WHICH ANTI-EPILEPTIC AGENT IS THE CHOICE FOR REFRACTORY STATUS EPILEPTICUS?

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STATUS EPILEPTICUS

SE is defined as 5 min or more of

(i) continuous clinical and/or electrographic seizure activity or

(ii) recurrent seizure activity without recovery between seizures

SE can be classified as
Convulsive SE
Non-convulsive SE

Refractory SE is the type of SE that does not respond to the standart treatment regimens (an initial benzodiazepine followed by another antiepileptic drug)

PROGNOSIS

Mortality at hospital discharge

- Convulsive SE 9-21 %
- Non-convulsive SE 18-52 %
- Refractory SE 23-61%

Return to functional baseline can only be seen in 39% of refractory SE patients

Factors associated with poor outcome:

- Underlying etiology
- >50 years of age
- Long seizure duration
- High APACHE-II scores

ETIOLOGY

- Metabolic disturbances
- Sepsis
- CNS infections, tumors
- Stroke
- Head trauma
- Drug toxicity or withdrawal
- Hypoxia
- Preexisting epilepsy
- Discontinuation of antiepileptic drugs
- Alcohol intoxication or withdrawal

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REVIEW

Guidelines for the Evaluation and Management of Status Epilepticus

Gretchen M. Brophy · Rodney Bell · Jan Claassen · Brian Alldredge · Thomas P. Bleck · Tracy Glauser · Suzette M. LaRoche · James J. Riviello Jr. · Lori Shutter · Michael R. Sperling · David M. Treiman · Paul M. Vespa · Neurocritical Care Society Status Epilepticus Guideline Writing Committee

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Class category	Level of evidence
I Intervention is useful and effective. Treatment benefits clearly exceed risks	A Adequate evidence is available from multiple, large, randomized clinical trials or meta-analyses
IIa Evidence/expert opinion suggest intervention is useful/effective. Treatment benefits exceed risk	B Limited evidence is available from less rigorous data, including fewer, smaller randomized trials, nonrandomized studies, and observational analyses
IIb Strength of evidence/expert opinion about intervention usefulness/effectiveness is less well established. More data are needed; however, using this treatment when warranted is not unreasonable	C Evidence relies on expert/consensus opinion, case reports, or standard of care
III Intervention is not useful or effective and may be harmful. Benefit does not exceed risk	

DIAGNOSTIC WORK-UP

All patients

- Fingerstick glucose
- Monitoring vital signs
- Head computed tomography scan
- Blood glucose, complete blood count, basic metabolic panel, calcium (total and ionized), magnesium, AED levels
- Continuous electroencephalograph (EEG) monitoring

Consider based on clinical presentation

- Brain MRI, Lumbar puncture, toxicology panel, coagulation studies, arterial blood gas

TREATMENT OF SE

- Non-invasive airway protection and gas exchange with head positioning (0–2 min)
- Intubation (0–10 min)
- Measurement of finger stick blood glucose (0–2 min)
- Vital signs, O2 saturation (0–2 min)
- Peripheral IV access (0–5 min)

- Emergent initial AED therapy (i.e. benzodiazepine)
- Fluid resuscitation, nutrient resuscitation (thiamine, dextrose)
- Urgent SE control therapy with AED should be given immediately after initial AED given (5–10 min)
- Refractory SE treatment (20-60 min after 2nd AED)

EMERGENT TREATMENT

- Critical care treatment and monitoring should be started simultaneously with emergent initial therapy
- Benzodiazepines should be given as emergent initial therapy (strong recommendation, high quality).
  - Lorazepam for IV administration
  - Midazolam for IM administration
  - Rectal diazepam can be given when there is no IV access and if IM administration of midazolam is contraindicated

Table 6 Treatment recommendations for SE

Treatment	Class/level of evidence
Emergent treatment	
Lorazepam	Class I, level A
Midazolam	Class I, level A
Diazepam	Class IIa, level A
Phenytoin/fosphenytoin	Class IIb, level A
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Urgent treatment	
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Phenytoin/fosphenytoin	Class IIa, level B
Midazolam (continuous infusion)	Class IIb, level B
Phenobarbital	Class IIb, level C
Levetiracetam	Class IIb, level C
Refractory treatment	
Midazolam	Class IIa, level B
Propofol	Class IIb, level B
Pentobarbital/thiopental	Class IIb, level B
Valproate sodium	Class IIa, level B
Levetiracetam	Class IIb, level C
Phenytoin/fosphenytoin	Class IIb, level C
Lacosamide	Class IIb, level C
Topiramate	Class IIb, level C
Phenobarbital	Class IIb, level C

Guidelines for the Evaluation and Management of Status Epilepticus, 2012

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Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus

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ABSTRACT

BACKGROUND

Early termination of prolonged seizures with intravenous administration of benzodiazepines improves outcomes. For faster and more reliable administration, paramedics increasingly use an intramuscular route.

METHODS

This double-blind, randomized, noninferiority trial compared the efficacy of intramuscular midazolam with that of intravenous lorazepam for children and adults in status epilepticus treated by paramedics. Subjects whose convulsions had persisted for more than 5 minutes and who were still convulsing after paramedics arrived were given the study medication by either intramuscular autoinjector or intravenous infusion. The primary outcome was absence of seizures at the time of arrival in the emergency department without the need for rescue therapy. Secondary outcomes included endotracheal intubation, recurrent seizures, and timing of treatment relative to the cessation of convulsive seizures. This trial tested the hypothesis that intramuscular midazolam was noninferior to intravenous lorazepam by a margin of 10 percentage points.

RESULTS

At the time of arrival in the emergency department, seizures were absent without rescue therapy in 329 of 448 subjects (73.4%) in the intramuscular-midazolam group and in 282 of 445 (63.4%) in the intravenous-lorazepam group (absolute difference, 10 percentage points; 95% confidence interval, 4.0 to 16.1; P<0.001 for both noninferiority and superiority). The two treatment groups were similar with respect to need for endotracheal intubation (14.1% of subjects with intramuscular midazolam and 14.4% with intravenous lorazepam) and recurrence of seizures (11.4% and 10.6%, respectively). Among subjects whose seizures ceased before arrival in the emergency department, the median times to active treatment were 1.2 minutes in the intramuscular-midazolam group and 4.8 minutes in the intravenous-lorazepam group, with corresponding median times from active treatment to cessation of convulsions of 3.3 minutes and 1.6 minutes. Adverse-event rates were similar in the two groups.

CONCLUSIONS

For subjects in status epilepticus, intramuscular midazolam is at least as safe and effective as intravenous lorazepam for prehospital seizure cessation. (Funded by the National Institute of Neurological Disorders and Stroke and others; ClinicalTrials.gov number, NCT00809146.)

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URGENT TREATMENT

- Urgent control AED treatment following administration of short acting benzodiazepines is required in all patients
  - For patients who respond to emergent initial therapy, the goal is rapid attainment of therapeutic levels of an AED
  - For patients who fail emergent initial therapy, the goal of urgent control therapy is to stop SE
- Clinical scenarios may be used on a case-by-case basis to select one of AEDs for urgent control treatment

Table 6 Treatment recommendations for SE

Treatment	Class/level of evidence
Emergent treatment	
Lorazepam	Class I, level A
Midazolam	Class I, level A
Diazepam	Class IIa, level A
Phenytoin/fosphenytoin	Class IIb, level A
Phenobarbital	Class IIb, level A
Valproate sodium	Class IIb, level A
Levetiracetam	Class IIb, level C
Urgent treatment	
Valproate sodium	Class IIa, level A
Phenytoin/fosphenytoin	Class IIa, level B
Midazolam (continuous infusion)	Class IIb, level B
Phenobarbital	Class IIb, level C
Levetiracetam	Class IIb, level C
Refractory treatment	
Midazolam	Class IIa, level B
Propofol	Class IIb, level B
Pentobarbital/thiopental	Class IIb, level B
Valproate sodium	Class IIa, level B
Levetiracetam	Class IIb, level C
Phenytoin/fosphenytoin	Class IIb, level C
Lacosamide	Class IIb, level C
Topiramate	Class IIb, level C
Phenobarbital	Class IIb, level C

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BMC Neurology

RESEARCH ARTICLE Open Access

The efficacy of intravenous sodium valproate and phenytoin as the first-line treatment in status epilepticus: a comparison study

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Abstract

Background: Status epilepticus (SE) is a serious neurological condition and requires prompt treatment. Sodium valproate has been used to treat SE successfully but its role as the first-line antiepileptic drug (AED) is still controversial. This study evaluated the efficacy of intravenous sodium valproate to determine if it is non-inferior to intravenous phenytoin in SE treatment.

Methods: Patients diagnosed as SE during 2003–2010 who were of an age of more than 15 years and received either intravenous sodium valproate or intravenous phenytoin as the first-line treatment were enrolled. Clinical characteristics and outcomes of SE were recorded and analyzed. The differences of outcomes between sodium valproate and phenytoin group were determined by descriptive statistics.

Results: During the study period, there were 37 and 17 SE patients who received intravenous phenytoin and intravenous sodium valproate as the first-line treatment, respectively. All patients received diazepam 10 mg intravenously as a rescue medication before starting the antiepileptic agents if uncontrolled except one patient in the sodium valproate group. There were no significant differences between the phenytoin and sodium valproate groups in all outcome variables including numbers of patients with clinically-controlled seizures, non-dependent patients, time to seizure control, and duration of hospitalization, and death. No serious cardiovasculars event such as hypotension occurred in either group.

Conclusion: Intravenous sodium valproate is non-inferior to intravenous phenytoin as the first-line treatment in SE with no significant cardiovascular compromises.

Keywords: Phenytoin, Sodium valproate, Efficacy, Status epilepticus, Comparison

IV sodium valproate is non-inferior to IV phenytoin as the first-line treatment in SE.

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doi: 10.1111/j.1528-1167.2011.03056.x

FULL-LENGTH ORIGINAL RESEARCH

Second-line status epilepticus treatment: Comparison of phenytoin, valproate, and levetiracetam

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Summary

Purpose: Phenytoin (PHT), valproic acid (VPA), or levetiracetam (LEV) are commonly used as second-line treatment of status epilepticus (SE), but comparative studies are not available.

Methods: Among 279 adult SE episodes identified prospectively in our tertiary care hospital over 4 years, we retrospectively identified 187 episodes in which PHT, VPA, or LEV were given after benzodiazepines. Patients with postanoxic SE were not included. Demographics, clinical SE features, failure of second-line treatment to control SE, new handicap, and mortality at hospital discharge were assessed. Uni- and multivariable statistical analyses were applied to compare the three agents.

Key Findings: Each compound was used in about one third of SE episodes. VPA failed to control SE in 25.4%, PHT in 41.4%, and LEV in 48.3% of episodes in which these were prescribed. A deadly etiology was more frequent in the VPA group, whereas SE episodes tended to be more severe in the PHT group. After adjustment for these known SE outcome predictors, LEV failed more often than VPA [odds ratio (OR) 2.69; 95% confidence interval (CI) 1.19–6.08]; 16.8% (95% CI: 6.0–31.4%) of second-line treatment failures could be attributed to LEV. PHT was not statistically different from the other two compounds. Second-line treatment did not seem to influence new handicap and mortality, whereas etiology and the SE Severity Score (STESS) were robust independent predictors.

Significance: Even without significant differences on outcome at discharge, LEV seems less efficient than VPA to control SE after benzodiazepines. A prospective comparative trial is needed to address this potentially concerning finding.

KEY WORDS: Epilepsy, Seizures, Intensive care neurology.

Levetiracetam seems less efficient than VPA to control SE, without significant differences on outcome

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A Systematic Review of Randomized Controlled Trials on the Theraputic Effect of Intravenous Sodium Valproate in Status Epilepticus

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ABSTRACT

We performed this systematic review to determine whether intravenous sodium valproate was more effective or safer than other drugs in patients with status epilepticus (SE). A literature search was performed using Medline, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL). From 544 articles screened, 5 were identified as randomized controlled trials and were included for data extraction. The main outcomes were SE controlled and risk of seizure continuation. The meta-analysis was performed with the Random-effect model. The quality of the included studies was evaluated by GRADE (Grading of Recommendations Assessment, Development, and Evaluation). There was no significant statistics in SE controlled between intravenous sodium valproate and phenytoin. Compared with diazepam, sodium valproate had a statistically significant lower risk of time interval for control of refractory SE (RSE) after having drugs; however, there was no statistically significant difference in SE controlled within 30 min between the two groups. There was no statistically significant difference in cessation from status between intravenous sodium valproate and levetiracetam. Intravenous sodium valprate was as effective as intravenous phenytoin for SE controlled and risk of seizure continuation.

IV sodium valproate is as effective as IV phenytoin for RSE
There is no difference between sodium valproate and levetiracetam

TREATMENT OF RSE

- The main decision point at this step is to consider repeat bolus of the urgent control AED or to immediately initiate additional agents
- It is recommended proceeding with additional treatment immediately, in combination with critical care treatment
- Treatment recommendations are to use continuous infusion AEDs to suppress seizures
- If the first continuous infusion or AED chosen for RSE fails, then switching to a different continuous infusion or starting another agent is recommended

Table 6 Treatment recommendations for SE

Treatment	Class/level of evidence
Emergent treatment	
Lorazepam	Class I, level A
Midazolam	Class I, level A
Diazepam	Class IIa, level A
Phenytoin/fosphenytoin	Class IIb, level A
Phenobarbital	Class IIb, level A
Valproate sodium	Class IIb, level A
Levetiracetam	Class IIb, level C
Urgent treatment	
Valproate sodium	Class IIa, level A
Phenytoin/fosphenytoin	Class IIa, level B
Midazolam (continuous infusion)	Class IIb, level B
Phenobarbital	Class IIb, level C
Levetiracetam	Class IIb, level C
Refractory treatment	
Midazolam	Class IIa, level B
Propofol	Class IIb, level B
Pentobarbital/thiopental	Class IIb, level B
Valproate sodium	Class IIa, level B
Levetiracetam	Class IIb, level C
Phenytoin/fosphenytoin	Class IIb, level C
Lacosamide	Class IIb, level C
Topiramate	Class IIb, level C
Phenobarbital	Class IIb, level C

Guidelines for the Evaluation and Management of Status Epilepticus, 2012

Table 8 RSE dosing recommendations

Drug	Initial dose	Continuous infusion dosing recommendations-titrated to EEG	Serious adverse effects
Midazolam	0.2 mg/kg; administer at an infusion rate of 2 mg/min	0.05–2 mg/kg/hr CI Breakthrough SE: 0.1–0.2 mg/kg bolus, increase CI rate by 0.05–0.1 mg/kg/hr every 3–4 h	Respiratory depression Hypotension
Pentobarbital	5–15 mg/kg, may give additional 5–10 mg/kg; administer at an infusion rate ≤50 mg/min	0.5–5 mg/kg/h CI Breakthrough SE: 5 mg/kg bolus, increase CI rate by 0.5–1 mg/kg/h every 12 h	Hypotension Respiratory depression Cardiac depression Paralytic ileus At high doses, complete loss of neurological function
Propofol	Start at 20 mcg/kg/min, with 1–2 mg/kg loading dose	30–200 mcg/kg/min CI Use caution when administering high doses (>80 mcg/kg/min) for extended periods of time (i.e., >48 h) Peds: Use caution with doses >65 mcg/kg/min; contraindicated in young children Breakthrough SE: Increase CI rate by 5–10 mcg/kg/min every 5 min or 1 mg/kg bolus plus CI titration	Hypotension (especially with loading dose in critically ill patients) Respiratory depression Cardiac failure Rhabdomyolysis Metabolic acidosis Renal failure (PRIS)
Thiopental	2–7 mg/kg, administer at an infusion rate ≤50 mg/min	0.5–5 mg/kg/h CI Breakthrough SE: 1–2 mg/kg bolus, increase CI rate by 0.5–1 mg/kg/h every 12 h	Hypotension Respiratory depression Cardiac depression

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ACTA NEUROLOGICA SCANDINAVICA

Intravenous lacosamide or ~~phenytoin~~ for treatment of refractory status epilepticus

Kellinghaus C, Berning S, Stögbauer F. Intravenous lacosamide or phenytoin for treatment of refractory status epilepticus. Acta Neurol Scand: DOI: 10.1111/ane.12174.

Objectives – To compare intravenous phenytoin (PHT) and intravenous lacosamide (LCM) for treatment of status epilepticus after failure of the first and second drug. *Methods* – We retrospectively identified patients from a large community hospital in northern Germany who had been diagnosed with SE between August 2008 and December 2010. Patients who had failed to respond to the first two drugs were selected for this analysis. *Results* – Forty-six patients (23 female, median age 68 years) were identified. LCM was used as third drug in 21 patients (median bolus 400 mg) and PHT in 15 patients (median bolus 1500 mg). Pretreatment was similar regarding substance groups (benzodiazepine as first line, levetiracetam as second line drug) and bolus doses. Status epilepticus was terminated in six patients (40%) of the PHT group and in seven patients (33%) of the LCM group. Four patients (27%) of the PHT group and no patient of the LCM group suffered from a relevant, treatment-related side effect during administration of the third drug. *Conclusion* – Lacosamide and PHT showed similar success rates for treatment of SE when used after failure of benzodiazepines and levetiracetam. However, PHT was associated with relevant side effects that were not seen with LCM.

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Key words: comparison; effect; refractory status epilepticus; retrospective; tolerability

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Lacosamide and phenytoin showed similar success rates for treatment of SE when used after failure of benzodiazepines and levetiracetam

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The efficacy of topiramate in adult refractory status epilepticus: Experience of a Tertiary Care Center

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KEYWORDS
Refractory status epilepticus;
Seizures;
Topiramate;
Antiepileptic drugs;
$GABA_A$ receptor;
Glutamate receptors

Summary Refractory status epilepticus (RSE) occurs in patients with SE when they fail to respond to traditional medical therapy. Because there are very few case reports of topiramate (TPM) treatment of RSE in adult patients, we examined our experience with TPM with regard to its safety and efficacy in seizure termination in RSE in an adult patient population. We report a retrospective review of 35 adult patients with RSE who were treated with TPM in addition to other antiepileptic drugs (AEDs) between 2003 and 2010. After failure of initial treatments of benzodiazepines and weight-based intravenous loading doses of standard AEDs, TPM tablets were crushed and administered via nasogastric tube. Data were collected on age, gender, history of epilepsy, etiology of RSE, daily dose of TPM, co-therapeutic agents, treatment response, and disposition. Following initiation of TPM use and discontinuation of continuous intravenous anesthetics with no additional AEDs administered, cumulative cessation of RSE in patients was 4/35 (11%) at one day, 10/35 (29%) at two days, and 14/35 (40%) at three days. However, when including all patients and comparing the two patient groups in which RSE was or was not terminated within three days of initiating TPM as the last or not last AED given, there was no significant difference. Time to TPM response was not associated with the type of seizures, etiology of SE, or whether there was a history of epilepsy. There were no documented side effects or complications of therapy with TPM. This study provides support for the use of TPM as an adjunctive agent in the treatment of RSE.

This study provides support for the use of topiramate as an adjunctive agent in the treatment of RSE

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Short communication

Efficacy of intravenous lacosamide as an add-on treatment in refractory status epilepticus: A multicentric prospective study

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ABSTRACT

Objective: Treatment of status epilepticus (SE) has not changed in the last few decades, benzodiazepines plus phenytoin or valproate being the most common treatment. Once this first and second line treatment has failed SE is considered refractory (RSE). This study aimed to assess the efficacy and tolerability of intravenous (iv) lacosamide (LCM) in RSE.
Method: Patients with RSE who were treated with ivLCM in six Spanish centers were prospectively included. Efficacy was defined as cessation of seizures after starting ivLCM, with no need for any further antiepileptic drug. All patients had been unsuccessfully treated following the standard protocol (benzodiazepines plus phenytoin or valproate) before ivLCM was added.
Results: Thirty-four patients were included, 52.9% men, with mean age of 60.15 years. In 58.9% of patients the etiology was symptomatic, and the most common type of SE was focal convulsive (82.4%). Mean initial bolus dose of LCM was 323.53 mg. ivLCM was effective in more than half of patients (64.7%), with termination of SE before 12 h in 50% of them. ivLCM was used as a fourth or later option in 76.5% of patients. No serious adverse events attributable to LCM were reported.
Conclusions: LCM might be a fast, effective and safe add-on treatment in RSE.

Lacosamide might be a fast, effective and safe add-on treatment in RSE

Table 9 Alternative therapies for RSE

	Number of articles related to treatment of RSE	Case series $n \geq 3$	Comments
Pharmacological			
Ketamine	9	2	Intravenous drip, potential neurotoxicity
Corticosteroids	16	2	Rasmussen's encephalitis, Hashimoto's encephalopathy
Inhaled anesthetics	19	2	High complication rate/morbidity
Immunomodulation (IVIG or PE)	3	1	Rasmussen's encephalitis, EPC
Non-pharmacological			
Vagus nerve stimulation	8	2	Catastrophic epilepsy in infants
Ketogenic diet	20	3	Landau-Kleffner syndrome, pediatrics
Hypothermia	4	2	Single or small case series only
Electroconvulsive therapy	5	1	Single or small case series only
Transcranial magnetic stimulation	9	1	EPC in most cases
Surgical management	13	4	Most often used and successful in pediatrics

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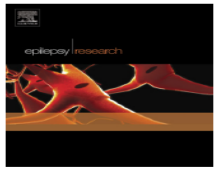

Ketamine use in the treatment of refractory status epilepticus

Andrea S. Synowiec[a], Deepinder S. Singh[a], Vamsi Yenugadhati[a], James P. Valeriano[a,b], Carol J. Schramke[a,b], Kevin M. Kelly[a,b,c,*]

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Ketamine;
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Refractory status epilepticus;
NMDA receptor

Summary Refractory status epilepticus (RSE) occurs when status epilepticus (SE) fails to respond to appropriate therapy with typical antiepileptic drugs (AEDs). Animal studies have shown ketamine to be a highly efficacious agent in this setting, but very few case reports describe use of ketamine in human SE or RSE. We report a retrospective review of 11 patients who were treated for RSE with ketamine infusion in addition to other standard AEDs over a nine-year period. Data collection included age, gender, history of epilepsy, etiology of RSE, daily dose of ketamine, co-therapeutic agents, duration of seizures, treatment response, and disposition. RSE was successfully terminated in all 11 patients treated with ketamine. Dosing ranged from 0.45 mg/kg/h to 2.1 mg/kg/h based upon the preference of the treating clinician and response to therapy, with maximal daily doses ranging from 1392 mg to 4200 mg. Ketamine was the last AED used prior to resolution of RSE in 7/11 (64%) cases. In the remaining four cases, one other AED was added after ketamine infusion had begun. Time from ketamine initiation to seizure cessation ranged from 4 to 28 days (mean = 9.8, SD = 8.9). In 7/11 patients, RSE was resolved within one week of starting therapy. Administration of ketamine was uniformly associated with improvement in hemodynamic stability. Six of the seven patients (85%) who required vasopressors during early treatment for RSE were able to be weaned from vasopressors during ketamine infusion. No acute adverse effects were noted. These findings suggest that ketamine may be a safe and efficacious adjunctive agent in the treatment of RSE.

Findings of the study suggest that ketamine may be a safe and efficacious adjunctive agent in the treatment of RSE

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Five cases of new onset refractory status epilepticus (NORSE) syndrome: Outcomes with early immunotherapy

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ABSTRACT

Cryptogenic new onset refractory status epilepticus (NORSE) syndrome has been described in both adults and children, and is often associated with poor outcome. A variety of terms have been used in the literature to refer to this syndrome. The condition may be triggered by as yet unidentified infections or an immunological mechanism. We present a series of 5 patients with NORSE syndrome treated at 2 neuroscience centres in the North of England, in whom early use of immunotherapy appears to be associated with good neurological outcomes.

Methods: Case note review of the index case and four other patients was undertaken to obtain details of clinical presentation, imaging and CSF findings, infectious/inflammatory tests, management of seizures, immunotherapy and outcome.

Results: Case 1 was a 26 year old male with a prodrome of headache and vomiting. He developed refractory multifocal and generalised seizures, which required admission to intensive care unit and administration of general anaesthetic. Seizures recurred on withdrawal of barbiturate anaesthetic until day 29. MR imaging, CSF examination and serological tests for viral and autoimmune aetiologies were normal apart from positive anti-TPO antibodies: the patient had previously treated hyperthyroidism. He was initially treated with aciclovir and antibacterials. IV steroids were administered day 12 and IV immunoglobulin day 18. He made a good recovery being discharged home 2 months after admission. Seizures recurred on withdrawal of steroid therapy, and required longer term immunosuppressant treatment with azathioprine. Clinical features and investigations of the four other patients were similar. Two were given early immunotherapy with steroids and intravenous immunoglobulins and survived with few deficits. One patient who was not given immunotherapy died from complications associated with prolonged ICU stay. Outcome was not known for the fourth patient as she was repatriated to her home country in thiopentone coma.

Conclusion: In our experience, early immunotherapy has been associated with good outcomes in NORSE. Multicentre collaboration is required to establish the diagnostic criteria and appropriate management of patients presenting with NORSE.

Early immunotherapy has been associated with good outcomes in NORSE

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Short communication

Plasma exchange in cryptogenic new onset refractory status epilepticus

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ABSTRACT

Objective: New onset refractory status epilepticus (NORSE) is a recently described entity and has been difficult to treat because the etiology is often cryptogenic. Our aim in each case was to stop status epilepticus while simultaneously searching for the etiology.
Methods: We describe three patients who presented with NORSE, who were refractory to multiple anticonvulsants and general anesthetics for at least 5 days. All patients had an extensive evaluation including MRI brain, CSF studies, radiologic scans for malignancy and serological autoimmune and infectious investigations.
Results: Each patient responded dramatically to the use of plasma exchange therapy with cessation of status epilepticus by the fourth day of treatment. Although an etiology was sought after, no appropriate cause for NORSE could be found.
Conclusion: We propose early use of plasma exchange therapy (Class IV evidence) in hopes to prevent the complications of status epilepticus and prolonged hospitalization.

Early use of plasma exchange therapy in hopes to prevent the complications of SE

WHAT FOR FUTURE?

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SHORT COMMUNICATION

A prospective, randomized, multicentre trial for the treatment of refractory status epilepticus; experiences from evaluating the effect of the novel drug candidate, NS1209

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KEYWORDS
Status epilepticus;
Refractory;
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NS1209

Summary Refractory status epilepticus (RSE) is a life-threatening condition that requires immediate and aggressive treatment. Unfortunately, sometimes standard antiepileptic treatment is insufficient. Furthermore, alternative therapeutic options are limited by low evidence of efficacy.
The primary objective of this study was to evaluate the effects of the novel drug candidate, NS1209 versus third-line standard treatment (phenytoin/valproate) for RSE. Having not reached the study end-points, the purpose of this paper is to discuss the challenges that are encountered in conducting a controlled study of RSE. This was a phase II, prospective, multicentre, single-blinded, randomized clinical trial and included patients to two separate protocols for convulsive and non-convulsive RSE (NS1209-006 and NS1209-007). In total, 28 patients were included and 14 patients were exposed to NS1209. At study conclusion, the study was insufficiently powered to detect any statistically significant difference between the two treatment groups. This was especially true for the convulsive RSE protocol. We conclude that high-quality studies in RSE are difficult to conduct owing to a number of ethical and practical problems associated with this critical illness. Challenges for further studies are discussed.

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This study was insufficiently powered to detect any significant difference between the two treatment groups

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SGE-102: A novel therapy for refractory status epilepticus

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Summary

Refractory status epilepticus (SE) has a mortality rate of up to 35%. Current treatment protocols for the treatment of SE begin with benzodiazepines and then proceed to conventional anticonvulsants. If seizures continue, SE is considered refractory (RSE) and treatment with anesthetic agents in undertaken. Twenty-four h to 48 h after initiation of anesthesia with midazolam, pentobarbital or thiopental, or propofol, an attempt is made to wean the anesthetic. If this fails and seizures recur, SE is considered highly refractory (HRSE) and repeated attempts are undertaken. No randomized trial data are available to guide the choice of anesthetic agent in either RSE or HRSE status. Medication resistance in established SE is thought to result, in part, from internalization of synaptic γ-aminobutyric acid (GABA) receptors, making them unavailable for modulation. Neurosteroids act on both synaptic and extrasynaptic $GABA_A$ receptors, which are not internalized, and are therefore hypothesized to have a role in the treatment of RSE. SGE-102 is a neurosteroid metabolite of progesterone with demonstrated anticonvulsant properties in animal seizure models. A randomized double-blind placebo-controlled adjunctive trial of SGE will include subjects randomized at the time that initial treatment with anesthesia is initiated. Subjects will receive midazolam and either SGE-102 or placebo. Midazolam will be tapered and discontinued between hours 24 and 48. SGE-102 or placebo will be continued through hour 120. The primary end point will be the difference in proportion of subjects from each arm who remain seizure free through hour 120. Secondary end points will include the proportion of subjects who are seizure free at hour 168, 2 days after discontinuation of the experimental agent. The study will be powered to have a 90% chance of detecting a clinically meaningful reduction in seizure recurrence at 120 h. Comprehensive safety and pharmacokinetic data will also be obtained during the course of the trial.

KEY WORDS: Clinical trial, Neurosteroid, Anticonvulsant, Randomized, Phase II.

Randomized, double-blind, placebo controlled, adjunctive trial has been planned. We are waiting for results…

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STATUS EPILEPTICUS 2013

Stiripentol in refractory status epilepticus

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Summary

Benzodiazepines (BZDs), which enhance γ-aminobutyric acid ($GABA_A$) receptor–mediated inhibition, are the first-line therapy for treatment of status epilepticus (SE). However, pharmacoresistance to BZDs develops rapidly after SE initiation. This is due to an activity-dependent internalization of BZD-sensitive $GABA_A$ receptors during SE. Stiripentol (STP) is a positive allosteric modulator of $GABA_A$ receptors with a unique subunit selectivity profile. We report that in a rodent model of SE, STP terminates behavioral seizures and remains effective in established SE when seizures have become BZD resistant. The anticonvulsant effects of STP are age dependent, with greater potency in juvenile animals. Whole cell recordings from dentate granule cells in hippocampal slices reveal that STP potentiates GABAergic inhibitory postsynaptic currents (IPSCs) and tonic GABAergic currents by acting at a site on the $GABA_A$ receptor that is separate from the benzodiazepine binding site. This potentiation persists in established SE, whereas potentiation of GABAergic inhibition by BZDs is lost. STP potentiates IPSCs in juvenile animals with greater potency than in adult animals. We suggest that STP, either alone or as add-on therapy, may prove useful in treating established and BZD-resistant status epilepticus. Furthermore, STP may be particularly effective in terminating SE in children when SE is most prevalent.

KEY WORDS: Benzodiazepine, GABAergic inhibition, Seizure, Anticonvulsant, Dentate gyrus, IPSC.

In animal studies, it has been reported that stiripentol terminates seizures and remains effective in SE

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The Established Status Epilepticus Trial 2013

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Summary

Benzodiazepine-refractory status epilepticus (established status epilepticus, ESE) is a relatively common emergency condition with several widely used treatments. There are no controlled, randomized, blinded clinical trials to compare the efficacy and tolerability of currently available treatments for ESE. The ESE treatment trial is designed to determine the most effective and/or the least effective treatment of ESE among patients older than 2 years by comparing three arms: fosphenytoin (fPHT) levetiracetam (LVT), and valproic acid (VPA). This is a multicenter, randomized, double-blind, Bayesian adaptive, phase III comparative effectiveness trial. Up to 795 patients will be randomized initially 1:1:1, and response-adaptive randomization will occur after 300 patients have been recruited. Randomization will be stratified by three age groups, 2—18, 19—65, and 66 and older. The primary outcome measure is cessation of clinical seizure activity and improving mental status, without serious adverse effects or further intervention at 60 min after administration of study drug. Each subject will be followed until discharge or 30 days from enrollment. This trial will include interim analyses for early success and futility. This trial will be considered a success if the probability that a treatment is the most effective is >0.975 or the probability that a treatment is the least effective is >0.975 for any treatment. Proposed total sample size is 795, which provides 90% power to identify the most effective and/or the least effective treatment when one treatment arm has a true response rate of 65% and the true response rate is 50% in the other two arms.

KEY WORDS: Comparative efficacy, Bayesian design, Fosphenytoin, Levetiracetam, Valproic acid.

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STATUS EPILEPTICUS 2013

The Established Status Epilepticus Trial 2013

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KEY WORDS: Comparative efficacy, Bayesian design, Fosphenytoin, Levetiracetam, Valproic acid.

Multicenter, randomized, double-blind, phase III, comparative trial for three AED has been planned. We are waiting for results…

CONCLUSION

- It is recommended proceeding with additional treatment immediately for RSE, in combination with critical care treatment
- Treatment recommendations are to use continuous infusion AEDs to suppress seizures
- If the first continuous infusion or AED chosen for RSE fails, it is recommended switching to a different continuous infusion or starting another agent
- There are many different antiepileptic drugs which can be used in SE
- The selection of AED should be planned on a case-by-case basis


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