A Clinical Trial for Prevention of Temporal Lobe Epilepsy following Febrile Status Epilepticus: Critical Considerations

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- The speaker has no relationships with entities producing, marketing, re-selling, or distributing health care goods or services consumed by, or used on, patients
Learning Objectives

• How clinical and preclinical observations inform the following questions:
• Is status epilepticus a risk factor for developing epilepsy?
• Is status epilepticus a risk factor for developing hippocampal sclerosis?
A Clinical Trial for Prevention of Temporal Lobe Epilepsy following Febrile Status Epilepticus

Critical Considerations

• Starting point: clinical problem amenable to prevention
• What might be key facets of clinical trial (design including outcome measures, biomarkers, others)
• Design and execute preclinical studies within this context
Thinking about a Prevention Trial: Key Questions

- Is status epilepticus a risk factor for developing TLE?
- Is status epilepticus a risk factor for developing hippocampal sclerosis?
- Is status epilepticus a risk factor for developing memory problems?
Intra-amygdala kainic acid model: status epilepticus

KA infusion
Beginning of EEG and Video Monitoring

Termination of SE

Monitoring at 2 Weeks Post-SE

Resuming EEG and video monitoring From Week 5 Post-SE

40 Minutes of SE

Emergence of SRS within 3 to 7 Days

Reliably induces status epilepticus which results in spontaneous recurrent seizures beginning 3-5 days later. Mortality less than 10%. Ben-Ari, Nadler, Henshall, others
Chemically or electrically induced status epilepticus is sufficient to induce TLE in diverse species including mice, rats, subhuman primates (Loscher et al Epil Res 50:105-123, 2002; Perez-Mendes et al Epil Res 96:45-57, 2011)

Status epilepticus induced by hyperthermia is sufficient to induce TLE in subset of rats (Dube et al J Neurosci 30:7484-7494, 2010)
Is status epilepticus a risk factor for developing TLE? Clinical Observations

Is status epilepticus a risk factor for developing TLE? Caveats

- A genetic predisposition may be the reason that the environmental insult evoked status epilepticus rather than a brief seizure or no seizure at all (e.g. Dravet syndrome caused by SCN1A mutation)
- Perhaps the genetic predisposition would result in epilepsy regardless of the status epilepticus
Is status epilepticus a risk factor for developing TLE? “My two cents”

- ABSOLUTELY!!!!!!!!
Thinking about a Prevention Trial: Key Questions

- Is febrile status epilepticus a risk factor for developing TLE?
- Is status epilepticus a risk factor for developing hippocampal sclerosis?
- Is status epilepticus a risk factor for developing memory problems?
Is status epilepticus a risk factor for developing hippocampal sclerosis? Historical Perspective

- Hippocampal Sclerosis: Progress Since Sommer
  Thom M  Brain Path 19:565-572, 2009

- Hippocampal Lesions Produced by Prolonged Seizures in Paralyzed Artificially Ventilated Baboons
  Meldrum B S et al  Experientia 29:561-563, 1973

- Sustained electrical stimulation of the perforant path duplicates kainate-induced electrophysiological effects and hippocampal damage in rats
Is status epilepticus a risk factor for developing hippocampal sclerosis? Clinical Observations

FEBSTAT MRI Data Reveal CA1 Predominance

One day after FSE

8 months after FSE

Vandlandingham et al Annals Neurol 1998
Intra-amygdala kainic acid model: status epilepticus

Reliably induces status epilepticus which results in spontaneous recurrent seizures beginning 3-5 days later. Mortality less than 10%. Ben-Ari, Nadler, Henshall, others
Serial T2 Weighted MRI in Kainic Acid Model

Similarity to Human

Baseline scanning

48 hr after KA-SE

10 week after KA-SE
Is status epilepticus a risk factor for developing hippocampal sclerosis? Caveats

- Induction of many (e.g. a hundred tonic-clonic) isolated seizures are sufficient to induce hippocampal sclerosis in experimental animals (Kotloski R et al. Prog Brain Res 135:95-110, 2002)


- Thus recurrent isolated seizures could contribute to hippocampal sclerosis evident following status epilepticus in this model and in humans
Is status epilepticus a risk factor for developing hippocampal sclerosis? “My two cents”

- ABSOLUTELY!!!!!!
Thinking about a Prevention Trial: Key Questions

- Is febrile status epilepticus a risk factor for developing TLE?
- Is status epilepticus a risk factor for developing hippocampal sclerosis?
- Is status epilepticus a risk factor for developing memory problems?
Is status epilepticus a risk factor for developing memory problems? Preclinical Observations

- **Cognitive and Behavioral Co-Morbidities of Epilepsy**

- **Seizures in the Developing Brain Cause Adverse Long-term Effects on Spatial Learning and Anxiety**
  Sayin U et al  Epilepsia 45:1539-1545, 2004

- **Impaired memory following status epilepticus antedates onset of epilepsy**
Is status epilepticus a risk factor for developing memory problems? Clinical Observations

Is status epilepticus a risk factor for developing memory problems? “My two cents”

- Absolutely!!!!!!!!!!!!!
Thinking about a Prevention Trial: Key Questions

- Is status epilepticus a risk factor for developing TLE? Yes
- Is status epilepticus a risk factor for developing hippocampal sclerosis? Yes
- Is status epilepticus a risk factor for developing memory problems? Yes
Thinking about a Prevention Trial: Key Unanswered Questions

- What is/are the molecular mechanism(s) by which status epilepticus causes memory impairment, death of hippocampal neurons, and temporal lobe epilepsy?
- Can a safe and effective drug targeting the mechanisms be developed?
- Will treatment with the drug commencing several hours after status epilepticus and continued for approximately two weeks be sufficient to prevent memory impairment and temporal lobe epilepsy?
Thinking about a Prevention Trial: Potential Outcome Measures

- Prevention of seizures as primary outcome is not feasible because of long latency (5-10 years)
- Prevention of comorbidity like memory impairment may be feasible
- Prevention of MRI evidence of hippocampal sclerosis: a secondary outcome measure
Challenging Problems and Creative Solutions

- Cause for optimism: FEBSTAT provides data essential to clinical trial design; Diverse animal models available; Identification of molecular targets in preclinical models is encouraging; Biomarkers needed
- Solution requires: continuous and effective interactions among expert clinicians, preclinical scientists, clinical trial design experts, NIH, biotech/pharma, FDA
- NINDS solution: Center without Walls
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