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Amantadine: A new treatment for refractory electrical status epilepticus in sleep

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ABSTRACT

Purpose: Electrical status epilepticus in sleep (ESES) is an electrographic abnormality linked to language abnormalities and cognitive dysfunction and specifically associated with Landau–Kleffner syndrome (LKS), the syndrome of continuous spike and wave in slow-wave sleep (CSWS), and autistic regression with epileptiform EEG (AREE). As first-line therapies for treatment of ESES display inadequate efficacy and confer substantial risk, we set out to describe our center's experience with amantadine in the treatment of ESES.
Methods: Patients with video-EEG-confirmed ESES who received amantadine were retrospectively identified in a clinical EEG database. Spike–wave index, before and after amantadine exposure, was compared in a pairwise fashion. In an exploratory analysis, we cataloged reported changes in language functioning, cognition, and autistic features, which accompanied treatment.
Results: We identified 20 patients with ESES-associated syndromes. Median cumulative weighted average amantadine dosage was 2.1 mg/kg/d (interquartile range (IQR): 1.1, 4.5), and median duration of therapy was 11.5 months (IQR: 7.8, 26.6). In comparison with median baseline spike–wave index (76%), post-amantadine spike–wave index (53%) was reduced, with $P = 0.01$. Six (30%) patients exhibited complete (or nearly complete) resolution of ESES. A majority of patients exhibited subjective cognitive, linguistic, or behavioral benefit. Amantadine was generally well-tolerated despite substantial dosage and duration of therapy.
Conclusions: This study suggests that amantadine may be effective in the treatment of ESES-associated syndromes but warrants replication in a more rigorous study.

1. Introduction

Electrical status epilepticus in sleep (ESES) is an electrographic pattern characterized by nearly continuous spike–wave discharges in slow-wave sleep, which has been linked to acquired impairment of cognition and behavior [1–3], and most notably, Landau–Kleffner syndrome (LKS) [4]. Although the classic electrographic criterion for ESES is a spike–wave index (SWI) exceeding 85%, such that at least 85% of 1-second epochs in slow-wave sleep "contain" an epileptiform discharge [1], several contemporary reports have suggested that lower burdens of spikes (SWI > 50%) may be associated with reversible cognitive impairment and thus warrant treatment [2,5–7]. Furthermore, a recent multicenter, long-term follow-up study of 117 patients confirmed that a broad range of SWI can be associated with encephalopathy and that the electroclinical criteria should be revised to accommodate such findings [8]. Electrical status epilepticus in sleep may be further conceptualized as a measure of epileptic encephalopathy such that the discovery of ESES indicates the presence of treatable encephalopathy and reductions in SWI associated with specific treatments may be used as a quantitative—albeit imperfect—surrogate measure of treatment response.

In contrast to LKS, in which ESES is linked specifically to language dysfunction [4,9], the syndrome of continuous spike and wave in slow-wave sleep (CSWS) has also been associated with the ESES pattern on EEG and global developmental regression [10]. A third syndrome associated with ESES is termed autistic regression with epileptiform EEG (AREE) and manifests with the emergence of autistic symptoms in the context of abnormal EEG. Unlike LKS and CSWS, the EEG in AREE is generally characterized by a lower spike burden than is typically encountered in LKS and CSWS, though some cases present with SWI approaching 100%. Although classification of AREE alongside LKS or CSWS is controversial, these syndromes exhibit considerable genetic overlap [11], and AREE is often treated with similar pharmacologic agents [12]. Across these syndromes, the elimination of ESES on EEG is thought to be necessary—though not necessarily sufficient—to impact cognitive functioning, and longer duration of ESES is thought to be associated with poorer outcomes [3].

Although the treatment of ESES is not supported by any large-scale, randomized controlled trials with blinded and standardized cognitive

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outcome assessment, a preponderance of available data suggests that corticosteroids and benzodiazepines are most efficacious [13] except for a small minority of patients whose ESES occurs in the setting of focal structural abnormalities and are favorable candidates for surgical resection [14]. Still, a large proportion of patients have seizures that are refractory to initial therapies, and the effectiveness of these agents is often compromised by poor tolerability, especially with regard to long courses of corticosteroids and benzodiazepines. It is within this context of refractory ESES that we have explored the potential utility of amantadine, guided by success in the treatment of refractory absence epilepsy [15–17] and with the hypothesis that amantadine may target mechanisms that underlie ESES and associated epileptic encephalopathy.

2. Methods

2.1. Institutional approvals

This study was approved by the Institutional Review Board at UCLA, and the requirement for informed consent was waived.

2.2. Study design

Using a database which includes all patients who underwent video-EEG (VEEG) at UCLA Mattel Children's Hospital, we retrospectively identified all patients that received amantadine to treat EEG-confirmed ESES between October 2003 and October 2016. We adopted a rather inclusive definition of ESES such that patients with a SWI ≥ 25% at any point prior to initiating amantadine therapy were included. Pertinent clinical and demographic data were abstracted from the electronic medical record.

For each patient, we quantified amantadine exposure with review of all neurology progress notes. Using patient weight, dosage (mg/d), and dates recorded at each visit, we calculated age at treatment onset, total treatment duration (mo), cumulative weighted average weight-based dosage (mg/kg/d), and peak weight-based dosage (mg/kg/d).

To evaluate electrographic responses to therapy, we tabulated SWI on sequential inpatient overnight VEEG studies before and after amantadine initiation. We compared each patient's baseline SWI with (1) the first follow-up SWI and (2) the most recent follow-up SWI. With regard to posttreatment SWI, we only considered VEEG studies in which amantadine treatment was continued and no new medications were initiated but allowed inclusion of studies performed after the discontinuation of presumably inefficacious or intolerable treatments. In those cases in which amantadine was discontinued, we reviewed the records to determine whether discontinuation was carried out for lack of efficacy, adverse side effects, both, or neither.

To explore clinical response to amantadine, sequential neurology follow-up notes were screened for statements in interval history and neurological exam findings indicating a change in overall cognition, language function, and behavior.

2.3. Statistical methods

Paired comparisons of median SWI before and after amantadine initiation were accomplished using the two-sided Wilcoxon signed-rank test. Statistical calculations were facilitated with STATA software (version 14; Statacorp, College Station, TX, U.S.A.).

3. Results

3.1. Patients

Clinical and demographic characteristics of the study population are summarized in Table 1. We identified 20 patients (6 females) with VEEG-confirmed ESES who were treated with amantadine. With regard to ESES syndrome classification, we identified patients with LKS (n = 2), CSWS (n = 12), and AREE (n = 6). Sixteen (80%) patients experienced comorbid epilepsy, with the discovery of ESES following epilepsy onset by a median of 2.9 years (interquartile range (IQR): 1.3, 5.2). Among the patients with comorbid epilepsy, we identified eight with multifocal epilepsy (no specific ILAE epilepsy syndrome), three with childhood epilepsy with centrotemporal spikes, two with generalized genetic epilepsy, two with atypical absence epilepsy, and one with epileptic spasms. Despite extensive investigations, underlying etiology was identified in only four patients and included partial duplication of chromosome X, hypoxic ischemic encephalopathy, perinatal stroke, and intraventricular hemorrhage. We identified nine (45%) patients who carried a diagnosis of autism spectrum disorder (ASD). Diagnosis of ASD was

Table 1
Clinical and demographic characteristics of the study population.

Patient	Age/sex	Etiology	Comorbid epilepsy	ESES syndrome	Autism (Y/N)	Prior unsuccessful treatments	Concomitant treatments
1	15 M	Unknown	GGE	CSWS	Y	IVIG, VNS, lithium (LTH), VPA[a], LTG[a], KETO[a]	DZP, CBD
2	6 F	Unknown	IS	CSWS	N	IVIG, DZP, CLB[a]	DZP, CLB[a], IVIG
3	8 M	Unknown	GGE	CSWS	Y	LEV[a], VPA[a]	LEV[a], VPA[a]
4	10 F	Partial dupX	MF	CSWS	N	DZP, IVIG, VPA, CLB, PRED, LTG[a]	LTG[a], GBP
5	5 M	Unknown	BRE	CSWS	N	DZP	DZP, LEV[a]
6	8 M	Unknown	MF	LKS	N	DZP, IVIG, PRED, VPA[a], LTG[a]	LTG[a], PRED, VPA[a]
7	6 M	Unknown	None	AREE	Y	DZP, PRED, VPA, LTG, CBD, BDS	None
8	11 M	Unknown	MF	AREE	Y	DZP, IVIG, PRED, LEV[a]	LEV
9	13 F	Unknown	MF	CSWS	N	DZP,CLB, VPA[a], LEV[a]	CLB
10	8 M	HIE	MF	AREE	Y	CLB	DZP, LTG
11	11 F	Unknown	AAE	CSWS	N	DZP, CLB, IVIG, LTG[a]	CLB, LTG[a]
12	10 M	Unknown	MF	CSWS	N	DZP, CLB[a], VPA[a], LEV[a], LTG[a]	None
13	9 M	Unknown	BRE	CSWS	Y	DZP, LTG[a], GBP[a]	LTG[a], GBP[a]
14	6 M	Unknown	AAE	CSWS	N	DZP, CLB[a], KETO[a], LTG[a], LEV[a], VPA[a]	CLB[a], LEV[a], LTG[a]
15	6 M	Stroke	MF	CSWS	N	DZP, PRED, CLB[a], LEV[a], LTG[a]	DZP, PRED, CLB[a], LEV[a], LTG[a]
16	8 F	Unknown	BRE	LKS	N	LEV[a]	DZP, LEV[a]
17	6 M	Unknown	None	AREE	Y	DZP, VPA[a], LEV[a]	VPA[a]
18	14 F	IVH	MF	CSWS	N	CLB, DCD, IVIG, KETO[a]	LEV, CLN
19	9 M	Unknown	None	AREE	Y	DZP, VPA, CBD,	VPA, DZP
20	15 M	Unknown	None	AREE	Y	CLB, VPA[a]	DZP, CLB

Abbreviations: AAE, atypical absence epilepsy; AREE, autistic regression with epileptiform EEG; BDS, budenoside; BRE, benign rolandic epilepsy; CBD, cannabidiol; CLB, clobazam; CLN, clonazepam; CSWS, epileptic encephalopathy with continuous spike and wave in slow-wave sleep; DCD, decadron; dupX, duplication of chromosome X; DZP, diazepam; GBP, gabapentin; GGE, generalized genetic epilepsy; HIE, hyposix ischemic encephalopathy; IS, infantile spasms; IVH, intraventricular hemorrhage; IVIG, intravenous, immunoglobulin; KETO, ketogenic diet; LEV, levetiracetam; LKS, Lanfau–Kleffner syndrome; LTG, lamotrigine; LTH, lithium; MF, multifocal epilepsy; PRED, prednisone; VNS, vagal nerve stimulator; VPA, valproic acid.
[a] Medication with dual indications, i.e., ESES and epilepsy or behavior improvement.