NEW AND EMERGING TREATMENTS FOR STATUS EPILEPTICUS

John Betjemann, MD
University of California
San Francisco, CA

Overview of Status Epilepticus

- Status epilepticus (SE) is a common neurologic emergency with an annual incidence of 10-41/100,000[1-5]
- Generalized convulsive SE (GCSE) is the most common form of SE representing approximately 45-74% of all SE cases[1-2]
- The overall mortality associated with SE approaches 20% and is largely dependent on the etiology for SE[6,7]
- Given the incidence, morbidity and mortality, the annual direct inpatient costs related to SE are estimated at more than $4 billion in the United States[8]

New ILAE Definition of SE

- "SE 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 that 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."[9]
- For GCSE t1=5 minutes and t2=30 minutes

Prehospital Treatment Trials for SE

- The first rigorous prehospital study showed that intravenous (IV) benzodiazepines (lorazepam and diazepam) were superior to placebo in terminating SE and patients treated with benzodiazepines also experienced lower rates of respiratory compromise necessitating intubation.[10]
- Rapid Anticonvulsant Medications Prior to Arrival Trial (RAMPART), a randomized, double-blind comparison found that the prehospital administration of intramuscular midazolam (10mg in adults) was at least as effective as IV lorazepam (4mg in adults) in the timely termination of SE (73.4% in the midazolam group and 63.4% in the lorazepam group; 95% confidence interval, 4.0 to 16.1; $P<0.001$ for both noninferiority and superiority) and was not associated with an increase in respiratory compromise or seizure recurrence.[11]

Alternate Routes of AED Administration

- Randomized controlled trials have established the efficacy of rectal diazepam for SE[12]
- More recently, intranasal, buccal and intramuscular routes have been studied
- Studies of intranasal midazolam and lorazepam[13,14] suggest that these are both viable alternative routes of administration for seizure cessation
- 8 randomized controlled trials have compared intranasal midazolam to either rectal or intravenous diazepam.[15-22] Overall, no differences were found between the midazolam and diazepam groups in terms of seizure cessation (OR: 0.92; 95% confidence interval 0.34 – 2.50) or serious adverse events.
- Buccal midazolam has been found to be more effective than rectal diazepam for seizure cessation in children (OR: 1.78; 95% confidence interval: 1.11-2.85)[12]
- Intrapulmonary administration of propofol hemisuccinate [4-(2,6-diisopropylphenoxy)-4-oxobutanoic acid)], a water soluble prodrug, has been shown to be seizure protective in rats.[23]

Established Status Epilepticus Treatment Trial (ESETT)

- Current practice patterns for the treatment of benzodiazepine-refractory SE are quite variable owing to a lack of class I, head-to-head, blinded comparisons
- ESETT is a multicenter, randomized, double-blind trial comparing fosphenytoin (20mg/kg), levetiracetam (60mg/kg) and valproic acid (40mg/kg).[24]
- The study is designed to determine either the most or least effective treatment for benzodiazepine-refractory SE
- Goal enrollment of 795 participants is about 40% complete

Therapeutic Hypothermia: HYBERNATUS

- Multicenter, open-label, parallel-group, randomized controlled trial conducted in France. Patients were randomized to standard care alone or standard care plus hypothermia[25]
- Convulsive SE defined as >5min of seizure activity or two seizures without return to baseline
- Enrolled 270 adults >18 years of age, intubated in the ICU
- Hypothermia defined as 32-34^{o}C for 24 hours
- No statistical difference in the primary outcome of functional impairment at 90 days as measured by Glasgow Outcome Scale
- Of secondary outcomes, the only statistically significant difference was seen among the treatment group having a lower rate of progression to EEG-confirmed SE.
- Adverse events, particularly pneumonia were more common in the therapeutic hypothermia group

Ketamine

- Most conventional anesthetics used in refractory SE (RSE) act on γ-aminobutyric acid ($GABA_A$) receptors
- Experimental models have shown that as SE continues inhibitory synaptic $GABA_A$ receptors become internalized while excitatory N-methyl-d-aspartate (NMDA) receptors are trafficked to the cell membrane.[26] This receptor trafficking results in SE becoming more difficult to control, particularly with benzodiazepines, as it continues.
- Ketamine has NMDA-glutamate receptor antagonist properties[27]
- Animal models have demonstrated the efficacy of ketamine in rats with RSE[28, 29]
- Three case series and a number of case reports of ketamine use in humans found an overall success rate 63% in aborting refractory SE[30]
- A multicenter, randomized, controlled, open-label Italian study (KETASER01) is actively recruiting (ClinicalTrials.gov identifier: NCT02431663)[31]
- KETASER01 is a study of pediatric patients with convulsive SE refractory to benzodiazepines and a second line antiepileptic drug (AED) (phenytoin and/or phenobarbital and midazolam infusion)
- Patients will be randomized to ketamine with low dose midazolam versus midazolam and either thiopental or propofol (if SE not controlled with midazolam)
- Primary outcome is the resolution of SE up to 24 hours after withdrawal of therapy

Neurosteroids

- There is a growing appreciation for the role of inflammation in epileptogenesis and recognition of the role of autoimmune encephalitis leading to SE.[32]
- Thus, more consideration is being given to the use of steroids, intravenous immunoglobulin and plasma exchange for the treatment of super refractory SE (SRSE) in cases of proven or suspected autoimmune encephalitis-induced SRSE
- Not surprisingly, there is little data other than individual case reports to support these treatments and there are potential adverse effects to immunosuppression. Careful consideration should be given to the appropriate use of these potentially harmful treatments (the reference provides a practical approach to diagnosing autoimmune/inflammatory conditions).[33]
- Allopregnanolone is an endogenous neuroactive steroid and acts as a positive allosteric modulator of both synaptic and extrasynaptic $GABA_A$ mediated inhibition.[34,35]
- SAGE-547 is a proprietary injectable formulation of allopregnanolone that has completed phase I/II studies (ClinicalTrials.gov Identifier: NCT02052739) and is the subject of an actively recruiting, multicenter, randomized, double-blind, placebo-controlled phase III trial (ClinicalTrials.gov Identifier: NCT02477618)[34]
- Participants (age 2 or older) with SRSE (failed to respond to first or second-line agents and either have not received or are unable to be weaned from a third-line agent) will be randomized to SAGE-547 plus a third-line agent or placebo plus a third-line agent with the potential for open-label crossover.
- Primary outcome is the cessation of SE for at least 24 hours after being weaned off the third-line agents

Other new/emerging medications worthy of further study

- Lacosamide enhances slow inactivation of voltage-gated Na channels and is available in an intravenous formulation. Experience with lacosamide for treating SE is limited to case reports and case series.[36]
- In a cumulative analysis of 20 reports totaling 195 episodes of RSE, lacosamide was most commonly given with a loading dose of 400mg and maintenance dosing of 200-400mg daily. Seizure cessation was seen in 56%.[36]
- Perampanel is a selective alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) antagonist

approved for focal and generalized seizures.[37]

- Perampanel use for SE is limited to case series (initial median dose 4-6mg).[38,39] The data is too sparse and the population to diverse to draw significant conclusions but given its novel mechanism of action, perampanel deserves further study.
- Brivaracetam is FDA approved as adjunctive treatment for focal seizures and binds synaptic vesicle protein 2A (SV2A). Its SV2A affinity is about 15- to 30-fold higher than levetiracetam and has been shown to have more potent seizure suppression in animal models. Three phase III trials have been completed in patients with focal epilepsy. It is available in IV form, which is desirable for SE, but has not yet been studied in this population.[34]
- Valnoctamide is a chiral isomer of valpromide, an active derivative of valproic acid. Valnoctamide has broad spectrum antiseizure properties and has been shown to be effective in pilocarpine rat models of SE. *sec*-butylpropylacetamide is a homologue of valnoctamide and also has potent, broad spectrum antiepileptic properties demonstrated in animal models.[40] In addition, both seem to have a more favorable side effect profile than valproic acid in terms of teratogenicity.

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