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ORIGINAL ARTICLE

Practice Variations in the Management of Status Epilepticus

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Abstract
Background Numerous anticonvulsant agents are now available for treating status epilepticus (SE). However, a paucity of data is available to guide clinicians in the initial treatment of seizures or SE. This study describes the current strategies being employed to treat SE in the USA.
Methods Fifteen American academic medical centers completed a retrospective, multicenter, observational study by reviewing 10–20 of the most recent cases of SE at their institution prior to December 31, 2009. A multivariate analysis was performed to determine factors associated with cessation of seizures.
Results A total of 150 patients were included. Most patients with SE had a seizure disorder (58 %). SE patients required a median of 3 AEDs for treatment. Three quarters of patients received a benzodiazepine as first-line therapy (74.7 %). Phenytoin (33.3 %) and levetiracetam (10 %) were commonly used as the second AED. Continuous infusions of propofol, barbiturate, or benzodiazepine were used in 36 % of patients. Median time to resolution of SE was 1 day and was positively associated with presence of a complex partial seizure, AED non-compliance prior to admission, and lorazepam plus another AED as initial therapy. Prolonged ICU length of stay and topiramate therapy prior to admission were negatively associated with SE resolution. Mortality was higher in patients without a history of seizure (22.2 vs 6.9 %, $p = 0.006$).

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Conclusions The use of a benzodiazepine followed by an AED, such as phenytoin or levetiracetam, is common as first and second-line therapy for SE and appears to be associated with a shorter time to SE resolution. AED selection thereafter is highly variable. Patients without a history of seizure who develop SE had a higher mortality rate.

Keywords Seizure · Phenytoin · Levetiracetam · Benzodiazepine · Epilepsy

Introduction

Approximately 150,000 admissions for status epilepticus (SE) occur in the United States annually, approaching nearly a 30 % mortality rate, with elderly individuals at a much higher risk of death than younger patients [1, 2]. SE occurs because of various causes including traumatic brain injury, brain tumor, stroke, and exacerbation of seizure disorders [3]. Outcomes after SE vary greatly in the existing literature. Patients treated for out-of-hospital SE returned to baseline upon discharge in 74 % of cases with an overall mortality rate of 9.4 %, whereas 30-day outcomes for patients with in-hospital SE are far worse [4]. The Veterans Affairs Cooperative Study demonstrated a mortality rate of 27 %, with 50 % of patients being discharged from the hospital at 30 days for patients in convulsive SE [5]. In general, the success rate of any single agent for the initial treatment of SE is low, ranging between 40 and 60 % and diminishes dramatically if the first agent fails and with a more prolonged seizure duration [5].

Clinical trials have demonstrated that the preferred agent for initial treatment of SE is lorazepam, though a recent major study suggests intramuscular midazolam is also a primary option for treatment [4–6]. Benzodiazepine therapy seems to have the highest initial response rate for early SE. However, over the last 10 years, numerous antiepileptic drugs (AEDs) have become available that may also have a role in treating acute seizure disorders such as SE. Although traditional AEDs for SE, such as phenytoin, valproic acid, and phenobarbital, represent the current cornerstone of SE therapy, the paucity of evidence demonstrating the efficacy of the various traditional AEDs has led to great interest in utilizing these newly available AEDs in this acute situation [5, 7–13]. AEDs such as valproic acid, levetiracetam, and lacosamide are available as intravenous preparations, which allows for rapid administration, and are generally safer to administer intravenously than the older traditional AEDs (particularly from a cardiovascular and dermatologic standpoint) [14, 15]. These agents, and others such as topiramate, have a broad spectrum of activity for a variety of different seizure types, which may extend the efficacy of these agents in SE [16, 17]. However, no rigorous comparative, clinical trials have been completed to test the efficacy and safety of any of these newer agents for SE. As a result, no definitive recommendations can be made on the preferential AEDs to be used after benzodiazepine therapy for SE, leading to significant practice variation [2, 18].

This study was conducted to evaluate the current strategies being employed to treat SE in the United States hospitals and describe patient characteristics in this population.

Methods

This study was a multicenter, retrospective, observational one conducted across 15 hospitals in the United States. Each center reviewed a target number of 10 cases of SE based on the corresponding ICD-9 code (345.3) and recorded their data in a secure online database (SurveyMonkey™, Palo Alto, CA). Patients were included if they were adults (at least 18 years of age) and were admitted with a primary or secondary diagnosis of SE between the dates of January 1, 2009 and December 31, 2009 in reverse chronological order. Each center obtained approval from their local institutional review board (IRB) and was subject to regulation by the primary governing IRB.

The primary objective of the study was to evaluate the current pharmacologic management and practice variation associated with the treatment of SE. Secondary objectives included describing the characteristics of patients with SE including etiology of SE, the seizure type on presentation, intensive care unit (ICU), and hospital length of stay, and disposition upon discharge. In addition, an analysis of the timing of treatment, the pharmacologic agents used to treat SE, and the order in which specific agents were used, was performed. For the purposes of this analysis, fosphenytoin and phenytoin were combined into the same category ("phenytoin"). SE was designated as terminated with the administration of the last AED or if a specific time was documented in the medical record. Organ dysfunction evident in patients with SE was identified via documentation in the medical record and specific laboratory value definitions. Renal dysfunction was defined as a serum creatinine >1.5 mg/dl, and hepatic dysfunction was defined as liver function tests values >3 times their normal value. In patients that received numerous doses of benzodiazepines, repeated doses that were near together in time were categorized as the same dose whereas doses that were remote or separated by the administration of another AED were characterized as different dose administrations. This categorization was based primarily by the investigator collecting the data.

The statistical analysis consisted of descriptive statistics for the population demographics. A multivariate analysis was performed to define the relationship between selection of AEDs, timing of therapy, etiology of SE, and seizure cessation and outcome. Subgroup analysis of patients with a history of seizure disorder was also performed, since those patients are suspected to have a different prognosis when presenting with SE as compared with patients with an acute reason for developing SE such as traumatic brain injury or stroke.

Multivariate analysis for time to resolution of SE was based on the GLIMMIX procedure (SAS Institute, Inc.) using gamma distribution with log link function for the outcome and using the random-effects model to account for variance among the hospitals. The GLIMMIX Procedure used for the multivariate analysis of these data is a relatively new type of statistical process. In our study, the random-effects model was chosen to model the relationship between each hospital, and gamma distribution was chosen to model the time to resolution. By using random-effects model, we are controlling for the correlation between patients from the same hospital by sharing specific but unobserved properties of the respective hospital site. The GLIMMIX Procedure incorporates both gamma distribution and the random-effects model into one succinct multivariate analysis.

Results

Patient Demographics

A total of 150 patients were included in this retrospective study of SE practice across 15 institutions. The characteristics of the population are summarized in Table 1. The study population was 56 % male with a mean (standard deviation) age of 51 years (17.7). Over half of the patients presenting with SE (58 %) had a documented, previous history of a seizure disorder. Of the patients with a seizure disorder, 93.1 % were receiving AED therapy before admission. Conversely, in patients with no seizure disorder, 14.3 % were receiving AED therapy when admitted to the facility where SE was treated. The majority of these patients appeared to be receiving prophylactic AEDs for other indications such as brain infection or TBI, and had been initiated at an outside facility. Only one patient with no documented seizure disorder appeared to have been receiving AEDs as an outpatient (a liver dysfunction patient admitted for drug withdrawal). Patients developing SE with no previous history of seizure disorder were significantly older than those who had a seizure disorder. A number of patients also presented with organ dysfunction likely to affect the prescribing and dosing of AEDs such as renal dysfunction (14.7 %) and hepatic dysfunction (7.3 %).

Table 1 Patient characteristics

Characteristic	Total population ($n = 150$)	With seizure history ($n = 87$)	Without seizure history ($n = 63$)	p value*
Age, years (SD)	51 (17.7)	44.9 (15.1)	59.3 (17.6)	<0.0001
Male gender, *n* (%)	84 (56 %)	48 (55.2 %)	36 (57.1 %)	0.872
Weight, kg (SD)	77 (20.6)	75.5 (19.4)	79.1 (22.1)	0.284
BMI, kg/m^2 (SD)	26.4 (6.3)	26.5 (6)	26.4 (6.8)	0.938
Taking antiepileptic drug prior to presentation, *n* (%)	90 (60 %)	81 (93.1 %)	9 (14.3 %)	<0.0001
Number of AEDs per patient prior to presentation, median (IQR) ($n = 90$)	2 (1–2)	2 (1–2)	1 (1–2)	0.100
EEG abnormalities				
Generalized epileptiform activity, *n* (%)	99 (66 %)	57 (65.5 %)	42 (66.7 %)	0.883
Complex partial, *n* (%)	26 (17.3 %)	18 (20.7 %)	8 (12.7 %)	0.202
Simple partial, *n* (%)	5 (3.3 %)	4 (4.6 %)	2 (3.2 %)	0.661
Non-convulsive SE, *n* (%)	10 (6.7 %)	4 (4.6 %)	6 (9.5 %)	0.232
Other, *n* (%)	10 (6.7 %)	4 (4.6 %)	5 (7.9 %)	0.395
Outcomes				
ICU LOS, median (IQR)	3 (1–8)	2 (0–7)	4 (2–10)	0.626
Hospital LOS, median (IQR)	7 (3–14)	5 (3–11)	10 (5–20)	0.227
Mortality rate, *n* (%)	20 (13.3 %)	6 (6.9 %)	14 (22.2 %)	0.006

Data are represented as mean (standard deviation) or median (interquartile range), as appropriate

* p value comparing patients with seizure history versus without seizure history

The etiology of SE varied among patients but was mostly associated with an exacerbation of the pre-existing seizure disorder (44 %), AED non-compliance (18.7 %), ischemic stroke (10.7 %), drug/alcohol withdrawal (9.3 %), traumatic brain injury (8.7 %), and brain tumor (7.3 %). In patients with a prior seizure disorder, AED non-compliance or exacerbation of their disease was the principal reason for admission with SE. Patients without a history of seizure disorder were more likely to develop SE after acute events such as intracerebral hemorrhage, ischemic stroke, drug overdose, and other causes (e.g., anoxic brain injury and sepsis; Fig. 1). Patients with a previous seizure disorder primarily presented because of an exacerbation of their disease or non-adherence to prescribed AED regimens.

AED Selection and Order of Use

Patients with SE required a median of 3 (IQR 2–4) AEDs for treatment (Fig. 2). The selection of AED for initial therapy was relatively predictable. Three quarters of patients received a benzodiazepine as the first agent (74.7 %) for SE, the majority of which was lorazepam. Only 8.7 % of the patients received phenytoin as the first agent (Fig. 3). Interestingly, 33.3 % of patients received a second regimen of benzodiazepine (in some cases, this represents a continuous infusion, whereas others gave separate bolus doses from the first round of agents). AEDs such as phenytoin (33.3 %) and levetiracetam (10 %) were more commonly selected as the second agent. Dosing of phenytoin products was inconsistently documented, but loading doses were typically used (ranging from 10 to 20 mg/kg). Overall, nearly all patients received a benzodiazepine plus an additional AED as the initial two agents in their treatment for SE. However, only 30 % of patients in this study required two or fewer agents for seizure resolution.

The selection of AEDs after the initial two agents was much more variable (Fig. 3). Numerous patients continued to receive benzodiazepines (both as repeated bolus doses and as an infusion, 23.3 % of patients outside of the initial 2 agents selected), while other AEDs such as phenytoin (30.7 %) and levetiracetam (24.7 %) were also commonly

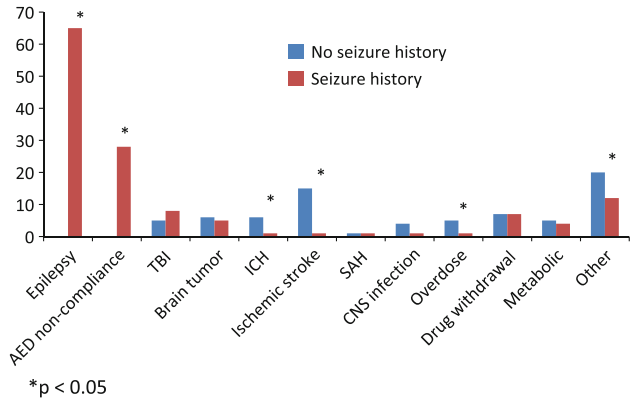

Fig. 1 Presumed etiology of SE

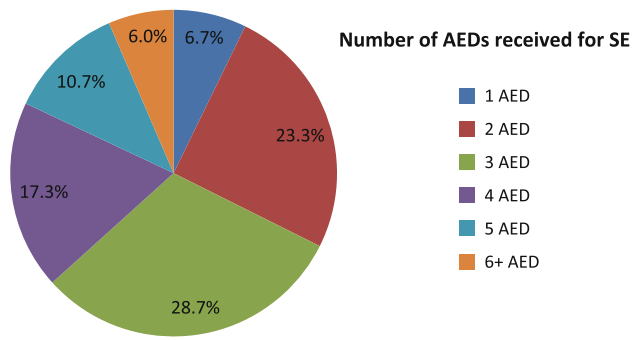

Fig. 2 % of patients that required 1, 2, 3, 4, 5, and 6+ AEDs

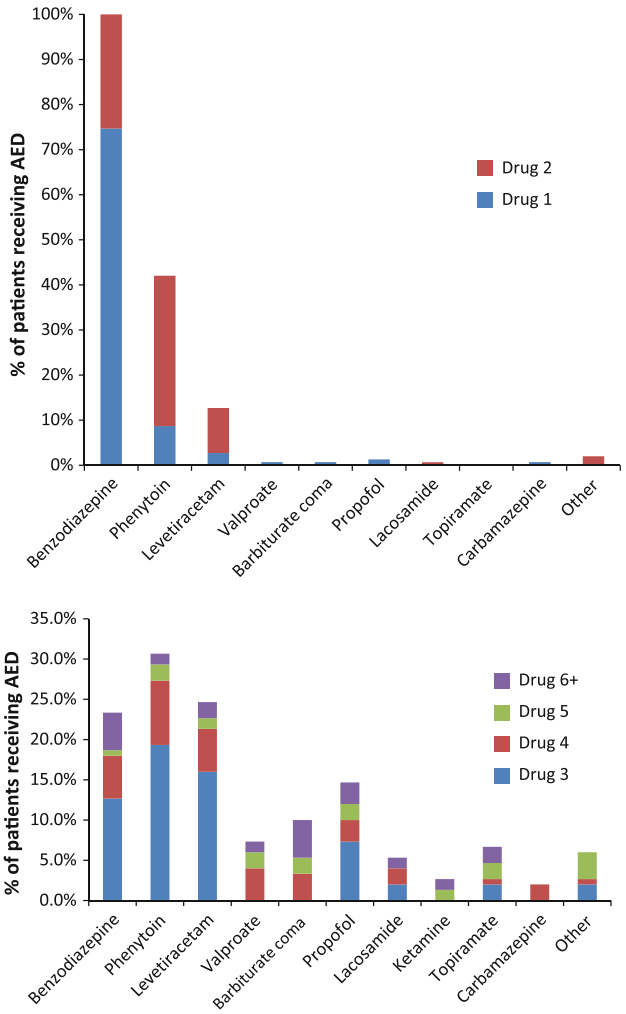

Fig. 3 % of patients that received AEDs in a cumulative manner

employed. Agents such as valproic acid and topiramate were used infrequently as initial agents and sparingly even in patients requiring 3 or more AEDs (valproic acid 8 %, topiramate 6.7 % overall). Lacosamide was approved just before the data collection period began, so the use of this agent for SE was also low overall (5.3 %) and was typically seen in patients requiring three or more AEDs. Continuous infusions of propofol, midazolam, or pentobarbital were used in 36 % of patients overall. The place in therapy for continuous infusions varied widely. Only 17 % of patients received a continuous infusion as the second AED, whereas 56 % of patients received a continuous infusion if they needed 5 or more AEDs.

Clinical response rate

The time to resolution of SE was a median of 1 day (IQR 1–2, with a maximum time to resolution of >21 days in three patients). Several factors were associated with a shorter time to resolution including the presence of complex partial seizure activity (hazard ratio 0.643, $p = 0.04$), or AED non-compliance as an etiology for SE (hazard ratio 0.574, $p = 0.03$). In addition, a faster resolution of SE was associated with a hospital stay <3 days (hazard ratio 0.603, $p = 0.01$). The selection of initial treatment was also significantly associated with a shorter time to resolution. Patients receiving lorazepam as the initial drug (hazard ratio 0.524, $p = 0.04$), or lorazepam plus another AED (hazard ratio 0.435, $p = 0.008$) had a lower time to resolution. Two factors were associated with a prolonged time to resolution: ICU stay >14 days (hazard ratio 2.24, $p = 0.001$) and receipt of topiramate as a home medication (hazard ratio 1.69, $p = 0.049$).

Outcomes at Discharge

The median ICU length of stay for the study population was 3 days (IQR 1–8), while the hospital length of stay was a median of 7 days (IQR 3–14). Nearly half of the patients included were discharged home (44.7 %), while 18.7 % continued with a long-term care facility, and 11.3 % referred to an acute rehabilitation facility. Only 4 % of patients were ventilator-dependent or in a persistent vegetative state, while 13.3 % of patients died during their admission for SE. The mortality rate was significantly higher in the patients who did not have a seizure history (22.2 vs 6.9 %, $p = 0.006$).

Before admission for SE, 40 % of the patients had been taking an AED (Fig. 4). Of the patients taking AEDs, the median number of AEDs per patient was 2 (IQR 1–2). The most common AEDs taken before admission were phenytoin (47.8 %), levetiracetam (40 %), valproic acid (20 %), carbamazepine (13.3 %), oxcarbazepine (10 %), topiramate (10 %), and lamotrigine (8.9 %). Interestingly, 96.9 % of patients were receiving an AED at discharge and the median number of AEDs per patient upon discharge was 2 (IQR 1–5). The most common AEDs prescribed upon discharge were levetiracetam (65.1 %), phenytoin (50 %), valproic acid (14.3 %), topiramate (11.1 %), phenobarbital (7.9 %), carbamazepine (7.1 %), and lacosamide (6.3 %).

Discussion

This observational study of the treatment of SE in US hospitals suggests that initial therapy for SE is relatively predictable, with benzodiazepines and an AED (phenytoin or levetiracetam), as the initial combination of agents used. This practice matches the most recent guidelines [19]. However, while our multivariate analysis does suggest that using a benzodiazepine (specifically lorazepam) and an AED as the first two agents was associated with a shorter duration of SE, the low response rate of 30 % to the first two selected agents suggests that our current treatment approach seems relatively lacking. This low response rate is similar or perhaps slightly lower than what has been

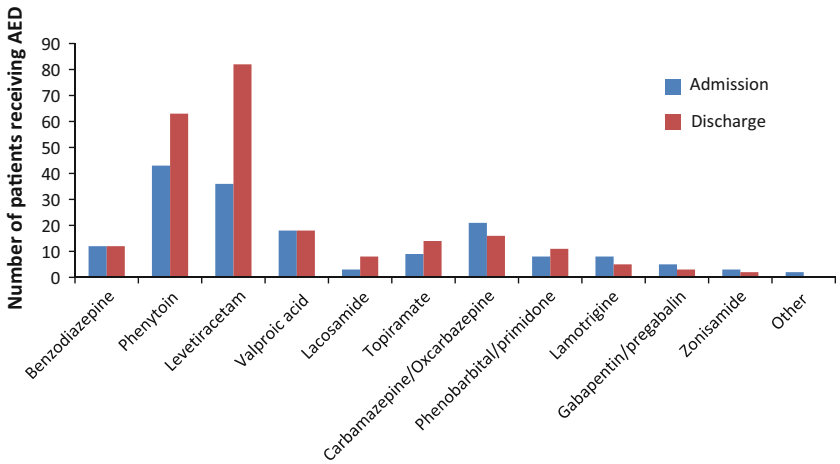

Fig. 4 AEDs before admission and upon discharge

demonstrated in the available clinical literature [4–6]. Most of the patients included in this study required three or more AEDs to stop their SE, with some requiring up to six or seven agents with duration of seizures lasting in a few cases of greater than 3 weeks. Although it is clear that most clinicians are practicing as recommended by the guidelines, it is also clear that this practice may not work for many of the patients with SE, who require numerous therapies before seizures abate.

The AEDs utilized after the initial two agents failed were far less static. A variety of AEDs were prescribed as the third, the fourth, the fifth (and so on) agents in the regimen, most commonly including phenytoin and levetiracetam, with other AEDs, such as valproic acid, lacosamide, topiramate, and carbamazepine seeing sporadic use as well. Our multivariate analysis failed to find any association with the use of a particular agent for the third line therapy and cessation of seizures. Several agents which have been postulated to have unique efficacy in patients with refractory SE, such as ketamine, lacosamide, and topiramate, were used in later stages of SE in this study [7, 9, 16, 17, 20–26]. However, these agents were not used with enough frequency for any meaningful conclusions to be garnered. The place in therapy for continuous infusions varied widely and midazolam, pentobarbital, or propofol infusions were not associated with cessation of seizures or any effect on mortality. This was not surprising due to the small sample size and lack of power to determine these outcomes.

The AEDs most commonly used as the first agents (aside from benzodiazepines) were phenytoin and levetiracetam. Similarly, these two agents were also the most commonly added agents after the initial benzodiazepine therapy had failed. Though the available clinical evidence is the most supportive of phenytoin at this point, there seems to be a growing trend among clinicians for using levetiracetam in the setting of acute seizure, which the results of our study also seem to corroborate. These two agents were also significantly most likely to be continued upon the patients' discharge from the hospital (phenytoin OR 1.69, $p < 0.001$; levetiracetam OR 2.63, $p < 0.001$). In general, patients with no seizure history were discharged from the hospital on either phenytoin or levetiracetam with few exceptions (20 % of patients received both on discharge), whereas the variety of AEDs prescribed to patients with a seizure disorder was far wider.

As might be expected, the cohort of patients presenting with SE who had a prior history of a seizure disorder differed greatly from those patients who developed SE from other causes. Patients with a history of seizure disorder, who were more likely to be admitted on prior AEDs from home, were younger, and had a significantly lower mortality rate than patients with no history of a seizure disorder. In most instances, patients with pre-existing seizure disorder were admitted because of an exacerbation of their disease or AED non-compliance. In contrast, the cohort of patients with no seizure disorder developed SE associated with a variety of different causes including stroke, brain trauma, and malignancy. The seizure type was similar between the two groups, as was the length of stay, both in the ICU and the hospital. The reasons for prolonged duration were not collected, and would be difficult to discern with a retrospective study design, but these data seem to indicate that patients developing SE often require prolonged hospital care, independent of the etiology. Mortality was higher in the patients with no seizure history, likely because the non-seizure disorder etiology such as stroke or brain trauma is the principal determining factor which factored in the ultimate outcome for those patients.

There was no relationship between the AEDs taken before admission in patients with a seizure disorder and the AEDs initiated upon developing SE in the hospital. In practice, this scenario typically results in one of two responses by the clinician. First, administration of the same AED as the patient was taking at home to optimize the serum concentrations, particularly in the case of known non-compliance. Conversely, a different AED (preferably one with a different mechanism of action) may be administered to have additive or synergistic activity with the AEDs already being taken by the patient. There did seem to be a significant association of the receipt of topiramate at home before developing SE. Interestingly, taking topiramate at home was associated with a longer time to seizure cessation (HR 1.69, $p = 0.049$). One possible explanation for this may be that topiramate is being used more commonly in patients with refractory seizure disorders. Therefore, patients already on topiramate may be less likely to respond well to initial benzodiazepine and AED therapy, and their seizure may be more treatment refractory. Another possibility is that topiramate is currently only available as an oral product and resuming effective home doses of this agent can be problematic in critically ill patients who lack enteral or oral access, thereby prolonging the time to effective therapy and seizure cessation.

This study has several limitations which merit mentioning. First, because of the retrospective study design, identifying the precise moment that seizures began for most patients was impossible. We relied upon ICD-9 codes to identify patients diagnosed with SE, rather than the clinical definition of unremitting seizure for greater than five minutes [2, 27]. Using ICD-9 codes is often fraught with difficulty, as some patients with brief episodes of SE may not have been appropriately coded and may have escaped inclusion in our analysis. As for refractory SE, it is well known that non-convulsive SE may occur for hours to days in some patients before being detected, yielding a treatment refractory situation in many cases. This was also

difficult to detect given the retrospective nature of the study. For the purposes of this study, we used the need for extensive clinical treatment (>2 agents) as a surrogate for refractory SE. Second, some data points were missing or were incompletely documented. This included the order in which the initial AEDs were administered, particularly if the agents were administered at another facility or en route to the admitting center. In this case, we assigned the benzodiazepine as the first drug given. In addition, some routes of administration were not available. For instance, nearly all the patients (94.7 %) received their first two AEDs by the intravenous route when the route was documented. However, 27 % of all the patients did not have the route of their initial therapies documented. Improvements in documentation of out-of-hospital AED administration routes may help facility in-hospital treatment practices.

Conclusion

This retrospective analysis of clinical practice revealed that patients with SE are receiving benzodiazepines as initial therapy the vast majority of the time. This analysis was conducted before the publication of the RAMPART study, and so it is likely that the use of intramuscular midazolam may supplant some of the intravenous lorazepam use as this study infiltrates the current practice. Subsequent AED options are prescribed with a great variety, though phenytoin is the most commonly used as the second agent. Continuous infusions of anesthetic agents were used in over one-third of patients, though typically after 2–3 other agents have been used in patients with refractory SE. The cohort of our study population with a history of a seizure disorder had a lower mortality rate compared to those presenting with SE because of other etiologies such as stroke or trauma. There is a wide variety of AEDs being prescribed for patients with SE and new, viable options continue to be developed for the treatment of acute seizures. A concerted effort to evaluate the safety and efficacy of various AEDs in the setting of SE, as well as developing an evidence-based treatment approach, is necessary to ensure utilization of the most effective AEDs and to optimize time to effective therapy.

References

1. DeLorenzo RJ, Pellock JM, Towne AR, Boggs JG. Epidemiology of status epilepticus. J Clin Neurophysiol. 1995;12(4):316–25.
2. Chen JW, Wasterlain CG. Status epilepticus: pathophysiology and management in adults. Lancet Neurol. 2006;5(3):246–56.
3. DeLorenzo RJ. Management of status epilepticus. Va Med Q. 1996;123(2):103–11.
4. Alldredge BK, Gelb AM, Isaacs SM, et al. A comparison of lorazepam, diazepam, and placebo for the treatment of out-of-hospital status epilepticus. N Engl J Med. 2001;345(9):631–7.
5. Treiman DM, Meyers PD, Walton NY, et al. A comparison of four treatments for generalized convulsive status epilepticus. Veterans Affairs Status Epilepticus Cooperative Study Group. N Engl J Med. 1998;339(12):792–8.
6. Silbergleit R, Durkalski V, Lowenstein D, et al. Intramuscular versus intravenous therapy for prehospital status epilepticus. N Engl J Med. 2012;366(7):591–600.
7. Goodwin H, Hinson HE, Shermock KM, Karanjia N, Lewin JJ III. The use of lacosamide in refractory status epilepticus. Neurocrit Care. 2011;14(3):348–53.
8. Hodges BM, Mazur JE. Intravenous valproate in status epilepticus. Ann Pharmacother. 2001;35:1465–70.
9. Kellinghaus C, Berning S, Besselmann M. Intravenous lacosamide as successful treatment for nonconvulsive status epilepticus after failure of first-line therapy. Epilepsy Behav. 2009;14:429–31.
10. Eue S, Grumbt M, Muller M, Schulze A. Two years of experience in the treatment of status epilepticus with intravenous levetiracetam. Epilepsy Behav. 2009;15(4):467–9.
11. Patel NC, Landan IR, Levin J, Szaflarski J, Wilner AN. The use of levetiracetam in refractory status epilepticus. Seizure. 2006;15(3):137–41.
12. Rossetti AO, Bromfield EB. Levetiracetam in the treatment of status epilepticus in adults: a study of 13 episodes. Eur Neurol. 2005;54(1):34–8.
13. Rupprecht S, Franke K, Fitzek S, Witte OW, Hagemann G. Levetiracetam as a treatment option in non-convulsive status epilepticus. Epilepsy Res. 2007;73(3):238–44.
14. Wilby J, Kainth A, Hawkins N, et al. Clinical effectiveness, tolerability and cost-effectiveness of newer drugs for epilepsy in adults: a systematic review and economic evaluation. Health Technol Assess. 2005;9(15):1–157, iii–iv.
15. Arif H, Buchsbaum R, Weintraub D, et al. Comparison and predictors of rash associated with 15 antiepileptic drugs. Neurology. 2007;68:1701–9.
16. Bensalem MK, Fakhoury TA. Topiramate and status epilepticus: report of three cases. Epilepsy Behav. 2003;4(6):757–60.
17. Tarulli A, Drislane FW. The use of topiramate in refractory status epilepticus. Neurology. 2004;62(5):837.
18. Tesoro EP, Brophy GM. Pharmacological management of seizures and status epilepticus in critically ill patients. J Pharm Pract. 2010;23(5):441–54.
19. Meierkord H, Boon P, Engelsen B, et al. EFNS guideline on the management of status epilepticus in adults. Eur J Neurol. 2010;17(3):348–55.
20. Pruss H, Holtkamp M. Ketamine successfully terminates malignant status epilepticus. Epilepsy Res. 2008;82:219–22.
21. Hsieh CY, Sung PS, Tsai JJ, Huang CW. Terminating prolonged refractory status epilepticus using ketamine. Clin Neuropharmacol. 2010;33(3):165–7.
22. Borris DJ, Bertram EH, Kapur J. Ketamine controls prolonged status epilepticus. Epilepsy Res. 2000;42(2–3):117–22.
23. Sheth RD, Gidal BE. Refractory status epilepticus: response to ketamine. Neurology. 1998;51(6):1765–6.
24. Albers JM, Moddel G, Dittrich R, et al. Intravenous lacosamide—an effective add-on treatment of refractory status epilepticus. Seizure. 2011;20(5):428–30.
25. Koubeissi MZ, Mayor CL, Estephan B, Rashid S, Azar NJ. Efficacy and safety of intravenous lacosamide in refractory nonconvulsive status epilepticus. Acta Neurol Scand. 2011;123(2):142–6.
26. Kellinghaus C, Berning S, Immisch I, et al. Intravenous lacosamide for treatment of status epilepticus. Acta Neurol Scand. 2010;123(2):137–41.
27. Lowenstein DH, Alldredge BK. Status epilepticus. N Engl J Med. 1998;338(14):970–6.