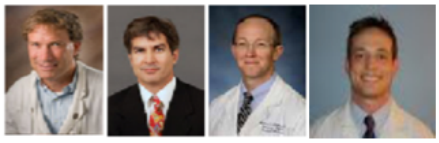
critical care perspectives in emergency medicine



The ESETT Trial

Key Article

- *Kapur J, et al. Randomized trial of three anticonvulsant medications for status epilepticus. N Engl J Med. 2019; 381:2103-2113.*

Introduction

- Benzodiazepines remain first-line treatment for patients with status epilepticus (SE)
- Up to 33% of patients do not respond to benzodiazepines
- Treatment of benzodiazepine-refractory SE is not well studied
- Convulsive and non-convulsive SE associated with brain injury
- Early termination of convulsive SE associated with decreased risk of cardiac and respiratory complications. Also associated with decreased admission to the ICU.
- Fosphenytoin is one of the only medications FDA approved for refractory SE in adults (No FDA approved medications for children with refractory SE)
- Levetiracetam and valproic acid are also commonly given for refractory SE
- Current guidelines do not provide guidance on which medication to chose in the setting of refractory SE

Objective

- Determine the superiority or inferiority of three commonly used anticonvulsant medications with regard to treatment success among ED patients with SE.

Study

- Investigator-initiated, multicenter, randomized, blinded, comparative-effectiveness trial
- Developed by the NIH and FDA; conducted by Neurological Emergencies Treatment Trials (NETT) and PECARN.
- 57 EDs across the US (academic and community; 18 only enrolled children, 26 only enrolled adults, 13 enrolled both)
- Patients - Included
    - Ages 2 years or older
    - Treated with a generally accepted cumulative dose of benzodiazepines for generalized convulsive SE lasting 5 minutes
    - Continued or recurrent convulsions in the ED for at least 5 min after the last dose of benzodiazepines and no more than 30 min after the last dose of benzodiazepines
- Patients – Excluded
    - Seizure caused by trauma, hypo/hyperglycemia, cardiac arrest, postanoxia
    - Pregnancy
    - Incarceration
    - Treated for SE with agents other than benzodiazepines
    - Intubated

    - Inborn errors of metabolism
    - Liver or renal impairment
- Minimum adequate cumulative dose
    - For body weight > 32 kg
        - Diazepam – 10 mg IV or PR
        - Lorazepam – 4 mg IV
        - Midazolam – 10 mg IV or IM
    - For body weight < 32 kg
        - Diazepam – 0.3 mg/kg IV or PR
        - Lorazepam – 0.1 mg/kg IV
        - Midazolam – 0.3 mg/kg IV or IM
- Treatment
    - Clinical team used an age-stratified trial "use next" medication box in proximity to patient care area in the ED
    - Trial drug administered by an infusion pump with a predetermined rate over 10 min
    - Levetiracetam: 60 mg/kg (max 4500 mg)
    - Fosphenytoin: 20 mgPE (max 1500 mgPE)
    - Valproic acid: 40 mg/kg (max 3000mg)
    - After 10 min infusion of trial drug stopped
- Primary outcome
    - Absence of clinically apparent seizures and improving responsiveness at 60 minutes after the start of the trial drug infusion, without additional anticonvulsant medication
- Secondary efficacy outcomes
    - Time to termination of seizures
    - ICU admission
    - ICU and hospital LOS
- Primary safety outcome
    - Composite of life-threatening hypotension or cardiac arrhythmia within 60 min after start of drug infusion
- Secondary safety outcomes
    - Death before end of participation in trial
    - ETI within 60 min of start of drug infusion
    - Acute seizure recurrent more than 60 min after drug infusion
    - Acute anaphylaxis
- Statistical analysis
    - Maximum sample was 795 patients
    - Randomization stratified according to age category

Results

- 384 patients
    - Enrollment discontinued after DMSB – trial met predefined futility criteria in the planned interim analysis at 400 patients
    - Did not include an interaction with age in predefined analysis, so they continued enrollment in the pediatric sub cohort

    - Baseline characteristics similar
        - 39% were 2 to 17 years of age
        - 48% were 18 to 65 years of age
        - 13% were > 65 years of age
- Deviations from the eligibility criteria occurred in 108 enrollments (27%)
    - Due to benzodiazepines administered too long before or to proximate to enrollment, inadequate cumulative doses of benzodiazepines, and enrollment of patients without SE
- Unblinding of investigators and treating clinicians was considered necessary for patient care in 200 of the 400 enrollments – most of these occurred after the primary outcome had been determined at 60 min
- Efficacy Analysis – Primary Outcome
    - Levetiracetam: 68 out of 145 patients (47%)
    - Fosphenytoin: 53 out of 118 patients (45%)
    - Valproic acid: 56 out of 121 (46%)
- Safety Analysis
    - Life-threatening hypotension
        - Levetiracetam: 0.7%
        - Fosphenytoin: 3.2%
        - Valproic acid: 1.6%
    - Arrhythmia
        - Levetiracetam: 0.7%
        - Fosphenytoin: 0
        - Valproic acid: 0
    - Intubation
        - Levetiracetam: 20%
        - Fosphenytoin: 26.4%
        - Valproic acid: 16.8%

Limitations

- Need for unblinding in order to choose a second anticonvulsant for ongoing seizures
- 10% of patients had psychogenic nonepileptic seizures
- EEG was not used to determine primary outcome of seizure cessation
- Authors chose doses of medications – could other doses have been more efficacious?
- Large percent of patients had eligibility deviations related to benzodiazepine dosing

Take home points

- Levetiracetam, fosphenytoin, and valproic acid were effective in stopping approximately 50% of benzodiazepine-refractory SE.
- No agent found to be superior or inferior to another.