Lacosamide for Refractory Pediatric Status Epilepticus
October 5th, 2018

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Objectives

- Describe the standard of care treatment of pediatric status epilepticus (SE)
- Evaluate the evidence for intravenous (IV) lacosamide use in pediatric refractory SE (RSE)
- Determine which patients may benefit from use of lacosamide
- Identify which patients should not use lacosamide

Patient Case

- JD is a 6 year old male who was playing outside when he had a witnessed fall
  - Weight: 20 kg
  - PMH: Non-contributory
  - Medications: none
  - Allergies: NKDA
  - Mom saw he was shaking his limbs and didn’t respond to her voice
  - EMS was called and upon arrival determined that the patient was having a convulsive seizure
  - Administered 6 mg (0.3 mg/kg) of intranasal midazolam with no effect
  - JD was immediately transferred to Dell Children’s Medical Center for presumed status epilepticus

Status Epilepticus (SE)

- SE: 5 minutes or more of continuous clinical or electrographic seizure activity or seizure activity without baseline recovery between seizures
  - Convulsive
  - Non-convulsive
  - Only recognizable with an electroencephalogram (EEG)

Pathophysiology of SE

- Seizures, hypermetabolic activity
- Gamma aminobutyric acid (GABA)
2012 Neurocritical Care Society Guidelines

Class I: Benefit clearly exceeds risk
Class IIa: Benefit exceeds risk
Class IIb: Using this treatment when warranted is not unreasonable

Pathophysiology of SE
Lowenstein and Aldredge 2001

Appendix B
Class I: Benefit clearly exceeds risk
Class IIa: Benefit exceeds risk
Class IIb: Using this treatment when warranted is not unreasonable

Patient Case
• Upon arrival at Dell Children’s Medical Center the patient’s seizures were still unresponsive to treatment
• IV access was obtained
• Lorazepam 2 mg (0.1 mg/kg) IV was administered
• There was no effect on seizure activity after 5 minutes

2012 Neurocritical Care Society Guidelines

Patient Case
• At 15 minutes after arrival, patient still had with ongoing convulsive seizures
• Phosphenytoin 400 mg phenytoin equivalents (20 mg/kg) was administered
• There was no change in convulsive seizures after administration

Refractory Status Epilepticus (RSE)
• Patients who do not respond to standard treatment
  - Continuing seizures after an adequate dose of a benzodiazepine followed by a second AED
  - Duration is no longer a valid determinant of RSE

Pathophysiology of Refractory SE

Seizures, hypermetabolic activity

Initial seizure control, followed by benzodiazepine tachyphylaxis

Initial seizure control, followed by benzodiazepine tachyphylaxis

Pre-synaptic neuron

Post-synaptic neuron

Glutamate

NMDA

GABA/benzodiazepine

Dell Children’s Seizure Management Pathway

- Benzodiazepine (IM, IV, buccal, rectal, intranasal)
- Establish IV access
- Repeat benzodiazepine
- Phenytoin, phenytoin, levetiracetam, or valproic acid
- Phenytoin
- Transfer patient to critical care area
- Start midazolam infusion +/- bolus
- If unable to suppress epileptiform activity, consider pentobarbital infusion

2012 Neurocritical Care Society Guidelines

Class I: Benefit clearly exceeds risk
Class IIa: Benefit exceeds risk
Class IIb: Using this treatment when warranted is not unreasonable

Timing and Selection of Medications

Cook et al. 2012
- Multicenter, retrospective, observational study across 15 hospitals in the United States
- Primary objective: to evaluate the current pharmacologic management and practice variation associated with SE
- Adult patients (n=150) with a diagnosis of SE
- Recorded which anti-epileptic drug (AED) was given and in what order

Prognosis of RSE

- Refractory SE damages the brain
- Primary goal: control seizures
  - Mortality increases the longer the episode continues
  - Refractory convulsive status mortality in pediatrics as high as 16 to 20%
- Secondary goals:
  - Neuroprotection
  - Avoidance and treatment of complications of prolonged anesthesia/hospitalization
Limitations of Anesthetic Medications

Use of anesthetic agents and prolonged hospitalization comes with significant risk:
- Hypotension
- Cardiorespiratory failure
- Hepatic/renal failure
- Hypersensitivity and allergic reactions
- Bleeding disorders
- Infection
- Rhabdomyolysis
- Ileus/Gastrointestinal disturbance
- ICU neuropathy
- Anesthetic coma

Lacosamide Overview

Formulations: tablets, oral solution, IV solution
Contraindications: hypersensitivity to any component
Warnings: cardiovascular effects, central nervous system effects, ophthalmic effects, multiorgan hypersensitivity reactions, suicidal ideation
Pediatric considerations: may have an effect on central nervous system development
Regulatory: Schedule V

Pharmacokinetics:
- Absorption (oral): complete
- Distribution: 0.6 L/kg
- Protein binding: <15%
- Metabolism: hepatic (CYP3A4, CYP2C9, CYP2C19)
- Bioavailability: 100%
- Half-life: 7-15 hours (pediatric)
- Excretion: urine

Dose adjustments:
- Renal: creatinine clearance <30 mL/min, reduce dose by 75%
- Hepatic: mild to moderate, reduce dose by 75%, not recommended in severe liver impairment
Clinical Questions

1. Should lacosamide be used for RSE before anesthetic medications?
   - Grosso et al. 2014
   - Arkilo et al. 2016
   - Poddar et al. 2016

2. Which subgroups should avoid use of lacosamide for RSE treatment?

Efficacy

Grosso et al. 2014

Objective:
To assess the efficacy and tolerability of IV lacosamide (LCM) in children with RSE

Primary outcome:
Cessation of RSE (disappearance of seizure activity on EEG)

Population: (n=11)
Pediatric patients with SE refractory to 2 or more agents

Study Design:
Retrospective single-center analysis

Methods:
IV lacosamide started after a trial of at least 2 other AEDs
Mean loading dose: 8.6 mg/kg
Mean maintenance dose: 12.3 mg/kg/day

Primary outcome: Cessation of RSE

<table>
<thead>
<tr>
<th>Total response</th>
<th>CRSE (n=6)</th>
<th>NCRSE (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Seizure cessation</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Persistent EEG seizures</td>
<td>--</td>
<td>2</td>
</tr>
<tr>
<td>No response</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

Conclusion:
IV lacosamide could be considered as an option for refractory convulsive or non-convulsive SE after a trial of 2 or more anti-epileptic medications
Clinical experience of intravenous lacosamide in infants and young children

**Objective:**
To review the clinical experience with IV lacosamide at a single center

**Primary outcome:**
Seizure cessation or >50% seizure reduction (physician observation and EEG monitoring)

**Population:** (n=9)
3 patients with refractory status epilepticus

**Study Design:**
Retrospective single-center analysis

**Methods:**
IV lacosamide started after at least 2 AEDs
Mean loading dose: 8.7 mg/kg (range 4-10 mg/kg)
Mean maintenance dose: 7.2 mg/kg/day (range 4-11 mg/kg/day)

<table>
<thead>
<tr>
<th>Age/gender</th>
<th>Seizure etiology</th>
<th>AEDs used/Concurrent medications</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 month, F</td>
<td>SR-SE, Meningitis</td>
<td>LEV, PB, continuous pentobarbital</td>
<td>Ineffective</td>
</tr>
<tr>
<td>16 months, M</td>
<td>SR-SE, Unknown</td>
<td>LEV, PB, continuous midazolam, continuous lorazepam</td>
<td>Ineffective</td>
</tr>
<tr>
<td>5 years, F</td>
<td>SR-SE, Unknown</td>
<td>OXC, VPA, PB, continuous pentobarbital</td>
<td>Ineffective</td>
</tr>
<tr>
<td>7 years, F</td>
<td>SR-SE, FRES</td>
<td>VPA, prop. FOS, LEV, FBM, continuous pentobarbital</td>
<td>Ineffective</td>
</tr>
<tr>
<td>7 years, M</td>
<td>R-SE, Lea syndrome</td>
<td>FOS, LEV, continuous prop.</td>
<td>Effective</td>
</tr>
<tr>
<td>6 months, F</td>
<td>R-SE, Unk outer l</td>
<td>FOS, LEV, continuous midazolam</td>
<td>Effective</td>
</tr>
<tr>
<td>6 months, F</td>
<td>SR-SE, Infection</td>
<td>LTG, LEV, OZP, FOS, continuous prop.</td>
<td>Effective</td>
</tr>
<tr>
<td>5 years, M</td>
<td>R-SE, Patonagia</td>
<td>LTG, LEV, ENZ, GABA, prop.</td>
<td>Effective</td>
</tr>
<tr>
<td>5 months, M</td>
<td>SR-SE, Unk outer l</td>
<td>LEV, ENZ, L2F, FOS</td>
<td>Effective</td>
</tr>
</tbody>
</table>

**Efficacy**
Arkilo et al. 2016

**Primary Outcome:**
56% with seizure response (n=5/9 refractory)

**Secondary Outcomes:**
Adverse effects: none noted, no effect on electrocardiogram (ECG), blood pressure, respiratory measurements
Application:
No children with super-refractory SE responded
3 patients who responded had another agent given at the same time as lacosamide

**Limitations:**
Subjective adverse events would not be quantifiable
Small patient population, retrospective
All patients on other AEDs when lacosamide was administered

**Conclusion:** IV lacosamide may be safe and effective for refractory status epilepticus and may be associated with higher efficacy earlier in seizure treatment

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Intravenous lacosamide in pediatric status epilepticus: an open label efficacy and safety study

**Objective:**
To review the use of IV lacosamide in children with SE at a single center

**Primary outcome:**
Seizure cessation or >50% reduction of seizures within 24 hours of lacosamide administration

**Population:** (n=9)
Mean age: 5.7 years (range 1-16 years)
SE defined as seizures >20 minutes or 2+ seizures without return to baseline, refractory status not specifically defined

**Study Design:**
Retrospective single-center analysis

**Methods:**
IV lacosamide started after 3 or more AEDs
Average total dose 13.8 mg/kg in 24h

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Efficacy
Arkilo et al. 2016

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Efficacy
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Average total dose 13.8 mg/kg in 24h
### Efficacy

Poddar et al. 2016

<table>
<thead>
<tr>
<th>Age, gender</th>
<th>Seizure history</th>
<th>Sensitive AEDs</th>
<th>AEDs before LCM</th>
<th>Efficacy (%) reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6 years, F</td>
<td>New onset</td>
<td>fos, lev, ptb</td>
<td>fos, lev, ptb</td>
<td>seizure free</td>
</tr>
<tr>
<td>3 months, M</td>
<td>New onset</td>
<td>levetiracetam</td>
<td>levetiracetam</td>
<td>seizure free</td>
</tr>
<tr>
<td>9 years, F</td>
<td>New onset</td>
<td>vpa</td>
<td>vpa</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>14 years, F</td>
<td>Lennox-Gastaut</td>
<td>lev, clob, clb, ltg</td>
<td>levetiracetam</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>4 months, F</td>
<td>West syndrome</td>
<td>lev, tsp, clob</td>
<td>levetiracetam</td>
<td>&gt;50%</td>
</tr>
<tr>
<td>1.4 years, M</td>
<td>New onset</td>
<td>lev, levetiracetam</td>
<td>levetiracetam, ptb</td>
<td>no change</td>
</tr>
<tr>
<td>1 year, M</td>
<td>localization-related</td>
<td>letr, clob</td>
<td>levetiracetam</td>
<td>seizure free</td>
</tr>
<tr>
<td>5 years, F</td>
<td>localization-related</td>
<td>levetiracetam</td>
<td>levetiracetam</td>
<td>seizure free</td>
</tr>
<tr>
<td>3.5 years, M</td>
<td>New onset</td>
<td>fos, levetiracetam</td>
<td>levetiracetam, fos, ptb</td>
<td>no change</td>
</tr>
</tbody>
</table>

FOS: fosphenytoin
LEV: levetiracetam
PTB: pentobarbital
VPA: valproic acid
TPM: topiramate
CLB: clobazam
CZP: carbamazepine

### Conclusion

IV lacosamide may be an appropriate adjunctive therapy for refractory status epilepticus treatment when administered with other AEDs

### Clinical Questions

1. Should lacosamide be used for RSE before anesthetic medications?
   - IV lacosamide may be an appropriate adjunct therapy for RSE treatment
   - Consider a loading dose of 4-10 mg/kg IV given over 15 minutes

### How to Administer: Loading Dose?

Intravenous lacosamide in status epilepticus: Correlation between loading dose, serum levels, and clinical response

- Retrospective case study evaluating the correlation between LCM serum levels after a loading dose and clinical response
- Population: 40 patients with trough LCM serum levels
  - 19 males, median age 68 years (range 34-88), median body weight 70 kg
  - 21 females, median age 58 years (range 27-86), median body weight 60 kg
- Intervention:
  - Median LCM loading dose was 600 mg (range 100-800 mg)
  - Median 7.5 mg/kg (range 1.3-16 mg/kg)
- Results:
  - Median LCM serum level was 10 mg/L (range 2.4-24.8 mg/L)
  - 50% of levels fell within the therapeutic reference range (10-20 mg/L)
  - Median time between blood sampling was 15.9h
  - A loading dose of ≥ 9 mg/kg was associated with more levels in the reference range compared to lower doses (p=0.003, χ²)
  - Highest level was 24.8 mg/L with patient experiencing transient vertigo and nystagmus
  - 40% of patients responded to LCM
  - No association between loading dose and clinical response

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  - 40% of patients responded to LCM
  - No association between loading dose and clinical response

### Patient Case

• At 30 minutes after the start of his seizure, the patient continues to be unresponsive
• Phenobarbital 400 mg IV (20 mg/kg) is administered
• At 40 minutes there is no change in EEG activity
• The team prepares to transfer the patient to the pediatric intensive care unit
• The fellow consults pharmacy regarding use of IV lacosamide while waiting for transfer
Clinical Questions

1. Should lacosamide be used for RSE before anesthetic medications?
2. Which subgroups should avoid use of lacosamide for RSE treatment?
   - Loomba et al. 2015
   - Biton et al. 2015
   - Verrotti et al. 2013

Safety

Loomba et al. 2015

- Retrospective case report
- 3 year old patient with RCSE
- PMH: left hypoplastic heart syndrome with significant cardiac comorbidities, cerebral palsy with subsequent epilepsy, eosinophilic esophagitis, J-tube dependent
- IV midazolam→IV lorazepam→levetiracetam→valproic acid→IV lacosamide
- LCM administered 15 minutes after ED arrival, re-dosed 4 hours after initial dose

Outcome:
- Patient developed wide-complex tachycardia with hemodynamic compromise 1 hour after 2nd dose of IV lacosamide
- IV amiodarone did not resolve tachycardia and patient eventually required electrical cardioversion at 6 hours which restored normal sinus rhythm

Conclusion: IV lacosamide should be avoided in pediatric patients with known structural cardiac abnormalities

Safety

Biton et al. 2015

Purpose:
- To describe protocol-defined a priori analyses to evaluate the safety and tolerability of adjunctive oral LCM

Design:
- Retrospective analysis of pooled data of three randomized controlled trials

Population:
- Adult patients (16-70 years) with partial-onset seizures for ≥2 years with a trial of ≥2 other AEDs
- 1368 patients randomized; 944 to LCM, 364 to placebo
- Most patients (84.4%) were taking 2 or 3 concomitant AEDs

Intervention:
- Oral LCM at 200, 300, or 600 mg/day or placebo

Outcome:
- Treatment-emergent adverse events (TEAEs) in patients with and without partial onset epilepsy: discontinuations due to TEAEs

Safety and tolerability of lacosamide as adjunctive therapy for adults with partial-onset seizures: analysis of data pooled from three randomized, double-blind, placebo-controlled clinical trials

Biton V et al. Epilepsy and behavior. 2015;52:119-127

Lacosamide-induced atrial tachycardia in a child with hypoplastic left-heart syndrome: the importance of assessing additional pro-arrhythmic risks

Safety
Biton et al. 2015

Outcome:
• Most common TEAEs:
  - Dizziness (30.6 vs 8.2%)
  - Nausea (11.4 vs 4.4%)
  - Diplopia (10.5 vs 1.9%)
• TEAEs were dose-related and lower during the maintenance phase
• Placebo-adjusted mean maximum PR interval increase was 1.5, 3.1, and 4.5 ms for LCM 200, 400, and 600 mg/day respectively
  - 4 patients on LCM experienced 1st degree atrioventricular block
  - No findings of second degree or higher block

Conclusion: IV lacosamide should be used with caution in patients with known cardiac conduction abnormalities

Safety
Verrotti et al. 2013

Purpose:
To investigate the efficacy and safety of lacosamide adjunctive therapy in pediatric and adult patients with uncontrolled epilepsy

Design:
Prospective, multicenter study

Population:
Pediatric (n=59) and adult patients (n=59) with uncontrolled generalized and focal epilepsy

Intervention:
Dose started at 1 mg/kg/day
Final maintenance dose 7.2 ± 2.45 mg/kg daily

Outcome:
Safety assessment: Withdrawal due to adverse events, changes in laboratory values, liver and kidney function tests, urinalysis, plasma concentrations of other AEDs, ECG, EEG, vital signs, weight, physical and neurologic exam findings

Conclusion: Lacosamide is generally well tolerated in pediatrics for uncontrolled seizure treatment

Clinical Questions

1. Should lacosamide be used for RSE?
2. Which subgroups should avoid use of lacosamide for RSE treatment?
   - IV lacosamide should be avoided in patients with structural or conductive cardiac abnormalities

Conclusions

• Consider use of IV lacosamide for the treatment of refractory status epilepticus
• Providers may consider using IV lacosamide in the seizure pathway before anesthetics if:
  - The patient has no history of structural or conductive cardiac abnormalities
  - If the patient may be at high risk for complications associated with anesthesia
  - Anesthetic therapy is not significantly delayed
Summary

• There is limited evidence available for the use of IV lacosamide for pediatric refractory status epilepticus
• Studies available suggest lacosamide may be efficacious and could be used as a third or fourth line agent
• Lacosamide has a generally benign safety profile which may provide benefit in patients at high risk for complications of prolonged anesthesia
• Further studies are needed to determine its ideal place in the SE management pathway

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• Evaluator
  - Deedee Hu, Pharm.D., MBA
• Preceptors
  - Molly McNaull, Pharm.D.
  - Derek Templet, Pharm.D.
  - Sarah Johnson, Pharm.D.
  - Lyndrick Hamilton, Pharm.D., BCPS, BCPPS
Appendices

Appendix A: Abbreviations


Appendix D: Table 1, Cook et al. Neurocrit care. 2012;17:24-30

Appendix E: Table 2, Cook et al. Neurocrit care. 2012;17:24-30


Appendix A: Abbreviations

AED: Antiepileptic drug
CLB: Clobazam
CRSE: Convulsive refractory status epilepticus
CSE: Convulsive status epilepticus
CZP: Carbamazepine
DZP: Diazepam
ECG: Electrocardiogram
EEG: Electroencephalogram
EMS: Emergency medical services
FIRES: Febrile infection-related epilepsy syndrome
FOS: Fosphenytoin
GABA: Gamma aminobutyric acid
IM: Intramuscular
IV: Intravenous
LCM: Lacosamide
LEV: Levetiracetam
LTG: Lamotrigine
LZP: Lorazepam
NCRSE: Non-convulsive refractory status epilepticus
NCSE: Non-convulsive status epilepticus
NKDA: No known drug allergies
NMDA: N-methyl-D-aspartate
OXC: Oxcarbazepine
PB: Phenobarbital
PMH: Past medical history
PRES: Posterior reversible encephalopathy syndrome
PRIS: Propofol infusion syndrome
SE: Status epilepticus
RSE: Refractory status epilepticus
TPM: Topiramate
VPA: Valproic acid
ZNS: Zonisamide
### Table 6: Treatment recommendations for SE

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Class/level of evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Emergent treatment</strong></td>
<td></td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Class I, level A</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Class I, level A</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Class IIa, level A</td>
</tr>
<tr>
<td>Phenytoin/fosphenytoin</td>
<td>Class IIb, level A</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Class IIb, level A</td>
</tr>
<tr>
<td>Valproate sodium</td>
<td>Class IIb, level A</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Class IIb, level C</td>
</tr>
<tr>
<td><strong>Urgent treatment</strong></td>
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</tr>
<tr>
<td>Valproate sodium</td>
<td>Class IIa, level A</td>
</tr>
<tr>
<td>Phenytoin/fosphenytoin</td>
<td>Class IIa, level B</td>
</tr>
<tr>
<td>Midazolam (continuous infusion)</td>
<td>Class IIb, level B</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Class IIb, level C</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>Class IIb, level C</td>
</tr>
<tr>
<td><strong>Refractory treatment</strong></td>
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</tr>
<tr>
<td>Midazolam</td>
<td>Class IIa, level B</td>
</tr>
<tr>
<td>Propofol</td>
<td>Class IIb, level B</td>
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<td>Pentobarbital/thiopental</td>
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<tr>
<td>Phenobarbital</td>
<td>Class IIb, level C</td>
</tr>
</tbody>
</table>
Appendix D: Cook et al. *Neurocrit care*. 2012;17:24-30
Fig. 3 % of patients that received AEDs in a cumulative manner
## Table 1 – Clinical findings and baseline data.

<table>
<thead>
<tr>
<th></th>
<th>CRSE (n = 6)</th>
<th>NCRSE (n = 5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>9.6</td>
<td>9.1</td>
</tr>
<tr>
<td>Sex (M/F)</td>
<td>3/3</td>
<td>2/3</td>
</tr>
<tr>
<td>Prior history of epilepsy</td>
<td>5 (83%)</td>
<td>4 (80%)</td>
</tr>
<tr>
<td>Etiology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
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<tr>
<td>Structural/metabolic</td>
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<tr>
<td>Neuronal migration disorders</td>
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<td>-</td>
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<tr>
<td>PRES</td>
<td>-</td>
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<td>Cerebral palsy</td>
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<td>2</td>
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</tr>
<tr>
<td>LCM loading dose (mg/kg): mean (range)</td>
<td>8.8 (6.9–9.9)</td>
<td>8.3 (6.7–9.5)</td>
</tr>
<tr>
<td>LCM maintenance dose</td>
<td>12.9</td>
<td>11.9 (8.8–13.4)</td>
</tr>
<tr>
<td>(mg/kg/day): mean (range)</td>
<td>(9.1–13.9)</td>
<td></td>
</tr>
<tr>
<td>Time from seizure onset to LCM therapy: mean (range)</td>
<td>52.5 h</td>
<td>63.5 h (31–90)</td>
</tr>
<tr>
<td>AEDs before RSE: mean (range)</td>
<td>3.1 (2–6)</td>
<td>2.8 (2–5)</td>
</tr>
</tbody>
</table>

CRSE: convulsive refractory status epilepticus; NCRSE: non-convulsive status epilepticus; PRES: posterior reversible encephalopathy syndrome; LCM: lacosamide; AED: antiepileptic drugs.
<table>
<thead>
<tr>
<th>Adverse eventsa</th>
<th>Group A (n=59)</th>
<th>Group B (n=59)</th>
<th>Total (n=118)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>2 (3.4%)</td>
<td>6 (10.2%)</td>
<td>8 (6.8%)</td>
</tr>
<tr>
<td>Headache</td>
<td>3 (5.1%)</td>
<td>4 (6.8%)</td>
<td>7 (5.9%)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>2 (3.4%)</td>
<td>3 (5.1%)</td>
<td>5 (4.3%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>3 (5.1%)</td>
<td>2 (3.4%)</td>
<td>5 (4.3%)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>4 (6.8%)</td>
<td>1 (1.7%)</td>
<td>5 (4.3%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>3 (5.1%)</td>
<td>1 (1.7%)</td>
<td>4 (3.4%)</td>
</tr>
<tr>
<td>Irritability</td>
<td>3 (5.1%)</td>
<td>1 (1.7%)</td>
<td>4 (3.4%)</td>
</tr>
<tr>
<td>Inappetence</td>
<td>–</td>
<td>2 (3.4%)</td>
<td>2 (1.7%)</td>
</tr>
<tr>
<td>Diplopia</td>
<td>–</td>
<td>2 (3.4%)</td>
<td>2 (1.7%)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>1 (1.7%)</td>
<td>1 (1.7%)</td>
<td>2 (1.7%)</td>
</tr>
<tr>
<td>Balance disorder</td>
<td>1 (1.7%)</td>
<td>–</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1 (1.7%)</td>
<td>–</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>1 (1.7%)</td>
<td>–</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Lightheadedness</td>
<td>–</td>
<td>1 (1.7%)</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Status epilepticus</td>
<td>–</td>
<td>1 (1.7%)</td>
<td>1 (0.8%)</td>
</tr>
</tbody>
</table>

a Patients could have more than one adverse event.