Seizure 22 (2013) 467–471

Contents lists available at SciVerse ScienceDirect

Seizure

journal homepage: www.elsevier.com/locate/yseiz

Treatment of electrographic seizures and status epilepticus in critically ill children: A single center experience

Nicholas S. Abend [a,b,*], Sarah M. Sanchez [a,b], Robert A. Berg [c], Dennis J. Dlugos [a,b], Alexis A. Topjian [c]

[a] Division of Neurology, The Perelman School of Medicine at the University of Pennsylvania, United States
[b] Department of Pediatrics, The Children's Hospital of Philadelphia and the Perelman School of Medicine at the University of Pennsylvania, United States
[c] Department of Anesthesiology and Critical Care Medicine, The Children's Hospital of Philadelphia and the Perelman School of Medicine at the University of Pennsylvania, United States

ARTICLE INFO

Article history:
Received 29 January 2013
Received in revised form 19 March 2013
Accepted 20 March 2013

Keywords:
Seizure
Status epilepticus
Pediatric
Critically ill
Electroencephalogram
Anticonvulsant
Phenytoin
Fosphenytoin
Phenobarbital
Levetiracetam

ABSTRACT

Purpose: Electrographic seizures (ES) and electrographic status epilepticus (ESE) are common in encephalopathic children in the pediatric intensive care unit (PICU) and associated with worse short-term outcome. Survey data indicate most physicians treat ES and ESE with antiepileptic drugs (AEDs), but few data are available regarding AED usage patterns. We aimed to describe AED usage for ES and ESE in critically ill children.
Methods: We performed an observational study of patients who underwent continuous electroencephalographic (cEEG) monitoring in the PICU of a single quaternary care children's hospital. We collected data regarding age, clinical diagnoses, ES and ESE occurrence, and AEDs utilized.
Results: 200 subjects underwent cEEG. ES occurred in 21% (41/200) and ESE occurred in 22% (43/200). Of the 84 patients with ES or ESE, 80 received non-benzodiazepine AEDs including 48% (38 of 80) with ES and 52% (42 of 80) with ESE. The most commonly administered first AEDs were levetiracetam in 38% (30/80), phenobarbital in 31% (25/80), phenytoin–fosphenytoin in 28% (22/80), and valproate in 4% (3/80). Seizures terminated after administration of the first AED in 74% (28/38) with ES and 22% (9/41) with ESE.
Conclusions: Levetiracetam, phenobarbital, and phenytoin–fosphenytoin are commonly used to manage ES and ESE at our center. Over half of subjects received multiple AEDs.

1. Introduction

Continuous EEG monitoring (cEEG) is often utilized to identify electrographic seizures (ES) and electrographic status epilepticus (ESE) in children in the pediatric intensive care unit (PICU),[1] and recent survey data indicate cEEG use is increasing in North America.[2] ES and ESE occur in 7–47% of critically ill children who undergo cEEG[3–14] and several studies have reported an association between ES and ESE and worse short-term outcome.[13–16] When surveyed, most physicians reported that they initiated antiepileptic drugs (AEDs) in response to ES or ESE, but there was substantial variability in the specific AEDs they reported administering.[17] Further, survey responses may not reflect true practice. Data regarding AED usage patterns will help guide clinical management and develop feasible prospective AED effectiveness studies. We aimed to determine which AEDs are used to manage ES and ESE in children in our PICU.

2. Patients and methods

Children treated in the PICU of a quaternary care referral hospital who underwent clinically indicated cEEG between July 2008 and January 2011 were enrolled in a prospective observational study aimed at identifying ES-ESE risk factors[18] and the impact of ES-ESE on short-term outcome.[15] Informed written consent was obtained from the parents/guardians of patients for inclusion in the database. Neonates (<1 month) were excluded. This study was approved by the Children's Hospital of Philadelphia Institutional Review Board.

Our institution's criteria for cEEG in the PICU were: (1) altered mental status persisting for 1–2 h after a convulsion or convulsive status epilepticus, (2) altered mental status without a preceding convulsion in a patient with an acute neurologic disorder, or (3) altered mental status and the presence of abnormal movements or vital sign fluctuations of unknown etiology. Per our clinical pathway, patients underwent cEEG for at least 24 h when screening for ES, unless they were undergoing therapeutic

* Corresponding author at: Division of Neurology, The Children's Hospital of Philadelphia, 34th Street and Civic Center Blvd, Philadelphia, PA 19104, United States. Tel.: +1 215 590 1719; fax: +1 215 590 1771.
E-mail address: abend@email.chop.edu (N.S. Abend).

1059-1311
http://dx.doi.org/10.1016/j.seizure.2013.03.008

hypothermia after cardiac arrest resuscitation, in which case they were monitored for 72 h. Patients with ES or ESE identified by cEEG were monitored for approximately 24 h after their last seizure. Continuous EEG monitoring was performed using a Grass-Telefactor (Grass Technology, West Warwick, RI) video-EEG system with 21 gold-over-silver scalp surface electrodes positioned according to the international 10–20 system and affixed with collodion adhesive. EEGs were interpreted by the Neurophysiology Service. Patients were managed by the Critical Care and Neurology Consult services. There is no institutional pathway for ES or ESE management so each physician made independent management decisions. Prophylactic AEDs are not administered.

Clinical and EEG data were prospectively collected including patient age, underlying acute neurologic disorder category, EEG findings including ES or ESE occurrence, and AED usage. Patients were assigned to one acute neurologic disorder category: (1) history of epilepsy with altered mental status following a seizure or status epilepticus, (2) hypoxic ischemic encephalopathy, (3) encephalitis, (4) traumatic brain injury, (5) stroke, (6) sepsis, (7) posterior reversible leukoencephalopathy syndrome, (8) neurosurgical procedure, (9) provoked seizures (such as febrile seizures), or (10) systemic/metabolic disorders (such as electrolyte abnormalities or hepatic encephalopathy). EEG tracings were reviewed by an investigator to provide standardized categorization of ES and ESE. Seizures were classified as ES or ESE based on the seizure burden at the administration time of the initial AED. ES was defined as an abnormal paroxysmal EEG event that was different from the background lasting longer than 10 s with a temporal-spatial evolution in morphology, frequency, and amplitude, and with a plausible electrographic field. ESE was defined as either a single 30-min ES or a series of recurrent independent ES totaling more than 30 min in any 1-h period (50% seizure burden).

We performed an exploratory analysis of seizure termination following administration of an initial AED. We described the use of intravenous benzodiazepines and AEDs. Patients received benzodiazepines for both sedation and seizures, but delineation of reason was not possible from the chart review. AED's described were levetiracetam, phenobarbital, phenytoin/fosphenytoin and valproate. An AED was considered effective if within 30 min of AED administration the patient became seizure free and had no seizure recurrence for at least 12 h without administration of any new AED. During the 12 h seizure-free period AED maintenance doses and benzodiazepines could be administered.

Descriptive statistics are reported as median and interquartile ranges (IQR) for non-parametric data. The Chi-squared or Fishers Exact tests were used to determine the association between categorical variables. The Wilcoxon rank-sum and Kruskal–Wallis tests were used to test the association between continuous non-parametric data.

3. Results

During the study period 241 patients underwent cEEG. Forty-one were not enrolled due to refusal (4), legal guardianship issues (2), lack of study staff available for enrollment during their hospitalization (17), or lack of parents available at bedside for in-person consent (18). This led to 200 enrolled subjects. ES occurred in 41 of 200 (21%) and ESE occurred in 43 of 200 (22%). AEDs were administered during cEEG to 95% (80 of 84) of subjects with ES or ESE including 48% (38 of 80) with ES and 52% (42 of 80) with ESE. Four subjects with seizures (3 with ES and 1 with ESE) did not receive AEDs: three had brief ES which resolved prior to treatment including 1 with stroke, 2 with hypoxic ischemic encephalopathy, and one with ESE hypoxic ischemic encephalopathy who had withdrawal of technologic support prior to seizure treatment. Descriptive characteristics regarding the 80 subjects who received AEDs are provided in Table 1. Prior to ES or ESE onset, benzodiazepines were being administered for sedation to 59% (47 of 80) of subjects. Midazolam was the only benzodiazepine administered as an infusion while boluses included diazepam, lorazepam, and midazolam. Once ES or ESE were identified, most patients continued to receive bolus doses of benzodiazepine but the indication (seizure management versus sedation) could not be determined from chart review so efficacy analyses were not performed. The most commonly administered first AEDs were levetiracetam in 38% (30 of 80) of subjects at a median dose of 23 mg/kg intravenously (IQR 20, 30), phenobarbital in 31% (25 of 80) of subjects at a median dose of 20 mg/kg intravenously (IQR 12, 23), phenytoin–fosphenytoin in 28% (22 of 80) of subjects at a median dose of 20 mg/kg intravenously (IQR 14, 20), and valproate in 4% (3 of 80) of subjects at a median dose of 22 mg/kg intravenously (IQR 20, 30) (Fig. 1). Phenobarbital was the first AED given to younger children with a median age 0.25 years (IQR 0.17, 0.5), compared to phenytoin–fosphenytoin at 4.6 years (IQR 1.75, 10) and levetiracetam at 5.4 years (IQR 1, 10) ($p < 0.001$). There was no difference in the frequency of AED administered based on gender ($p = 0.17$) or seizure classification as ES or ESE ($p = 0.13$).

Of the 80 subjects administered AEDs, 48% (38 of 80) received one AED, 23% (18 of 80) received two AEDs, 8% (7 of 80) received three AEDs, and 21% (17 of 80) received $\geq$4 AEDs (Fig. 2). Of the 38 subjects with ES, 76% (29 of 38) received one AED, 16% (6 of 38) received two AEDs, 5% (2 of 38) received 3 AEDs, and 3% (1 of 38) received $\geq$4 AEDs. Of the 42 subjects with ESE, 21% (9 of 42) received one AED, 29% (12 of 42) received two AEDs, 12% (5 of 42) received 3 AEDs, and 38% (16 of 42) received $\geq$4 AEDs. ESE management required pentobarbital infusion, midazolam infusion, or isoflurane in 26% (11 of 42) subjects. Seizures terminated after administration of the first AED in 46% (37 of 80) of subjects including 74% (28 of 38) with ES and 21% (9 of 42) with ESE. One

Table 1
Descriptive characteristics of subjects who received AEDs.

Variable	All $N = 80$	ES (38 of 80, 48%)	ESE (42 of 80, 52%)
Age (years) median (IQR)	2.2 (0.6, 8.1)	1.4 (0.4, 3.9)	5.4 (0.6, 9.8)
Male	46 (58%)	19 (50%)	27 (64%)
AEDs prior to hospitalization	22 (28%)	12 (32%)	10 (24%)
Acute neurologic disorder			
Epilepsy	23 (29%)	13 (34%)	10 (24%)
Hypoxic ischemic encephalopathy	15 (19%)	8 (21%)	7 (17%)
Infection-autoimmune	10 (13%)	2 (5%)	8 (19%)
Stroke	7 (9%)	3 (8%)	4 (10%)
Traumatic brain injury	6 (8%)	1 (3%)	5 (12%)
Metabolic–systemic	6 (8%)	6 (16%)	0 (0%)
Neurosurgical procedure	5 (6%)	3 (8%)	2 (5%)
Posterior reversible encephalopathy syndrome	3 (4%)	1 (3%)	2 (5%)
Provoked seizures	3 (4%)	1 (3%)	2 (5%)
Sepsis	2 (3%)	0 (0%)	2 (5%)

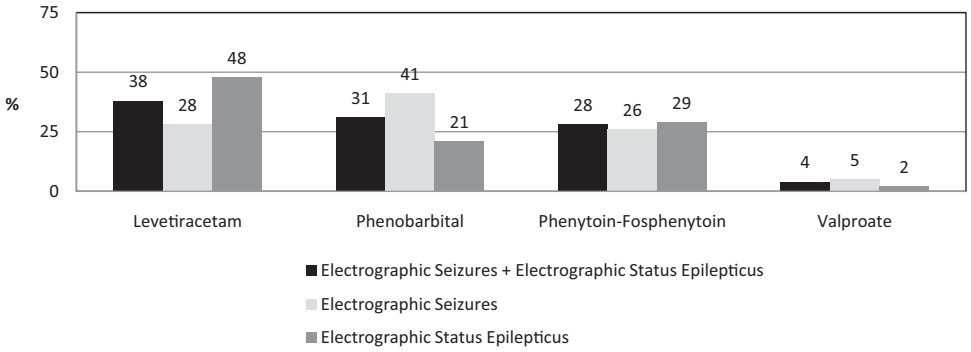

Fig. 1. Initial antiepileptic drug administered.

subject had continued ES following AED administration and was not administered additional AEDs, explaining the discrepancy between 38 receiving one AED and only 37 having ES terminated by the first AED.

We performed exploratory analyses of seizure termination following administration of various first AEDs. In this single center cohort, we failed to demonstrate a significant difference in seizure termination depending on the first administered AED (phenobarbital 64% (16 of 25), levetiracetam 40% (12 of 30), phenytoin–fosphenytoin 36% (8 of 22), and valproate 33% (1 of 3) ($p = 0.19$)). Furthermore, we failed to demonstrate a significant difference in the efficacy of any first administered AED to terminate ES ($p = 0.58$) or ESE ($p = 0.47$). For each of the first administered AEDs, we failed to demonstrate a significant difference in the median dose between those in whom seizures did and did not terminate: phenobarbital (21 mg/kg vs. 20 mg/kg, $p = 0.28$), levetiracetam (28 mg/kg vs. 20 mg/kg, $p = 0.12$), phenytoin–fosphenytoin (20 mg/kg vs. 19 mg/kg, $p = 0.19$), and valproate (30 mg/kg vs. 21 mg/kg, $p = 0.22$).

4. Discussion

This single center observational study of children with acute encephalopathy undergoing cEEG demonstrated levetiracetam, phenobarbital and phenytoin–fosphenytoin are used with similar frequencies, although phenobarbital is administered more often to younger children. ES terminated after administration of the first AED in 74% of children while ESE terminated after administration of the first AED in only 21% of children. Exploratory analysis in this small cohort failed to demonstrate a significant difference in seizure termination after administration of any of the first AEDs.

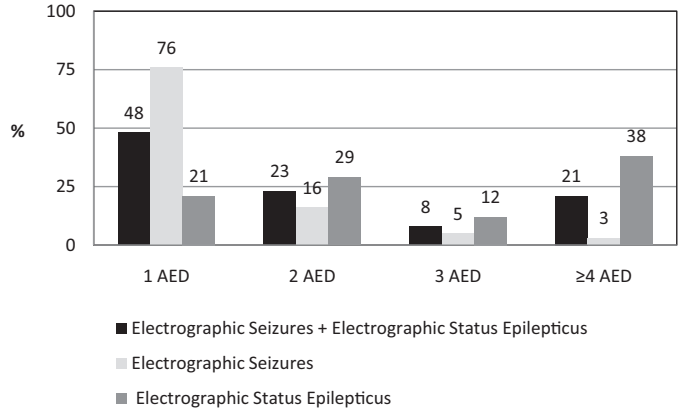

Fig. 2. Number of antiepileptic drugs (AED) administered.

When surveyed, the majority of neurologists indicate that they initiate an AED after a single ES is identified, and the majority aim to terminate all ES, escalating to utilize multiple AEDs and even pharmacologic coma induction for ES or ESE refractory to two or three typical AEDs.[17] Those survey data are consistent with data from actual practice which indicated that the most common change to clinical management as a result of cEEG was AED adjustment.[19] The current data demonstrate that when ES or ESE were identified most patients at our center received AEDs. These findings are in line with the recent Neurocritical Care Society guidelines for the evaluation and management of status epilepticus which describe that "treatment of status epilepticus should occur... until electrographic seizures are halted."[20]

Survey data indicate that lorazepam, phenytoin–fosphenytoin, and levetiracetam are the most commonly utilized AED when ES or ESE are identified.[17] However, reported use in surveys may not accurately reflect true clinical practice. Although many subjects in our cohort were receiving benzodiazepines for sedation prior to seizure identification and continued to receive benzodiazepines for sedation after seizure identification, we could not determine if benzodiazepine boluses were routinely administered or if infusions were routinely escalated due to ES or ESE. Instead, levetiracetam, phenobarbital, and phenytoin–fosphenytoin were commonly administered when ES or ESE were identified, partially establishing a state of clinical equipoise needed for future clinical trials at our institution. Recent guidelines regarding the management of convulsive and electrographic status epilepticus suggest that benzodiazepines should be given as emergent initial therapy and that most patients should also receive "urgent control therapy" with fosphenytoin–phenytoin, valproate sodium, or levetiracetam.[20] Our cohort was managed prior to publication of these guidelines and subjects generally received "urgent control therapy." The variability in the AED chosen for "urgent control therapy" is consistent with surveys[21] and observational studies[22] of status epilepticus management. While few conclusions can be drawn regarding effectiveness from these open-label observational data, there is at least a suggestion that no AED had substantially better efficacy than the other AEDs. The variability in management along with no clear signal regarding efficacy help establish that prospective rigorous comparative effectiveness investigations are necessary.

These data demonstrate that only about half of patients with ES and a quarter of patients with ESE had seizure termination after a single AED, and polypharmacy is often required at our center. Further, seizures terminated after administration of each AED in only about 30–60% of patients. While this response is disappointingly low, it is consistent with studies of AED efficacy in other populations. In a study of neonatal seizures,

phenobarbital and phenytoin only controlled 43% and 45% of seizures, respectively. Even together, the two AEDs only controlled seizures in 57–62% of neonates.[23] In 542 children, convulsive status epilepticus terminated after first-line treatment in 42%, second-line treatment in 35%, and was refractory in 22%.[24] Similarly, in children with convulsive status epilepticus upon arrival to an emergency department, seizures terminated after a first-line benzodiazepine in 65% (121/187) and after a second-line AED in 50% (41/82), with 50% (41/82) remaining refractory and requiring thiopental infusion.[25] In a study of adults with convulsive status epilepticus a median of three AEDs were administered and only 30% of subjects required two or fewer AEDs for seizure termination.[22]

Dosing of AEDs was variable, but averaged 20 mg/kg for each of the four medications. This dosing is consistent with the recent Neurocritical Care Society status epilepticus management guidelines[20] but may be on the low end. As described in the guidelines, second doses of phenytoin or phenobarbital may be administered at 5–10 mg/kg and dosing may be higher for valproate (40 mg/kg) and levetiracetam (60 mg/kg). Higher dosing may have terminated seizures in more patients, although at these middle doses no difference was found in dosing between patients in whom seizures did and did not terminate for any of the AEDs.

This observational study has limitations. First, this was a single center study which limits generalizability. Different centers may have different treatment practices regarding the speed of seizure identification, overall management approach, and specific AED choices. Thus, the state of equipoise at out center may not reflect an overall state of equipoise across centers. Surveys regarding AED management and/or multi-center studies of actual AED use are needed to better evaluate the current practice across centers. If practice regarding AED choice is not uniform then this inter-center variability could be harnessed to perform comparative effectiveness studies evaluating AED effectiveness.[26] Second, AED use was open-label and determined clinically. Thus, there was likely variability in the manner in which AEDs were escalated, peak AED doses administered, and the time interval for progressing to the next AED if seizures persisted. Treatment delays have been associated with lower response rates in children with convulsive status epilepticus.[25,27,28] However, the knowledge that ES and even ESE sometimes terminate after administration of available AEDs indicates that ES-ESE identification by cEEG has the potential to improve outcome using our current pharmacologic armamentarium. This motivates future rigorous comparative effectiveness studies of the available AEDs and overall management pathways. Third, seizure burden classification and AED refractoriness are intertwined. Seizures were classified as ES or ESE at the onset of AED management. Using this classification approach, even 50% of subjects with ESE had seizure termination with 1–2 AEDs indicating that ESE is not always a hopeless refractory condition. These data may have differed had we classified subjects as having ESE if they experienced ESE at any point. If ES responded to AED therapy then it would be unlikely to evolve into ESE. In contrast, if ES did not respond to AED therapy then it would be more likely to achieve a sufficiently high seizure burden to be classified as ESE, thereby making ESE appear even more refractory to AED therapy. Fourth, this study aimed to describe current AED use and was not powered to compare the medications. There was a non-significant trend toward seizures terminating more often following administration of phenobarbital than phenytoin–fosphenytoin or levetiracetam. However, phenobarbital was administered more often to younger patients which may bias the results. Further studies powered to compare AED efficacy are needed.

5. Conclusions

These data indicate that at our center almost all patients with ES or ESE receive AEDs that AED choice is currently in a state of equipoise, and that AED administration is often followed by ES and ESE termination. These data suggest that management is possible for many patients with ES and ESE using existing AEDs. Further study is needed to establish whether current practice across centers is at a similar state of equipoise. This framework will help ensure that future rigorous comparative effectiveness studies of AEDs for ES and ESE in critically ill children are designed in a manner that is ethical and feasible.

Funding

Dr. Abend is supported by NINDS K23NS076550.

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