RESEARCH ARTICLE

The Effect of Carbamazepine on Interictal Epileptic Discharges in Patients with Focal Epilepsy

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Received: 12th June, 2021; Revised: 26th August, 2021; Accepted: 22nd November, 2021; Available Online: 25th December, 2021

ABSTRACT

Background: According to the International League Against Epilepsy (ILAE) recommendations, carbamazepine (CBZ) is considered at the top of the first-line antiepileptic drugs in treating partial epileptic paroxysms with or without secondary generalization.

The CBZ act on cortical neurons by different types of actions, electroencephalographic (EEG) examination of patients placed on CBZ therapy is of special importance due to this ability of medication, the administration of CBZ and its derivative should be scheduled concerning the form of epilepsy, specificity of individual EEG, EEG dynamics and clinical manifestation during the treatment.

Objective: This study aimed to evaluate the impact of carbamazepine on interictal epileptic discharge for patients with focal epilepsy.

Patients and Method: This is a prospective study conducted in Basra general hospital from first of March to first of November 2014, one hundred ten (110) patients recently diagnosed as having partial epilepsy were included in the study. Their age range from 15 to 45 years, no one of them had a history of encephalitis, meningitis, head trauma or cerebrovascular accident (CVA), with normal neurological exam and normal MRI and CT scan. All patients were exposed to EEG exam at the starting of the study by using digital EEG machine according to the 10 to 20 International system. All EEG records that presented with changes suggestive of interictal epileptic discharges (IEDs) were then independently reviewed. The frequency of IED was calculated. Patients began the drug therapy with carbamazepine (20 mg/kg/day), and a second EEG exam was done after six months. Patients who show no compliance to treatment or resistance to treatment (continue to experience clinical attacks of seizure) were excluded. All patients who missed their follow-up visits after three months of starting a treatment or did not attend the second EEG exam appointment after six months of treatment were excluded.

Results: From one hundred ten patients included in the study only 77 patients continued the study and 33 patients were excluded. The results revealed that 68 patients (88.3%) had a significant reduction in mean epileptic discharge in the second EEG exam after six months of treatment with carbamazepine. Furthermore, among them, 42 patients (61.8%) had no more clinical seizure attacks during study time, and 26 patients (38.2%) continued having seizure attacks until the end of third month after starting treatment, and most of them experienced one attack during the first or second month.

Conclusion: Carbamazepine is still a very effective drug in the management of partial epilepsy. Besides, EEG is an essential tool in the assessment of patient's response to carbamazepine and reduction in interictal epileptic discharges on subsequent EEG studies may predict the chance of developing further clinical epileptic attacks in patients with partial epilepsy using carbamazepine drug.

Keywords: Carbamazepine, Electroencephalography, Epileptic discharge.

International Journal of Drug Delivery Technology (2021); DOI: 10.25258/ijddt.11.4.58

How to cite this article: Hammady MM, Mohammed SJ, Sabbar OS. The Effect of Carbamazepine on interictal epileptic discharges in patients with focal epilepsy. International Journal of Drug Delivery Technology. 2021;11(4):1460-1465.

Source of support: Nil.

Conflict of interest: None

INTRODUCTION

According to the ILAE recommendations, CBZ is considered at the top of the first-line antiepileptic drugs in treating partial epileptic paroxysms with or without treatment without secondary generalization. Considering the prevalence of partial seizure (localization-dependent seizures) making up to 60% of all forms of epilepsy in children and about 80% in adults, the share of CBZ and its derivatives among the total volume

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of antiepileptic drugs used is not less than 50%.[1] Although the mechanism of action of CBZ is not fully understood. It is widely accepted that the drug produces its antiepileptic effect by blocking sodium channels which reduces the ability of neurons to conduct high-frequency impulse flow.

Moreover, CBZ is also known to have a variety of other actions, including inhibiting the reuptake of norepinephrine, and blocking adenosine and N-methyl-D-aspartate (NMDA) receptors. However, it is not clear if these mechanisms are related to its antiepileptic effect. The EEG examination of patients placed on CBZ therapy is of special importance due to this medication ability: the administration of CBZ and its derivate should be scheduled with due regard to the form of epilepsy, specificity of individual EEG, EEG dynamics, and clinical manifestation during the treatment.[2] The use of EEG to detect IEDs in patients with a history of seizures is routine. The presence of IEDs can help confirm a clinical diagnosis of epilepsy, and their location and characteristics can help identify the epileptogenic zone or suggest a particular epilepsy syndrome.[3] Besides that, some clinicians may also use the presence or frequency of IEDs to help predict clinical epilepsy severity, much of the evidence on this subject had been studied in specific subpopulations and is quite dated. Generally, our understanding of the ability of IEDs to predict measures of epilepsy severity such as seizure frequency is remarkably developing.[4] Also, several factors may affect the rate and appearance of interictal epileptiform discharges like antiepileptic drugs (AEDs) such as carbamazepine, which may suppress interictal epileptiform activity. Moreover, in some patients with focal seizure disorders, there is a positive correlation between the number of seizures and interictal epileptiform activity (IEA).[5] In this study, we investigated the impact of CBZ on interictal epileptic discharges in patients with focal epilepsy.

METHODOLOGY

This is a prospective study conducted in Basra general hospital from the first of March to the first of November 2014, and designed to evaluate the effect of carbamazepine treatment on interictal epileptic discharge in the group of patients having partial epilepsy. All patients included in the study were recently diagnosed with epilepsy and have no more than two attacks of seizure within the last one-month duration. Their age range from 15 to 45 years, no one of them had a history of encephalitis, meningitis, head trauma, CVA with a normal neurological exam done by a consultant neurologist, and a normal MRI and/ or CT scan of the brain. The total numbers of patients included in the study were 110 patients (65 females and 45 males).

All patients did EEG exam at the beginning of the study in Basra children specialty hospital using digital EEG machine according to the 10 to 20 International system, with measured impedances of less than 5 k. Ohms at all electrodes. All studies utilized both bipolar and referential montages. Initial analog signal conditioning included a 0.3 to 1 Hz high pass filter, a 35 to 70 Hz low pass filter and a 50 Hz notch filter. The digital sampling rate was 200 to 500 per second. EEG recordings last for 30 minutes. Activating techniques including hyperventilation and intermittent photic stimulation were used. All EEG records with findings suggestive of IEDs were then independently reviewed in their entirety by a neurophysiologist, and the IEDs were defined as spike or sharp wave discharges that stood out from the background rhythms with or without an aftergoing slow wave. Subjects demonstrating IEDs consistent with a diagnosis of primary (idiopathic) generalized epilepsy, myoclonic or absence epilepsy were excluded from further analysis. Only patients with focal IEDs were included in the study. The frequency of IED was calculated by manually counting the total number of IEDs seen in the entire routine study and dividing by study duration. Patients were divided into two groups according to the changes in epileptic discharge obtained by EEG exam:

Group A: Patients who show a reduction in ED in the second visit.

Group B: Patients who show an increase in ED in the second visit.

Patients began the drug therapy with carbamazepine 20 mg/kg/day as prescribed by their neurologist, A total body weight accepted for patients were not exceeding 70 kg because larger weights need high doses from the beginning, which is usually associated with the early appearance of side effects as suggested by the neurologist doctors.

All patients were asked to visit their doctor if they experienced any seizure attacks. Patients who did not complain well to the treatment or show resistance to treatment (continue to experience clinical attacks of seizure which necessitate the use of other drugs) were excluded. All patients who missed their follow-up visits after three months of starting a treatment or did not attend the second EEG exam appointment after six months of treatment were excluded. This study was conducted following a protocol approved by the Committee on Clinical Investigations at Basra collage of Medicine and Basra health directorate, all patients were informed about the aim of study and their acceptance obtained.

Statistical Analysis

Data analysis was done by using Statistical Package for the Social Sciences (SPSS) version 20 computer software. Descriptive statistics for all data of each set was expressed as mean ± 2SD. The difference in mean epileptic discharge between groups was assessed by independent sample t-test, $p < 0.05$ considered statistically significant, spearman test was used to assess the correlation between a number of seizure attacks and mean epileptic discharge.

RESULTS

Out of the total, 110 included in the study only 77 patients continued the study and 33 patients were excluded from the study. The number of females was 46 (59.7%) and number of males were 31 (40.3%), and no significant difference was found in epileptic discharge between males and females as illustrated in Table 1, which also shows the number and percentage of all patients included and excluded from the study.

Patients were divided into two groups according to the changes in epileptic discharges (ED) obtained by EEG exam:

Group A: Patients who show a reduction in ED in the second visit.

Group B: Patients who show an increase in ED in the second visit.

The results obtained in Table 2 show that (68) patients (88.3%) show a reduction in an epileptic discharge after six months of treatment with carbamazepine, and (9) patients (11.7%) show an increase in epileptic discharge.

The total number of patients who still had clinical seizure attacks during the period of treatment, whether one or more attacks were (31) patients (40.3%), and those who had no more seizure attacks after starting treatment were (46) patients (59.7%). Moreover, no significant difference was found between males and females regarding seizure attacks (Table 3).

Also, from the total number of patients who showed a reduction in epileptic discharge, which was (68) patients, forty-two patients (61.8%) did not experience any seizure attacks during the next six months of treatment, and (26) patients (38.2%) continue having seizure attacks. Moreover, from the nine patients who showed an increase in epileptic discharge, five patients (55.5%) still experienced seizure attacks during the study period, and four patients (44.5%) did not experience any seizure attack during the six months study period, as illustrated in the Table 4.

Table 5 showed that thirty one patients continue having seizure attacks after three months of treatment, twenty six of them in group A (who have a reduction in epileptic discharge) and five in group B who have increased in epileptic discharge). After six months of treatment, only two patients from group A and three patients from group B continue having seizure attacks, so a totally five patients only experience seizure attacks after three months of treatment.

Statistically, there was no significant difference in mean epileptic discharge between male and female in first and second visits $p = 0.15$. However, a highly significant reduction in mean epileptic discharge was noticed in second visit (49.38 ± 28.37) as compared to the first visit (79.44 ± 28.98), $p > 0.00$ as demonstrated in the Table 6.

Figure 1 shows a significant positive linear correlation between number of seizure attacks and mean epileptic discharge (p significant at 0.032 level), so as the mean epileptic discharge increases, this will increase the risk for patients to develop seizure attacks.

DISCUSSION

This study included 110 patients with focal epilepsy; only 77 patients continued the study, and 33 patients were excluded from the study either for irregular treatment or still experience clinical seizures, which make it necessary to use drugs other than carbamazepine or not attending the second visit for EEG

Table 1: The number and percentage of patients included and excluded from the study with their gender distribution

	Male		*Female*		*Total*	
	NO.	*%*	*NO.*	*%*	*NO.*	*%*
1st visit	45	40.9	65	59.1	110	100
2nd visit	31	40.3	46	59.7	77	70
Excluded	14	31	19	29.5	33	30

Table 2: Number and percentage of patients in groups A and B

	Male		*Female*		*Total*	
ED	*No.*	*%*	*No.*	*%*	*No.*	*%*
Group A	28	90.3	40	87	68	88.3
Group B	3	9.7	6	13	9	11.7
Total	31		46		77	

Table 3: Number and percentage of patients who continue having clinical seizure attacks after treatment and patients that have no more attacks after treatment

	Male		*Female*		*Total*	
Clinical attacks	*No.*	*%*	*No.*	*%*	*No.*	*%*
Patients with no attacks	18	58.1	28	60.9	46	59.7
Patients still having attacks	13	41.9	18	39.1	31	40.3
Total	31		46		77	

Table 4: Number and percentage of patients in group A (have reduction in ED) & group B (have increase in ED) who still having seizure attacks and those who have no more attacks.

	Patient have no seizure attacks		*Patient still having seizure attacks*		*Total*	
ED	*No.*	*%*	*No.*	*%*	*No.*	*%*
Group A	42	61.8	26	38.2	68	88.3
Group B	4	44.5	5	55.5	9	11.7
Total	46		31		77	

Table 5: Number of patients in group A & B who continue having seizure attacks after three and six months of treatment consecutively

	End of third month of treatment		*End of six months of treatment*	
	No.	*%*	*No.*	*%*
Group A	26	83.9	2	40
Group B	5	16.1	3	60
Total	31		5	

Table 6: Mean epileptic discharge for patients in first and 2nd visit after treatment

	No.	*1st visit*	*2nd visit*	*p-value*
Male	31	78.5 ± 30.3	48.8 ± 29.5	H.S
Female	46	80.11 ± 26.6	50.74 ± 27.85	H.S
Total	77	79.44 ± 28.98	49.38 ± 28.37	H.S
p-value		N.S	N.S	

N.S: *p-value* = 0.15, H.S: *p-value* = 0.00

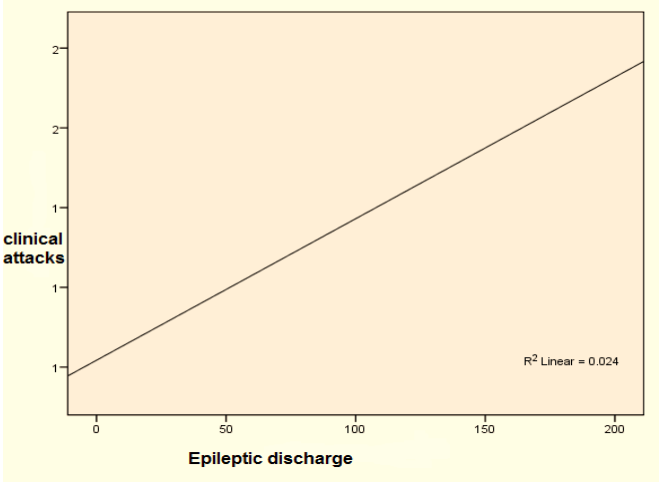

Figure 1: Correlation between number of seizure attacks and mean epileptic discharge, correlation is significant at the 0.05 level (*p-value*=0.032)

exam. The number of females was 46 (59.7%) and number of males were 31 (40.3%), and no significant difference was found in mean epileptic discharge between males and females, indicating no gender variation in epileptic discharge between male and female. These results also reported in other studies, which show no difference in epileptic discharge or response to treatment between male and female.[7,19]

The results also revealed that 68 patients (88.3%) had a highly significant reduction in mean epileptic discharge in second EEG exam after six months of treatment with carbamazepine (Table 2 and 4). Moreover, among them, forty-two patients (61.8%) had no more clinical seizure attacks during study time, and twenty six patients (38.2%) continued having seizure attacks until the end of third month after starting treatment, most of them experienced one attack during the first or second month, and that is why they kept on the same dose of treatment. At the end of the sixth month of treatment there were only two out of the above twenty-six patients experienced one seizure attack in the fourth month after treatment, and the dose of carbamazepine changed to 30 mg/kg/day, and no more seizure attacks developed in the fifth and sixth months of treatment.

In group B, which includes nine patients (11.7%) who had an increase in an epileptic discharge after six months of treatment, five patients (55.5%) continued having seizure attacks, two of them their seizure attacks stopped before the third month of treatment and three patients experience seizure attacks in the fourth month. Thus, the dose of carbamazepine increased to 30 mg/kg/day, so no more attacks were recorded for them in fifth and six months. When we chart these seizure attacks, we found that most of them were in the first and second months of treatment either because of a gradual increase in the dose of treatment in the first month or because of the trouble of patient obedience to treatment but later on when the dose became fixed as 20 mg/kg/day in two divided doses and patients accommodated for the schedules of their treatment, the seizure attacks decline.

Even though five patients experienced seizure attacks in the fourth month which necessitated the increase in the dose of carbamazepine to become 30 mg/kg/day to stop their clinical attacks, and actually seizure attacks stopped for all of them and two of them show reduction in epileptic discharge in second visit as compared to first visit. However, still three patients their second EEG exam showed increase in epileptic discharge as compared to first exam.

This group of patients might need further follow-up after increasing their treatment dose because they might show reduction in epileptic discharge during the next six months after changing treatment, especially because they develop no more seizure attacks (for the last two months of study) after increasing the dose of carbamazepine. This possibility had been reported by other studies, which showed that prolonged use of carbamazepine is associated with significant reduction in epileptic discharge.[6,16]

Besides, some studies showed that some mechanisms might affect the action of AEDs and two main hypotheses attempt to explain that the first is the multidrug transporter hypothesis which suggests that AEDs cannot achieve sufficient concentrations in the brain to be effective and this occurs because of the blood-brain barrier that is actively "empty" the brain of small organic molecules. Moreover, the second is the altered target hypothesis which states that there is an alteration of drug target by some chemical modification (phosphorylation, glycosylation etc.).[7,17]

However, we cannot judge from the data obtained in this study whether patients show an increase in epileptic discharge by EEG exam. However, with no clinical seizure, attacks are due to one of the mechanisms above, especially because 88.3% of patients included in the study showed a significant reduction in mean epileptic discharge and no more seizure attacks were recorded. Thus we assume that patients who show an increase in epileptic discharge need further follow-up to carefully assess their response to carbamazepine monotherapy especially if they had no seizure attacks.

Furthermore, from the 88.3% of patients who show a reduction in mean epileptic discharge, only 2.9% of them have seizure attacks in fourth month, and these attacks stopped after increasing the dose of carbamazepine in fifth and sixth months. Hence, carbamazepine was effective in reducing both clinical seizure attacks and epileptic discharge at EEG exam. Moreover, the efficacy of carbamazepine in the treatment of focal epilepsy could be related to the binding rate constant of carbamazepine onto the inactivated Na channels, which is five times faster than that of other antiepileptic drugs, especially phenytoin. Therefore, it is speculated that carbamazepine may be more effective than other antiepileptics in treating seizures whose ictal depolarization shift is relatively short.[8,18] Moreover, if a drug can frequently induce normalization of EEG, it may be a better drug for treating that seizure type.[9,15]

These findings are consistent with the results obtained by Devazio G. *et al.,* that the effect of carbamazepine on group of patients with complex partial seizures results in decline in seizure attacks in response to carbamazepine monotherapy.

Although, he did not correlate the reduction in seizure attacks with the epileptic discharge on EEG exam because he did a single EEG exam at the starting of his research to decide seizure type (focal, absence, myoclonic etc.) and only patients with focal epileptic discharge were included in his study.[10] But later on, different studies showed that quantitative EEG measures are a useful tool in the objective determination of antiepileptic drugs related to neurotoxicity and follow-up response to treatment.[11, 20] Moreover, other studies conducted by Marciani *et al.* showed a significant reduction in mean epileptic discharge after two months of treatment of patients with focal epilepsy using carbamazepine monotherapy.[12] However, in his study, he found that changes in background EEG activity inform of slow waves for some patients whose first EEG exam shows highly active epileptic foci before starting treatment. However, other studies could not trace such effect of carbamazepine on cerebral activity and they found that carbamazepine inhibits epileptiform activity without affecting the membrane resting potential or input resistance; thus it is unlikely to affect cerebral background activity.[13,21]

And since patients with focal epilepsy who are taking carbamazepine as a treatment showed a reduction in epileptic discharge by EEG exam. They also showed a reduction in seizure attacks, which was consistent with the findings of Marson *et al.* when he studied carbamazepine versus valproate monotherapy for epilepsy. His results support the policy of using carbamazepine as the treatment of first choice in people with partial epilepsy, and it was effective in reducing clinical seizure attacks and epileptic discharge by EEG exam.[2,7,22-27]

CONCLUSION

Carbamazepine is still a very effective drug in the management of partial epilepsy. Besides, EEG is an essential tool in the assessment of patient's response to carbamazepine, and reduction in interictal epileptic discharges on subsequent EEG studies may predict the chance of developing further clinical epileptic attacks in patients with partial epilepsy using carbamazepine drug.

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