Comparison of three anticonvulsive agents for benzodiazepine resistant status epilepticus

Tyson Savage¹ · Marshall Ross¹

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epilepticus in regard to (1) efficacy of terminating seizure, and (2) associated safety outcomes.

Methods

Design

Multicentre, randomized, blinded clinical trial.

Settings

Fifty-seven emergency departments across the United States consisting of a mix of academic, community, adult, and children's hospitals.

Subjects

Inclusion criteria:

- Age ≥ 2 .
- Generalized convulsive seizure lasting greater than 5 min that was treated with adequate dose(s) of benzodiazepines, but seizure was persistent or recurrent in the emergency department at least 5 min after the last benzodiazepine dose.

Exclusion criteria:

- Inadequate benzodiazepine dose or more than 30 min from the last dose.
- Acute precipitant of seizure was major trauma, hypoglycemia, hyperglycemia, cardiac arrest, or post anoxia.
- Patient was pregnant, pre-emptively opted out, incarcerated, intubated, or already treated with a non-benzodiazepine anticonvulsant.

Introduction

Background

Prior to this study, there was a paucity of high-quality evidence comparing anticonvulsant medications in the treatment of benzodiazepine refractory status epilepticus. This randomized, blinded, multicentre study evaluates the efficacy and safety of three anticonvulsants by head-to-head comparison.

Objective

Comparison of fosphenytoin, levetiracetam, and valproic acid in treating benzodiazepine-resistant convulsive status

✉ Tyson Savage
tyson.savage@ucalgary.ca

¹ Department of Emergency Medicine, University of Calgary, C231 3280 Hospital Dr. NW, Calgary, AB T2N 4Z6, Canada

- Known allergy.
- Liver disease or severe renal impairment.

Intervention

Patients were randomized to receive one of the three masked trial drugs: levetiracetam (60 mg/kg, max 4500 mg), fosphenytoin (20mgPE/kg, max 1500 mg), or valproate (40 mg/kg, max 3000 mg) infused over 10 min.

Outcomes

The primary outcome was absence of clinically apparent seizures and improving responsiveness at 60 min from the start of trial-drug infusion without additional anticonvulsant medications, including medications required for endotracheal intubation.

Secondary outcomes included time to termination of seizure, ICU admission rate, rate of life-threatening hypotension, cardiac arrhythmia, intubation within 60 min of receiving trial drug, and rate of death before end of participation in trial.

Main results

A total of 384 unique patients were enrolled and enrollment was stopped early based on a planned interim analysis suggesting futility of finding one drug to be superior or inferior.

Primary Outcome: There was no statistically significant difference among the trial drugs in cessation rate of clinically apparent seizures with improvement in level of consciousness 60 min after the start of drug infusion. Rates of primary outcome were 47%, 45%, and 46% in the levetiracetam, fosphenytoin, valproate arms, respectively.

Secondary Outcomes: There were no statistically different differences in secondary efficacy or safety outcomes.

Appraisal

Strengths

- Multicenter, randomized, blinded.
- Includes both adult and pediatric patients.
- Intention to treat protocol, with secondary sensitivity analysis using per-protocol analysis which had similar findings.

Limitations

- EEG was not used to confirm primary outcome.
- Inclusion of “increasing level of alertness” in the primary outcome criteria may undermine the number of

patients in which status epilepticus was successfully terminated as this may have been confounded by post-ictal state and/or medication-induced sedation.

- 27% of patients enrolled had deviations from the eligibility criteria.
- Unblinding occurred in 46 patients before 60 min after trial drug was given (11.9%).
- Fosphenytoin dose was limited to 1500 mg given the standardized 10 min infusion rate among all trial medications, which means patients over 75 kg were underdosed.

Context

Two recently published, multicentre, open-label, randomized trials also failed to detect a significant difference between levetiracetam and phenytoin in their efficacy of terminating clinically apparent seizures in pediatric patients with benzodiazepine-resistant status epilepticus [1, 2]. These studies were not powered to detect a difference in serious safety outcomes, but based on their data, report similar safety profiles between levetiracetam and phenytoin [1, 2].

Arguments against using phenytoin as the first choice for benzodiazepine-resistant status epilepticus relate to its need for careful administration and its multiple drug interactions, including with midazolam and corticosteroids, which may be needed for patients in refractory status epilepticus [3].

Bottom line

This high-quality, multicentre, blinded, randomized control trial showed no statistically significant difference in the efficacy or safety outcomes of fosphenytoin, levetiracetam, or valproic acid when used for patients with benzodiazepine refractory status epilepticus. These agents were only effective about half the time in stopping clinically apparent seizures and improving level of alertness within 60 min of infusion.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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