

Electroencephalographic Findings after Eslicarbazepine Therapy in Focal Epileptic Syndrome Patients

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Abstract

The efficacy and the tolerance of the AEDs have been extensively studied in the past, however the effects of them on the EEG activity of epileptic patients have been scarcely studied. Eslicarbazepine is a third generation blocker-sodium channels AED associated with a high reduction in the rate of partial seizures in epileptic patients. We designed an open label, non control study to determine the effects of Eslicarbazepine on the EEG activity of EP with focal seizures in a 12-week follow up. The EP with focal paroxysmal activity enrolled in this study showed a statistical significant reduction in the rate of monthly seizures when Eslicarbazepine 800 mgs was added to a previous AED compared to those patients who only received an increase of the AED in monotherapy, concomitantly, EP treated with ESL added to a previous AED showed a statistically significant reduction in the mean occipital frequency and voltage amplitude in the central and parietal regions in the twelfth-week EEG compared to the control group.

Keywords

EEG, Focal Epilepsy, Anti-Epileptic Drugs

1. Introduction

The clinical and molecular effects of antiepileptic drugs (AEDs) have been extensively investigated in the past, however much less is known about their effects on Electroencephalography [1] [2] [3].

Some AEDs as carbamazepine and lamotrigine (both, channel blockers) and valproic acid have been related to electroencephalography changes in epileptic patients. Slowing of the posterior (occipital) frequency has been related to the im-

provement in the rate of seizures in epileptic patients (EP) after some AEDs therapy [4]. Even though, there is little information about the effects of new generation AEDs on the EEG activity in epileptic patients, some AEDs, such as levetiracetam are associated with acceleration of background EEG frequencies and improved cognitive function. Other AEDs have been related with changes in the paroxysmal EEG activity, however these findings couldn't be reproduced in further studies. Most of the past studies about AEDs have stressed the focus on the efficacy and tolerance of the AEDs leaving behind in a second place the pharmacological mechanism of action of these drugs. Interestingly, some authors have pointed out the usefulness of EEG not only in the diagnosis but in the prognosis of the EP patients as a diagnostic tool in order to follow up the epileptic focus nevertheless there are not scientific evidences that can confirm this statement. On the other hand, there are basic and neurophysiological studies that give some clues about possible action mechanism of some AEDs, for example, change in frequency power band could predict improvement in several cognitive domains across Levetiracetam therapy [5]. Lacosamide modulates interictal spiking and high-frequency oscillations in a model of mesial temporal lobe epilepsy [6]. Eslicarbazepine treatment prevented acute latrunculin A-induced seizures, as well as chronic seizures and all EEG chronic signs of paroxysmal activity, supporting a possible anti-epileptogenic effect of Eslicarbazepine in mice [7] [8]. There are few studies related to the EEG activity pre and post AED in EP patients to our knowledge. We designed a prospective, open label, parallel controlled follow up of EP with a focal syndrome to study the EEG characteristics pre and post Eslicarbazepine therapy using QEEG analysis.

2. Patients and Methods

Epileptic patients with clinical and EEG criteria of focal epileptic syndrome were enrolled in this 12-week, prospective, open label, parallel control-study.

2.1. Inclusion and Exclusion Criteria

Focal EP of both sexes, from 18 to 80 years old with a poor control of seizures, with only one anti-epileptic drug, and who needed an adjustment of the AED therapy according to the real clinical practice, in order to control seizures frequency were included in this study. Patients should have a focal-paroxysmal EEG activity at the screening visit and clinical criteria of partial simple or complex seizures at the beginning of the study. Patients and/or caregivers should understand adequately how to fill up the seizures diary. Patients with pseudo-seizures even having real seizures were excluded of the study as well as EP patients under therapy with drugs that can potentially can modify the EEG activity finally EP patients with non control systemic disease also were not included in this study.

2.2. Methods

Patients were randomized subsequently into two groups (A and B), Group A pa-

tients received Eslicarbazepine (ESC) as an add-therapy to another anti-epileptic drug. 400 mgs once a day the first week then after, 800 Mgs once a day from the second week until the end of the study (12 weeks), and Group B patients received an AED in monotherapy, but adjusting the therapy through an increase in dose according to the usual clinical practice.

Patients were visited every four weeks: Visit 1—screening visit and Basal EEG; Visit 2—1 week later, randomization; Visits 3 and 4—clinical control, 4 and 8 weeks later; Visit 5—final EEG and clinical control, 12 weeks after randomization.

Patients were instructed to fill up seizures diary and adverse effects questionnaires, which were asked in all the visits after randomization. All the patients signed a written consent form before being included in the study.

Two EEGs were performed to all the patients of both groups: the first one at the screening visit and the second one at the end of the study. The EEG was a 30 minute registering (Nihon Kohden Co., Japan) with activation maneuvers. The EEG was analysed by visual objective experience and by a software of EEG parameters analyser, in all the EEG regions; 80 ephocs free of artifacts with paroxysmal EEG activity were analysed, and other 80 ephocs without paroxysmal activity. QEEG analysis of bands power: Alfa (8 - 13 Hz), theta (4 - 8 Hz), Delta (1 - 4 Hz), beta (14 - 18 hz) and gamma (>18). The QEEG of the Paroxysmal activity were analysed separately.

2.3. Statistical Analysis

The endpoint assessment measures were the EEG-parameters and the seizures diary changes from baseline to the end of the study. The Statistical analysis was performed comparing the basal data to the twelve-week evaluation data of both groups.

Statistical significance was determined $p < 0.05$ T student was the statistical method used and SPSS pack statistical analysis was used.

3. Results

40 EP were screened, 3 of them were excluded because they did not meet an EEG focal paroxysmal activity at the screening visit. Other 5 patients were excluded because they showed no clear partial seizures.

32 patients were included in the study, all of whom were able to finish the 12-week follow up, they were randomized into two groups (A and B), 15 EP patients in group A, Eslicarbazepine added to another anti-epileptic drug (SCL + AED), and 17 EP patients were included in Group B (AED monotherapy).

Patients of Group A showed a mean age of 57 yo (Aged from 36 to 67 SD \pm 8 years), 9 women and 6 men. Mean Years of diagnostic of 14 years \pm 3. Patients of the Group B showed similar demographic characteristics with a mean of age of 42 yo, (20 to 56 SD \pm 9, 11 years) 11 women and 6 men, years of diagnostic 9 \pm 3 (Table 1).

Table 1. Demographic characteristics.

N = 32	N	Sex: F/M	Age (mean)	Years onset	Monthly seizures	Simple/complex seizures
Group A (ESC + AED)	15	9/6	57 (36 - 67)	14 ± 3	3.4 ± 0.4	6/9
Group B (AED monotherapy)	17	11/6	42 (20 - 56)	9 ± 3	3.2 ± 0.2	7/8

With regard to epileptic seizures, patients of Group A (ESC + AED) showed at basal evaluation a mean of monthly seizures of 3.8 ± 0.4 , posteriorly they showed a mean of monthly seizures of 1.5 ± 0.2 in the twelfth week evaluation (average of reduction of -59.3% , $p < 0.05$). Patients of Group B (AED in monotherapy) showed a reduction of monthly seizures from 3.2 ± 0.2 at basal evaluation to 2.2 ± 0.8 seizures in the twelfth week evaluation visit (average of reduction of -31% , $p < 0.05$) (**Table 2**).

With regard to EEG findings in areas of non paroxysmal activity, EP of group A showed a reduction in the occipital rate from 12.3 to 8.3 Hz (-35% , $p < 0.05$) and also showed a reduction in the central parietal amplitude from $20 \text{ v} \pm 2$ to $10 \text{ v} \pm 1$ (-50% , $p < 0.05$) at the end of the follow up, however the rest of the brain regions showed no changes in the neurophysiological parameters.

Patients of Group B showed reduction in the occipital frequency from 10.2 Hz to 9.2 Hz (-9.9% , $p > 0.05$) at the end of the study. They showed no other relevant changes in the rest of neurophysiological parameters in the different brain areas at the end of the study (**Table 3**).

In relation to the EEG characteristics in the areas of paroxysmal activity, patients of Group A showed changes in the mean frequency of the paroxysmal activity from 4.3 Hz to 2.6 Hz. (reduction 30%, $p < 0.05$) at the 12 week follow up. They showed no significant changes in the mean of amplitude from 42.4 to 42.3 V ($p > 0.05$) at the end of the study. There were no changes in relation to the location and the morphology of the focal paroxysmal activity at the end of the study. Patients of Group B showed no significant reduction in the mean of frequency of the Paroxysmal activity from 4.6 to 4.2 ($p > 0.05$). They showed no changes in the mean of amplitude of the paroxysmal activity at the end of the study (**Table 4** & **Table 5**).

4. Discussion

Both groups of Epileptic patients of this study showed a statistical significant reduction of monthly frequency seizures at the end of the study. However, Patients treated with ESL-in ADD-on therapy to another AED showed a greater reduction in monthly seizures (-59.3% monthly seizures) compared to the monotherapy group (-33% monthly seizures). This is not a novel data because it has been published in the past that partial syndrome EP had shown a greater

Table 2. Follow up of the frequency of monthly seizures in both groups.

	Basal seizures (mean)	12-week (mean)	% reduction seizures	<i>p</i> < 0.05
Group A (ESC + AED)	3.8 ± 0.4	1.5 ± 0.2	59.3%	<i>p</i> < 0.001
Group B (AED monotherapy)	3.2 ± 0.2	2.2 ± 0.8	31%	<i>p</i> < 0.001

Table 3. EEG findings in the epochs of free paroxysmal activity, basal and at 12-week evaluation in the Esc + AED group.

Esc + AED	Basal	12-week	% reduction	<i>p</i>
Occipital				
Rate	12.3 Hz	8.3 Hz	-35	<i>p</i> < 0.001
Voltage	20 v ± 2	10 v ± 1	-50	<i>p</i> < 0.001
Parietal				
Rate	7.2 Hz	6.8 Hz	-0.6	<i>p</i> > 0.001
Voltage	10 v ± 1	10.3 v ± 1	+0.3	<i>p</i> > 0.001
temporal				
Rate	6.3 Hz	6.4 Hz	+0.1	<i>p</i> > 0.001
Voltage	8 v ± 0.8	7.8 ± 0.4	-2.5	<i>p</i> > 0.001
Frontal				
Rate	18 ± 1	17.3 ± 0.4	-3.8	<i>p</i> > 0.001
Voltage	5 v ± 0.4	5 v ± 0.4	0	<i>p</i> > 0.001

Table 4. EEG parameters in the epochs free of paroxysmal activity, basal and at the 12-week evaluation in the AED monotherapy group.

AED monotherapy	Basal	12-week	% reduction	<i>p</i>
Occipital				
Rate	10.2 Hz	9.2 Hz	-0.8	<i>p</i> > 0.001
Voltage	18 v ± 3	17 v ± 0.7	-0.5	<i>P</i> > 0.001
Parietal				
Rate	6.2 Hz	5.9	-0.1	<i>P</i> > 0.001
Voltage	12 v ± 1	12.5 ± 1	+0.5	<i>P</i> > 0.001
temporal				
Rate	5.8 Hz	5.6 Hz	+0.1	<i>p</i> > 0.001
Voltage	6v ± 0.4	7.8 ± 0.4	-2.5	<i>p</i> > 0.001
Frontal				
Rate	16.3 ± 0.7	16.8 ± 0.4	+3	<i>p</i> > 0.001
Voltage	4 v ± 0.5	5.2 ± 0.3	+2.5	<i>p</i> > 0.001

Table 5. EEG parameter in the epochs of paroxysmal activity, basal and at the 12-month evaluation.

Paroxysmal activity	Basal	12-week	<i>p</i>
Esc + AED			
Rate Hz	4.3	2.6	<i>p</i> < 0.01
Amp	42.4	42.3	<i>p</i> > 0.01
AED monotherapy			
Rate	4.6	4.8	<i>p</i> > 0.01
Amp	34	36	<i>p</i> > 0.01

reduction in the monthly seizures when a second AED is added in order to control seizures [9] [10].

In regards to the EEG findings in the epochs of free paroxysmal activity, we observed interesting data in the ESC group which consists in the slowing of the mean posterior frequency from 12.3 to 8.3 Hz (-35% , $p < 0.05$) at the end of this study. This finding is consistent with other studies published before in which had reported that other AEDs decreased the posterior frequency presumably related to the blockage of the sodium/potassium voltage gated channels [11] simultaneously, patients of this group showed a reduction in the centre parietal voltage amplitude from $20 \text{ v} \pm 2$ to $10 \text{ v} \pm 1$ (-50% , $p < 0.05$) at the end of the study, this data has not been reported in other studies in the past to our knowledge, unlike the monotherapy-group which showed a mild and not statistical representative change in the EEG parameters at the end of the study. Even though patients of group B (Monotherapy) showed a reduction in the monthly frequency seizures the decrease in the rate of seizure was greater in ESL group, and we also observed that the greater reduction in the posterior EEG activity is directly related to the decrease in the frequency of monthly seizures; some authors have published that Carbamazepine and Oxcarbazepine (Na/K blockers channels) could cause similar EEG findings in epileptic patients [12] [13], but this has not been stated in EP patients treated with Eslicarbazepine to our knowledge.

In regards to the EEG activity in the epochs of paroxysmal activity, the patients of ESL group also showed a reduction in the mean frequency of the paroxysmal activity decreasing from 4.3 Hz at the basal EEG to 2.6 Hz (reduction 30%, $p < 0.05$) at the end of the study, however there were no changes in the mean voltage amplitude in the epochs of paroxysmal activity (from basal 50 ± 8 to the end point 55 ± 7 $p > 0.05$). Patients of the monotherapy group showed no EEG changes, neither in frequency nor in amplitude in the epochs of paroxysmal activity at the end of the study.

There were no relevant changes in the location and the morphology of the focal paroxysmal activity of both groups at the end of the study.

There is some published data about important changes in the EEG parameters in EP after AED therapy as we pointed out above, interestingly AEDs, such as Phenytoin, valproic acid and carbamazepine have been shown to change EEG parameters in EP patients and in models' rats [14]. However there is little published information in relation to EEG changes in EP patients treated with ESL as well as in mice.

ESL treatment prevented acute latrunculin A-induced seizures, as well as chronic seizures and all EEG chronic signs of paroxysmal activity, supporting a possible antiepileptogenic effect in mice.

We have not a clear scientific explanation in regards to the EEG changes in the ESL group, however ESL has shown in mice a greater selectivity of the inactive state of Voltage gate sensitive channel, which is the common feature of the

rapidly firing neurons, over their resting state as compared to CBZ, OXC [15].

We could hypothesize that this selectivity of interaction of the ESL with the inactive state of the voltage-gated sodium channel (VGSC) could determine greater effects on the EEG of EP patients [16]. ESL in add on therapy to another AED could cause a greater blockage of the Na⁺/K⁺ depending channels, which could decrease the posterior EEG frequency and the voltage-amplitude in all the EEG in the free-paroxystic activity epochs, as well as in the epochs where the paroxystical focal activity was observed in the EP patients of this study.

5. Conclusions

The EP with focal paroxystical activity of this study showed a statistical significant reduction in the rate of monthly seizures when Eslicarbazepine 800 mgs was added to a previous AED compared to those patients who only received an increase of the AED in monotherapy, concomitantly, EP treated with ESL added to a previous AED showed a statistically significant reduction in the mean occipital frequency and voltage amplitude in the central and parietal regions in the twelfth week EEG compared to the control group.

There was a strong correlation between the reduction in the monthly seizures and the reduction in the EEG electrical activity (occipital frequency and voltage amplitude in central and parietal regions) in the Eslicarbazepine group in the twelfth week evaluation.

We are aware of the limitation of this study (short sample, open study), however this data gives us a clue about possible neurophysiological effects and action mechanism of ESL as AED Voltage-gated sodium channels blocker and also a possible forecast value of EEG in the control of seizures frequency in EP patients treated with Eslicarbazepine, however better designed studies should confirm these results taking into account the outcomes and complications in longer clinical trials.

Consent

All the patients signed a written consent before being included into the study, this Study was ap-proved by the local committee of ethic.

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