propofol infusion syndrome: acute refractory bradycardia leading to asystole, in the presence of one or more of the following: metabolic acidosis, rhabdomyolysis, hyperlipidaemia, and enlarged or fatty liver) (n=1)
- Supraventricular tachycardia (n=2)
- Atrial fibrillation (n=1)
KETAMINE FOR REFRACTORY STATUS EPILEPTICUS: A SYSTEMATIC REVIEW.

BACKGROUND: Ketamine is an emerging third line medication for refractory status epilepticus, a medical and neurological emergency requiring prompt and appropriate treatment. Owing to its pharmacological properties, ketamine represents a practical alternative to conventional anesthetics.

RESULTS: We found no results from randomised controlled trials. The literature included 27 case reports accounting for 30 individuals and 14 case series, of which included children. Overall, 248 individuals (20 children) with a median age of 43.5 years (range 2 months to 67 years) were treated in 12 case series whose sample size ranged from 5 to 67 patients (median 11). Regardless of the status epilepticus type, ketamine was twice as effective if administered early, with an efficacy rate as high as 64% in refractory status epilepticus lasting 3 days and dropping to 32% when the mean refractory status epilepticus duration was 26.5 days. Ketamine doses were extremely heterogeneous and did not appear to be an independent prognostic factor. Endotracheal intubation, a negative prognostic factor for status epilepticus, was unnecessary in 12 individuals (10 children), seven of whom were treated with oral ketamine for non‐convulsive status epilepticus.

CONCLUSIONS: Although ketamine has proven to be effective in treating refractory status epilepticus, available studies are hampered by methodological limitations that prevent any firm conclusions. Results from two ongoing studies (ClinicalTrials.gov identification number: NCT02431663 and NCT03115489) and further clinical trials will hopefully confirm the better efficacy and safety profile of ketamine compared with conventional anesthetics as third-line therapy in refractory status epilepticus, both in paediatric and adult populations.

SYSTEMIC COMPLICATIONS OF GENERALIZED CONVULSIVE STATUS EPILEPTICUS

<table>
<thead>
<tr>
<th>Metabolic</th>
<th>Renal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactic acidosis</td>
<td>Acute renal failure from rhabdomyolysis</td>
</tr>
<tr>
<td>Hyperventilation</td>
<td>Myoglobinuria</td>
</tr>
<tr>
<td>Hypoglycemia</td>
<td>Cardiac/respiratory</td>
</tr>
<tr>
<td>Hyperkalemia</td>
<td>Hypoxia</td>
</tr>
<tr>
<td>Hyponatremia</td>
<td>Arrhythmia</td>
</tr>
<tr>
<td>CSF/serum leukocytosis</td>
<td>High output failure</td>
</tr>
<tr>
<td>Autonomic</td>
<td>Pneumonia</td>
</tr>
<tr>
<td>Hyperpyrexia</td>
<td></td>
</tr>
<tr>
<td>Failure of cerebral autoregulation</td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
<td></td>
</tr>
<tr>
<td>Incontinence</td>
<td></td>
</tr>
</tbody>
</table>

LONG-TERM COMPLICATIONS

Epilepsy (20% to 40%),
Encephalopathy (6% to 15%), and
Focal neurologic deficits (9% to 11%).

Neuronal injury leading to temporal lobe epilepsy is probably mediated by excess excitation via activation of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors and consequent elevated intracellular calcium that causes acute necrosis and delayed apoptotic cell death.
<table>
<thead>
<tr>
<th>Rapid Sequence Termination (RST) for adult hypophagia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Objectives</strong>:</td>
</tr>
<tr>
<td>1. <strong>Check</strong> hypophagia planer</td>
</tr>
<tr>
<td>2. <strong>Verify</strong> information (depth of tone device? protruded)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Items</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ventilation</strong></td>
</tr>
<tr>
<td>Check airway</td>
</tr>
<tr>
<td>Placing device (brachial plexus may be advanced)</td>
</tr>
<tr>
<td><strong>2 minutes</strong></td>
</tr>
<tr>
<td>Begin Bag/Bag/Bag (B/B/B) or pre-procedural device</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Additional Items</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Airway</strong></td>
</tr>
<tr>
<td>Intubation device</td>
</tr>
<tr>
<td><strong>Additional</strong></td>
</tr>
<tr>
<td><strong>Cricothyrotomy</strong></td>
</tr>
<tr>
<td><strong>Cricothyrotomy</strong></td>
</tr>
</tbody>
</table>

**THANK YOU**