STATUS EPILEPTICUS

CAN WE UNDERSTAND ITS PATHOPHYSIOLOGY?
CAN WE IMPROVE TREATMENT?

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STATUS EPILEPTICUS: THE CURRENT STATE OF AFFAIRS

• ABOUT 150,000 CASES/YEAR IN THE USA

• MORTALITY (Richmond study): age, etiology, duration
  Children: 3%
  Young adults: 14%
  Elderly: 38%
  VA Cooperative Study 55%

• ONLY 3 DOUBLE-BLIND STUDIES OF TREATMENT OF SE

• NO TREATMENT OF SE HAS EVER INTRODUCED WITH TYPE 1 EVIDENCE OF EFFICACY

• MOST NEWER AEDs ARE NOT AVAILABLE BY IV ROUTE OR ARE NOT INDICATED FOR TREATMENT OF SE (FDA)
CONSEQUENCES OF SE

CONTROL

STATUS EPILEPTICUS
Time-dependent pharmacoresistance in SE

- Early treatment more effective than late treatment

- Good response to first drug used: 53%
- Good response to third drug used: 2%
- Regardless of which drug was used

Treiman et al, NEJM 1998
STATUS EPILEPTICUS

WE HAVE VERY EFFECTIVE MECHANISMS FOR STOPPING SEIZURES, YET IN SE THEY FAIL

“SEIZURES TEND TO BECOME SELF-SUSTAINING TIME-DEPENDENT PHARMACORESISTANCE

HIPPOCAMPAL SWELLING THEN ATROPHY

Experimental SE: Pharmacoresistance, neuronal injury in 30 min.
• What mechanism accounts for the transition from single seizures to status epilepticus?

• What mechanism accounts for the time-dependent development of pharmacoresistance? (seizure-induced tachyphylaxis)
Video-EEG seizure monitoring in rodents

CONTINUOUS EEG MONITORING (Stellate software)

RECORDING ON CD-ROM

TIME CODE GENERATOR

VCR

VIDEO MONITOR

VIDEO CAMERAw

INFRARED LIGHT

Record

Stimulate

Hippocampus

Perforant path

8 CHANNEL AMPLIFIERS

STIMULATOR
SELF-SUSTAINING STATUS EPILEPTICUS

- 20 min
- 3 hrs
- 8 hrs
- 1 hr
- 6 hrs
- 12 hrs

Cumulative seizure time:
- 330 (200-610)
- 1020 (480-1320)

Bars: M±SEM;
Numbers: Median (min-max)
TIME-DEPENDENT PHARMACORESISTANCE IN SE

PRETREATMENT DIAZEPAM 5 MG/KG

40 MIN SE DZ 5 MG/KG

70 MIN SE DZ 5 MG/KG
GABA AND STATUS EPILEPTICUS

- GABA is the primary CNS inhibitor
- Many convulsants are GABA antagonists (e.g. bicuculline, picrotoxin, penicilllin, PTZ)
- Decreased GABA receptors in SE (Kapur, ‘94)
- Decreased BZD response during SE (Kapur & MacDonald, ‘97)
- Increased failure of BZDs to terminate SE as it progresses (Mazarati et al, ‘98; Treiman et al., ‘98)
Effect of SE on mIPSCs

- Control
- SE

Normalized

10 pA

5 ms
$\text{GABA}_\text{A}$ Receptor Trafficking

C

SE
CONTROL OF SYNAPTIC FUNCTION

• Milliseconds to sec.:
  protein phosphorylation, allosteric changes

• Minutes to hours:
  Trafficking of receptors, other proteins

• Minutes to weeks:
  Gene expression

Example: physiology of short-term memory
GABA$_A$ receptor

Gephyrin scaffold

Clathrin AP2 adaptor

GABARAP NSF

Golgi

Endosome

Endosomal system
GABA RECEPTOR TRAFFICKING IN SE

- Internalized receptors are no longer functional

- Fewer GABA receptors at the synapse means loss of inhibition

- Benzodiazepines and other drugs have fewer receptors to work on: development of pharmacoresistance

- There is less defense against seizures: development of self-sustaining seizures.
NMDA synapses during SE
• Time is of the essence (TIME IS BRAIN)

• Pre-hospital treatment should help avoid pharmacoresistance

• Start with high dose

• Combine benzodiazepines with a non-GABAergic agent
PRE-HOSPITAL TREATMENT OF SE

- Rectal diazepam is effective
- Lorazepam (LZ) and Diazepam (DZ) given i.v. are equally effective *(Alldredge, Lowenstein)*
- Complication rates are similar for LZ and DZ and are lower than placebo.
- Buccal/nasal midazolam is effective in children, should be evaluated in adults.

A trial of IM midazolam is under way.
WHERE CAN WE SAVE TIME = BRAIN?

TIME TO TREATMENT IN STATUS EPILEPTICUS
Retrospective review of treatment access time of 30 patients with SE admitted to the emergency department of St. Bernardino Medical Center

- Onset of SE to arrival of EMT: 30 min (15-40 min)
- Arrival of EMT to arrival at ED: 20 min (10-40 min)
- Arrival at ED to initiation of treatment: 35 min (15-83 min)

IN THE ER, WHEN SHOULD WE TREAT?

1. The concept of impending SE

Duration of tonic-clonic seizures *(Theodore et al 1984)*

<table>
<thead>
<tr>
<th>Patients</th>
<th>Mean duration</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>120</td>
<td>62 sec</td>
<td>8-118 sec</td>
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</table>

Five min. of continuous GC seizures is a rare event, the risk that SE is present or impending is high

2. SE lasting over 30 min. causes neuronal loss

3. SE lasting over 15 min. becomes self-sustaining and pharmacoresistant

**CONCLUSION:** TREAT WITH HIGH DOSES OF INTRAVENOUS DRUGS AFTER 5 MINUTES OF REPEATED SEIZURES WITHOUT RECOVERY OF CONSCIOUSNESS BETWEEN SEIZURES
INITIAL TREATMENT OF GCSE

• **RESTORE HOMEOSTASIS:**
  • maintain airway and blood pressure,
  • start an IV line and draw blood
  • inject 50ml of 50% DW and 100 mg thiamine. Take hx of allergy if possible, then

• **INJECT ANTICONVULSANTS:**
  • IV fosphenytoin 20 mg/kg PE
  • IV midazolam 0.2 mg/kg bolus followed by 10 μg/kg/hr for 1 hr.
EMERGENCY EVALUATION OF SE

- Accucheck
- CBC
- Chemistries
- Monitoring EKG, EEG
- Pulse oxymetry, ABGs
- CXR
- Toxicology screen
EVIDENCE-BASED MEDICINE: WHICH AEDS ARE EFFICACIOUS FOR TC SEIZURES LASTING > 10 MIN IN ADULTS?

One vs two drugs? No difference between Lorazepam (LZ) and Diazepam (DZ) + Phenytoin (PHT).

**But:** LZ 0.1 mg/kg vs DZ 0.15 mg/kg. Doses were not equivalent.

Best regimen? No difference in efficacy or toxicity between LZ, DZ + PHT, Phenobarbital (PB). PHT alone less efficacious than LZ.

Best benzodiazepine? No difference between LZ, DZ.
Currently available IV formulations of AEDs

<table>
<thead>
<tr>
<th>Benzodiazepines</th>
<th>Hydantoins</th>
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<tbody>
<tr>
<td>diazepam</td>
<td>fosphenytoin</td>
</tr>
<tr>
<td>lorazepam</td>
<td>phenytoin</td>
</tr>
<tr>
<td>clonazepam</td>
<td></td>
</tr>
<tr>
<td>midazolam</td>
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<table>
<thead>
<tr>
<th>Barbiturates</th>
<th>Valproate sodium</th>
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<tr>
<td>phenobarbital</td>
<td></td>
</tr>
<tr>
<td>thiopental</td>
<td></td>
</tr>
<tr>
<td>pentobarbital</td>
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</table>

• **Levetiracetam**

• **Lacosamide**

IV = intravenous
# GCSE: CHOICE OF BENZODIAZEPINES

<table>
<thead>
<tr>
<th></th>
<th>DIAZEPAM</th>
<th>LORAZEPAM</th>
<th>MIDAZOLAM</th>
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</thead>
<tbody>
<tr>
<td>Peak brain concentr.</td>
<td>1 min.</td>
<td>5 min.</td>
<td>5 min</td>
</tr>
<tr>
<td>Redistributes to general body fat, [brain] falls after</td>
<td>15 min.</td>
<td>Little secondary fall.</td>
<td>Little secondary fall.</td>
</tr>
<tr>
<td>Elimination</td>
<td>½ life 48-60 hrs.</td>
<td>½ life 20 hrs.</td>
<td>½ life 1½ hr+</td>
</tr>
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## CGSE: INITIAL TREATMENT

<table>
<thead>
<tr>
<th>PHENYTOIN</th>
<th>FOSPHENITOIN</th>
</tr>
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<tbody>
<tr>
<td>- Solvent propylene glycol, PH 12</td>
<td></td>
</tr>
<tr>
<td>- Purple glove syndrome</td>
<td></td>
</tr>
<tr>
<td>- Cardiac arrhythmias</td>
<td></td>
</tr>
<tr>
<td>- Max IV infusion rate 50 mg/m</td>
<td></td>
</tr>
<tr>
<td>- Water-soluble, few local complications</td>
<td></td>
</tr>
<tr>
<td>- Fewer cardiac complications reported</td>
<td></td>
</tr>
<tr>
<td>- Max rate 150 mg/m</td>
<td></td>
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<tr>
<td>- Free [phenytoin] increases faster</td>
<td></td>
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</tbody>
</table>
INITIAL TREATMENT OF GCSE: EXCEPTIONS

• **Hx of drug intolerance:** avoid specific antigen

• **GCSE associated with PME or JME:** replace hydantoins by IV valproate 40-50 mg/kg, 3 mg/kg/min.

• **GCSE with hepatic encephalopathy:** lorazepam may deepen coma, phenytoin may damage liver; replace by IV levetiracetam 50 mg/kg, 250 mg/min.

• **Acute intermittent porphyria:** avoid all P450 inducers. IV levetiracetam
**Impending SE**

**PreER**

- Diazepam rectal gel
  - 15-20 mg
  - or
  - iv Lorazepam
    - 2 mg, may repeat once
  - or
  - iv Diazepam
    - 5 mg, may repeat once

**ER**

- iv Midazolam
  - 0.2 mg/kg bolus
  - 0.05 mg/kg/hr
  - or
  - iv Lorazepam
    - up to 0.1 mg/kg
  - or
  - iv Diazepam
    - up to 0.25-0.4 mg/kg

**Established SE**

- iv Fosphenytoin/Phenytoin
  - 20-30 mg/kg

**EEG monitoring?**

Airway, BP, Temp, IV access, EKG, CBC, glucose, electrolytes, AED levels, ABG, tox screen; central line?
We define refractory SE by the failure of seizures to stop after intravenous injection of adequate amounts of 2 appropriate anticonvulsants.

- Adequate treatment = high therapeutic serum levels of anticonvulsants.

- Treatment should start IMMEDIATELY after the end of the previous injection. No waiting!
THERAPEUTIC ALGORITHM FOR REFRACTORY SE

- Intubate, maintain BP>90

- First maximize anticonvulsant dosage. Add IV fosphenytoin up to 30mg/kg PE

- Complete diagnostic work-up

- After failure of 2 drugs, consider anesthesia

- The place of new drugs is unclear
EMERGENCY EVALUATION OF SE

• Accucheck
• CBC
• Chemistries
• Monitoring EKG, EEG
• Pulse oxymetry, Arterial Blood Gazes
• CXR
• Toxicology screen

• Detailed history from chart and family
• Physical examination
• Anticonvulsant plasma levels
• Consider lumbar puncture and other tests
I.V. levetiracetam for status epilepticus

- Maximal rate of i.v. administration: 4000 mg in 15 minutes well tolerated by healthy volunteers (Ramael et al 2007).
- Little effect on vital signs or level of consciousness (Zaatreh, Clin Neuropharmacol, 2005; Baulac et al Epilepsia, 2007; Schulze-Bonhage et al JNNP 2007; Ruppert at al Epilepsy Res 2007).
- No hemato- or hepatotoxicity, no reported psychiatric side-effects to date.
- Synergistic with benzodiazepines in animal models.
- Too little experience to know its place, looks promising.
<table>
<thead>
<tr>
<th></th>
<th>Case reports:</th>
<th>Abstracts:</th>
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<tbody>
<tr>
<td><strong>Patients with SE:</strong></td>
<td>87</td>
<td>65</td>
</tr>
<tr>
<td><strong>Dose:</strong></td>
<td>500-7500 mg</td>
<td>500-5000 mg</td>
</tr>
<tr>
<td><strong>Seizure control:</strong></td>
<td>31-80%</td>
<td>80%</td>
</tr>
<tr>
<td><strong>Seizure type:</strong></td>
<td>CPSE&gt;GCSE</td>
<td>CPSE&gt;GCSE</td>
</tr>
<tr>
<td><strong>Specific sz types:</strong></td>
<td>AIP</td>
<td>Myoclonic 2</td>
</tr>
<tr>
<td></td>
<td>(acute intermittent porphyria)</td>
<td>(1 Lafora)</td>
</tr>
<tr>
<td><strong>Complications:</strong></td>
<td>somnolence 6</td>
<td>intubation 2, aggresssivity 1</td>
</tr>
</tbody>
</table>
I.V. valproate for status epilepticus

- Maximal rate of infusion 3 mg/kg/min
- Aim: serum levels of 150 μg/ml usually achieved with a dose of 40 mg/kg
- Little effect on vital signs or level of consciousness (Cattrell et al, Epilepsia, 2000, 41: 253)
- Mitochondrial myopathy, liver dis.
I.V. VALPROATE FOR SE: meta-analysis

3 randomized unblinded studies:

• Misra 2006: valproate 30 mg/kg vs phenytoin 18 mg/kg (n= 35 V, 33 Ph). Success: V 1st tr. 66%, 2d tr. 79%; Ph 1st 42%, 2d 25%.

• Mehta 2007: valproate vs diazepam in children (n=20+20). V 80% success, sz stop 5 min., Dz 85%, sz stop 17 min.

• Agarwal 2007: valproate vs phenytoin (n = 50+50, benzo-refractory) Success: V 88%, Ph 84%.

Case series: 139 pts, V 15-31.5 mg/kg, success SE 63-77%, serial sz 85%. Success w. treatment < 3 hrs 95%, 3-24 hrs 62%, > 24 hrs 40% (Olsen et al 2007). Complications: few but beware of publication bias.
THERAPEUTIC ALGORITHM FOR REFRACTORY SE: GENERAL ANESTHESIA

• **Option 1:** Propofol 1.5 mg/kg followed by continuous IV drip at 5-10 µg/kg/hr.
• If still seizing after 1 hr: option 5

• **Option 2:** Midazolam bolus 0.2 mg/kg followed by continuous iv infusion up to 0.05 mg/kg/hour
THERAPEUTIC ALGORITHM FOR REFRACTORY SE

- **Option 3:** Phenobarbital 20 mg/kg IV (100 mg/min).
- **Option 4:** Pentobarbital: loading dose 15 mg/kg - maintenance ≥ 1.5 mg/kg/hr
- **Option 5:** Ketamine bolus 1.5 mg/kg, then continuous iv 0.01-0.05 mg/kg/hour. Does not raise intracranial pressure*. Neuroprotective in experimental SE ** Safety in neonates is uncertain ***

THERAPEUTIC ALGORITHM FOR REFRACTORY SE: ANESTHESIA

- Adjust to burst suppression pattern
- Stop IV every morning and monitor seizures
- If recurrence, another 22 hrs of anesthesia
Management of GCSE in adults

**Pre-emergency room**
- Diazepam rectal gel 15–20 mg
- or
- IV lorazepam 2 mg, repeat x1
- or
- IV diazepam 5 mg repeat x1
- or
- Buccal midazolam in children

**Emergency room**
- midazolam 0.2 mg/kg bolus
- or
- lorazepam up to 0.1 mg/kg
- or
- diazepam up to 0.25–0.4 mg/kg
- + fosphenytoin/phenytoin 20–30 mg/kg

**Intensive care unit**
- valproate 40–60 mg/kg
- 3 mg/kg/min
- or
- Propofol loading 2–5 mg/kg civ
- 2–10 mg/kg/h
- or
- Midazolam loading 0.2 mg/kg civ
- 0.1–2 mg/kg/h
- or
- Pentobarbital loading up to 10 mg/kg
- ≤25 mg/min civ
- 0.5–2 mg/kg/h
- or
- Phenobarbital 20 mg/kg
- 50–100 mg/min

**EEG monitoring?**
- Airway, BP, temp, IV access, EKG, CBC, glucose, electrolytes, AED levels, ABG, tox screen, central line?

GCSE = generalised convulsive status epilepticus

Chen & Wasterlain, 2006
COMPLEX PARTIAL STATUS EPILEPTICUS

- Two forms: cyclic or continuous
- Partial responsiveness with reactive automatisms ↔ total unresponsiveness with reactive automatisms
- May be distinguished from absence SE by EEG or presence of complex automatisms
- Response to benzos, interictal focus help dx
COMPLEX PARTIAL SE: PRINCIPLES OF TREATMENT

- Causes brain damage,
- Treat like CGSE
- Two drugs IV (benzo+ fosphenytoin)
- Time is of the essence
- Refractory CPSE: EFNS guidelines* levetiracetam or valproate
- general anestheisia if necessary

*Meierkord et al EJN 2010
• Distinguish from partial complex status
• Most common in children
• Not responsive to phenytoin or fosphenytoin
• Responsive to benzodiazepines
ELECTROGRAPHIC SE

• With impaired consciousness:
  IV fosphenytoin and midazolam

• Without impairment of consciousness:
  - No need for IV treatment
  - Load p.o. or rectally

• During sleep:
  - No need for IV treatment
Conclusions: don’t be “too low, too slow”

- SE should be treated early, vigorously, in ICU.
- Pre-hospital treatment should be used.
- Refractory SE should quickly lead to general anesthesia.
- Indications of valproate & levetiracetam uncertain.
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West Los Angeles VAMC