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A retrospective observational study of current treatment for generalized convulsive status epilepticus

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ABSTRACT

Objectives: This study aimed at determining the current state of practice of treatment for acute generalized convulsive status epilepticus (GCSE) and responsiveness to therapy.
Methods: This observational study was performed by retrospectively identifying patients with GCSE presenting to an emergency room setting. The primary outcome was seizure cessation following medication administration. Secondary outcomes were rates of intubation and mortality.
Results: One hundred seventy-seven episodes of GCSE were identified. All patients, except 1, received a benzodiazepine for first-line treatment. Only 11% of these patients, all children, were treated with at least 0.1 mg/kg of lorazepam or an equivalent dose of an alternative benzodiazepine. A first-line treatment was effective in 56% of the patients, a second-line treatment in an additional 28%, and a third-line treatment in 12%. Phenytoin was the most prescribed second-line treatment (41%) but statistically significantly least effective (22% versus 86% seizure cessation, $p < 0.0001$) compared with all other second-line agents together. Propofol was the most prescribed third-line treatment.
Conclusions: Results emphasize that, in clinical practice, approximately half of GCSE patients respond to first-line therapy and, among nonresponders, approximately two-thirds respond to second-line and approximately three-quarters respond to third-line therapies. The variations in treatment selection reflect that there are no randomized controlled trials to guide treatment beyond use of benzodiazepines for first-line treatment. The observation that phenytoin is statistically substantially worse than other second-line treatments raises the possibility that the most commonly selected second-line treatment is the least effective and provides equipoise for a large randomized controlled trial of second-line therapies.

1. Introduction

Status epilepticus (SE) is a common medical and neurological emergency. The Richmond-based population study projected an estimated 126,000–195,000 cases of SE per year in the United States with annual mortality of 22% despite aggressive medical treatment [1]. Along with high mortality, SE is associated with significant morbidity, including cognitive dysfunction and risk of subsequent epilepsy [2].

Benzodiazepines (BZDs) are considered first-line treatment based on randomized controlled trials. The VA Cooperative Study, a large multicenter randomized controlled trial, compared 4 treatments for SE and found that, in patients with overt SE, 0.1 mg/kg lorazepam was the most successful, terminating episodes in 65% of the patients which was statistically significantly greater compared with phenytoin (PHT) and numerically greater compared with the other treatments [3]. Two other randomized controlled trials also suggest superiority of lorazepam [4,5]. Although a recent double-blind placebo controlled trial found superiority of intramuscular midazolam over intravenous lorazepam for out-of-hospital initial treatment for status epilepticus, it is likely that many emergency physicians still use lorazepam [6]. It is probable that BZDs are used almost uniformly for patients with SE, but it is unclear what types or doses are being used in current clinical practice.

While there are excellent data to support the use of BZDs for first-line treatment, there are no large prospective randomized controlled trials to guide second-line treatment. The majority of data come from case reports or case series of individual drugs. There have been two single center randomized controlled trials that found equivalent efficacy of VPA and PHT [7,8] and one which found VPA to be statistically significantly more effective than PHT (66% vs 42%, $p = 0.046$) [9]. Alvarez et al. recently reported a retrospective analysis of patients in a clinical protocol who received a standardized dose of benzodiazepine followed by a choice of PHT = 20 mg/kg, VPA = 20 mg/kg, or LEV = 20 mg/kg and found that VPA failed to control SE in 25.4% of the patients, PHT in 41.4%, and LEV in 48.3% [10].

There have been no observational studies to determine what the current state of clinical practice is for the treatment for GCSE. A 2003 survey of members of the critical care or epilepsy sections of the American Academy of Neurology reported that 95% of participants

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would use fosphenytoin or PHT as a second-line agent [11]; however, this study was based on a response to a clinical vignette and may not reflect true clinical practice. More recently, a 2012 survey of the American Critical Care Society also came to a similar conclusion [12].

The lack of rigorous systematic data to support decision-making beyond BZDs, especially the lack of data about second-line therapy, prompted us to study how GCSE is actually treated in routine emergency room practice. We hypothesize that treatment is likely to be highly variable, especially benzodiazepine use, and that some routinely used treatments may be more effective than others.

2. Methods

We retrospectively reviewed the ICD9 coding database for visits to the University of Virginia Medical Center from 1/1/2006 to 12/31/2010 for the primary codes of 345.3 "grand mal status", 345.2 "petit mal status", and 345.7 "epilepsia partialis continua" and reviewed the medical records from each case to determine if they met criteria for acute GCSE originally presenting to an emergency department during that admission. The remaining primary epilepsy codes from the same database, 345.0–345.9, excluding those mentioned above, were systematically sampled and reviewed and did not yield additional patients.

Patients either presented initially to the University of Virginia Emergency Department or were seen at a local emergency room and transferred to the University of Virginia Emergency Department. Acute GCSE was defined as seizing on EMS or emergency room arrival or greater than 2 seizures without return to baseline. The seizure was deemed convulsive if there was any mention of "jerking", "twitching", or similar movements. Subjects younger than 1 month, post anoxic SE, and non-convulsive status epilepticus were not included.

At our institution and other local emergency rooms, there was no established treatment protocol for SE at the time of the study. We defined first-line treatment as BZD administration. Second-line treatment was defined as the treatment received immediately after BZD administration. Third-line treatment was defined as the treatment given after second-line treatment. Prehospital treatment was defined as treatment received prior to arrival in the emergency room and could include treatment administered by nonmedically trained caregivers at home or en route or by medically trained personnel via emergency transport services.

Age, gender, history of epilepsy, place of original presentation (University of Virginia or outside hospital), treatment, need for intubation, and disposition were extracted from the medical record. Epilepsy type was categorized as symptomatic, cryptogenic, or idiopathic and localization-related or generalized according to the ILAE classification of epilepsies and epileptic syndromes [13]. The etiology was considered acute symptomatic if related to a known injury at the time of GCSE presentation, chronic symptomatic if related to a remote injury, due to epilepsy if related to underlying epilepsy only with no other cause found, due to febrile seizure, or unknown if the evaluation did not reveal a cause of the episode.

The primary outcome was seizure cessation following medication administration. Secondary outcomes included intubation, disposition, and in-hospital mortality. If a timed flow chart was available, then a response was considered seizure cessation within 10 min following benzodiazepine administration or 30 min following second- or third-line treatment administration. If no timed flow chart was available, then a descriptive report of seizure response following medication administration was used. Drug levels in closest proximity to administration of treatment drug were recorded if available.

3. Statistical analysis

Comparisons among the treatment groups were performed using two-tailed Fisher's exact test. The significance level for all tests was $p < 0.05$. Ninety-five percent confidence levels surrounding mean antiepileptic doses and antiepileptic levels were calculated when available.

4. Results

We identified 177 episodes of acute GCSE occurring in 170 patients. Of these episodes, 121 (68%) first presented to the University of Virginia Emergency Department, while 56 (32%) were seen initially in a community hospital. Demographic data and other characteristics of the population are presented in Table 1.

All patients except for one received BZDs as first-line treatment either in the prehospital or emergency room setting. The single patient who did not receive benzodiazepine was described as a 67-year-old woman with no history of epilepsy who had waxing and waning mental status and intermittent twitching of her arm. This patient was not included in the subsequent analysis, which was performed on the remaining 176 episodes.

First line BZD treatment was given for 176 episodes of GCSE and 56% responded with seizure cessation following administration. Figure 1 presents a flowchart of patient responsiveness to treatment. Fig. 1 presents a flowchart of seizure responsiveness to treatment. Prehospital treatment was given to 48% of the patients, typically by an EMS provider, with 73% receiving diazepam (Table 2). A single dose of medication was given to 54% of those receiving prehospital treatment, with the remaining patients receiving multiple doses of often a variety of BZDs. Most patients received BZDs in the emergency room (86%) regardless of whether they had received them previously, with the majority receiving lorazepam (86%). Of those patients receiving BZDs in the emergency room, only 17 (11%) patients received a single dose of at least 0.1 mg/kg lorazepam or an equivalent dose of another BZD, and all of these patients were children (2 months–8 years old).

Second-line treatment was effective in seizure cessation in 49 (63%) of the 78 patients whose seizures did not respond to BZDs (Fig. 1). Seizures in 22% of the patients responded to PHT/fosphenytoin, 78% to levetiracetam, 83% to midazolam, 89% to phenobarbital, 93% to propofol, and 50% to valproic acid. The response to PHT/fosphenytoin

Table 1
Demographic data.

Population	Number (%)
Age	
<1 year	10 (6%)
1–18 years	65 (38%)
19–65 years	65 (38%)
>65 years	30 (18%)
Gender	
M	77 (45%)
F	93 (55%)
H/O epilepsy	
Y	117 (69%)
N	53 (31%)
Type of epilepsy	
SLRE	69 (59%)
SGE	20 (17%)
CLRE	18 (15%)
IGE	3 (3%)
UNK	7 (6%)
Etiology of GCSE	
Acute symptomatic	61 (34%)
Chronic symptomatic	12 (7%)
Epilepsy	88 (50%)
Febrile seizure	6 (3%)
UNK	10 (6%)
First place of treatment	
Academic hospital ED	121 (68%)
Community hospital ED	56 (32%)

SLRE = symptomatic localization related epilepsy, SGE = symptomatic generalized epilepsy, CLRE- cryptogenic localization related epilepsy, IGE = idiopathic generalized epilepsy, UNK = unknown, GCSE = generalized convulsive status epilepticus.