Guideline of status epilepticus management 2017

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Guideline
Guideline of status epilepticus

- Initial treatment: pre-hospital; hospital
- Second step treatment
- Refractory status epilepticus
- Super-refractory status epilepticus
Guideline

Type of antiepileptic drugs and alternatives therapy
Initial or emergent or early status epilepticus

- Lorazepam [1, 2, 3, 4]
- Midazolam [2, 3, 4]
- Diazepam [1 (+PHT), 2, 3 (+PHT), 4]
- Phenytoin/fosphenytoin [1 (+DZP), 2, 4 (+DZP)]
- Phenobarbital [2, 3, 4]
- Valproate [1?, 2]
- Levetiracetam [2]

1 European Foundation Neurology Society 2010
2 American Neurocritical care Society and American epilepsy society 2012
3 American epilepsy society 2016
4 Hong Kong Epilepsy Society Society 2017
<table>
<thead>
<tr>
<th>AEDs</th>
<th>European Foundation Neurology Society 2010</th>
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</tr>
</thead>
<tbody>
<tr>
<td>Lorazepam</td>
<td>0.1 mg/kg (4 mg) 5 mg</td>
<td>0.1 mg/kg (4 mg) 0.15 mg/kg (10mg) 20 mg/kg add 5-10 mg/kg (10 min after loading) = PHT 20-40 mg/kg add 20 mg/kg 3-6 mg/kg/min</td>
<td>0.1 mg/kg (4 mg) 0.15-0.2 mg/kg (10mg)</td>
</tr>
<tr>
<td>Diazepam</td>
<td>5 mg + 18mg/kg</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Diazepam + Phenytoin</td>
<td>5 mg</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>-</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Valproate</td>
<td>-</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.1 mg/kg max. 10 mg</td>
<td>0.2 mg/kg max. 10 mg</td>
<td>10 mg IM; 5-10 buccal</td>
</tr>
</tbody>
</table>
Urgent, established Status epilepticus

- Valproate [2, 3, 4]
- Phenytoin/fosphenytoin [2, 4 (no document fosphenytoin)]
- Midazolam [2]
- Phenobarbital [2, 4]
- Levetiracetam [2, 3?, 4]

3American epilepsy society 2016

2American Neurocritical care Society and American epilepsy society 2012

4Hong Kong Epilepsy Society Society 2017
# Urgent or establish status epilepticus

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<tr>
<td>Phenytoin</td>
<td>20 mg/kg add 5-10 mg/kg (10 min after loading) (up to 50 mg/min)</td>
<td>15-20 mg/kg (up to 50 mg/min)</td>
</tr>
<tr>
<td>fosphenytoin</td>
<td>20 mg/kg add 5 mg/kg (10 min after loading) (up to 150 mg/min)</td>
<td>15 mg/kg (max rate 100 mg/min)</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>= PHT (50-100 mg/min)</td>
<td>40 mg/kg, max 3,000 mg (infusion &gt; 5-10 min)</td>
</tr>
<tr>
<td>Valproate</td>
<td>20-40 mg/kg add 20 mg/kg</td>
<td>-</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.2 mg/kg max. 10 mg</td>
<td>-</td>
</tr>
<tr>
<td>Levetiracetam</td>
<td>1-3 g IV (2-5 mg/kg/min)</td>
<td>60 mg/kg, max 4,500 mg/dose (infusion &gt;10 min)</td>
</tr>
</tbody>
</table>
Refractory Status epilepticus

- Midazolam [1, 2, 4]
- Propofol [1, 2, 4]
- Pentobarbital/thiopental [1, 2, 4]
- Lacosamide [2]
- Topiramate [2]

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## Initial or emergent or early status epilepticus

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<tr>
<td><strong>Midazolam</strong></td>
<td>0.2 mg/kg (maintenance 0.05-4 mg/kg/h)</td>
<td>0.2 kg/kg (initial rate 2 mg/min) (maintenance 0.05-2 mg/kg/hr increase CI 0.05-0.1 mg/kg/hr q 2-4 h)</td>
<td>0.1-0.2 mg/kg (maintenance 0.05-3 mg/kg/h)</td>
</tr>
<tr>
<td><strong>Propofol</strong></td>
<td>2-3 mg/kg bolus 1-2 mg/kg (maintenance 4-10 mg/kg/h)</td>
<td>1-2 mg/kg (initial rate 20 mcg/kg/min) (maintenance 30-200 mcg/kg/hr ถ้าให้นานกว่า 48 ห ระวังไม่ควรเกิน 80 mcg/kg/min)</td>
<td>3-5 mg/kg (maintenance 2-15 mg/kg/h)</td>
</tr>
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<tr>
<td>Thiopental</td>
<td>3-5 mg/kg bolus 1-2 mg/kg q 2-3 min (maintenance 3-7 mg/kg/h)</td>
<td>2-7 mg/kg (&lt; 50 mg/min) (maintenance 0.5-5 mg/kg/h) Increase CI 0.5-1 mg/kg/h q 12 h with bolus 1-2 mg/kg</td>
<td>2-3 mg/kg (maintenance 3-5 mg/kg/hr)</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>5-10 mg/kg (&gt; 1 hr) (maintenance 0.5-1 mg/kg/h Increase 1-3 mg/kg/hr)</td>
<td>5-15 mg/kg add 5-10 mg/kg (&lt; 50mg/min) (maintenance 0.5-5 mg/kg/h) Increase CI 0.5-1 mg/kg/h</td>
<td>-</td>
</tr>
</tbody>
</table>
Guideline: Super-refractory

- Ketamine
  - 1-3 mg/kg CI up to 5 mg/kg/hr
  - [4]

- Immunotherapy: methylprednisolone
  - 1g/d 3-5 d
  - IVlg
  - 0.4 g/kg/d x 5 d
  - [4]

- Ketogenic diet
  - [4]

- Magnesium
  - 2-6 g/h (obtain serum level 3.5 mmol/L)
  - [4]

- Pyridoxime (young children)
  - [4]

- Hypothermia
  - [4]

- Lacosamide
  - [4]

- Electroconvulsive therapy
  - [4]

- Epileptic surgery
  - [4]

*Hong Kong Epilepsy Society Society 2017*
คำถาม

- Lorazepam ดีกว่า diazepam จริงหรือ
- Second-line treatment status epilepticus: LEV vs. PHT vs VPA
- การศึกษาของ valproate พบว่าดีกว่า phenytoin ในการรักษาแบบ first line นอกจากนี้พบว่าเมื่อ failure ต่อ phenytoin แล้ว มาใช้ valproate จะได้ผลดีกว่าเมื่อ failure ต่อ valproate แล้วมาใช้ phenytoin (25% vs. 71%)
- ความแตกต่างของ efficacy ระหว่างยาที่ใช้รักษาผู้ป่วย benzodiazepine resistance status epilepticus ?
- lacosamide มีข้อมูลที่สามารถนำมาใช้ใน guideline ได้หรือยัง
Is IV LZP more efficacy than DZP or MZP as a first-line treatment status epilepticus

- Basic knowledge of pharmacokinetics
- Study population
- Pre-hospital or hospital treatment
- Outcome of study: the proportion of patients with clinical seizure cessation
Is IV LZP more efficacy than DZP or MZP as a first-line treatment status epilepticus: Meta-analysis

- Seizure cessation: RR 0.64; 95% CI 0.45-0.90  
  Prasad et al. Cochrane Database Syst Rev 2014;9 CD003723

- RR 1.09; 95% CI 1.00-1.20  
Is IV LZP more efficacy than DZP or MZP as a first-line treatment status epilepticus: Meta-analysis


Continuation of SE requiring a different drug

Seizure cessation after a single dose of medication
Meta-analysis outcome

PHT VS. VPA. LEV

Direct comparison
- PHT VS. VPA: OR 1.07 95% CI 0.57-2.03 \( (I^2 = 0) \)
- PHT VS. LEV: OR 1.18 95% CI 0.50-2.78 \( (I^2 = 26\%) \)

Indirect comparison
- LEV VS. VPA: OR 1.16 95% CI 0.45-2.97\%
Absence of evidence of a statistically significant difference in seizure control between LEV and VPA or between VPA or LEV and PHT

This finding is not synonymous with evidence of no evidence
the critical difference in the response 20%, the efficacy of PHT 40%
The sample size calculate = 85% (the power of the test 90%
Recruit 68 patients power of the test 71%
Overall, in 3 of 36 children (age range 4 weeks–17 years), side effects were described; however, no serious adverse events occurred in the studies in pediatric patients, suggesting that LCM seems to be a safe and efficacious treatment option in SE in pediatric patients.

### Overall Efficacy of LCM in SE

In total, 522 episodes of SE in 486 adults and 36 minors could be extracted from the literature, including the data already evaluated by Höfler and Trinka. Efficacy data were available for a total of 471 episodes (51.7% female). Overall LCM efficacy was 57%, which is similar to the efficacy ranged from 100% to 50% with 92% (34/39) overall, which seems better than in GCSE (p = 0.013) and NCSE (p < 0.001).

LCM is currently not approved for use in SE. Consequently, most studies used LCM as an adjunctive therapy in patients with refractory SE. This impacts the evaluation of LCM efficacy and may have led to an underestimation of the efficacy of LCM in SE treatment. AEDs are commonly less effective in terminating SE when they are afforded a later position in the succession of anticonvulsive drugs, which is reflected in the findings from several studies. The efficacy with later positioning decreased from 60% to 20%, 100% to 75%, 84.6% to 55.6%, and 72.2% to

- Retrospective study > prospective study
- Small study population
- Adjunctive therapy (4-5 AEDs)
A randomized controlled trial of lacosamide versus sodium valproate in status epilepticus

Usha K. Misra, Deepanshu Dubey, and Jayantee Kalita

Epilepsia, 58(5):919–923, 2017
doi: 10.1111/epi.13706

SUMMARY

Objective: To compare the efficacy and safety of lacosamide (LCM) and sodium valproate (SVA) in lorazepam (LOR)–resistant status epilepticus (SE).

Methods: Patients with LOR-resistant SE were randomized to intravenous LCM 400 mg at a rate of 60 mg/kg/min or SVA 20 mg/kg at a rate of 100 mg/min. The SE severity score (STESS), duration of SE and its etiology, and magnetic resonance imaging (MRI) findings were noted. Primary outcome was seizure cessation for 1 h, and secondary outcomes were 24 h seizure remission, in-hospital death and severe adverse events (SAEs).

Results: Sixty-six patients were included, and their median age was 40 (range 18–90) years. Thirty-three patients each received LCM and SVA. Their demographic, clinical, STESS, etiology, and MRI findings were not significantly different. One hour seizure remission was not significantly different between LCM and SVA groups (66.7% vs. 69.7%; p = 0.79). Twenty-two seizure freedom was higher in SVA (20, 66.6%) compared with LCM group (15, 45.5%), but this difference was not statistically significant. Death (10 vs. 12) and composite side effects (4 vs. 6) were also not significantly different in LCM and SVA groups. LCM was associated with hypotension and bradycardia (one patient) and SVA with liver dysfunction (six patients).

Significance: In LOR-resistant SE patients, both LCM and SVA have comparable efficacy and safety. SVA resulted in slightly better 24 h seizure remission.

KEY WORDS: Status epilepticus, Lacosamide, Sodium valproate, Antiepileptic drug, Adverse events, Mortality.
แนวทางการรักษาในเป็นเครื่องมือส่งเสริมคุณภาพในการบริการด้านสุขภาพที่เหมาะสมกับทุกยาง และมีประโยชน์ต่อสุขภาพของคนไทยอย่างมีประสิทธิภาพและคุ้มค่า ข้อเสนอแนะต่าง ๆ ในการดูแลสุขภาพตั้งแต่ ไม่ใช้ยาขัดบังคับของการปฏิบัติตามใช้ยาตามที่ปรากฏปฏิบัติแตกต่างไปจากข้อแนะนำโดยไม่เก็บค่าทำสิ่งที่สุขภาพน่ายังแตกต่างออกไปหรือมีเหตุผลที่สมควรโดยใช้วิเคราะห์ฐานที่เป็นที่ยอมรับในสังคม