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Research Article

COMPARISION OF EFFICACY AND SAFETY OF CARBAMAZEPINE AND ESLICARBAZEPINE IN ADULT PARTIAL AND GENERALIZED SEIZURES

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ABSTRACT

The treatments for seizures are usually aimed at improving the clinical condition of the patient by reducing the seizure frequency and adverse drug reactions.

Objective: The objective of this study is to evaluate the efficacy of monotherapy Carbamazepine in comparision with Eslicarbazepine and also to assess adverse drug reactions of Carbamazepine and Eslicarbazepine.

Methods: This study was a prospective interventional study.A total of 44 patients were included in the study, of which, 22 patients were under Carbamazepine (Group A) and 22 patients were under Eslicarbazepine (Group B).

Results: On comparision with GroupA patients, the seizure frequency was found to be less in Group B with very low incidence of adverse effects.

Conclusion: Eslicarbazepine monotherapy was found to be better than carbamazepine in partial and generalized seizure patients.

Keywords: Seizures, Carbamazepine, Eslicarbazepine

INTRODUCTION

Epilepsy is defined as a chronic neurological condition characterized by recurrent epileptic seizures, [1] characterized by periodic and unpredictable occurrence of seizures that usually recur in the absence of a consistent provoking factor [2]. The neuronal activity is usually excessive and synchronous in character and produces characteristic paroxysmal discharges (epileptic form activity) [3,4,5,6,7]. Seizures are categorized as being symptomatic, reactive, or idiopathic. Symptomatic or secondary seizures occurs secondary to a structural brain lesion. Brain trauma, hydrocephalus, encephalius, and neoplasia are potential inducers of structural damage. Reactive seizures arise as a consequence of an extracranial metabolic or toxic insult. Idiopathic or primary epilepsy refers to seizures for which no underlying etiology can be detected [6,8,9,10,11].

Seizures can also be classified by their clinical features [6,8,11] as either partial (synonymous with focal) or generalized. Partial seizures are those in which the seizure activities restricted to discrete areas of the cerebral cortex [8,9]. Generalized seizures involve diffuse regions of the brain simultaneously [10]. Partial seizures are usually associated with structural abnormalities of the brain. In contrast, generalized seizures are from cellular, biochemical, or structural abnormalities [12].

Medical treatments for seizures are usually aimed at improving the clinical condition of the patient by reducing the seizure frequency and adverse drug reactions. The seizure frequency in some conditions and patient condition may get worse with many adverse drug reactions. Eslicarbamazepine is new anti-epileptic drug of dibenzazepine family. It is a high affinity antagonist of the voltage-gated sodium channel. Eslicarbazepine has similar affinity to inactivated sodium channels (channels in just activated neurons) as carbamazepine [13,14,15].

The Carbamazepine and Eslicarbazepine are structurally related, but their biotransformation is different Carbamazepine is mainly metabolized to Carbamazepine-epoxide. The plasma concentration of Carbamazepine-epoxide may range from 5 to 40% of that of Carbamazepine in long-term therapy [16,17]. Eslicarbazepine binds avidly and blocks the inactivated voltage-gated sodium channel (VGSC). The VGSC is the major source of sodium entry when a neuron depolarizes, and consequently allows for the action potential to propagate. Eslicarbazepine binds to the inactivated form of the VGSC and prevents its reversion to the receptive resting or deactivated form which means that Eslicarbazepine binds to more active neurons preferentially [18,19]. This mechanism is shared by carbamazepine, Oxcarbazepine, and other anticonvulsants. The affinity of Eslicarbazepine to the inactivated form of the VGSC is similar to that of carbamazepine, but its affinity to the resting form of VGSC is some 3 times less. This suggests that Eslicarbazepine is less likely to bind to normally active neurons, and it does not form the epoxide compound like carbamazepine which is responsible for many adverse drug reactions and therefore, less likely to cause adverse neurological consequences. Indeed when compared with either carbamazepine or Oxcarbazepine, Eslicarbazepine had less neurologic impairment in rats, and was less toxic to cultured hippocampal neurons [20,21].

Untill no comparative study is done on monotherapy of Eslicarbazepine and carbamazepine in patients with seizures. Hence, the study has been designed to evaluate the efficacy and safety of Eslicarbazepine in comparision with carbamazepine.

MATERIALS AND METHODS

The study protocol was approved by the Institutional Ethics Committee in SRM Medical college hospital and research center, Kancheepuram, Tamil Nadu, India.The patients who had visited in the department of neurology for consultation were selected for the study according to the inclusion criteria. Patients having 18-65 years of age, both inpatient and outpatient with partial and generalized seizures were taken for the study. Pregnant women, lactating women, paediatric patients, geriatric patients, patients with concomitant liver, kidney, thyroid diseases, atrioventricular block, thrombocytopenia, leukopenia, patients treated concomitantly with oral anticoagulants, propoxyphene and dextropropoxyphene, tetracyclines, clofibrate, monoamine oxidase inhibitors and tricyclic

anti-depressants were excluded from the study. A total of 48 patients were enrolled into the study, of which 26 patients were under Carbamazepine 200mg (Group A) twice a day,4 patients were excluded due to lack of exact information and 22 patients were under Eslicarbazepine 400mg (Group B) once a day based on inclusion and exclusion criteria. At the beginning of the study the purpose, importance of the study was explained to the patients participated in the study and obtained the informed consent form. Details like name, age, sex, past medical history, past medication history, family history, telephone number, address were collected. Baseline details for Haemoglobin, Haematocrit, RBC, total and differential WBC count, platelet count, SGOT, SGPT, alkaline phosphatase, sodium, potassium and electroencephalography were collected before taking the medication and after taking medication. Symptoms and seizure frequencieswere collected by patient interview during the therapy period. Data were analysed using SPSS software and methods like student t-test and chi-square test were used to calculate the significance of efficacy (*P<0.05).

RESULTS

A total of 44 patients were included into the study, of which 22 patients were under Carbamazepine 200mg (Group A) and 22 patients were under Eslicarbazepine 400mg (Group B) Table 1 shows age wise distribution of patients in Group A and Group B. In Group A, 8 (36%) were males and 14 (64%) were females and in Group B, 10 (45.5%) were males and 12 (54.5%) were females. In Group A, 6 (27.3%) patients had family history of seizures and 16 (72.7%) patients did not have any family history of seizures. In Group B patients, 4 (18.2%) patients had family history of seizures and 18 (81.8%) patients did not have any family histories of seizures.

Table 1: It shows age wise distribution.

S.NO	Age	Group - A (n=22)	Percentage (%)	Group - B (n=22)	Percentage (%)
1	<20 years	5	22.7%	4	18.2%
2	20-30 years	9	40.9%	9	40.9%
3	31-40 years	6	27.3%	5	22.7%
4	>40 years	2	9.1%	4	18.2%
5	Total	22	100%	22	100%

In Group A, 7 (87.5%) patients were having smoking and alcohol habits, 1 (12.5%) was only smoker and 1 (12.5%) was only alcoholic patient and in Group B, 3 (37.5%) patients were having smoking and alcohol habits, 2 (25%) were only smokers and 3 (37.5%) were alone alcoholic patient.

The comorbid conditions associated with seizure patients were collected in the data entry form. Table 2 shows comorbid conditions of patients.

Table 2: It shows comorbid conditions of patients

S.NO	Comorbid condition	Group - A No. of patients (n=22)	Percentage	Group - B No. of patients (n=22)	Percentage
1	Hypertension	2	9.10%	0	0%
2	Diabetes mellitus	1	4.50%	1	4.50%
3	Anaemia	0	0%	1	4.50%
4	Tuberculosis	2	9.10%	0	0%
5	Hypogonoidism	1	4.50%	0	0%
6	None	16	72.80%	20	91%
	Total	22	100%	22	100%

The haematological parameters (haemoglobin, haematocrit, RBC, total WBC, lymphocytes, eosinophil's, neutrophils, monocytes, basophils, platelet count) were measured. The liver enzymes (SGOT, SGPT, and ALP) tests were done to evaluate the effect of drug on liver enzyme. The electrolytes were also checked.The laboratory parameters were obtained before and after the Carbamazepine and Eslicarbazepine therapy in order to assess the efficacy [22, 23].

The Mean±SD of haemoglobin base and review value in Group A patients were 12.3455±1.03958 and 13.3636±0.67863g% respectively. The Mean±SD of haemoglobin base and review levels in Group B patients were 12.6455±1.30412 and 14.2455±1.02700g% respectively. The haemoglobin base and review levels of both Groups shows the significance of P value 0.028S.

Table 3 shows the seizure frequency i.e., recurrence of seizure after the drug therapy. In Group A, 4 (18.2%) patients had seizure recurrence and 18 (81.8%) patients were seizure free. In Group B patients, there is no recurrence of seizure and all the 22 (100%) patients were seizure free. The mean value of seizure frequency in Group A and Group B was found to be significant with p value of 0.036.

Adverse drug reaction categorization

The adverse drug reactions were collected in the ADR documentation form. Table 4 shows adverse drug reactions observed in patients after taking Carbamazepine and Eslicarbazepine respectively.

Table 3: It shows seizure frequency of patients.

S.NO	Seizure frequency	Group – A No. of patients (n=22)	Percentage (%)	Group – B No. of patients (n=22)	Percentage (%)	P value
1	Yes	4	18.2%	0	0%	
2	No	18	81.8%	22	100%	0.036*S*
	Total	22	100%	22	100%	

S- Significant (*P < 0.05), NS – Not Significant (*P > 0.05)

Table 4: It shows adverse drug reactions in Group A and Group B.

S.NO	ADR	Group – A		Group – B	
		No. of patients (n=22)	Percentage (%)	No. of patients (n=22)	Percentage (%)
1	Dizziness	14	63..6%	1	4.5%
2	Sleepiness	22	100%	17	77.3%
3	Headache	9	40.9%	9	40.9%
4	Blurred or double vision	1	4.5%	4	18.2%
5	Nausea or vomiting	4	18.2%	1	4.5%
6	Diarrhea	0	0%	0	0%
7	Skin rash	0	0%	0	0%
8	Fatigue	12	54.5%	21	47.7%
9	Abnormal coordination	2	9.1%	0	0%
10	Problems concentrating	5	22.7%	5	22.7%
11	Tremor	3	13.6%	2	9.1%
12	Anaemia	0	0%	1	4.5%
13	Hypothyroidism	0	0%	0	0%
14	Abdominal pain	2	9.1%	2	9.1%
15	Dry mouth	4	18.2%	0	0%
16	Irritable bowel	0	0%	1	4.5%
17	Inflammation of mouth and gums	0	0%	2	9.1%
18	Changes in appetite and body weight	7	31.8%	3	13.6%
19	Dryness of skin	0	0%	0	0%
20	Redness of skin	0	0%	0	0%
21	Excessive sweating	6	27.3%	9	40.9%
22	Hair loss	11	50%	8	36.4%
23	Dehydration	1	4.5%	0	0%
24	Swelling of legs	1	4.5%	0	0%
25	Nocturia	4	18.2%	2	9.1%
26	Oedema	0	0%	0	0%
27	Nosebleed	2	9.1%	1	4.5%
28	Changes in sense	4	18.2%	0	0%
29	Confusion	10	45.5%	14	63.6%
30	Insomnia	2	4.5%	1	4.5%
31	Depression	7	31.8%	2	9.1%
32	Mood swings	10	45.5%	8	36.4%
33	Red or painful eye	1	4.5%	0	0%
34	Agitation	15	68.2%	18	81.8%
35	Problems with speech	7	31.8%	2	9.1%
36	Memory problems	11	50%	10	45.5%
37	Muscle, back, neck pain	9	40.9%	6	27.3%
38	Palpitations	0	0%	0	0%
39	Bradycardia	0	0%	0	0%
40	Tingling or numb Sensations	2	9.1%	2	9.1%
41	Others	1	4.5%	1	4.5%

The main adverse effects noticed were dizziness in 14 (63.6%) patients in Group A and 1 (4.5%) patients in Group B, sleepiness were observed in 22 (100%) patients in Group A and 17 (77.3%) patients in Group B, headache were seen in 9 (40.9%) patients in both Groups, fatigue were seen in 12 (54.5%) patients in Group A and 21 (47.7%) patients in Group B, hair loss were seen in 11 (50%) patients in Group A and 8 (36.4%) patients in Group B, confusion were seen in 10 (45.5%) patients in Group A and 14 (63.6%) patients in Group B, mood swings were seen in 10 (45.5%) patients in Group A and 8 (36.4%) patients in Group B, agitation were seen in 15 (68.2%) patients in Group A and 18 (81.8%) patients in Group B, excessive sweating were observed in 6 (273%) patients in Group A and 9 (40.9%) patients in Group B, memory problems were seen in 11 (50%) patients in Group A and 10 (45.5%) patients in Group B, muscle, back or neck pain were seen in 9 (40.9%) patients in Group A and 6 (27.3%) patients in Group B, the remaining adverse effects were seen less than 40% patients in both groups.

DISCUSSION

In our study, maximum numbers of patients were in the age group of 20-30 years (40.9%). The seizure frequency and adverse drug reaction were reported more in this age group. Most of the patients participated in the study were females in both groups. Recurrent seizures and adverse drug reactions were observed more in patients with family history of seizures.

Patients with smoking and alcoholic habits were not seen with recurrence of seizures but having adverse drug reactions comparatively high. In present study population we observed that patient with hypertension in Group A only had recurrence of seizure and recurrence was not seen in any other comorbid condition.

The mean haemoglobin levels in Group A and Group B patients after the treatment were significantly higher when compared with the levels before the treatment. The rest of the parameters were not found to be significant and therefore it was found that there is no association between the values before and after the treatment. These results were found to be controversial with the earlier studies done on Carbamazepine by Kari Juha Reinikainen, etal [24].

On comparision with the Carbamazepine monotherapy, the seizure frequency of the Eslicarbazepine monotherapy was found to be better. In earlier study it was proved that Eslicarbazepine had a better pharmacokinetic profile than Carbamazepine with low potential for drug-drug interactions and no auto induction of metabolism by Rajinder P. Singhetal and a study done by Almeida L etal [13] stated that Eslicarbazepine adjunctive therapy is comparatively more effective than carbamazepine therapy. Hence this study is similar to the above mentioned studies.

In earlier studies on Carbamazepine, patients experienced dizziness, skin rash, sleepiness, nausea or vomiting, hypernatremia, diplopia

were some of the adverse effects reported to higher extent in patients [24, 25, 26, 27].

In previous studies on Eslicarbazepine adjunctive and monotherapy, the adverse effects observed to higher extent in patients were sleepiness, abnormal coordination, somnolence, blurred vision, vertigo, fatigue, diplopia and nausea are reported [28,29,30].

In the present study, it was observed that safety profile of the Eslicarbazepine was found to be better when compared to Carbamazepine. Adverse drug reactions like dizziness, sleepiness, hair loss, mood swings, memory problems, muscle, neck or back pain, nausea or vomiting, tremor, dry mouth, changes in body weight and appetite, abnormal coordination, dehydration, swelling of legs, Nocturia, nose bleed, changes in sense, insomnia, depression, red or painful eye and problems with speech were more reported more in Group A patients which is similar to study done by Mogens Dam etal, Radhakrishnan K etal [26,27]. The adverse drug reactions like fatigue, excessive sweating, irritable bowl, inflammation of mouth and gums, confusion, agitation and blurred or double vision were reported more in Group B patients which was similar to study done by Enrique Serranoetal and Steve S. Chung etal.[28,29] The adverse drug reactions like headache, problems in concentrating, tingling or numb sensation and other effects were reported in the same ratio in both Groups.

CONCLUSION

It is concluded that Eslicarbazepine monotherapy was found to be better in partial and generalized seizure with very low seizure frequency and less adverse drug reactions compared with the Carbamazepine monotherapy.

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