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Original Article

Short-Term Response of Sleep-Potentiated Spiking to High-Dose Diazepam in Electric Status Epilepticus During Sleep

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ABSTRACT

We describe the short-term effects of high-dose oral diazepam on sleep-potentiated epileptiform activity in patients with electric status epilepticus during sleep. We enrolled patients treated with high-dose oral bedtime diazepam from 2001-2009. We defined spike percentage as the percentage of 1-second bins containing at least one spike, and calculated it during three randomly selected 5-minute samples of wakefulness throughout the day and during the first 5 minutes of every hour of non-rapid eye movement sleep at night. In this study, patients were considered to demonstrate sleep-potentiated epileptiform activity when their spike percentage during sleep was increased by ≥50% compared with wakefulness. Twenty-nine children (18 boys) were included (median age, 7.4 years). Twenty-four hours after receiving high-dose diazepam, epileptiform activity was significantly reduced (76.7% at baseline vs 40.8% 24 hours after high-dose diazepam; Wilcoxon signed ranks test, $Z = -4.287$, $P < 0.0001$). Seven patients (24.1%) manifested mild, reversible side effects during the first 48 hours after diazepam administration. High-dose oral diazepam effectively and safely reduced epileptiform activity in patients with electric status epilepticus during sleep.

Introduction

Epileptiform activity on electroencephalograms is frequently potentiated during non-rapid eye movement sleep [1,2]. The most dramatic sleep potentiation of epileptiform activity is observed during electric status epilepticus during sleep. This pattern is characterized by an increase in frequency and wider distribution of epileptiform discharges during non-rapid eye movement sleep. Epileptiform discharges may present as a near-continuous bilateral (or occasionally lateralized) pattern of slow spikes and waves that occupy a significant proportion of non-rapid eye movement sleep [3-6]. Frequent and prolonged epileptiform activity is thought to disrupt cortical information processing and the mechanisms to consolidate learning and memory [7-15]. Therefore, reducing interictal epileptiform activity could improve the prognosis of patients with electric status epilepticus in sleep [6,16-18].

However, the response of epileptiform activity to treatment has not been quantified. The transitory arrest of sleep potentiation of epileptiform activity in electric status epilepticus during sleep was observed after the administration of clonazepam [5,17,19], suggesting the usefulness of benzodiazepines in the treatment of sleep-potentiated epileptiform activity.

The shorter half-life of diazepam makes it another attractive benzodiazepine for the treatment of epileptiform activity in electric status epilepticus during sleep. The response of sleep-potentiated spiking to high-dose diazepam was described in several patients with electric status epilepticus during sleep, but this response has never been systematically quantified [10,17,20]. Accordingly, the present study was designed to close this gap. We aim to describe quantitatively the short-term response to high-dose oral diazepam treatment of sleep-potentiated

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epileptiform activity in patients with electric status epilepticus during sleep.

Methods

This study was approved by the Internal Review Board of Children's Hospital Boston (Boston, MA).

Study design

We performed a retrospective study of patients who received high-dose oral diazepam treatment as part of their clinical management.

Patients

We enrolled patients aged less than 21 years who had been admitted to the Epilepsy Monitoring Unit at Children's Hospital Boston between 2001 and 2009 for a clinical suspicion of electric status epilepticus in sleep. All patients underwent (1) at least one continuous electroencephalogram for a period of 44-96 hours, and (2) focal or generalized sleep-potentiated epileptiform activity, defined as an increase in epileptiform activity of ≥50% during non-rapid eye movement sleep, compared with wakefulness.

Inclusion in monitoring for electric status epilepticus during sleep was based on a neuropsychologic regression in at least one domain of development, accompanied in most cases by a seizure disorder. This clinical picture evolved over time, with seizure onset in infancy to early childhood, worsening of the seizure disorder and neuropsychologic regression during childhood, and eventual improvement or remission around puberty [4].

Analysis of clinical data

Clinical variables were obtained, including demographics, clinical seizures types, and comorbid neuropsychiatric conditions such as motor or language developmental delay, autistic spectrum signs, attention deficit hyperactivity disorder, learning or memory deficits, acquired epileptic aphasia, and behavioral problems, defined as any recurrent behavior that was significantly disruptive to family functioning. Concomitant antiepileptic treatments were also documented.

Overnight electroencephalogram monitoring

All patients underwent continuous electroencephalogram monitoring to diagnose and quantify electric status epilepticus during sleep. Patients were monitored for 44-96 hours. Scalp electroencephalogram recordings were performed according to the 10-20 international system of electrode placement. Electroencephalogram recordings were continuously monitored throughout the day and night by dedicated electroencephalogram technologists. All electroencephalogram and video data were saved and interpreted by two board-certified clinical neurophysiologists.

Electroencephalogram analysis

For the purposes of this study, all electroencephalogram data were scored by two clinical neurophysiologists who identified the different stages of the sleep-wake cycle, and selected wakefulness and non-rapid eye movement sleep samples for calculating epileptiform activity. Wakefulness samples consisted of three randomly selected 5-minute segments. All the available samples of wakefulness were distributed in chronologic order, and a series of three random numbers from 1-50 was used to select the minutes at which the three samples began. When samples overlapped, a fourth random number was selected.

The non-rapid eye movement sleep sample consisted of the first 5 minutes of non-rapid eye movement sleep in all cases. We defined the beginning of non-rapid eye movement sleep as the segment that began 1 minute after the first appearance of vertex waves. We defined spike percentage as the percentage of 1-second bins containing at least one spike, and calculated it during the three 5-minute samples of wakefulness and during the first 5 minutes of every hour of non-rapid eye movement sleep during the night. The electroencephalogram data were retrospectively collected, and the neurophysiologists who reviewed the electroencephalogram data were blinded to the time of diazepam administration. In case of discrepancy by more than 10% in spike percentage, the electroencephalogram was reviewed and assessed by a third reviewer.

Sleep potentiation of epileptiform activity: Focal vs generalized

For the purposes of this study, a patient was considered to exhibit sleep-potentiated epileptiform activity when the spike percentage during sleep was increased by ≥50% compared with wakefulness. None of the patients had a normal electroencephalogram during wakefulness with the epileptiform activity present only during sleep. All spikes were mapped on bipolar and referential montages. If spikes were evident in all head regions on different montages at the same time, they were considered generalized.

High-dose diazepam treatment protocol

We administered oral diazepam at a dose of 1 mg/kg, at a maximum of 40 mg, before sleep at night, and continued the electroencephalogram monitoring for a minimum of an additional 24 hours. The second assessment of electroencephalogram epileptiform activity was performed 24 hours after the administration of diazepam. After the first dose, diazepam was administered at 0.5 mg/kg, with a maximum of 20 mg, every night for 3 weeks, and was then gradually withdrawn. Our treatment protocol was based on the classical diazepam rectal protocol of De Negri et al. [20], and the modifications were based on those of Inutsuka et al. [17], who also administered high-dose diazepam orally. In the study by Kramer et al., published at the end of our study period, diazepam was also administered orally [10]. Patients' electroencephalograms were monitored to determine overnight treatment response. Acute side effects were registered during the first 48 hours after treatment, with monitoring for the appearance of hypotonia, excessive somnolence, dizziness, dysarthria, amnesia, ataxia, respiratory depression, and hypotension or paradoxic reactions with irritability, excitement, and insomnia.

Statistical analysis

We used nonparametric tests for comparisons of continuous variables, i.e., the Mann-Whitney U test for independent samples, and the Wilcoxon signed ranks test for dependent samples. Associations between categorical variables were assessed using the χ^2 or Fisher exact test, as appropriate. All tests were performed at a "two-sided" significance level of 0.05. We used SPSS version 19 software (SPSS, Inc., Chicago, IL) for all analyses.

Results

Patients

Our retrospective review revealed 208 children with a clinical suspicion of electric status epilepticus in sleep during the period 2001-2009 in our unit. We did not observe any patients who had been admitted for a clinical suspicion of other epileptic syndromes and were accidentally revealed to manifest electric status epilepticus during sleep. Of those 208, 85 patients demonstrated the sleep potentiation of epileptiform activity, and 29 children (34.1%) met the inclusion criteria for the high-dose diazepam treatment protocol.

Demographic and clinical data

The median age was 7.4 years (range, 3.8-17.3 years). Eighteen children (62.1%) were boys. The clinical presentation of this population is summarized in Table 1, and the specific types of seizures in the 24 patients with a seizure disorder are listed in Table 2. Thirteen patients (44.8%) demonstrated two or more clinical features at presentation, whereas 16 patients (55.2%) presented with three or more features (Table 1). Sixteen patients (66.7%) manifested only one seizure type, seven patients (29.2%) manifested two, and one patient (4.2%) manifested three (Table 2). Fourteen (48.3%) patients demonstrated a spike percentage of

Table 1. Clinical presentations in our population of 29 patients treated with high-dose diazepam treatment

Seizure disorder	24 (82.8%)
Language disorder	16 (55.2%)
Global developmental delay	9 (31%)
Motor problems	7 (24.1%)
Acquired epileptic aphasia	6 (20.7%)
Autistic spectrum symptoms	5 (17.2%)
Behavioral problems	4 (13.8%)
Attention deficit hyperactivity disorder	3 (10.3%)
Learning and memory problems	3 (10.3%)

Percentages do not sum up because several patients manifested more than one clinical feature. Six patients (20.7%) manifested only one feature, seven patients (24.1%) manifested two features, 10 patients (34.5%) manifested three features, three patients (10.4%) manifested four features, and three patients (10.4%) manifested five features.

Table 2. Types of seizures in 24 patients with a seizure disorder treated with high-dose diazepam treatment

Absences	11 (45.8%)
Generalized tonic-clonic	8 (33.3%)
Complex partial	4 (16.7%)
Tonic	3 (12.5%)
Atonic	3 (12.5%)
Myoclonic	3 (12.5%)
Clonic	1 (4.2%)
Aphasic	0 (0%)

Percentages do not sum up because several patients manifested more than one seizure type. Sixteen patients (66.7%) manifested one seizure type, seven patients (29.2%) manifested two seizure types, and one patient (4.2%) manifested three seizure types.

at least 85% during non-rapid eye movement sleep. In 27 of 29 patients, magnetic resonance imaging was performed, and of those 27, 15 (55.6%) manifested structural lesions (Table 3). We did not observe other potential etiologies in the remaining patients.

Sleep potentiation of epileptiform activity: Focal vs generalized

The potentiation of epileptiform activity from wakefulness to sleep was focal in 21 (72.4%) patients, and generalized in eight (27.6%). No significant differences were evident in the demographic and clinical features of patients with a focal compared with a generalized sleep potentiation of epileptiform activity (Table 4).

Antiepileptic drug regimen of patients entering the high-dose diazepam protocol

Data on drugs at the time of the high-dose diazepam treatment are presented in Table 5.

Response to high-dose diazepam treatment

The mean spike percentage was significantly reduced after high-dose diazepam treatment (76.7% at baseline vs 40.8% 24 hours after high-dose diazepam treatment, Wilcoxon signed ranks test, $Z = -4.287$, $P < 0.0001$). The decrease in spike percentage was significant and of a similar degree in the 21 patients with focal sleep potentiation of epileptiform activity (77.2% at baseline vs 40.8% 24 hours after high-dose diazepam treatment, Wilcoxon signed ranks test, $Z = -3.516$, $P < 0.0001$) and in the eight patients with generalized sleep-potentiated epileptiform activity (40.6% vs 75.4%, Wilcoxon signed ranks test, $Z = -2.527$, $P = 0.012$). Fifteen out of 29 patients (51.7%) demonstrated a decrease in epileptiform activity by at least 50%, and we referred to them as significant responders. We could not discern a difference between significant responders and nonsignificant responders regarding focal vs generalized activity, sex, age, brain structural lesions, seizure disorder, language disorder, autistic spectrum signs, attention deficit hyperactivity, learning and memory problems, acquired epileptic aphasia, or behavioral problems. We observed that seven out of 14 nonsignificant responders exhibited motor problems, whereas none of the 15 significant responders exhibited motor problems (Fisher exact test, $P = 0.002$). In parallel, seven out of 14 nonsignificant responders demonstrated global developmental delay, whereas two out of 15 significant responders demonstrated global developmental delay (Fisher exact test, $P = 0.05$).

Table 3. Distribution of MRI findings in our patient population

Normal MRI	12
Periventricular leukomalacia	8
Vascular lesion in the distribution of the left middle cerebral artery	4
Polymicrogyria	2
Abnormal myelinization	1
MRI not performed	2

Abbreviation:
MRI = Magnetic resonance imaging

Side effects

Seven patients (24.1%) manifested side effects during the first 48 hours after the administration of diazepam. Four of them exhibited excessive sedation, and three exhibited hyperactivity and agitation. All of these side effects were mild in nature and reversible.

Discussion

Our results support the efficacy of high-dose oral diazepam treatment in the reduction of sleep-potentiated spiking in electrical status epilepticus during sleep. Our 29 patients constitute, to the best of our knowledge, the largest series reported to date on this treatment. Moreover, we have expanded on previous results from the literature, because our study indicates that improvement with diazepam treatment occurs not only in patients with generalized epileptiform activity, but also in patients with focal sleep potentiation of epileptiform activity.

Demographic and clinical data

The median age at electroencephalogram monitoring of 7.4 years and the sex distribution of two males per female in our series are consistent with previous data, in which the age at diagnosis of electric status epilepticus in sleep peaks at around 5-8 years [18,21,22] and males predominate [17,18,22-24]. As in most studies of electric status epilepticus during sleep, the major clinical features in our series included seizures and different forms of developmental regression [4,6,18,21,22]. The proportion of patients with a brain abnormality in our study (55.6%) was consistent with findings in the previous literature, in which 45-59% of patients manifested a brain structural abnormality [23,25]. The distribution of lesions, with a predominance of lesions of vascular etiology (periventricular leukomalacia, infarcts, and hemorrhages) and malformations of cortical development, was also consistent with that in previous reports [23,25].

Treatment of electric status epilepticus in sleep

Some series suggest that longer durations of electric status epilepticus in sleep may be related to worse cognitive outcomes [10,13,14]. Even if some series could not confirm this correlation [26], a potential window of opportunity for better outcomes exists when electric status epilepticus in sleep is diagnosed early and appropriately treated.

Treatment choices in electric status epilepticus in sleep are mostly based on case reports and small case series, and whether any one anticonvulsant is better than another anticonvulsant remains unclear [27]. The transitory arrest of electric status epilepticus in sleep was observed after the administration of clonazepam [5,17,19], suggesting the usefulness of benzodiazepines in the treatment of sleep-potentiated epileptiform activity.

Treatment with high-dose diazepam

Because diazepam exhibits a shorter half-life than clonazepam, its effects have waned by the time the patient awakens, which

Table 4. Comparison of main demographic and clinical features of patients with focal and generalized sleep-potentiated epileptiform activity in the group of patients treated with high-dose diazepam

Variable	Focal Sleep-Potentiated Epileptiform Activity (n = 21) (72.4%)	Generalized Sleep-Potentiated Epileptiform Activity (n = 8) (27.6%)	Difference
Sex (male/female)	12/9	6/2	$P = 0.671$
Median (range) age in years	7.3 (3.8-14.3)	8.6 (4.6-17.3)	$P = 0.354$
Median spike-wave percentage before treatment	82%	79.5%	$P = 0.767$
Median spike-wave percentage after treatment	29%	31%	$P = 0.625$
Brain structural lesions	10/20 (50%)	5/7 (71.4%)	$P = 0.408$
Seizure disorder	16 (76.2%)	8 (100%)	$P = 0.283$
Language disorder	13 (61.9%)	3 (37.5%)	$P = 0.406$
Autistic spectrum signs	4 (19.1%)	1 (12.5%)	$P = 1.00$
Attention deficit hyperactivity	2 (9.5%)	1 (12.5%)	$P = 1.00$
Learning and memory problems	2 (9.5%)	1 (12.5%)	$P = 1.00$
Global developmental delay	8 (38.1%)	1 (12.5%)	$P = 0.371$
Acquired epileptic aphasia	4 (19.1%)	2 (25%)	$P = 1.00$
Motor problems	6 (28.6%)	1 (12.5%)	$P = 0.635$
Behavioral problems	3 (14.3%)	1 (12.5%)	$P = 1.00$

could be advantageous because electric status epilepticus during sleep involves an electroencephalogram pattern that affects patients during sleep. In a series of patients with different forms of electric status epilepticus treated with high-dose diazepam, all 15 patients with electric status epilepticus during sleep and one out of one patient with acquired epileptic aphasia responded to acute treatment [20]. In a study of four patients with electric status epilepticus during sleep refractory to valproate and ethosuximide, a short cycle of high-dose oral or intrarectal diazepam (0.5-1 mg/kg per day for 6-7 days) was effective for the short term in two patients [17]. High-dose oral diazepam (0.75-1.00 mg/kg/day for 3 weeks) was also efficacious in three out of eight patients (37.5%), but the response was temporary [10]. However, in another series, nine of 10 patients did not respond to valproate and benzodiazepines, and three patients demonstrated an adverse behavioral reaction [28]. No objective quantification of the reduction in epileptiform activity was available in previous publications. Our data indicate that high-dose diazepam constitutes an effective treatment in the short-term reduction of sleep-potentiated epileptiform activity. Motor problems and global developmental delay were factors predicting nonsignificant responses to high-dose diazepam oral treatment.

Side effects

Treatment with high-dose diazepam appeared safe on a short-term basis, with mild and reversible side effects observed. Our results are consistent with those in the series of De Negri et al., in which only minor and transient side effects (drowsiness, hypotonia, and hyperexcitability) were evident [20], and in the series of Inutsuka et al., in which only sleepiness and hyperactivity were evident [17].

Because of the heterogeneous treatment strategies reported in the literature regarding electric status epilepticus during sleep, comparing the safety of high-dose diazepam with other therapeutic approaches is difficult. Conventional antiepileptic drugs appear quite safe in electric status epilepticus in sleep. In a series of 15 patients on valproate, valproate and ethosuximide, and diazepam and/or adrenocorticotropic hormone, adverse effects were mild and did not require discontinuation in any case [17]. In a study of 17 patients treated with clonazepam, no adverse effects were reported [19], and only moderate adverse behavioral reactions were observed in three of 10 patients treated with valproate and benzodiazepines [28]. However, other treatments appear to entail a higher risk of serious adverse effects. Buzatu et al. reported an absence of serious or life-threatening side effects in a series of 44 patients receiving corticosteroids, but all patients were instructed to follow a very strict diet to avoid weight gain or hypertension, all manifested mild to moderate side effects, and severe hyperkinesias and sleep disorders contributed to the decision to discontinue treatment in seven of the 11 patients in whom steroids were prematurely discontinued [25]. Intravenous immunoglobulin has not been associated with serious adverse effects in electric status epilepticus during sleep, but the risks inherent in the use of a blood derivative should be considered [29]. The risks and potential side effects of surgical treatment limit its use to a small number of selected patients [30].

Although high-dose diazepam treatment may not be useful in the long term because of tolerance issues, it appears to be useful in the reduction of epileptiform activity in an acute setting where other treatment strategies may be associated with a higher risk of adverse effects.

Limitations

Our results were limited to a population of patients with electric status epilepticus and a particularly severe electroencephalogram pattern, and are not intended to be generalized to other epileptic syndromes. Data collection at a tertiary referral center may have selected a subpopulation of patients with a more severe clinical presentation of electric status epilepticus during sleep, and this approach may limit overall generalizations of our results to less severely affected patients because of selection and referral bias. However, high-dose diazepam treatment is usually administered only to patients with severe electric status epilepticus during sleep who are refractory to first-line treatment protocols. The small number of patients did not allow us to adjust for other medications, but doses of other antiepileptic medications were not changed during the study interval. High-dose diazepam treatment was used mainly in patients with moderate to severe neuropsychologic regression, thought to be related to their very frequent interictal epileptiform activity. The final decision on enrolling patients into this protocol was made by each treating neurologist, which could be associated with selection bias. Because of our retrospective study design, data on clinical and neuropsychologic evolution were limited by the amount of information collected in the clinical charts. We think that to answer questions on clinical and neuropsychologic responses to treatment, a multicenter prospective study with evaluations of these features at regular intervals is required.

Data collection on demographic and clinical features may have been subject to information bias. Rather than relying on study reports, to standardize interpretations from the original data and reduce interobserver variability, our study involved a specific review of each magnetic resonance imaging scan for the presence

Table 5. Individual details of patients in our study

	Sex	Age	Baseline Pathology	MRI	Concomitant Treatment	Seizures	EEG Activity	SP Before Treatment	SP After Treatment	Side Effects	NPS REG	NPS R	SF R
1	F	7.3	LA, ADHD, GDD	N	No	No	FO	50	50	No	‡	++	=
2	M	7.3	LA, LE	N	LEV, LTG	No	FO	85	85	No	‡	++	=
3	F	7.7	LA, AU	ND	VPA	T	FO	85	0	No	‡	++	=
4	F	7.7	LA, SD	N	VPA	C	FO	50	5	No	†	+	++
5	F	7.1	SD	ND	VPA	AB	GE	50	30	No	†	=	=
6	M	11.9	LA, AU, SD, GDD, MD	A (PVL)	No	GTC	FO	95	95	H	‡	++	=
7	M	4.7	LA, SD, AEA	A (sellar mass)	VPA, LEV	AB	GE	60	9	No	†	+	=
8	F	14.3	SD, GDD, MD	A (PVL)	No	AB	FO	85	65	No	†	=	=
9	M	8.2	LA, SD, AEA, BP	N	VPA	AB	GE	85	30	H	†	+	=
10	M	4	LA, GDD	N	No	No	FO	85	45	No	*	=	=
11	F	9.8	SD	N	LEV, CBZ	MY	FO	85	50	No	†	=	+
12	M	17.3	SD, MD	A (polymicrogyria)	VPA	GTC	GE	85	65	No	‡	=	=
13	M	9	SD	A (hemorrhage)	VPA	MY	GE	85	30	No	‡	=	=
14	M	6.5	SD	A (PVL)	LEV, CBZ	GTC	FO	60	0	No	*	=	=
15	M	5.5	LA, AU, SD, AEA, BP	N	VPA	AB, GTC	FO	90	20	No	‡	+	=
16	M	10	SD	A (hemorrhage)	LTG, TPM	CP, GTC	FO	50	20	No	†	=	+
17	M	8.6	LA, SD, MD	A (atrophy and gliosis)	LTG	AB	FO	70	70	No	†	+	+++
18	M	9.5	SD, GDD, MD	A (Infarct)	VPA, LEV, LTG, CBZ, ZNS	CP	FO	80	55	S	*	=	=
19	F	5.75	SD, ADHD, AEA, MD, BP	N	VPA	AB, GTC	FO	70	60	S	†	=	=
20	M	4.75	LA, SD, GDD	N	No	No	FO	88	27	S	†	+++	++
21	F	6.4	SD	A (infarct)	ZNS, LEV	AB	FO	100	0	No	†	=	=
22	F	7.4	LA, AEA, BP	N	STR, LTG	No	FO	65	27	No	†	++	++
23	F	14.9	AU, SD, ADHD, LE	N	VPA, STR, LEV	AB, AT	GE	74	32	S	*	=	=
24	M	10.7	SD, GDD	A (polymicrogyria and heterotopia)	LTG, TPM	CP	GE	70	45	No	‡	++	+
25	M	4.6	LA, SD	A (right hemisphere atrophy)	VPA	AB, CP, GTC	GE	94	84	No	‡	++	++
26	M	4.8	LA, SD, LE	N	VPA, LEV	AB, GTC	FO	82	28	No	†	=	=
27	M	3.8	LA, AU, SD, AEA	A (delayed myelination)	VPA, LTG	AT, T	FO	70	26	H	*	++	++
28	F	6.8	LA, SD, GDD	A (hypoxic-ischemic injury)	VPA	MY	FO	76	29	No	*	++	=
29	M	10.3	SD, GDD, MD	A (PVL)	VPA, LEV, OXC	AT, T	FO	100	100	No	*	=	+++

Abbreviations:

A = Abnormal
AB = Absence
ADHD = Attention deficit hyperactivity disorder
AEA = Acquired epileptic aphasia
AT = Atonic
AU = Autistic features
BP = Behavioral problems
C = Clonic
CBZ = Carbamazepine
CP = Complex partial
EEG = Electroencephalogram
F = Female
FO = Focal
GDD = Global developmental delay
GE = Generalized
GTC = Generalized tonic-clonic
H = Hyperactivity
LA = Language deficit
LE = Learning deficit
LEV = Levetiracetam
LTG = Lamotrigine
M = Male
MD = Motor deficits
MRI = Magnetic resonance imaging
MY = Myoclonic
N = Normal
ND = Not done
NPS = Neuropsychologic evaluation
OXC = Oxcarbazepine
PVL = Periventricular leukomalacia
R = Response to treatment
REG = Regression
S = Excessive sedation
SD = Seizure disorder
SF = Seizure frequency
SP = Spike percentage
STR = Steroids
T = Tonic
TPM = Topiramate
VPA = Valproate
ZNS = Zonisamide

+, mild improvement; ++, moderate improvement; +++, marked improvement; = , no significant change.

* Mild regression
† Moderate regression
‡ Severe regression

of brain structural abnormalities, and of each electroencephalogram to assess epileptiform activity.

Moreover, our analysis was restricted to the first 24 hours after the introduction of high-dose diazepam treatment, and therefore we do not describe the clinical correlation between reduced epileptiform activity and overall tolerability over a longer period of time. The clinical improvement after treatment was registered in the clinical charts of all patients, and a study on the long-term effects of this protocol, comparing seizure frequency and severity before and after treatment, is underway.

It can be argued that the classic definition of electric status epilepticus during sleep requires that at least 85% of non-rapid eye movement sleep should be occupied by generalized spike-wave activity [5,6,31]. The authors who initially described the electroencephalogram patterns of electric status epilepticus during sleep proposed that no less than 85% of the total duration of slow sleep should be occupied by slow spike-waves [6,31]. This cutoff value has generally been followed in defining the electroencephalogram pattern of electric status epilepticus [6,16,18,19,26,32-36]. However, the definition of the International League Against Epilepsy does not

consider a specific cutoff percentage, and only requires that spike-waves be "continuous" and "diffuse" [3]. Several authors used lower cutoff percentage values [17,23,37,38]. Others used terms such as "sleep overactivation pattern" [39] or "near electrical status epilepticus in sleep" [26] when referring to patients with electrographic features consistent with electric status epilepticus during sleep but not meeting the percentage cutoff criterion. In the series from the Venice Colloquium on Electrical Status Epilepticus in Sleep, a percentage of less than 85% was reported in more than one third of the cases [40]. Therefore, a cutoff value of less than 85% was frequently used in the previous literature on electric status epilepticus during sleep, given that the potentiation of epileptiform activity from wakefulness to sleep is marked, and the resulting electroencephalogram tracing during non-rapid eye movement sleep contains continuous or almost continuous spike-waves. Whether patients with a threshold below 85% are significantly different from patients with electric status epilepticus during sleep remains unknown and requires further investigation [17,23,26,38-40]. For the purposes of this study, we gathered a population of patients with a significant sleep potentiation of epileptiform activity, and we arbitrarily set a potentiation of spike percentage at 50%. The patients' clinical and demographic characteristics did not differ significantly from those in previous series on electric status epilepticus during sleep.

Conclusion

Our data indicate that high-dose oral diazepam is an efficacious and safe treatment for the reduction of sleep-potentiated spiking in patients with electric status epilepticus during sleep in the short term. No significant differences in response to this treatment protocol were evident between patients with sleep-potentiated epileptiform activity of focal or generalized predominance. Future studies will need to focus on long-term follow-up and neuropsychologic outcomes.

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