SMACC 2015:
Controversies in the acute management of status epilepticus

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Director, Clinical Neurophysiology, Rush University Medical Center

Disclosures

• I am a current member of the ABIM Critical Care Subspecialty Exam Committee.
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  – As a member of an ABIM exam committee, I agree to keep exam information confidential.
  – As is true for any ABIM candidate who has taken an exam for Certification, I have signed the Pledge of Honesty in which I have agreed not to share ABIM exam questions with others.
  – No exam questions will be disclosed in my presentation.
Standard disclosures

• Research support from NINDS, AHA, Zoll
• Consultant for USAMRICD (nerve agent protection)
• DSMB chair for Sage phase 3 trial of allopregnenolone in RSE
• DSMB member for a trial of ketogenic diet in RSE
• DSMB chair for a trial of intraventricular nimodipine in SAH

• Many of the treatments discussed are not approved by the FDA for SE

SE Controversies

1. What is the best initial treatment to terminate SE?
2. What is the best second line therapy if the initial therapy fails?
3. How should one treat refractory SE?
4. When is immunologic treatment indicated?
PHTSE

Time to end of status

Proportion Seizing

Time (minutes)

- Placebo
- Diazepam
- Lorazepam

P = 0.0002
Intramuscular versus Intravenous Therapy for Prehospital Status Epilepticus

Robert Silbergeld, M.D., Valerie Durakis, Ph.D., Daniel Luekenstein, M.D., Robert Carret, M.D.,
Arthjo Fincel, M.D., Fuku Peltz, Ph.D., and William Barron, M.D., for the NETT Investigators*.

ABSTRACT

BACKGROUND

Early elimination of prolonged seizures with intravenous administration of benzodiazepines improves outcomes, for faster and more reliable administration, patients increasingly use an intramuscular route.

METHODS

This double-blind, randomized, noninferiority trial compared the efficacy of intramuscular lorazepam with that of intravenous lorazepam for children and adults with 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 or intravenous infusion. The primary outcome was absence of seizures at the time of arrival to the emergency department without the need for rescue therapy. Secondary outcomes included endotracheal intubation, intubation times, and timing of treatment relative to the occurrence of convulsive seizures. This trial tested the hypothesis that intramuscular midazolam or lorazepam is noninferior to intravenous lorazepam at a margin of 3 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 (34.7% of subjects with intramuscular midazolam and 34% with intravenous lorazepam and occurrence of seizures (34.7% and 31.4%, respectively). Among subjects whose seizures ceased before arrival in the emergency department, the median time to active treatment was 3.2 minutes in the intramuscular-midazolam group and 4.5 minutes in the intravenous-lorazepam group, with corresponding median times from active treatment to cessation of convulsions of 3.2 minutes and 3.6 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, NCT00389194.)

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40 kg: MDZ 10 mg, LRZ 4 mg
13-40 kg apply the neurosurgical dose rule

Figure 3. Intervals between Active Treatment and Cessation of Convulsions, Box Opening and Cessation of Convulsions, and Box Opening and Active Treatment.

The shorter time to IM drug administration was offset by the faster onset of action after IV drug administration, resulting in similar latency periods until convulsions were terminated. Time to IV administration includes the nominal time (about 20 seconds) needed to administer the drug by means of IM autoinjector. Asterisks indicate means, boxes interquartile ranges, bold vertical lines within boxes medians, 1 bars 1.5 times the interquartile range, and circles outliers.

40 kg: MDZ 10 mg, LRZ 4 mg
13-40 kg: just cut the dose in half

Figure 3. Intervals between Active Treatment and Cessation of Convulsions, Box Opening and Cessation of Convulsions, and Box Opening and Active Treatment.

The shorter time to IM drug administration was offset by the faster onset of action after IV drug administration, resulting in similar latency periods until convulsions were terminated. Time to IV administration includes the nominal time (about 20 seconds) needed to administer the drug by means of IM autoinjector. Asterisks indicate means, boxes interquartile ranges, bold vertical lines within boxes medians, 1 bars 1.5 times the interquartile range, and circles outliers.
Only the first conventional anticonvulsant has a reasonable chance of working in SE.

DVA cooperative study of SE: treatment success

<table>
<thead>
<tr>
<th>response rates (%)</th>
<th>Overt SE</th>
<th>Subtle SE</th>
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</thead>
<tbody>
<tr>
<td>LRZ</td>
<td>64.9</td>
<td>17.9</td>
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<tr>
<td>PB</td>
<td>58.2</td>
<td>24.2</td>
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<tr>
<td>DZ + PHT</td>
<td>55.8</td>
<td>8.3</td>
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<tr>
<td>PHT alone</td>
<td>43.6</td>
<td>7.7</td>
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<tr>
<td>means</td>
<td>55.5</td>
<td>14.9</td>
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</table>
### VACSP 265: lorazepam arm (overt SE)

<table>
<thead>
<tr>
<th>drug</th>
<th>response rate (%)</th>
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<tbody>
<tr>
<td>lorazepam</td>
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<tr>
<td>phenytoin</td>
<td>7.2</td>
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<tr>
<td>phenobarbital</td>
<td>2.1</td>
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<tr>
<td>other drugs</td>
<td>17.5</td>
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</table>

### VACSP 265: phenobarbital arm (overt SE)

<table>
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<th>response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenobarbital</td>
<td>58.2</td>
</tr>
<tr>
<td>phenytoin</td>
<td>3.3</td>
</tr>
<tr>
<td>lorazepam</td>
<td>2.2</td>
</tr>
<tr>
<td>other drugs</td>
<td>25.3</td>
</tr>
</tbody>
</table>
**VACSP 265: diazepam/phenytoin arm (overt SE)**

<table>
<thead>
<tr>
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<th>response rate (%)</th>
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</thead>
<tbody>
<tr>
<td>diazepam/phenytoin</td>
<td>55.8</td>
</tr>
<tr>
<td>lorazepam</td>
<td>3.2</td>
</tr>
<tr>
<td>phenobarbital</td>
<td>2.1</td>
</tr>
<tr>
<td>other drugs</td>
<td>23.2</td>
</tr>
</tbody>
</table>

**VACSP 265: phenytoin arm (overt SE)**

<table>
<thead>
<tr>
<th>drug</th>
<th>response rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>phenytoin</td>
<td>43.5</td>
</tr>
<tr>
<td>lorazepam</td>
<td>13.9</td>
</tr>
<tr>
<td>phenobarbital</td>
<td>3.0</td>
</tr>
<tr>
<td>other drugs</td>
<td>26.7</td>
</tr>
</tbody>
</table>
All patients received LRZ

34/50 = 68%
39/50 = 78%

(LRZ alone ~65%)

7/150 = ~5% refractory
We need a large clinical trial to guide the choice of second-line agents.
Established SE Treatment Trial (ESETT) proposal

- Planned sample size = 795 patients
- Use same sites as RAMPART and SHINE
- Randomize after BZ failure to
  - FOS, 20 mg/kg; > 75 kg receive 1500 mg
  - VAL, 40 mg/kg; > 75 kg receive 3000 mg
  - LEV, 60 mg/kg; > 75 kg receive 4500 mg
- All study drugs masked, infused over 10 min
- Parallel studies in US and Europe

High-dose benzodiazepines

- Midazolam
  - loading dose: 0.2 mg/kg
  - maintenance: 0.1 - 2.0 mg/kg/hr (2.0 - 40 µg/kg/min)
  - goal: seizure suppression
- Lorazepam
  - up to 9 mg/hr
  - goal: seizure suppression
High-dose midazolam infusion for refractory status epilepticus

Andres Fernandez, MD
Hector Lantigua, MD
Christine Lesch, PharmD
Bethesda Has, BA
Brando Fuentes, MD
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ABSTRACT

Objective: This study compares 2 treatment protocols allowing low vs high continuous IV midazolam (cIV-MDZ) doses.

Methods: We compared adults with refractory status epilepticus treated with a protocol allowing for high-dose cIV-MDZ (n = 100; 2002–2011) with those treated with the previous lower-dose cIV-MDZ (n = 29; 1996–2000). We collected data on baseline characteristics, cIV-MDZ doses, seizure control, hospital course, and outcome.

Results: Median maximum cIV-MDZ dose was 0.4 mg/kg/h (interquartile range [IQR] 0.2–1.0) for the high-dose group and 0.2 mg/kg/h (IQR 0.1–0.3) for the low-dose group (p < 0.001) with similar duration of infusion. Median time from status epilepticus onset to cIV-MDZ start was 1 day (IQR 1–3) for the high-dose group and 2 days (IQR 1–5) for the low-dose group (p = 0.016). "Withdrawal seizures" (occurring within 48 hours of discontinuation of cIV-MDZ) were less frequent in the high-dose group (15% vs 64%, odds ratio 0.10, 95% confidence interval 0.03–0.27). "Ultimate cIV-MDZ failure" (patients requiring change to a different cIV antiepileptic medication) and hospital complications were not different between groups. Hypertension was more frequent in the high-dose group, but was not associated with worse outcome. Discharge mortality was lower in the high-dose group (49% vs 65%, odds ratio 0.34, 95% confidence interval 0.13–0.62 in multivariate analysis).

Conclusions: High-dose cIV-MDZ treatment of refractory status epilepticus can be performed safely, is associated with a lower seizure rate after cIV-MDZ discontinuation, and may be associated with lower mortality. Neurology® 2014;82:350–365.

Table 4

| Table 4 Multivariate analysis of mortality at hospital discharge |
|---------------------------------|--------------------|-----------------|-----------------|
| Discharge mortality             | Alive (n = 71)     | Dead (n = 58)   | OR (95% CI)     |
| APACHE II score*                | 17 (12, 20)        | 21 (18, 26)     | 1.18 (1.09–1.27) |
| Epilepsy as presumptive cause of RSE | 22 (31)            | 4 (7)           | 0.17 (0.05–0.81) |
| High-dose cIV-MDZ group         | 60 (85)            | 40 (69)         | 0.34 (0.13–0.62) |

Abbreviations: APACHE II = Acute Physiology and Chronic Health Evaluation II; CI = confidence interval; cIV-MDZ = continuous IV midazolam; OR = odds ratio; RSE = refractory status epilepticus.

Values are median (interquartile range) and n (%).

* Three patients had missing APACHE II scores.
Midazolam vs. propofol

- Retrospective review of 20 RSE cases with continuous EEG monitoring
  - 14 propofol, 6 midazolam
  - Overall mortality:
    - 57% propofol, 17% MDZ (NS)
    - Subgroup with APACHE II scores > 20 did show a statistically significantly higher mortality with propofol

Prasad A et al Epilepsia 2001;42:380-386
Intravenous lacosamide or phenytoin for treatment of refractory status epilepticus


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 2005 and December 2010. Patients who had failed to respond to the first two drugs were selected for this analysis. Results – Forty-six patients (37 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 (benzodiazepines 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.

Table 3 Outcome

<table>
<thead>
<tr>
<th>Variable</th>
<th>All 3rd AED (n = 46)</th>
<th>PHT 3rd AED (n = 15)</th>
<th>LCM 3rd AED (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SE finally treated successfully</td>
<td>36 (83%)</td>
<td>13 (87%)</td>
</tr>
<tr>
<td>mRS at discharge</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>3.92 ± 1.93</td>
<td>3.98 ± 1.4</td>
<td>3.98 ± 2.2</td>
</tr>
<tr>
<td>Median</td>
<td>4 (0-6)</td>
<td>4 (1-6)</td>
<td>4 (1-6)</td>
</tr>
<tr>
<td>1 ± 2</td>
<td>4</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>5</td>
<td>10</td>
</tr>
<tr>
<td>5</td>
<td>10</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>6</td>
<td>11</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td>mRS Difference</td>
<td>28</td>
<td>8</td>
<td>15</td>
</tr>
</tbody>
</table>

mRS, modified Rankin scale; SD, standard deviation; AED, antiepileptic drug; PHT, phenytoin; LCM, lacosamide.
Hypothermia for Refractory Status Epilepticus

Jackson L. Curry - Rajat Dhar - Theresa Murphy - Michael N. Orfali
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Abstract
Introduction Status epilepticus (SE) can be refractory to conventional anticonvulsants, requiring anesthetic doses of medications to suppress seizures. This approach carries significant morbidity, is associated with a high mortality rate, and may not always control SE. Hypothermia has been shown to suppress epiileptiform activity experimentally, but has not previously been used as a primary modality to control SE in humans.

Methods Four patients with SE refractory to benzodiazepine and/or barbiturate infusions were treated with hypothermia (target temperature: 31-33°C) using an endovascular cooling system. All received continuous EEG monitoring, three were on midazolam infusions and one had recurrent seizures on weaning from pentobarbital.

Results Therapeutic hypothermia was successful in aborting seizure activity in all four patients, allowing midazolam infusions to be discontinued; three achieved a burst-suppression pattern on EEG. After controlled rewarming, two patients remained seizure-free, and all four demonstrated a marked reduction in seizure frequency. Adverse events included shivering, coagulopathy without bleeding, and venous thromboembolism. Two deaths occurred, neither directly related to hypothermia; however, immunosuppression related to the use of barbiturates and hypothermia may have contributed to an episode of fatal sepsis in one patient.

Conclusions Hypothermia was able to suppress seizure activity in patients with SE refractory to traditional therapies with minimal morbidity. It appears promising as an alternative or an adjunct to anesthetic doses of other agents, but requires further study to better evaluate its safety and efficacy.

Keywords Induced hypothermia - Status epilepticus - Endovascular cooling - Barbiturates

Introduction

Status epilepticus (SE) affects up to 150,000 patients each year in the United States, with a mortality between 3 and 33% [1-8]. Initial treatment with benzodiazepines, phenytoin, and/or pentobarbital fails to terminate SE in 30-50% of cases, with cases of longer duration becoming more difficult to treat [6, 9-12]. Even infusions of anesthetic doses of agents, such as midazolam, pentobarbital, and propofol, that are traditionally used to control refractory SE, fail in 8-21% of cases [13]. Refractory SE has a greater mortality than SE that can be controlled by first-line interventions.

Ketogenic Diet for Adults in Super-refractory Status Epilepticus

Kiran T. Thakur, MD* - John C. Fedderson, MD* - Matthew D. Sullivan, MD - Sara E. Hucker, MD - Kelly Rech, MS, RD - Bobbie Henry, RD - Eric H. Kosoff, MD - Peter W. Kaplan, MB, FRCP - Ranjana G. Gogia, MD - Adam L. Hartman, MD - Anni Venhamxonia, MD - PDR - Michael C. Cervenka, MD*

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E-mail: mcervenka@uth.edu

ABSTRACT

Objective: To describe a case series of adult patients in the intensive care unit in super-refractory status epilepticus (SRSE), refractory status lasting 24 hours or more despite appropriate anesthetic treatment who received treatment with the ketogenic diet (KD).

Methods: We performed a retrospective case review at 4 medical centers of adult patients with SRSE treated with the KD. Data collected included demographic features, clinical presentation, diagnosis, EEG data, anticonvulsant treatment, and timing and duration of the KD. Primary outcome measures were resolution of status epilepticus (SE) after initiation of KD and ability to wean from anesthetic agents.

Results: Ten adult patients at 4 medical centers were started on the KD for SRSE. The median age was 33 years (interquartile range [IQR] 21), 4 patients (40%) were male, and 7 (70%) had encephalitis. The median duration of SE before initiation of KD was 21.5 days (IQR 28), and the median number of antiepileptic medications used before initiation of KD was 7 (IQR 7). Ninety percent of patients achieved ketosis, and SE ceased in all patients achieving ketosis in a median of 3 days (IQR 8). Three patients had minor complications of the KD including transient acidosis and hypoglycemia, and 2 patients ultimately died of causes unrelated to the KD.

Conclusions: We describe treatment of critically ill adult patients with SRSE with the KD, with 90% of patients achieving resolution of SE. Prospective trials are warranted to examine the efficacy of the KD in adults with refractory SE.

Classification of evidence: This study provides Class IV evidence that for intensive care unit patients with refractory SE, a KD leads to resolution of the SE. Neurology® 2014;82:1-5
Depth of EEG suppression and outcome in barbiturate anesthetic treatment for refractory status epilepticus

- Retrospective review of 40 patients with RSE treated with pentobarbital
- 5 died during treatment
- Survival correlated best with the etiology of SE

Krishnamurthy and Drislane *Epilepsia* 1999;40:759-762
Depth of EEG suppression and outcome in barbiturate anesthetic treatment for refractory status epilepticus

<table>
<thead>
<tr>
<th>EEG pattern</th>
<th>Slow</th>
<th>S-B</th>
<th>Flat</th>
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<tbody>
<tr>
<td>N</td>
<td>3</td>
<td>12</td>
<td>20</td>
</tr>
<tr>
<td>SE duration</td>
<td>6h</td>
<td>16h</td>
<td>14h</td>
</tr>
<tr>
<td>PB duration</td>
<td>26h</td>
<td>72h</td>
<td>14h</td>
</tr>
<tr>
<td>survival</td>
<td>3 (100%)</td>
<td>3 (25%)</td>
<td>12 (60%)</td>
</tr>
</tbody>
</table>

RESEARCH

Is pentobarbital safe and efficacious in the treatment of super-refractory status epilepticus: a cohort study

Deborah Puglisi, Brandon Foreman, Gian Marco De Marchi, Andreas Fernandez, J Michael Schmidt, Berry M Collier, Stephan A Mayer, Sahin Agawal, Christine Leicht, Hector Carriaga and Jan Claassen

Abstract: Seizure refractory to third-line therapy are also labeled super-refractory status epilepticus (SRE). These seizures are extremely difficult to control and associated with poor outcome. We aimed to characterize efficacy and side-effects of continuous infusions of pentobarbital (CI-PTB) treating SRE.

Methods: We retrospectively reviewed continuous electroencephalographic (cEEG) reports for all adults with SRE treated with CI-PTB between May 1997 and April 2015 at our institution. Patients with post-anoxic SE and those resolving CI-PTB for reasons other than SRE were excluded. We collected baseline information, cEEG findings, side-effects and functional outcome at discharge and one year.

Results: Thirty one SRE patients treated with CI-PTB for SRE were identified. Mean age was 48 years old (interquartile range (IQR) 28/63), 20% (N = 6) had a history of epilepsy. Median SE duration was 6 days (IQR 3.14-18), 74% (N = 23) presented with convulsive SE. Underlying etiology was acute symptomatic seizures in 52% (N = 10), 12/16 with encephalitis, remote 30% (N = 6), and unknown 16% (N = 3). CI-PTB controlled seizures in 96% (N = 30) of patients but seizures occurred in 48% (N = 15) while weaning CI-PTB, despite the fact that suppression-burst was attained in 96% (N = 28) of patients and persisted >7 hours in 58% (N = 17). Waking was successful after adding phenobarbital in 86% (13/15) of the patients with withdrawal asci. Complications during or after CI-PTB included pneumonia (20%, N = 4), hypotension requiring pressors (20%, N = 4), urinary tract infection (16%, N = 3) and one patient each with paralytic ileus and cardiac arrest. One-third (10%, N = 11) had no identified new complication after starting CI-PTB. At one year after discharge, 74% (N = 23) were dead or in a state of unresponsive wakefulness, 16% (N = 5) severely disabled, and 10% (N = 3) had no or minimal disability. Death or unresponsive wakefulness was associated with catastrophic etiology (p = 0.003), but none of the other collected variables.

Conclusions: CI-PTB effectively aborts SRE and complications are infrequent, outcome in this highly refractory cohort of patients with devastating underlying etiologies remains poor. Phenobarbital may be particularly helpful when weaning CI-PTB.
Burst-suppression myths

- EEG burst-suppression has been demonstrated to be necessary for RSE control
- achieving burst-suppression means that the patient will not have seizures
- the burst-suppression pattern is easily recognized and taught, even for non-neurologists
Nitwiticisms

- EEG burst-suppression has been demonstrated to be necessary for RSE control
- achieving burst-suppression means that the patient will not have seizures
- the burst-suppression pattern is easily recognized and taught, even for non-neurologists

Other approaches to RSE

- lidocaine
- high-dose phenobarbital
- paraldehyde
- clonazepam
- isoflurane
- magnesium
- surgery
  - resection
  - subpial transection
  - vagus nerve stimulator
AnaConDa device for recirculating volatile anesthetic gases in the ICU

Our increasing recognition of inflammatory causes of SE suggests that we need to pay early attention to treating the etiology of SE ('source control')
Table 1. Antibodies associated with encephalitides and seizures

<table>
<thead>
<tr>
<th>Antibody</th>
<th>Syndrome</th>
<th>Clinical significance</th>
<th>Location of epitopes</th>
<th>Response to immunotherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hu</td>
<td>Limbic, cortical encephalitis</td>
<td>High</td>
<td>Intracellular</td>
<td>Infrequent</td>
</tr>
<tr>
<td>GY2/GMPS</td>
<td>Limbic encephalitis</td>
<td>High</td>
<td>Intracellular</td>
<td>Infrequent</td>
</tr>
<tr>
<td>Ma2</td>
<td>Limbic, diencephalon, upper brainstem encephalitis</td>
<td>High</td>
<td>Intracellular</td>
<td>Moderate</td>
</tr>
<tr>
<td>AMPH</td>
<td>Limbic encephalitis, stiff-person syndrome</td>
<td>High</td>
<td>Intracellular</td>
<td>Poor</td>
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<td>GAD</td>
<td>Limbic encephalitis, refractory epilepsy, stiff-person syndrome</td>
<td>Moderate</td>
<td>Intracellular</td>
<td>Moderate</td>
</tr>
<tr>
<td>VGKC (Kv1.1, Kv1.2)</td>
<td>Psychosis, dyskinesia, autonomic instability, hyperventilation</td>
<td>High</td>
<td>Extracellular</td>
<td>Frequent</td>
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<tr>
<td>NMDAR (NR1)</td>
<td>Limbic encephalitis, Morvan’s syndrome</td>
<td>High</td>
<td>Extracellular</td>
<td>Frequent</td>
</tr>
<tr>
<td>NMDAR (NR2B or GluN2)</td>
<td>Multiple types of encephalitides</td>
<td>Unclear</td>
<td>Extracellular and intracellular</td>
<td>N/A</td>
</tr>
<tr>
<td>NMDAR (NR3A/2B)</td>
<td>Neurophysiologic lupa</td>
<td>Low</td>
<td>Extracellular (DWEYS)</td>
<td>N/A</td>
</tr>
<tr>
<td>AMPAR (GluR1/2)</td>
<td>Limbic encephalitis (frequent relapses)</td>
<td>N/A</td>
<td>Extracellular</td>
<td>Frequent</td>
</tr>
<tr>
<td>AMPAR (GluR3)</td>
<td>Rasmussen’s encephalitis</td>
<td>Low</td>
<td>Extracellular</td>
<td>Infrequent/moderate</td>
</tr>
<tr>
<td>Thyroid peroxidase, thyroglobulin</td>
<td></td>
<td>Low</td>
<td>Intracellular</td>
<td>Frequent</td>
</tr>
</tbody>
</table>

*Italicics indicate syndromes that are almost always paraneoplastic.

CRMP5, collapsin response mediator protein-5; GAD, glutamic acid decarboxylase; VGKC, voltage-gated potassium channels; NMDAR, N-methyl-D-aspartate receptor; AMPAR, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor.

1*Described in multiple unrelated disorders, including among others: limbic encephalitis, non-specific encephalitis, viral encephalitis, and degenerative disorders.

2*DWEYS pentapeptide consensus sequence present in NR2A and NR2B.

N/A: not available, too early to assess significance.

Dalmau, *Epilepsia*, 2009
The Frequency of Autoimmune N-Methyl-D-Aspartate Receptor Encephalitis Surpasses That of Individual Viral Etiologies in Young Individuals Enrolled in the California Encephalitis Project

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Background. In 2007, the California Encephalitis Project (CEP), which was established to study the epidemiology of encephalitis, began identifying cases of anti-N-methyl-D-aspartate receptor (anti-NMDAR) encephalitis. Increasing numbers of anti-NMDAR encephalitis cases have been identified at the CEP, and this form rivals commonly known viral etiologies as a causal agent. We report here the relative frequency and differences among encephalitis caused by anti-NMDAR and viral etiologies within the CEP experience.

Methods. Demographic, frequency, and clinical data from patients with anti-NMDAR encephalitis are compared with those with viral encephalitis, encephalitis due to herpes simplex virus type 1 (HSV-1), varicella-zoster virus (VZV), and West Nile virus (WNV). All examined cases presented to the CEP between September 2007 and February 2011 and are limited to individuals aged ≥30 years because of the predominance of anti-NMDAR encephalitis in this group. The diagnostic costs incurred in a single case are also included.

Results. Anti-NMDAR encephalitis was identified >4 times as frequently as HSV-1, WNV, or VZV and was the leading encephalitis identified in our cohort. We found that 60% of anti-NMDAR encephalitis occurred in patients aged ≤18 years. This disorder demonstrated a predilection, which was not observed with viral etiologies, for females (P < .01). Seizures, language dysfunction, psychosis, and electroencephalographic abnormalities were significantly more frequent in patients with anti-NMDAR encephalitis (P < .05), and autonomic instability occurred exclusively in this group.

Discussion. Anti-NMDAR encephalitis rivals viral etiologies as a cause of encephalitis within the CEP cohort. This entity deserves a prominent place on the encephalitis differential diagnosis to avoid unnecessary diagnostic and treatment costs, and to permit a more timely treatment.

Encephalitis with refractory seizures, status epilepticus, and antibodies to the GABA\(_\text{A}\) receptor: a case series, characterisation of the antigen, and analysis of the effects of antibodies

Weill-Pitié-Salpêtrière, Paris, France; University Hospital, Essen, Germany; University of Camerino, Italy; University of Padua, Italy; University of Bologna, Italy; University of Cambridge, UK; Imperial College, UK; and Department of Neurology, Hospital Clínico, University of Barcelona, Spain

Summary

Methods. In this observational study, we selected serum and CSF samples for antigen characterization from 144 patients with encephalitis, seizures, status epilepticus, and antibodies to unknown neuronal antigens. The samples were obtained from 4000 referrals of patients with disorders suspected to be autoimmune between April 28, 2006, and April 25, 2013. We used samples from 73 healthy individuals and 416 patients with a range of neurological disorders as controls. We assessed the samples using immunoprecipitation, mass spectrometry, cell-based assays, and analysis of antibody effects in cultured hippocampal neurons with confocal microscopy.

Findings. Neuronal cell membrane immunoprecipitation with serum of two index patients revealed GABA\(_\text{A}\) receptor subunits, which were confirmed in the GABAA receptor family. Cell-based assays with HEK293 expressing wild-type GABA\(_\text{A}\) receptors showed that CSF antibodies from six patients. All six patients (age 14–63 years, median 22 years; five male patients) developed refractory status epilepticus and epilepsy partialis continua along with extensive cortical-subcortical MRI abnormalities. Five patients needed pharmacological induction coma, 12 of 416 control patients with other diseases, but none of the healthy controls, had in vitro GABA, receptor antibodies detectable in only one serum sample, but four of them also had GAD-65 antibodies. Four of 14 patients (age 2–7 years, median 3 years; seven male patients) showed T cell reactivity to GABA\(_\text{A}\) receptor antibodies in sera with mass spectrometry, and all patients exhibited GABA receptor antibodies in sera with mass spectrometry. Overall, 11 of 15 patients for whom treatment and outcome were assessed had full (three patients) or partial (eight patients) response to immunotherapy or symptomatic treatment, and three died. Patients antibodies caused a selective reduction of GABA\(_\text{A}\) receptor subunits in synapses, but not along dendrites, without shunting NMDA receptors and glutamate transporters that anchors the GABA\(_\text{A}\) receptor.

Interpretation. High titers of serum and CSF GABA\(_\text{A}\) receptor antibodies are associated with a severe form of encephalitis with seizures, refractory status epilepticus, and both antibodies cause a reduction of synaptic GABA\(_\text{A}\) receptors. The disorder often occurs with GABA\(_\text{A}\)-ergic and other corticostriatal neurons and is refractory to treatment.
Immunomodulatory therapy

• With or without a definitive diagnosis of an immunologic cause of status
• Choices:
  – Steroids
  – IgIV
  – Plasma exchange
  – Calcineurin antagonists and other antirejection drugs
  – Rituximab
  – Cytotoxic agents

We need to prevent or ameliorate secondary injury (sometimes from our treatment) while controlling SE
Early Ketamine to Treat Refractory Status Epilepticus

Andreas H. Kramer

Intravenous ketamine for the treatment of refractory status epilepticus: A retrospective multicenter study


SUMMARY

Purpose: To examine patterns of use, efficacy, and safety of intravenous ketamine for the treatment of refractory status epilepticus (RSE).

Methods: Multicenter retrospective review of medical records and electroencephalography (EEG) reports in 18 academic medical centers in North America and Europe, including 18 subjects, representing 16 episodes of RSE that were identified between 1998 and 2012. Seven episodes occurred after acute brain injury.

Key Findings: Perioperative control of RSE was achieved in 17% (4 of 24) of episodes. Ketamine was initiated in all patients to treat refractory status epilepticus (100% of cases). The first dose was 0.5 mg/kg (median, 0.25-1.0 mg/kg). The median total dose was 50 mg/kg (range, 25-100 mg/kg). Ketamine was administered in a median of 4.5 hours (range, 0.25-14.6 hours) after the onset of RSE. No adverse effects were observed when infusion rates were less than 0.5 mg/kg/h, but ketamine was introduced at least 8 days after severe brain injury. Ketamine was discontinued to possible adverse events in five patients. Complications were mostly attributed to concurrent drugs, especially other anesthetics. Mortality rate was 43% (8 of 19), but was lower when SE was controlled within 24 h of ketamine administration (2 of 5, p = 0.041).

Significance: Ketamine appears to be a relatively effective and safe drug for the treatment of RSE. This retrospective series provides preliminary data on effective dose and appropriate time of intervention to aid in the design of a prospective trial to further define the role of ketamine in the treatment of RSE.

NET WORTH: Ketamine, Treatment, Refractory status epilepticus, Anesthetics, Antiepileptic drugs.
Allopregnenolone (SAGE-547)

- Modulates *extra*synaptic GABA<sub>A</sub> receptors
  - Company claims no nuclear hormone receptor action
- Preliminary data suggests success controlling SE in 70% of 20 very super-refractory patients.
- Phase 3 study planned.

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**REVIEWS ARTICLE**

*The outcome of therapies in refractory and super-refractory convulsive status epilepticus and recommendations for therapy*

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In a previous paper, we reviewed the range of therapies available for the treatment of super-refractory status epilepticus. Here we report a review of the outcome of therapies in refractory and super-refractory status epilepticus. Patients (n=116) are reported who had therapy with: thiopental, pentobarbital, midazolam, propofol, ketamine, inhalational anesthetics (isoflurane, desflurane), antiepileptic drugs (topiramate, levetiracetam, pregabalin, lacosamide), hypothermia, magnesium, pyridostigmine, intracarotid, intravenous diazepam, emergency neurosurgery, electroconvulsive therapy, craniocerebral fluid drainage, vagal nerve stimulation and deep brain stimulation. The outcome parameters reported include control of status epilepticus, episode on withdrawal, breakthrough status and mortality. Where reported (66 cases), the long-term outcome was found to be death (35%), severe neurological deficit (13%), mild neurological deficit (13%), undefined defect (4%) and recovery to baseline (35%). The quality of reported outcome data is generally poor and the number of cases reported for all non-anesthetic therapies is low. Outcome assessment is complicated by changes in co-medication, delay in response and publication bias. Given these deficits, only broad recommendations can be made regarding optimal therapy. An approach to therapy, divided into first-line, second-line and third-line therapy, is suggested on the basis of this outcome evaluation. The importance of treatments directed at the causes of the status epilepticus, and of supportive ITU care, is also emphasized.
Table 3 Long-term outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>n = 596</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>207 (35%)</td>
</tr>
<tr>
<td>Severe neurological deficit</td>
<td>79 (13%)</td>
</tr>
<tr>
<td>Mild neurological deficit</td>
<td>80 (13%)</td>
</tr>
<tr>
<td>Undefined neurological deficit</td>
<td>22 (4%)</td>
</tr>
<tr>
<td>Recovery to baseline</td>
<td>208 (35%)</td>
</tr>
</tbody>
</table>

*In the reports of 596 cases (51% of the total of 1168), the long-term outcome was recorded. In the other 575 cases, no long-term outcome data were provided.*
For copies of slides, email

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