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Original Research Article

To Study the Efficacy and Tolerability of Lamotrigine in Comparison with Carbamazepine as A First Line Drug in Newly Diagnosed Untreated Epilepsy Patients

Baldeep Singh[1], Jasleen Kaur Narula[2]

[1]Assistant Professor, Department of Medicine, GMC Amritsar
[2]Professor, Department of Pharmacology, Gian Sagar Medical College, Rajpura

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Corresponding author: Dr. Jasleen Kaur Narula
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Abstract:

Epilepsy is a common neurological disorder affecting humans. The conventional antiepileptic drugs (AEDs) control seizure in 80% of the patients and possess various side effects like sedation, ataxia, teratogenicity etc. Lamotrigine(LTG), a phenyltriazine is safe and effective AED, both as add-on and monotherapy in patients with partial as well as generalised seizures. Thus, the present study was undertaken in 100 patients divided in two groups, to study the effect of lamotrigine as a first-line drug in the management of newly diagnosed untreated adult epileptics and to compare the efficacy and tolerability in comparison to carbamazepine(CBZ), a conventional antiepileptic drug.

Thus, we found that LTG was equally efficacious to carbamazepine as measured by reduction in seizure frequency. Sedation was the main side effect in CBZ group due to which nine withdrew from the study. Other side effects in CBZ study group were headache, rash, ataxia. Maculopapular rash was the main side effect in lamotrigine group, due to which two withdrew from the study. Other side effects in LTG study group were headache, asthenia, sedation. Thus, on comparing lamotrigine was better tolerated than carbamazepine and equally efficacious to carbamazepine in various types of seizure. Thus, lamotrigine may be useful as monotherapy in epilepsy.

Keywords: Epilepsy, Antiepileptic drugs, Lamotrigine, Carbamazepine

Introduction

Epilepsy is a common neurological disorder affecting humans and is one of the oldest conditions known to mankind. Antiepileptic drugs (AEDs) are the mainstay of treatment of epilepsy and have to be given lifelong. The conventional antiepileptic drugs control seizure in 80% of the patients and possess various side effects like sedation, ataxia, teratogenicity etc. Carbamazepine (CBZ) is widely used for the treatment of partial and generalized convulsive disorder. Diplopia, drowsiness and paraesthesia are associated with this drug. In India 30% do not respond to conventional pharmacological therapy.[1] The standard drugs do not control all patients with seizures. Newer AEDs have been designed with an aim to counteract specific mechanism in epilepsy. Newer drugs represent valuable tools in the treatment of epilepsy, but because of cost and limited experience their first line cannot be recommended in most situations.[2]

Lamotrigine (LTG), a newer AED is safe and effective AED, both as add-on and monotherapy in patients with partial as well as generalised seizures. It inhibits voltage sensitive sodium channel, thereby stabilizing neuronal membranes and modulating presynaptic transmitter release of excitatory aminoacids eg. Glutamate and aspartate. It has promising potential due to long half-life and minimal drug interactions.

Lamotrigine has proved to be efficacious in treating 2000 patients with partial and generalised tonic-clonic seizures not satisfactorily controlled with other AEDs.[3] Double blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy was conducted and efficacy was measured by seizure reduction.[4] The efficacy was similar with both the drugs in patients with partial seizures with or without secondary generalization. Another study evaluated the efficacy of lamotrigine and carbamazepine as monotherapy. In their study lamotrigine is more efficacious than carbamazepine in controlling seizures. [5]Thus, the present study was done to study the effect of lamotrigine as first line drug in the management of newly diagnosed untreated adult epileptics and to compare the efficacy of lamotrigine with carbamazepine in control of epilepsy and compare the tolerability and side effect of both the drugs.

Material and methods

The study was conducted in 100 newly diagnosed untreated epileptic patients of either sex aged 14 years and above attending medicine and neurology department of Government Medical College, Patiala. The diagnosis was based on

- The clinical assessment of the epilepsy syndrome,
- Electroencephalogram when required was done
- Computerized tomography of the head when required was done

Seizures were classified according to the classification given by International League against epilepsy, 1981.[6] Patients eligible in the study were those who had two or more seizures in the previous six months and at least one in the previous three months. Written informed consent was taken from the patients. The study was approved by Institutional Review and Ethics committee.

The following group of patients were excluded:

- On any other AED drug
- Ladies who are pregnant or likely to conceive or
- Evidence of liver dysfunction, renal disease,
- Progressive neurological illness
- Other serious medical disorders
- History of alcohol or substance abuse
- Epilepsy related to drugs
- Seizures precipitating medical illnesses
- Encephalopathies or structural CNS lesions
- Subjects not likely to be compliant about medication's usage were excluded.

The patients were divided in two groups:

- Group A patients receive lamotrigine tablet 25 mg during first week and then dose was increased every week by 25mg till dose of 150-200 mg was reached.
- Group B patients received carbamazepine according to their weight with usual dose of 300 mg daily and gradually increase till dose of 600-1000 mg was reached.

All patients were followed for six months for seizure recurrence and side effects for both the drugs. Thorough clinical examinations including a detailed neurological assessment and complete

haematological and biochemical investigations were carried out.

Patients were informed of the total number of drugs to be taken daily. Patients were told to maintain a seizure dairy card and report any side effect with the drug to the doctor. Patients were reassessed after every four weeks and followed for up to six months. Complete haematological and biochemical investigations were carried out during follow up. Compliance was assessed by questioning the patients. The primary determinant of efficacy was a reduction in seizure frequency. Other efficacy parameter included the number of days on which the seizure of any type occurred (seizure days). Assessment of the patients overall clinical status as compared with baseline (Global evaluation), a subjective assessment included the factors as seizure frequency and intensity, occurrence of adverse experiences and patients' functional status.All patients who showed more than 50% reduction in the seizure frequency were considered to have positive response. The recovery was where reduction of 75 -100% from the baseline seizure frequency at the end of the study. Patients who had no reduction from the baseline seizure frequency were considered as with no response.

Tolerability was measured by recording adverse events during the trial. Patients were informed about the common side effects like ataxia, headache, dizziness, somnolence, diplopia, nausea, vomiting, rash. Patients were asked to follow up if any side effect occurred. The drug was withdrawn if any side effects seriously hampered the patient's routine activity. All the data recorded was statistically analysed.

Results

Table 1: Showing Comparison in Frequency of Seizure and Reduction in Seizure in Group A And B

	Group A				Group B			
Time	No.	Range	Mean±SD	p	No.	Range	Mean±SD	p
Before	50	3-20	4.5±2.98	<0.001	50	2-10	4.66±2.07	<0.001
After	45	0-5	0.8±1.05*		38	0-3	0.84±0.82*	

Table 2: Showing Percentage Reduction of Seizure in Group A And B

Percentage reduction in seizures	Group A	Group B
≤50%	-	1
50-75%	18	12
75-100%	27	25
Total	45	38

Table 3: Showing Comparison of Side Effects in Group A And B.

Side Effect	Group A	Group B
Rash	2 (4%)	1 (2%)
Headache	4(8%)	2(4%)
Dizziness	1 (2%)	1(2%)
Somnolence	2(4%)	9*(18%)
Nausea/Vomiting	1(2%)	1 (2%)
Asthenia	2(4%)	1(2%)
Ataxia	1(2%)	2(4%)

*Statiscally Significance (P>0.001)

Table 4: Showing Comparison of Reduction in Seizures of Group A And B at Different Time Intervals

Time Interval (Week)	Group (N=50)	Mean±Sd
0	**A**	**4.5±2.98**
	B	**4.66±2.07**
4	**A**	**0.32±0.55**
	B	**0.20±0.40**
8	**A**	**0.54±0.70**
	B	**0.48±0.73**
12	**A**	**0.64±0.56**
	B	**0.64±0.80**
16	**A**	**0.62±0.96**
	B	**0.64±0.80**
20	**A**	**0.62±0.96**
	B	**0.64±0.80**
24	**A**	**0.68±0.99**
	B	**0.78±0.84**

P>0.05.No Statistical Significance In The Seizure Frequency Among The Both Group.

The following results were found in the study

1) patients in the LTG group were aged 14 - 47 years and in CBZ group were 14 to 40 years
2) 58% patients were male and 42% were female in LTG group 48% were male and 52% were female in CBZ group
3) Among the seizure frequency main type with which the patients presented with seizures were generalised type of clonic seizure (n=72). Other type of seizures were partial (n=15) complex partial (n=6) and focal with secondary generalization (n=7).
4) In LTG Group A 45 patients completed the study. One patient left the treatment in between and four withdrew due to side effect. Mean range of seizure frequency before the start of treatment was 3-20 which decreased to 0-5 after the treatment. Thus, lamotrigine was found to be equally efficacious to CBZ as measured by reduction in seizure frequency (Results are shown in Table 1 and 2). The reduction in seizure frequency occurred at 4 weeks which continued upto 24 weeks in both the groups as shown in table 4.
5) In carbamazepine group B only 38 patients completed the study. Two patients withdrew due to noncompliance. One patient left the treatment in between and nine patients withdrew due to side effect. The mean range of seizure frequency was 2-10 before the start of the treatment which decreased to 0-3 after the treatment. (Results are shown in Table 1 and 2).
6) Out of 50 patients recruited in the study in the carbamazepine group, nine patients were withdrawn from study due to serious side effects which did not disappear after reduction in dose. Nine patients had somnolence out of which 8 withdrew due to affecting their daily life. One withdrew due to eruption of rash along with eosinophilia during the 11th week of study. The various side effects reported with carbamazepine with number of patients reporting those side effect are shown in Table: 3.
7) 12 patients reported side effect with lamotrigine. Two patients had to withdrew from the study due to

eruption of maculopapular rash on the whole body and two due to severe headache which limited their routine life activity. Other side effects are shown in the table:3.

Thus, on comparing the various side effects reported by both the drug lamotrigine was better tolerated than carbamazepine and somnolence was higher in carbamazepine group which was statistically significant.

Discussion

The present study was carried to assess the efficacy and tolerability of LTG, a new AED in newly diagnosed untreated adult epileptics attending Government Medical College and Hospital, Patiala and comparing with CBZ which is one of the established first line drug for the treatment of partial and generalised convulsive disorder. The first line drugs for partial and generalised tonic-clonic seizure are carbamazepine, phenytoin and sodium valproate.[7] Carbamazepine was chosen as shown to be more tolerable than valproate for partial seizures.[8] The present study of 100 patients aged 14 to 50 years with newly diagnosed epilepsy of different types was divided into two groups. The groups were well matched in the demographic data this was in comparison to other studies showed but one study had more female population.[9] Monotherapy with lamotrigine was as effective as monotherapy with carbamazepine. Four Patients receiving lamotrigine were withdrawn from the study due to adverse events compared with carbamazepine, in which 9 patients withdrew suggesting superior tolerability with lamotrigine. This finding was in comparison to other studies by who showed that monotherapy with LTG is as effective as CBZ in age group from two years and above and patient could tolerate LTG better than carbamazepine.[10] Lamotrigine has been shown to be effective in treatment of partial seizures in adults and in both as add on and as monotherapy in various studies. Another comparative study, found 100 mg/day of lamotrigine to be equally efficacious as 600 mg/day of carbamazepine in newly diagnosed partial and generalised epilepsy (5% and 5.5% seizure free after weeks), with higher dose of lamotrigine 200mg/day more effective (60% seizure free)[11] The dose used in the present study was 150 to 200 mg and most of the patients were well controlled in the dosage of 100-150 mg. The other studies have used higher doses of lamotrigine ie 300-500 mg. In our study more withdrawal with carbamazepine was there due to sedation and CNS side effects which was in comparison to other studies who also reported similar side effects. In our study two patients withdrew due to rash in lamotrigine group which is related to the starting dose of lamotrigine whereas in other study the starting dose was 25mg/day only 2.2% withdrew because of rash.[11] Adverse effect profile was in accordance with Cochrane review which conducted metanalysis of 14 randomized controlled trial of lamotrigine with carbamazepine whose results suggested that people are more likely to withdraw earlier from carbamazepine than lamotrigine treatment.[12] The most common medicine-related reason for withdrawal was side effects: 52% of total withdrawals in participants on carbamazepine and 36% of total withdrawals in participants on lamotrigine. The second most common cause for withdrawal was seizure recurrence 8% on carbamazepine and 15% withdrawals on lamotrigine. Comparing the cost of therapy in our study lamotrigine tablets cost was ₹400 per month whereas carbamazepine cost was 200 rupees per month thus carbamazepine was more cost-effective drug but CNS side effects are more. Patients on lamotrigine are more likely to continue the treatment due to better tolerability of the agent. Thus, at the outset lamotrigine is a new drug with broader

spectrum of antiepileptic effect. Thus, it holds a promising future for the treatment of epilepsy and will help many patients to lead a seizure free and peaceful life. Thus, lamotrigine is equally efficacious as measured by reduction in seizure frequency to carbamazepine and has antiepileptic effect in various types of seizure and has better tolerability than carbamazepine. Therefore, lamotrigine may be used as monotherapy in epilepsy.

Bibliography

1. Kamal JA, Nadig RS, Joseph T, David J. Effect of calcium channel blockers on experimentally induced seizures in rats. Indian Journal of Experimental Biology 1990; 28:605-8.
2. Mahapatra AK. Role of lamotrigine in the treatment of epilepsy. Neurosciences Today 2000; 4:190-5.
3. Richens A and Yuen AWC. Overview of the clinical efficacy of lamotrigine. Epilepsia 1991; 32(suppl2): S13-S16.
4. Brodie MJ, Richens A and Yuen WC. Double-blind comparison of lamotrigine and carbamazepine in newly diagnosed epilepsy. Lancet 1995; 345:476-9.
5. Romanio De and Sopranzi N. Lamotrigine: monotherapy in refractory seizures. Clin Ter 1997; 148:153-8.
6. Commission on Classification and terminology of the International League aagainst epilepsy. Proposal for revised classification of epilepsies and epileptic syndromes. Epilepsia 1989; 30:389-99.
7. Brodie MJ, Dichter MA. Established antiepileptic drugs. N Engl J Med 1997; 342:700-08.
8. Mattson RH, Cramer JA, Collins JF. A comparison of valproate with carbamazepine for the treatment of compex partial seizures and secondarily generalised tonic-clonid seizures in adults. N Engl J Med 1992; 327: 765-71.
9. Matsuo F, Bergen MD, Faught E, Messenheimer JA, Dren AT etal. Placebo-controlled study of the efficacy and safety of lamotrigine in patients with partial seizures. Neurology 1993; 43: 2284-91.
10. Neito Barrera M, Brozmanova M, Capovilla G, Christie W, Pedersen B etal. A comparison of monotherapy with lamotrigine or carbamazepine in patients with newly diagnosed partial epilepsy. Epilepsy Research 2001; 46: 145-55.
11. Reunaen M, Dam M, Yuen AWC. A randomized open multicentre comparative trial of lamotrigine and carbamazepine in patients with newly diagnosed recurrent epilepsy. Epilesy Res 1996; 23: 149-55.
12. Nevitt SJ, Tudur Smith C, Weston J, Marson AG. Lamotrigine versus carbamazepine monotherapy for epilepsy: an individual participant data review. Cochrane Database of Systematic Reviews 2018; 6:CD001031. Accessed on 19 June 2023.