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Current and emerging pharmacological treatment for status epilepticus in adults

Abstract

Status epilepticus is a neurological disorder requiring emergent control with medical therapy. Based on guideline recommendations for adults with status epilepticus, the first line treatment is to start a benzodiazepine, as they are quick at seizure control. The second step is to initiate a non-benzodiazepine anti-epileptic drug to prevent refractory seizures. Studies show that the anti-epileptic drugs are approximately equivalent in status epilepticus control once a benzodiazepine has been given. This review provides a brief overview of the management of status epilepticus based on evidence from the literature, and evidence-based guidelines.

Keywords: neurological disorder, seizure, status epilepticus, benzodiazepines, antiepileptic agents

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Introduction

Status epilepticus (SE) is considered a common neurological emergency with high morbidity and mortality. SE is characterized as a state in which seizures persist for 5 minutes or more in several forms: 1) Repeated partial seizures characterized as focal motor/ sensory symptoms, or focal dysfunction (e.g., aphasia); 2) conclusive status epilepticus manifested as repeated generalized tonic clonic (GTC) seizure with depression of neurological function between seizures; 3) nonconvulsive status epilepticus refers to state with a prolonged seizures without the dramatic conclusions or a typical tonic-clonic event.[1-3]

Etiology and clinical presentations

The incidence of SE has been estimated to be about 150,000 admissions per year in the United States, accounting for 40,000 deaths per year, making SE a common neurological emergency with high morbidity and mortality. Mortality increases with age, the duration of SE, and the underlying causes. Worsen outcomes have been documented in patients with concomitant conditions such as acute stroke, trauma, CNS infection, and metabolic disturbances.[4]

Medical management of status epilepticus

This is a life-threatening condition and can cause irreversible brain damage, therefore, the goal of therapy is to promptly stop both electrical and clinical seizure activity and prevent their recurrence. There is no clear pharmacologic treatment algorithm for SE, however most evidence supports the use of benzodiazepine, potent gamma aminobutyric acid agonists, as an initial treatment for SE followed by anti-epileptic drug to prevent benzodiazepine refractory seizures. Drug selection should consider patient history with seizures and maintenance medications. Medications for the management of SE are summarized in Table 1.

Table 1 Medication dosages and routes of administration for the treatment of SE

Medication	Route	Dose	Common side effects	Agent selection	Considerations
Lorazepam	IV	0.1 mg/kg (max 4 mg/dose) up to 8 mg total	Sedation, hypotension	First-line	-Stability is compromised in non-refrigerated conditions - IV formulation contains propylene glycol
Midazolam	IM, intranasally	IM-5 mg (patient weight 13-40 kg) IM-10 mg (patient weight > 40 kg) Intranasally- 5 mg (1 spray) into 1 nostril	Sedation, hypotension	First-line	-Preferred due to the quicker access with IM versus IV -Use of mucosal atomizer device is recommended in children
Diazepam	IV	0.15-0.2 mg/kg up to 10 mg total	Sedation, hypotension	First-line	-Available rectally - IV formulation contains propylene glycol
Fosphenytoin	IV, IM	15-20 mg PE/kg (not to exceed 150 mg PE/min)	Cardiac arrhythmia, dizziness, hepatotoxicity	Second-line	-Caution in patients with certain cardiovascular comorbidities such as AV block, A-fib, and atrial flutter

Table Continued...

Medication	Route	Dose	Common side effects	Agent selection	Considerations
					-Several DDIs
Phenytoin	IV	15-20 mg/kg (not to exceed 50 mg/min)	Cardiac arrhythmia, dizziness, hepatotoxicity, phlebitis, purple glove syndrome	Second-line	-Caution in patients with certain cardiovascular comorbidities such as AV block, A-fib, and atrial flutter
					-Several DDIs
Valproic acid	IV	20–40 mg/kg (not to exceed 6 mg/kg/min)	Hyperammonemia, thrombocytopenia, hepatotoxicity	Second-line	-Contraindicated in patients with liver disease
					-Many DDIs (CYP450 inhibitor)
Levetiracetam	IV	1–3 g IV (not to exceed 5 mg/ kg/min) or 60 mg/kg as a single dose (max 4.5 g)	Sedation/ paradoxical excitation, irritability	Second-line	-Need dose adjustment in renally compromised individuals
					-Minimal DDIs
Lacosamide	IV	200-400 mg	Dizziness , sleepy, tired, blurred eyesight, brady arrhythmia	Second-line	-Minimal DDIs
Pentobarbital	IV	5-15 mg/kg (loading dose)	Sedation, hypotension, respiratory depression, constipation, cardiac depression	Third-line (RSE)	-IV formulation contains propylene glycol
		0.5 mg/kg			-Several DDIs
Midazolam high-dose	IV	0.05–2 mg/kg/hr	Sedation, hypotension, respiratory depression	Third-line (RSE)	-Lorazepam and diazepam are options but have a greater risk of side effects stemming from propylene glycol toxicity
		continuous infusion			-Caution with use in renal compromised and geriatrics
Propofol	IV	20–200 mcg/kg/min, titrate by 5 mcg/kg/min	Sedation, hypotension, respiratory depression	Third-line (RSE)	-Risk of propofol infusion related syndrome
		continuous infusion			-Hypertriglyceridemia at higher doses
Ketamine	IV	0.5–7 mg/kg/hr	Excitation, hypertension, possible neurotoxicity, hallucinations	Third-line (RSE)	May be more effective in prolonged refractory status epilepticus

Abbreviations: IV, intravenous; IM, intramuscular(ly); PO, by mouth; RSE, refractory status epilepticus; DDIs, drug-drug interactions

Overview of current and emerginf pharmacological treatment for status epilepticus

Lorazepam

In the study levetiracetam versus lorazepam in status epilepticus is described as a randomized open, label pilot study. The purpose of the study aimed at comparing the efficacy and safety of both levetiracetam and lorazepam in status epilepticus with endpoint of seizure cessation within 30 minutes with secondary endpoints to include 24 hour seizure freedom, mortality, and adverse effects. Study was conducted from January 2008 to 2010 and patients that were included were patients with convulsive status epilepticus or subtle convulsive status epilepticus. Patients were randomized to receive either lorazepam 0.1 mg/kg in 10 ml saline IV -over 2 to 4 minutes or levetiracetam 20 mg/kg infused in 15 minutes. Patients with ongoing status epilepticus would be treated with the agent that is not administered.

Results showed that both levetiracetam (76.3%) and lorazepam (75.6%) were equally effective in seizure cessation. Secondary endpoint of evaluating 24 hour cessation of seizure was statistically insignificant with a p-value of 0.38 resulting in both levetiracetam and lorazepam being comparable. Significant adverse events in the

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lorazepam group included artificial ventilation and hypotension for levetiracetam. Other adverse events include rash, thrombocytopenia, pneumonia, urinary infection, and liver dysfunction.[5]

Midazolam

In a Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART): A double bind randomized clinical trial of efficacy of IV midazolam versus IV lorazepam in the prehospital treatment of status epilepticus by paramedics shows that IM midazolam is not inferior to IV lorazepam in prehospital treatment of status epilepticus. Primary outcome measured whether or not there is termination of convulsive seizure without the need for additional administration of benzodiazepine. Secondary outcomes included EMS arrival to termination of seizure, initiation of treatment to termination of seizure, frequency of endotracheal intubation, frequency and duration of hospitalization, ICU admission, and acute seizure occurrences. Patient population includes adults and pediatrics and those who weigh >/= to 40 kg would be randomized midazolam 10 mg IM followed by IV placebo or IV active therapy and IM placebo followed by lorazepam 4 mg IV. Children whose weight < 40kg will receive either midazolam 5 mg IM or lorazepam 2 mg IV. Results are statistically significant in midazolam IM (73.4%) and lorazepam IV (63.4%) with a p-value of 0.001 for noninferiority and superiority. Secondary outcomes reported no differences.[6]

Diazepam

In the study reviewing the question of whether IV lorazepam is more effective and safer as a first line in convulsive status epilepticus? The study involved a search of literature centered on randomized clinical trials that were blinded and not blinded while those excluded are trials not controlled, not randomized, and nonconvulsive status epilepticus. Objective of the study was to assess the efficacy and tolerability of IV lorazepam and IV diazepam in convulsive status epilepticus. The following outcomes evaluated are seizure cessation within 15 minutes after administration of benzodiazepines, patients with continuous seizure activity after administration of benzodiazepines requiring antiepileptic therapy, and patients with cessation of seizure after drug administration and additional medication. 5 studies were included with 3 children studies and 2 adult studies with a focus on adult studies.

In the first adult study by Leppik et al, patients were randomized to lorazepam 2 mg IV or or diazepam 5 mg IV and the second study by Alldredge et al, patients were randomized to similar doses listed in the other adult study. The three outcomes discussed above were statistically insignificant with the following supporting data: seizure cessation after drug administration (RR 1.27; 95% CI 0.99 to 1.63), continuation of SE requiring different drugs (RR 0.72; 95% CI 0.51 to 1.02), and seizure cessation after a single dose of medication (RR 1.05.72; 95% CI 0.79 to 1.41). Adverse events included hypotension, cardiac dysrhythmia, and respiratory intervention.[7]

Levetiracetam

A prospective, open label, randomized study shows the effectiveness of IV levetiracetam versus IV phenytoin after the initiation of an IV benzodiazepine. Study was conducted at a teaching hospital. 52 patients in the status epilepticus group and 63 patients in the cluster seizure group. Patients who had ongoing seizures were initiated on benzodiazepine- lorazepam 4 mg or diazepam 5 to 10 mg over 2 minutes for the seizure episode. After providing the benzodiazepine, patients were randomized via computer generated and initiated on IV phenytoin 20mg/kg over 30 minutes or IV levetiracetam 30 mg/kg over 30 minutes. Primary end point of the study was to control the seizures for a 24 hour time period with no recurrent episode, and the secondary endpoints were side effects of the medications administered and outcome of hospital discharge based on the modified Rankin Score (mRS).

In the status epilepticus group, 22 patients were randomized to receive IV levetiracetam and 30 patients received IV phenytoin. Results show that levetiracetam and phenytoin are equally effective in controlling status epilepticus with no statistical significance (p= 0.33). Minimal adverse effects are reported with hypotension occurring in 2 patients in the phenytoin group and transient thrombocytopenia occurring in 1 patient, but not normalized. In the cluster seizure group, 38 received levetiracetam and 25 received phenytoin, and there was no statistical significance reported with levetiracetam being superior. And adverse effects were minimal in both groups.[8]

An investigator-initiated, multicenter, randomized, blinded, and comparative-effectiveness study, evaluates and compares the efficacy and safety of the three agents of levetiracetam, fosphenytoin, and valproate in treatment of SE. This study was conducted at 57 hospitals. There were 18 sites recruiting children, 26 sites enrolling adults, and 13 sites that enrolled both.

Medications utilized are the following: levetiracetam at 60 mg/kg (max: 4500 mg), valproate at 40 mg/kg (max: 3000 mg), and fosphenytoin at 20 mgPE/kg (max: 1500 mgPE); these drugs were administered by an infusion pump with a predetermined rate over a period of 10 minutes. The primary outcome was assessing absence of clinical apparent seizures and improving responsiveness at 60 minutes with any additional adjunct medication provided. Secondary outcomes included time to termination of seizures, admission to ICU, and length of ICU and hospital stays.

Baseline characteristics were the same in all 3 groups. There were slight deviations from the eligibility criteria in cases such as benzodiazepines being administered too long before or too close to enrollment of patients, enrollment of patients without status epilepticus, psychogenic nonepileptic seizures, and lastly certain investigators and clinicians were not blinded in cases that were deemed necessary for unblinding. In the intention to treat analysis, there were 68 out of 145 patients (47%) in the levetiracetam group, 53 of 118 patients (45%) in the fosphenytoin, and 56 of 121patients (46%) in the valproate group that had absence of seizures or had an improvement in response without additional antiepileptic at 60 minutes. In the per-protocol and adjudicated-outcome analyses on the other hand did not show any difference. 39 patients met the primary outcome and of those 39 patients there was no statistically significant difference in the 3 drugs. Safety concerns identified were life threatening hypotension, arrhythmia, and endotracheal intubation and those concerns did not illustrate significant difference. Adverse effects occurred in 248 patients at 42% and those events involved convulsions after 60 seconds, respiratory distress and depressed state of consciousness.[9]

Lacosamide

In the review of lacosamide as a new treatment option in status epilepticus, 19 studies were identified utilizing PubMed from the time frame of January 2009 to May 2012. In the 19 studies, there were 136 episodes of refractory status epilepticus. The articles were considered eligible if intravenous lacosamide were reported in the treatment of status epilepticus. 10 cases were single case reports while the rest of 9 were retrospective case series. The objective of the study was to assess all published studies on the use of IV lacosamide in

the treatment of SE and to monitor acute recurrent seizures. The dose most used was a lacosamide bolus dose of 200 to 400 mg over 3 to 5 minutes. There was no duration of treatment reported with either single case reports or retrospective case series. Outcomes were not truly defined, but provided the review of 19 studies, the outcome was to assess the role of lacosamide in therapy and whether it prevented SE. In the 10 single case reports, one of the cases did not report an initial dose, and the other 9 cases had a median initial dose of 100 mg. The use of lacosamide was listed as the fourth treatment algorithm. In the 9 retrospective case series, it was divided into 2 subgroups based on the number of patients with group 1 having a population of 3 to 29 patients and group 2 having greater than 30 patients. In group seizure control varied from 0 to 100%. In studies with 100% responder, the initial dose ranged from 50 to 100 mg versus 100% non-responders, the initial dose ranged from 100 to 300 mg. The conclusion was no difference. In the group, seizure control varied from 44 to 81%. The median initial dose ranges from 200 to 400 mg. In both studies, lacosamide was considered as the third drug in the treatment algorithm. Lastly, rates of adverse effects were low. The following adverse effects were reported, sedation, possible angioedema, hypotension, allergic skin reactions, and pruritus. In addition, there was one patient who developed a third degree of AV block and paroxysmal asystole.[10]

Phenytoin

A randomized study looks at the use of IV valproate versus phenytoin at patients with SE refractory to IV diazepam admitted to the ICU or the emergency room from the time frame of Dec 2004 to Feb 2006. 100 patients were taken from a pool of 3000 patients that were considered benzodiazepine resistant SE. Patients were randomly split 50/50 in the IV valporic group that received 20 mg/kg loading dose at rate of 40mg/min whereas the other group which was the IV phenytoin group received 20 mg/kg at max rate of 50 mg/min. These patients prior to being randomized have received IV diazepam dose at 0.2 mg/kg at 2 mg/min up to max of 20 mg before being considered as refractory. Primary outcome was being seizure free and that was defined as all motor or electroencephalogram (EEG) seizure activity stopped within 20 minutes when medication is given and no return of seizure activity within 24 hours. Secondary endpoints included in-hospital outcomes and neurological outcomes at discharge.

There were no significant results reported that highlights IV valproate as a preferred choice over IV phenytoin other than a side effect profile perspective. In addition, recurrence was no different. Additional significant information includes that there is no difference in adverse effects.[11]

Fosphenytoin

A study compares the efficacy of levetiracetam versus fosphenytoin for recurrence of seizures after status epilepticus. The study pulled patients using a database of the Emergency and Critical Care Center of Hitachi General Hospital between the time frame of April 2013 and May 2016. Total of 63 patients were evaluated with 42 in the fosphenytoin group and 21 in the levetiracetam group. In the study, levetiracetam did not become available till December thus it was not till December where levetiracetam was implemented. All patients at Hitachi hospital were administered diazepam 5 mg or 10 mg before being placed on levateracetam 1000 mg in 100 ml of normal saline or fosphenytoin 22.5 mg/kg. Primary outcome was the presence or absence of recurrent convulsions. Those defined to have achieved epilepsy control are said to no longer present with convulsions. Secondary outcomes included both the presence and absence of adverse events when switching from IV formulation to oral formulation.

Baseline characteristics were similar for both groups. The primary outcome was statistically insignificant (p=0.69). Another significant result was the switching of IV to PO in both fosphenytoin and levetiracetam ($p < 0.0001$). Adverse events reported were minimal in the fosphenytoin group where the reported side effect was reduced blood pressure where there was no adverse events in the levetiracetam group.[12]

Valproate

A study evaluates phenytoin, valproate, and levetiracetam as a second line agents were assessed by retrospectively analyzing data from a prospective registry at a tertiary hospital. Data obtained over a time period from April 1, 2006, to March 31, 2010 included patients with SE. Drug regimen utilized included IV benzodiazepines initially with clonazepam 0.015 mg/kg or lorazepam 0.1mg/kg followed by phenytoin 300 to 400 mg, valproate 1000 to 2500 mg, and levetiracetam 1000 to 3000 mg. Second agent choices were administered over 30 minutes after benzodiazepines. The basis for the study was to evaluate the efficacy of the agents discussed and where they fall in therapy after the utilization of benzodiazepines. The primary outcome assessed the failure of the second line treatment. The significance is the necessity to now evaluate additional therapy to control SE. Reports of 167 patients were given IV benzodiazepine followed by second line treatments.

Notable results in an unadjusted analysis are fewer unfavorable outcomes with valporate that is supported by the following p-values for failure of second line agent p= 0.032, new morbidity or death (p=0.011), and mortality (p=0,045). Valporate had a smaller percentage of failed control of SE at 25.4% as compared to phenytoin at 41.4% and levetiracetam at 48.3%. Additionally, valporate and levetiracetam had less severe SE episodes when compared to phenytoin (p=0.007). Follow up analysis was done with the three outcomes mentioned in the adjusted analysis, but valproate was used as a reference treatment. The p-value this time around was insignificant.[13]

Midazolam, Propofol, Pentobarbital

A systemic review compares pentobarbital, propofol, and midazolam at the treatment response, complications, and mortality in patients with refractory status. Data was obtained via a literature review that dates from the timeframe of January 1970 to September 2001. Medication doses administered for treatment of SE are as follows: pentobarbital loading dose of 13 mg/kg, minimum infusion of 1.84 +/- 1.59 mg/kg/h, and max infusion of 3.17 +/- 2.11 mg/kg/h with a continuous infusion duration of 30 hours; propofol loading dose of 1 mg/kg, minimum infusion of 2.94 +/-2.00 mg/kg/h, and max infusion of 6.98 +/- 5.34 mg/kg/h with a continuous infusion duration of 36 hours; midazolam loading dose of 0.2 mg/kg, minimum infusion of 0.08 +/-0.04 mg/kg/h, and max infusion of 0.23 +/- 0.17 mg/kg/h with a continuous infusion duration of 96 hours; Outcome measures varied from assessing immediate treatment failure, breakthrough seizures, withdrawal seizures, and switching of continuous intravenous antiepileptic therapy due to treatment control of seizures. Results of statistical significance include the following: midazolam being associated with more breakthrough seizures and changes in pharmacological agents; second pentobarbital was associated with the least amount of short term treatment failure, breakthrough seizures, and not needing changes.[14]

Ketamine

A multicenter, retrospective study reviews the medical records and electroencephalography (EEG) reports from the time frame of 1999 to 2012 involving 58 subjects with 60 cases of refractory status

epilepticus treated with IV ketamine. The objective of the study was to assess the use of efficacy and safety of IV ketamine in refractory status epilepticus. Primary outcome was measurement at discharge utilizing the modified Rankin Scale (mRS) and mortality. Ketamine was administered after a median of 9 days since the initial presentation of status epilepticus. Median loading dose was 1.5 mg/kg and 5 mg/kg max followed by continuous infusion median of 2.75 mg/kg/h and max of 10 mg/kg/h with a duration that spanned from 6 hrs to 27 days. Results included 12% where ketamine resulted in permanent control of SE within 24 hrs of ketamine being added to a multidrug regimen. Overall 34 episodes (57%) cases of status epilepticus cases were controlled with. Response to ketamine is significant provided a p-value of 0.0014 for a univariate analysis and p-value of 0.001 for a multivariate analysis. Additional results include mortality rate of 45%, younger age patients with a median age of 27 providing statistical significance. Adverse events include a case of propofol related infusion syndrome, 2 patients developing supraventricular tachycardia, atrial fibrillation, and elevated intracranial pressure.[15]

Discussion and conclusions

The intent of evaluating various studies was to determine the selection of antiepileptics in both benzodiazepines refractory status epilepticus and maintenance therapy after the initiation of benzodiazepines to ensure the cessation of seizures.

The 2012 report of the guideline committee of the American epilepsy society by Brophy GM, Bell R, Claassen J, et al shows the recommendations for adults with status epilepticus to first initiate treatment with benzodiazepines and choices include lorazepam, diazepam, and midazolam. In addition, Misra et al have recommended the levetiracetam as an alternative option to lorazepam for the treatment of SE in patients with hypotension and respiratory distress. After initiation of benzodiazepines, the non-benzodiazepine anti-epileptic drugs are utilized either as an adjunct or for refractory cases. Studies show that the anti-epileptic drugs are approximately equivalent in status epilepticus control once a benzodiazepine has been given. Additionally, based on the evidence from the literatures reported in this review, there is no statistical difference amongst the various agents described. Further evaluation of non-benzodiazepine anti-epileptic drugs are necessary to determine the efficacy and safety of agents as it pertains to maintenance therapy and refractory cases.

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Conflicts of interest

Authors declare that there is no conflict of interest.

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