The Management of Status Epilepticus

4th East Mediterranean Epilepsy Congress,
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Dr Aidan Neligan PhD MRCP
HUH and NHNN
Why treat seizures urgently?

Two physiological points

New approaches to treatment of acute seizures and the stage of early SE
Key points in emergency drug treatment of seizures

- Short seizures do not carry risk of brain damage
- Drug treatment is not usually needed to terminate a normal seizures, as most seizures are self limiting
- A prolonged seizure carries the risk of evolving to status epilepticus and status epilepticus carries risks of brain damage
- Time is therefore crucial – TIME IS BRAIN
Time is brain - excitotoxic cerebral damage

Rat hippocampus – control

Rat hippocampus – 3 hrs of status epilepticus, terminated with diazepam and examined 3 weeks later
- Excitotoxic damage
- Due to electrographic activity
- Initiation after 1-2 hrs
- Processes progress over weeks
Progressive Brain Atrophy in Super-refractory Status Epilepticus

Sara Hocker, MD; Elanagan Nagarajan, MD; Alejandro A. Rabinstein, MD; Dennis Hanson, MA; Jeffrey W. Britton, MD

Figure 2. Association of Duration of Anesthetic Agent Use and Change in Vetricular Brain Ratio (ΔVBR)

The diagonal line represents the linear correlation of the duration of anesthetic agent use and the development of brain atrophy. Data points represent the 19 individual patients. See the Methods section for an explanation of how ΔVBR is calculated.
Risk of seizures: loss of drug efficacy over time

Tonic-clonic status epilepticus is a dynamic condition - One consequence is the loss of effect of GABAergic drugs over time

- Classic experiment showed, in rat model of SE, a 10 fold greater dose of diazepam is needed to control seizures lasting 45 mins, compared to those lasting 10 mins

(Kapur & Macdonald Neurosci 1997 17: 7532; 6)
- **GABA receptor trafficking**

- Rapid (minutes)

- Activity dependent (ie in seizures)

- Responsible for development of GABAergic drug resistance?
Staged protocol for the treatment of Tonic Clonic Status Epilepticus (SE) – and importance of early therapy

Stage 1: **Prodromal/early SE**  
Usual treatment - benzodiazepine: CLZ, DZP, LZP  
New therapies - out of hospital new routes of admin

⇒

Stage 2: **Established SE**  
Usual treatment - PHT or PB (or VPA or LEV)

⇒

Stage 3: **Refractory super/ refractory SE**  
Usual treatment - general anaesthesia
Current evidence base: stage 1 – early status epilepticus

- Lorazepam 4 mg (IV bolus; rate not critical), can be repeated after 10 mins if no response
- Diazepam 10-20mgs (IV bolus; not more than 5mg/min; can be repeated after 10 mins if not response)

In-hospital IV therapy in early SE
- Lorazepam vs diazepam – 3 RCTs (n=289)
- Lorazepam vs placebo – 1 RCT (n=137)
- Lorazepam vs diazepam/phenytoin – 1 RCT (n=192)
- Diazepam vs placebo – 1 RCT (n=139)

Conclusions (10 RCTs)
1. DZP and LZP are better than placebo
2. LZP may be better than DZP (2 out of 3 measures)
RCT comparing lorazepam, diazepam and placebo

• In out-of—hospital treatment: Study from San Francisco; 205 adult patients randomised to lorazepam 2mg, diazepam 5mg or placebo

(From: Alldredge et al NEJM 2001 345: 631)
• New out-of-Hospital routes of administration and therapies
  - Midazolam: buccal, IN, IM routes
  - Diazepam: IN
  - Lorazepam: IN
  - Propofol: Intrapulmonary
  - Other strategies
Out-of-hospital treatment with midazolam

- **Midazolam**
  - The only water soluble benzodiazepine but must be buffered at pH 3 to go into solution.
  - In an acidic solution, midazolam mainly in an open-ring form.
  - At physiological pH, exists mainly in closed-ring form.
  - Therefore, the drug is water soluble for injection facilitating rapid absorption over mucous members, and lipid soluble in the circulation facilitating rapid entry into the brain.
  - Licensed in EU in Nov 2011 PUMA programme.
Buccal midazolam: Pharmacokinetic (PK) profile of midazolam HCL in children (3 months - 18 years)

Buccal midazolam as effective as rectal diazepam in time to seizure cessation from drug administration

- Prolonged seizure in 42 patients aged 5–19 years
  
  (median time = 6 min [IQR 4-10] for BM and 8 min [4-12] for RD; p=0.31)

(Scott RC et al., Lancet 1999; 353: 623-26)
RCT: buccal midazolam v. rectal diazepam in children

- Multicentre RCT - buccal midazolam v. rectal diazepam 0.5mg/kg (approx). 219 episodes

<table>
<thead>
<tr>
<th>OUTCOME</th>
<th>MDZ</th>
<th>DZP</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=109)</td>
<td>(n=110)</td>
</tr>
<tr>
<td>Seizure control (within 10 mins)</td>
<td>56%</td>
<td>27%</td>
</tr>
<tr>
<td>Time to seizure control (median)</td>
<td>8 mins</td>
<td>15 mins</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>5%</td>
<td>6%</td>
</tr>
<tr>
<td>Required additional therapy</td>
<td>33%</td>
<td>57%</td>
</tr>
</tbody>
</table>

- Conclusion – buccal midazolam is more effective than rectal diazepam

Proprietary formulations of buccal midazolam
- Epistatus®
- Buccolam®
RAMPART study (Rapid Anticonvulsant Medication Prior to Arrival Trial)

- Academic-originated study - NIH funded
- IM midazolam v. IV lorazepam in out-of-hospital in seizures of ≥ 5mins in duration
- Treatment by paramedics
- Dose - adults 10mg MDZ .v. 4mg LZP (children – dosed by weight)
- Double blinded RCT, non-inferiority design
- Dummy design with IM autoinjectors, and IV injections in all patients
- Assume 70% response rate on lorazepam, hypothesis 10% difference (90% power, 5% significance)
- Target - 1024 subjects

RAMPART study

Value of network (and quality of academic leadership)

- Recruitment rate exceeds expectation!
- NETT
  - 17 Hub sites
  - 112 Spokes (EMS agencies & regional hospitals)
  - 4000 paramedics
- Across whole of United States
Intramuscular (IM) MDZ versus intravenous (IV) LZP therapy for pre-hospital status epilepticus

- Intervals between active treatment and cessation of convulsions, box opening and cessation of convulsions, and box opening and active treatment

Rampart study: IM midazolam v. IV lorazepam

- 893 subjects in an double blind RCT
- By time of arrival at ER, seizures were absent in 73% of IM MDZ v. 63% of IV LPZ (ns difference)
- 14% of both group required intubation
- 11% recurrence of seizures in both groups

- Two drugs show similar effects
- Shorter time of drug administration by IM route offset by slightly faster speed of action after IV administration

(Silbergleit et al NEJM 2012; 366:591-600)
Intranasal midazolam: is this the future?

- Nasal mucosa is richly vascular – rapid absorption of water soluble substances of small molecular weight
- Avoids hepatic first pass through liver
- ‘Nose-brain’ pathway – [CSF] can exceed [Blood]
- Spray or atomised pump – no need for active inhalation
- Position of head not important
- Pharmacokinetics (Rey et al Eur J Clin Pharm 1991)
  - Tmax 12 mins
  - Half life 2.2 hrs
  - Absolute bioavailability 55%
- Long experience of safety as used as a sedative in dental and other anaesthesia (since 1988) in children and adults. (Wilton et al Anesthesiology 1988)
- Low incidence of side-effects
Intranasal midazolam - is this the future?

- Intranasal midazolam used in acute seizures since 2000
- Scheepers et al (2000): 22 pts, 84 episodes, 94% success
  Dose: 5mg if <50kgs and 10mg >50kgs
- 4 studies compare IN midazolam with rectal diazepam
  3/4 showed IN midazolam to be more effective
- 4 studies compare IN midazolam with IV diazepam
  All showed that time to control was faster with IN and similar control rates 65-100%
- Prior respiratory infection had no effect on results
- Risk of respiratory depression very low
  - Supplementary oxygen required in 4%
  - Intubation required in 1%

intranasal midazolam versus rectal diazepam: Time from treatment administration to seizure cessation:

- Intranasal midazolam versus rectal diazepam for the home treatment of acute seizures in paediatric patients with epilepsy

(difference, 1.3 min; 95% CI, 0.0–3.5; P = 0.09)

(Holsti H et al., Arch Pediatr Adolesc Med 2010; 164 (8): 747–753)
IN midazolam: USL261 or intravenous solution in normal Subjects (Bancke LL et al Epilepsia 2015: 56: 1723)

Tmax 10–12 min)
Dose related pharmacodynamic effects
Intranasal administration of midazolam

Full Nasal Kit - Store in one place

Connect Atomizer

Connect tightly with twisting motion
Prehospital treatment with levetiracetam plus clonazepam or placebo plus clonazepam in status epilepticus (SAMUKeppra): a randomised, double-blind, phase 3 trial

Vincent Navarro, Christelle Dagron, Caroline Elie, Lionel Lamberth, Sophie Demeret, Saik Urien, Kim An, Francis Bolgert, Jean-Marc Telkuyr, Michel Baulac, Pierre Carli, for the SAMUKeppra investigators

Summary

Background Generalised convulsive status epilepticus (GCSE) should be treated quickly. Benzodiazepines are the only drug treatment available so far that is effective before admission to hospital. We assessed whether addition of the antiepileptic drug levetiracetam to the benzodiazepine clonazepam would improve prehospital treatment of GCSE.

Methods We did a prehospital, randomised, double-blind, phase 3, placebo-controlled, superiority trial to determine the efficacy of adding intravenous levetiracetam (2.5 g) to clonazepam (1 mg) in treatment of GCSE in 13 emergency medical service centres and 26 hospital departments in France. Randomisation was done at the Paris Descartes Clinical Research Unit with a list of random numbers generated by computer. Adults with convulsions lasting longer than 5 min were randomly assigned (1:1) by prehospital physicians to receive levetiracetam or placebo in combination with clonazepam. All physicians and paramedics were masked to group assignments. If the status epilepticus lasted beyond 5 min after drug injection, a second dose of 1 mg clonazepam was given. The primary outcome was cessation of convulsions within 15 min of drug injection. We analysed the modified intention-to-treat population that had received at least one injection of clonazepam and levetiracetam or placebo, excluding patients without valid consent and those randomised more than once. The trial is registered at EudraCT, number 2007-005782-35.

Findings Between July 20, 2009, and Dec 15, 2012, 107 patients were randomly assigned to receive placebo and 96 were assigned to receive levetiracetam. The trial was discontinued on Dec 15, 2012 when interim analysis showed no evidence of a treatment difference, and 68 patients in each group were included in the modified intention-to-treat analysis. Convulsions stopped at 15 min of drug injection in 57 of 68 patients (84%) receiving clonazepam and placebo and in 50 of 68 patients (74%) receiving clonazepam and levetiracetam (percentage difference -10·3%, 95% CI -24·0 to 3·4). Three deaths, 19 of 47 (40%) serious adverse events, and 90 of 197 (46%) non-serious events were reported in the levetiracetam group, and four deaths, 28 of 47 (60%) serious events, and 107 of 197 (54%) non-serious events were reported in the placebo group.

Interpretation The addition of levetiracetam to clonazepam treatment presented no advantage over clonazepam treatment alone in the control of GCSE before admission to hospital. Future prehospital trials could assess the efficacy of clonazepam alone as a first-line treatment in status epilepticus and the efficacy of a second injection of clonazepam with another antiepileptic drug as second-line treatment.

Funding UCB Pharma.
Intranasal diazepam/lorazepam: is this the future?

**Intranasal diazepam**
- Rate of absorption is faster than with rectal admin, but slower than with IN midazolam, and effect longer
- Feasibility study completed in EMU
- No clinical studies
- Plumiaz® (Accorda Pharma) granted orphan drug status by FDA in 2012, but in May 2016 development was discontinued because failure to demonstrate bioequivalence to rectal diazepam

**Intranasal lorazepam**
- 2 randomised open-label clinical studies.
- Bioavailability of 77%. Tmax variable and may prolonged
- As effective as IV lorazepam and paraldehyde

Other approaches to drug treatment of acute seizures and early SE

• The introduction of buccal midazolam was perhaps the most important development in epilepsy in several decades

• This is a fast-moving field with major advances occurring

• Some studies of other drugs in place of benzodiazepines:
  - IV propofol (subanaesthetic doses)
  - IV ketamine (subanaesthetic doses)

• Combination of diazepam and second-line drug rather than sequential use

• Neurosteroids

• Neuroprotective agents with antiepileptic drugs
Treatment of stage of established SE (30-90mins): conventional protocol

- Phenobarbitone 10 mg/kg at a rate of 100 mg/min
  
  or

- Phenytoin 15 - 18 mg/kg at a rate of 50 mg/min
  
  or

- Fosphenytoin 15 mg PE/kg at a rate of 100 mg PE/min

Alternatives: valproate, levetiracetam, lacosamide, benzodiazepine infusion
Stage of established SE – Should valproate be a drug of choice?

- **Efficacy – rates of seizure control**
  - 18/18 children with SE within 20 mins and 21/22 children with acute seizures at dose of 25mg/kg *(Yu Epilepsia 2003 44:74)*
  - 5/11 patients with overt convulsive SE (45%) and 2/6 (33%) with subtle SE *(Naritoku Neurology 2001: 56: A235)*
  - 41 (78%) children with NCSE, very rapidly *(Kaplan EEG 1999 30:1)*
  - 40/63 (63%) response rate in retrospective survey as 1st-4th AED used 10-78 mg/kg *(Lindi Neurology 2005 64: 353)*
  - 83/95 (86%) in SE/acute seizures, effect within 15 mins and seizure freedom for 12 hrs. *(Peters Seizures 2005 14 164)*

- **Dose – no consensus**
  - 25-60 mg/kg (some studies used higher doses to obtain high levels (100-150 mg/l). Max rate used has been 6mg/kg/min
  - 30-60 mg/kg in children
Stage of established SE – Sodium Valproate

- Side effects and toxicity
  - No fall in BP, Ht rate, ECG abnormalities
    → Low-dose/slow-rate IV infusion
      (Ann Neurol 1995 43: 483)
    → High dose rapid IV infusion (24 infusions - mean dose 24.2 mg/kg at rate of 3-6 mg/kg/min (Clin N’pharm 1999 22; 102)
    → Children SE (40 children; 25 mg/kg, 2.8 mg/kg/min)
      (Epilepsia 2003 44:724)
    → Adults, doses up to 78mg/kg (Neurology 2005 64 353)

- No local reaction at infusion site
- Other side effects ? - hyperammonaemia common,
  platelet function, in stroke ?, comedication with LTG
Stage of established SE – Levetiracetam?

- Intravenous formulation available
- Licensed for replacement therapy, but not for SE

- Pharmacokinetics established *(Stockis et al 2007)*
  Study of 1500mg IV over 15 mins compared to 3X500mg oral medication for 7 days (2-way cross over with a single dose)
  - Cmax and AUC equivalent to oral
  - Bioequivalence
  - Safety and tolerability equivalent
  - Commonest side effects dizziness and somnolence

- Children 30mg/kg/day dose equiv 1500mg IV adults
Stage of established SE – Levetiracetam?

II

- Case reports and small series show excellent efficacy
  - 20 abstracts presented at London colloquium 2009 presenting efficacy data in 128 patients with SE
  - Efficacy in TCSE, NCSE, CPSE, focal SE, myoclonic SE
  - Efficacy in symptomatic, idiopathic, de novo SE and SE in chronic ep, children, adults, acute brain injury, SE in tumours
  - Dose varied between 500-2000mg IV bolus (to 9000mg/day in one report)
  - No effect on cardiovascular or respiratory function
  - No adverse effects at infusion site

- Need a RCT - ESTAT Trial ongoing
  https://clinicaltrials.gov/ct2/show/NCT01960075
Stage of established SE – SVP vs PHY vs LEV

II

FULL-LENGTH ORIGINAL RESEARCH

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

*Vincent Alvarez, †Jean-Marie Januel, †Bernard Burnand, and *Andrea O. Rossetti

*Department of Clinical Neurosciences, Lausanne University Hospital (CHUV) and University of Lausanne (UNIL), Lausanne, Switzerland; and †Center of Clinical Epidemiology, Institute of Social and Preventive Medicine, Lausanne University Hospital (CHUV) and University of Lausanne (UNIL), Lausanne, Switzerland

• 187 episodes of SE retrospectively identified over a 4 year period treated with either SVP, PHY or LEV
### Table 1. Status Epilepticus Severity Score (STESS), a favorable score is 0–2

<table>
<thead>
<tr>
<th>Features</th>
<th>STESS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consciousness</td>
<td></td>
</tr>
<tr>
<td>Alert or somnolent/confused</td>
<td>0</td>
</tr>
<tr>
<td>Stuporous or comatose</td>
<td>1</td>
</tr>
<tr>
<td>Worst seizure type</td>
<td></td>
</tr>
<tr>
<td>Simple-partial, complex-partial, absence, myoclonic&lt;sup&gt;a&lt;/sup&gt;</td>
<td>0</td>
</tr>
<tr>
<td>Generalized-convulsive</td>
<td>1</td>
</tr>
<tr>
<td>Nonconvulsive status epilepticus in coma</td>
<td>2</td>
</tr>
<tr>
<td>Age</td>
<td></td>
</tr>
<tr>
<td>&lt;65 years</td>
<td>0</td>
</tr>
<tr>
<td>≥65 years</td>
<td>2</td>
</tr>
<tr>
<td>History of previous seizures</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0</td>
</tr>
<tr>
<td>No or unknown</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>0–6</td>
</tr>
</tbody>
</table>

<sup>a</sup>Complicating idiopathic generalized epilepsy.
Adapted from Rossetti et al. (2008).

Alvarez et al., 2011
Stage of established SE – SVP vs PHY vs LEV

### Table 2. Comparison of the groups of second-line treatment and the SE epilepticus characteristics

<table>
<thead>
<tr>
<th></th>
<th>VPA</th>
<th>PHT</th>
<th>LEV</th>
<th>p-value (test)</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 59 (29.8%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deadly etiology</td>
<td>15</td>
<td>39</td>
<td>34</td>
<td>&lt;0.001 (χ²)</td>
<td>88</td>
</tr>
<tr>
<td>Acute etiology</td>
<td>27</td>
<td>45</td>
<td>39</td>
<td>0.035 (χ²)</td>
<td>111</td>
</tr>
<tr>
<td>STESS ≥3</td>
<td>26</td>
<td>49</td>
<td>29</td>
<td>0.007 (χ²)</td>
<td>104</td>
</tr>
<tr>
<td>Alert/confus/somnolent</td>
<td>28</td>
<td>23</td>
<td>29</td>
<td>0.101 (χ²)</td>
<td>70</td>
</tr>
<tr>
<td>Stupor/coma</td>
<td>31</td>
<td>47</td>
<td>29</td>
<td>0.101 (χ²)</td>
<td>107</td>
</tr>
<tr>
<td>GCSE + NCSEC</td>
<td>22</td>
<td>41</td>
<td>17</td>
<td>0.002 (χ²)</td>
<td>80</td>
</tr>
<tr>
<td>No previous seizure</td>
<td>24</td>
<td>48</td>
<td>30</td>
<td>0.006 (χ²)</td>
<td>102</td>
</tr>
<tr>
<td>Age: mean (SD)</td>
<td>64</td>
<td>57.8</td>
<td>66.1</td>
<td>0.02 (ANOVA)</td>
<td>62.4</td>
</tr>
<tr>
<td>Failure of second-line treatment</td>
<td>15</td>
<td>29</td>
<td>28</td>
<td>0.032 (χ²)</td>
<td>72</td>
</tr>
<tr>
<td>New morbidity or death at discharge</td>
<td>25</td>
<td>45</td>
<td>39</td>
<td>0.011 (χ²)</td>
<td>109</td>
</tr>
<tr>
<td>Mortality/patients</td>
<td>4/48</td>
<td>17/64</td>
<td>9/47</td>
<td>0.045 (Fisher)</td>
<td>30/159</td>
</tr>
</tbody>
</table>

GCSE, generalized convulsive status epilepticus; NCSE, nonconvulsive status epilepticus in coma; STESS, Status Epilepticus Severity Score; VPA, valproate; PHT, phenytoin; LEV, levetiracetam.
### Stage of established SE – SVP vs PHY vs LEV

**Table 3.** Deadly etiology, Status Epilepticus Severity Score (STESS) ≥3, PHT and LEV compared with VPA with logistic regression for the different outcomes: failure of second-line treatment; new morbidity or death; and mortality

<table>
<thead>
<tr>
<th></th>
<th>OR</th>
<th>95% CI</th>
<th>p-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Failure of second-line treatment</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deadly etiology</td>
<td>0.997</td>
<td>0.53–1.89</td>
<td>0.995</td>
</tr>
<tr>
<td>STESS ≥3</td>
<td>1.51</td>
<td>0.8–2.85</td>
<td>0.201</td>
</tr>
<tr>
<td>Treatment (ref VPA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHT as second line</td>
<td>1.88</td>
<td>0.85–4.14</td>
<td>0.119</td>
</tr>
<tr>
<td>LEV as second line</td>
<td>2.69</td>
<td>1.19–6.08</td>
<td>0.017</td>
</tr>
<tr>
<td><strong>New morbidity or death at discharge</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deadly etiology</td>
<td>3.92</td>
<td>1.97–7.88</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>STESS ≥3</td>
<td>3.83</td>
<td>1.95–7.52</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Treatment (ref VPA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHT as second line</td>
<td>1.35</td>
<td>0.6–3.02</td>
<td>0.463</td>
</tr>
<tr>
<td>LEV as second line</td>
<td>1.98</td>
<td>0.86–4.57</td>
<td>0.109</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deadly etiology</td>
<td>3.69</td>
<td>1.47–9.3</td>
<td>0.005</td>
</tr>
<tr>
<td>STESS ≥3</td>
<td>3.56</td>
<td>1.32–9.61</td>
<td>0.012</td>
</tr>
<tr>
<td>Treatment (ref VPA)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PHT as second line</td>
<td>1.34</td>
<td>0.43–4.12</td>
<td>0.607</td>
</tr>
<tr>
<td>LEV as second line</td>
<td>1.08</td>
<td>0.33–3.52</td>
<td>0.894</td>
</tr>
</tbody>
</table>

STESS, Status Epilepticus Severity Score; VPA, valproate; PHT, phenytoin; LEV, levetiracetam. Bold type, statistically significant values.
The Established Status Epilepticus Treatment Trial (ESETT)

- Multi-centre randomised double-blind, comparative, effectiveness study of Fos-Phenytoin, Levetiracetam and Valproic Acid in subjects with benzodiazepine-refractory status epilepticus (SE)

- Sample size n=795, over 4 years, 1:1:1

- https://clinicaltrials.gov/ct2/show/NCT01960075
The 6th London-Innsbruck Colloquium on Status Epilepticus and Acute Seizures

6-8 April 2017
Salzburg, Austria