Role of new antiepileptic medications in status epilepticus?"

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Status epilepticus

► Continuous or rapidly repeating seizures
  ■ Seizure that persists for a sufficient length of time
  ■ Repeated frequently enough that recovery between attacks does not occur.

► More recent publication
  ■ Seizures that persist for 20-30 min “neuronal injury”
  ■ Should begin Rx for status epilepticus
    ► Before 20 minutes
    ► Isolated GTC rarely last more than a few minutes

Coeytaux A. Neurology 2000
DeLorenzo R.J. Neurology 1996
Hesdorffer DC. neurology 1998
Knake S. Epilepsia 2001
Status epilepticus

- One of the most common neurologic emergencies

- New definition of status epilepticus should
  - Continuous seizures lasting > 5 min
  - > 2 discrete seizures which incomplete recovery of consciousness

- Burden
  - 3 million people throughout the world per year
  - Estimates of the overall incidence ~ 10 to 60 per 100,000 person-years
  - A life-threatening condition
    - Associated with high morbidity and mortality (Overall mortality ~ 20%)
    - esp. generalized convulsive status epilepticus

- Cause of death
  - Underlying condition > status epilepticus

- Prognosis related to
  - Aetiology
  - Age (higher mortality in elderly)

- Controlled clinical trial: difficult to conduct
Definition

► Refractory status epilepticus

- severe form of SE that does not respond to first (benzodiazepines) and second (phenytoin, phenobarbital) treatment efforts with antiepileptic drugs (AEDs)

- Seizure continuing after 30 min of treatment above

Ferlisi M et al. Brain 2012

Definition

► Super-refractory status epilepticus

- status epilepticus that continues or recurs 24 h or more after the onset of anaesthetic therapy, including those cases where status epilepticus recurs on the reduction or withdrawal of anaesthesia

Ferlisi M et al. Brain 2012
Phases of status epilepticus

Stage 1 - Early Status Epilepticus
Treat with benzodiazepines - for instance IV lorazepam, buccal midazolam, IV or rectal diazepam

Stage 2 - Established Status Epilepticus
Treat with IV antiepileptic drugs - for instance, phenytoin, phenobarbital or valproate

Stage 3 - Refractory Status Epilepticus
Treat with general anaesthesia – for instance, propofol, midazolam, or thiopental/pentobarbital

Super-refractory Status Epilepticus: Status epilepticus which has continued or recurred despite therapy with general anaesthesia for 24 hours or more
General concepts for status Rx

► Emergency treatment

- Life support measures
- Identification and treatment of the underlying cause
- Rapid institution of intravenous antiepileptic drugs (AEDs)

Cause: acute process

► Metabolic disturbances

- Electrolyte abnormalities
- Renal failure
- Sepsis

► Central nervous system

- Infection
- Stroke
- Head trauma
- Drug toxicity
- Hypoxia
### Acute process: CNS

- Often difficult to control
- Associated with a higher mortality
- Especially after hypoxia and in older patients
- Myoclonic status epilepticus after hypoxia
  - Grave prognosis

### Cause: chronic process

- Breakthrough seizures
- Discontinuation of antiepileptic drugs
- Chronic ethanol abuse
- CNS tumors or strokes

* Respond well to anticonvulsant Rx*
Principles of Drug Treatment

► Goal of Rx

▪ Antiepileptic drugs

► Easy to use
► Immediate or rapid action
► A long-lasting antiepileptic effect
► Minimal cardiopulmonary and other side-effects
► Prompt cessation of seizure activity
Refractory status epilepticus (RSE)

- An emergency
  - A risk of physiological compromise, neuronal damage
  - Progressive drug resistance, ICU for early anesthesia

- Prolonged ICU and hospital stays
  - Requiring
    - neurointensive care
    - aggressive management (therapeutic coma)
    - multiple antiepileptic drugs (AEDs)
    - continuous infusions of propofol, midazolam, or pentobarbital, ketamine, inhalational anaesthetics (isoflurane, desflurane)

- Prognosis: poor, mortality 48%, morbidity 70%
Mechanism of drug resistance in status epilepticus

► From rat models SE>30 minutes

- Progressive alterations of GABAA receptors, including reduced surface expression of these receptors by receptor trafficking, which would explain the loss of efficacy of benzodiazepines

- SE-induced overexpression of drug efflux transporters, such as P-glycoprotein (Pgp), in the brain may be involved in the resistance to AEDs (including phenytoin and phenobarbital) that are Pgp substrates

Loscher W. Epilepsia 2007

Figure 2. Cartoon summarizing our model of the role of receptor trafficking in the transition from single seizures to status epilepticus (SE). After repeated seizures, and massive γ-aminobutyric acid (GABA) release, the synaptic membrane of GABA$_A$ receptors forms clathrin-coated pits (C), which internalize. This inactivates the receptors, which are no longer within reach of the neurotransmitter. These vesicles evolve into endosomes (E), and reach a phosphorylation-dependent decision point where they are transported toward the soma to lysosomes (L), where the receptors are destroyed, or to the Golgi apparatus (G) from where they are recycled to the membrane.

Epilepsia ©ILAE
Traditional AEDs

- Current standard treatment of established status epilepticus after failure of benzodiazepines is intravenous phenytoin/fosphenytoin, phenobarbital, or valproate

- If RSE → cIV-AED: Pentobarbital, midazolam, propofol
  - Titration goal "seizure suppression" or "EEG background suppression"
  - EEG background suppression, may be more effective but increase frequency of hypotension,
  - No effect on mortality


Side effect of standard treatment

- Respiratory depression
- Hypotonia
- Cardiac arrhythmia
- Pharmacokinetic interactions
  - Inducer or inhibitor for hepatic enzymes
New antiepileptic drugs in status epilepticus

► Alternative treatment of refractory status epilepticus (RSE)

► No prospective randomized studies

► Levetiracetam, pregabalin, topiramate, lacosamide

Evidence-based

New antiepileptic drugs in the treatment of status epilepticus

► Oral topiramate

► Oral and intravenous levetiracetam

► Intravenous lacosamide

► Pregabalin
Topiramate

- A potent broad-spectrum AED
- Several modes of action
  - Blockade of sodium channels
  - Enhancement of GABAergic transmission
  - Antagonism of alpha amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA)/kainate receptors
- An adjunctive treatment in RSE
- No commercially available intravenous formulation

Selvitelli & Drislane, 2007
<table>
<thead>
<tr>
<th>N</th>
<th>Bolus</th>
<th>Dose/d</th>
<th>Efficacy</th>
<th>Safety</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 RSE</td>
<td>300-1,600</td>
<td>good</td>
<td>Lethargy, no SAE</td>
<td>Towne AR. Neurology 2003</td>
<td></td>
</tr>
<tr>
<td>3 RSE children</td>
<td>2-3 mg/Kg</td>
<td>5-6 MKD</td>
<td>Terminate all in 24 hours</td>
<td>Kahrirman M. Epilepsia 2003</td>
<td></td>
</tr>
<tr>
<td>3 RSE</td>
<td>500 mg BID for 2-5 d</td>
<td>200 mg BID</td>
<td>2/3</td>
<td>Bensalem MK, Epilepsy Behav 2003</td>
<td></td>
</tr>
<tr>
<td>3 RSE children</td>
<td>10 mg/Kg (x2d)</td>
<td>5 MKD</td>
<td>Aborted in 21 h after initial dose</td>
<td>Epilepsia. 2006</td>
<td></td>
</tr>
<tr>
<td>14 RSE children</td>
<td>5 mg/Kg</td>
<td>5 MKD (x2d)</td>
<td>5.5 h (2-48 h) 9 full responders 3 partial responders 2 non-responders</td>
<td>X3 mild metabolic acidosis Akyildiz BN. Childs Nerv Syst 2011</td>
<td></td>
</tr>
<tr>
<td>6 GCSE, 7 NCSE With medical co-morbidity</td>
<td></td>
<td>100% in 3.7 days</td>
<td>No AE</td>
<td>Kim W. J Epilepsy Res 2011</td>
<td></td>
</tr>
<tr>
<td>35/113 RSE Rx in 2 days</td>
<td>Up to 800 mg/ d</td>
<td>71% in 72 h 3rd-86% 4th+-67% Mortality 31% (~etiology)</td>
<td>No SAE</td>
<td>Hottinger A. CNS Drug 2012</td>
<td></td>
</tr>
<tr>
<td>35 RSE</td>
<td></td>
<td></td>
<td>No AE</td>
<td>Szyrowiec AS. Epilepsy Res 2012</td>
<td></td>
</tr>
</tbody>
</table>

Oral and intravenous levetiracetam in SE
Levetiracetam

► A wide spectrum of action
► Good tolerability and a favorable pharmacokinetic profile
► Easy to use and administration and limited side effects
► Effectiveness in the treatment of focal and generalized epilepsies
► LEV may safely be used in porphyria

Levetiracetam

► The mechanism of action of LEV is poorly understood

- Alters glutamatergic neurotransmission
- Delayed rectifier channels and N- and P/Q-type calcium Channels
- Reduces the calcium release from intraneuronal stores
- The synaptic vesicle protein 2A (SV2A)
- Inhibits HVA-Ca2 channels (N-type)
- Reverses the inhibition of negative allosteric modulators such as zinc and beta-carbolines of GABA- and glycine-gated currents

Surges et al., 2008
LEV in status epilepticus

► Several reports of levetiracetam in animal models
  ▪ Possible efficacy in experimental models of SE

► Human studies
  ▪ Open-label experience in reported cases or retrospective case series are accumulating
  ▪ No randomised controlled studies (class I or II) in this field
  ▪ Firstly used the oral formulation
  ▪ Most often applied via a nasogastric tube

Ramael S. Clin Ther 2006, Ramael S. Epilepsia 2006
Baulac M. Epilepsia 2005, Baulac M. Epilepsia 2007

Oral LEV in status epilepticus

► 58 patients reported in 13 case reports or case series

► Various forms of SE

► Oral LEV (500-9,000 mg/day)
  ▪ The most often used effective dose was 2,000-3,000 mg/day.

► Responder rates of 69% (43-100%) within 12 hours to 4 days after onset

► Adverse events (n = 3)
  ▪ Somnolence, dizziness

Ramael S. Clin Ther 2006, Ramael S. Epilepsia 2006
Baulac M. Epilepsia 2005, Baulac M. Epilepsia 2007
Intravenous levetiracetam

- Available 2006, approval for the treatment of patients with epileptic seizures who are temporary unable to swallow
  - It has been widely used since its availability to treat all forms of acute seizures and status epilepticus
  - Bioequivalent to the oral preparation
- IV levetiracetam was administered over a period of 15-30 minutes; each 500 mg of levetiracetam was diluted in 100 mL of normal saline
- Well tolerated even at higher doses and/or at faster infusion rates
- Non-randomised, uncontrolled open-label experience in retrospective case series is accumulating.

Ramael et al. 2006

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<th>Dose/d</th>
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</tr>
</thead>
<tbody>
<tr>
<td>6 RSE</td>
<td></td>
<td>500 - 3000</td>
<td>Good control in 12-36 h</td>
<td>No SAE</td>
<td>Patel NC, Seizure 2006</td>
</tr>
<tr>
<td>16 (focal +/- sec gen)</td>
<td></td>
<td></td>
<td>Good</td>
<td>No SAE</td>
<td>JNNP 2008</td>
</tr>
<tr>
<td>156</td>
<td>2,000-3,000 in 15 minutes</td>
<td>85.4</td>
<td>Adverse events</td>
<td>7.1% (mild and transient)</td>
<td>Gorny 2008; Ruepp 2008; Kraupe 2007; Schulze-Bonhage A. JNNP 2007; Kraupe S. JNNP 2008</td>
</tr>
<tr>
<td>34 RSE (92% focal)</td>
<td>1,000</td>
<td>2,000 (1,000-3,000)</td>
<td>71%</td>
<td>No AE</td>
<td>Games-Leyva G. CNS Drugs 2005</td>
</tr>
<tr>
<td>32 (20 NCSE) Rx in 6 h</td>
<td>2,000</td>
<td>3,500</td>
<td>Good 23/32</td>
<td>Not improve 7/32</td>
<td>1 n, v 1 abn LFT (on VPA)</td>
</tr>
<tr>
<td>11 RSE children</td>
<td>30 mg/Kg</td>
<td>40 mg/kg/day</td>
<td>45% (5/11) in 1.5 days (1-4 days)</td>
<td>No SAE</td>
<td>Gallentine WB. Epilepsy Behav 2010</td>
</tr>
<tr>
<td>36</td>
<td>500-2000 in 1 h</td>
<td>3000 (1000-9000)</td>
<td>89% responder (assoc with loading dose) Mortality 17% (Responder 4%, non-responder 45%)</td>
<td>No SAE</td>
<td>Moulder G. JNNP 2009</td>
</tr>
<tr>
<td>40 (90% partial sei)</td>
<td></td>
<td></td>
<td>97.5% in 14.4 h</td>
<td>Mild AE 15%</td>
<td>Algabeha M. Seizure 2011</td>
</tr>
<tr>
<td>707</td>
<td>2,000-3,000 in 15 minute</td>
<td>78%</td>
<td>&lt;10% (mild and transient)</td>
<td></td>
<td>Eugen Trinka. Epilepsia, 2011</td>
</tr>
<tr>
<td>34 Thai'</td>
<td></td>
<td></td>
<td>61.6% (- co-morbidity)</td>
<td></td>
<td>Thongdee S. Neurology Asia 2013</td>
</tr>
</tbody>
</table>
Levetiracetam versus lorazepam in SE

► A randomized, open labeled pilot study. N 79 patients

► Comparing the efficacy and safety of LEV and LOR in convulsive or subtle convulsive SE

► IV LEV 20 mg/kg IV over 15 min or LOR 0.1 mg/kg over 2-4 min

► Failure to control SE within 10 min of administration of one study drug was treated by the other study drug.

► Primary endpoint was clinical seizure cessation

► Secondary endpoints were 24 h freedom from seizure, hospital mortality, and adverse events


Levetiracetam versus lorazepam in SE

► Result

► LEV and LOR were equally effective

► SE was controlled
  ► LEV in 76.3% (29/38)
  ► LOR in 75.6% (31/41)

► In those resistant to the above regimen, controlled SE
  ► LEV in 70.0% (7/10)
  ► LOR in 88.9% (8/9) patients.

► The 24-h freedom from seizure was also comparable
  ► LEV in 79.3% (23/29)
  ► LOR in 67.7% (21/31)

Levetiracetam versus lorazepam in SE

► Side effect
  ▪ LOR was associated with significantly higher need of artificial ventilation and insignificantly higher frequency of hypotension

► Conclusion
  ▪ For the treatment of SE, LEV is an alternative to LOR and may be preferred in patients with respiratory compromise and hypotension.


Lacosamide
Lacosamide

► A functionalized amino acid with anticonvulsant properties

► Mechanism of action
  ▪ A novel dual mechanism of action
    ► Selective enhancement of sodium channel slow inactivation
    ► Modulation of collapsin response mediator protein (CRMP)-2 activity

► Available 2008, for adjunctive treatment of partial onset epilepsies

Beyreuther et al., 2007

Lacosamide

► Approval from the European Medicines Agency (EMEA) as adjunctive treatment for refractory partial-onset seizures

► IV bioequivalence to the oral formulation

► No sedating effects

► A potent treatment option for RSE

► intravenous (i.v., 10 mg/ml) LCM as an add-on treatment in adult RSE patients

Beyreuther et al., 2007
<table>
<thead>
<tr>
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<th>Dose/d</th>
<th>Efficacy</th>
<th>Safety</th>
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</thead>
<tbody>
<tr>
<td>126 SE+other</td>
<td>400</td>
<td>200–400</td>
<td>67%</td>
<td></td>
<td>Beyreuther. 2007</td>
</tr>
<tr>
<td>9 RSE Initiate in 0-14 d (X 2 d)</td>
<td>200</td>
<td>200 mg q 12 h</td>
<td>No</td>
<td>2 angioedema 3 withdrawn</td>
<td>Goodwin H. Neurocrit Care 2011</td>
</tr>
<tr>
<td>7 RSE</td>
<td>100% in 24 hours</td>
<td>No AE</td>
<td></td>
<td></td>
<td>Alber JM. Seizure 2011</td>
</tr>
<tr>
<td>31/48 SE</td>
<td>200 (200–400)</td>
<td>88% 1st or 2nd, 100% 3rd - 81%, 4th - 75%</td>
<td>No serious AE 2 skin rash and pruritus</td>
<td>Hofler J. Epilepsia 2011</td>
<td></td>
</tr>
<tr>
<td>4 NCSE</td>
<td>Good</td>
<td>No AE</td>
<td></td>
<td></td>
<td>Koubeissi MZ. Acta Neurol Scand 2011</td>
</tr>
<tr>
<td>9 RSE</td>
<td>50-100</td>
<td>20% (~ age)</td>
<td></td>
<td></td>
<td>Rantsch K. Seizure 2011</td>
</tr>
<tr>
<td>53% of 111 RSE</td>
<td>Good (OR 2.34)</td>
<td>30% Mortality Reduce (OR0.34)</td>
<td>No serious AE</td>
<td>Sutter RI. NS Drugs 2013</td>
<td></td>
</tr>
<tr>
<td>136 RSE</td>
<td>200-400 in 3-5 min</td>
<td>56% (76/136)</td>
<td>25% Mild sedation 1 angioedema 1 arrhythmia</td>
<td>Hofler J. Epilepsia 2013</td>
<td></td>
</tr>
</tbody>
</table>

Pregabalin
Pregabalin

► 21 patients with non-convulsive seizures and non-convulsive status epilepticus

► Criteria
  ▪ Effective = terminate seizure within 24h of initiation of PGB without the addition of another antiepileptic agent

► via a nasogastric tube, the 2nd to 4th agent used

► The average initial dose and total daily dose of PGB 342mg

Swisher CB et al. Seizure 2013

Pregabalin

► 11/21 (52%) were responders
  ▪ aborting NCS (9 patients, 82%)
  ▪ Aborting NCSE (2 patients, 18%)

► All patients with hypoxic injury (4) did not respond to PGB

► The responders were noted to have better clinical outcome (64% vs. 9% discharged home)

► Side effect: 2 dizziness and sedation

Swisher CB et al. Seizure 2013
Pregabalin

- 11 SE episodes (10 patients) treated with PGB
- Mostly had refractory, partial SE
- A definite electroclinical response in 5 of 11, already evident 24 h after PGB introduction
  - NB: a possible response (concomitantly with other AEDs) in 3 of 11 of the episodes
- 3/11 did not respond
- Well tolerated

Novy J et al. Epilepsia 2010

Summary (1)

- Identify causes of status epilepticus and address them
- Standard Rx
  - lorazepam, phenytonin, fosphenytoin, valproic acid, phenobarbital
- Anaesthetic agents
  - thiopental, pentobarbital, midazolam, propofol
  - inhalational anaesthetics (isoflurane, desflurane)
- Anti-epileptic drugs
  - topiramate, lacosamide, pregabalin, levetiracetam
Summary (2)

► Other options
  - ketamine: blocks NMDA receptor, which is over-expressed in prolonged SE
  - hypothermia, ketogenic diet
  - magnesium infusion, pyridoxine, steroids and immunotherapy.
  - emergency resective neurosurgery and multiple subpial transection
  - transcranial magnetic stimulation, electroconvulsive therapy
  - vagal nerve stimulation, deep brain stimulation
  - trigeminal nerve stimulation, drainage of the cerebrospinal fluid

Summary (3)

New AEDs in status epilepticus

► Enteral or parenteral
  - Improve outcome, low or non-related side effect

► Evidence based: NO RCT with some publication biases
  - Case reports
  - Case series
  - Retrospective chart review
  - Non randomized open label head-to-head study
  - Randomized open label label head to head (pilot) study

► Third line treatment (add-on treatment), ? 2nd line

► Future direction: ??large control (head-to-head) study
Thank You