A COMPARATIVE TRIAL OF LAMOTRIGINE AND CARBAMAZEPINE IN PATIENTS WITH PRIMARY GENERALIZED TONIC CLONIC SEIZURES

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Abstract- Lamotrigine has been used widely in the treatment of partial and secondary generalized seizures. In this study use of lamotrigine as monotherapy for the newly diagnosed primary generalized tonic–clonic seizure has been investigated and compared with carbamazepine. After dose escalation (3 weeks for carbamazepine and 6 weeks for lamotrigin), patients were followed every 4 weeks for the first 16 weeks and then every 8 weeks for the next 32 weeks. Total number of patients was 91, randomly divided in two groups, 46 patients in lamotrigine group and 45 patients in carbamazepine group. The efficacy of the two drugs against primary generalized tonic clonic seizure was almost the same. The proportion of patients with seizure episodes in the last 40 weeks of treatment in both groups was similar (24.2% versus 24.6%). Overall, fewer patients in lamotrigine group than in the carbamazepine group withdrew because of adverse events (6.5% vs. 24.5%, P = 0.0216). The commonest side effect leading to withdrawal with lamotrigine was rash and with carbamazepine was drowsiness. More lamotrigine than carbamazepine recipients completed the study (88.9% vs. 73.3%, P = 0.0961). Lamotrigine and carbamazepine showed similar efficacy against primary generalized tonic clonic seizure in newly diagnosed epilepsy. Lamotrigine, however, was better tolerated.

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INTRODUCTION

Lamotrigine (3,5-diamino-6 (2,3-di chlorophenyl) - 1,2,4 triazine) is a new antiepileptic drug, which acts by blocking voltage–dependent sodium channels (1), thus stabilizing neuronal membranes and reducing the release of excitatory neurotransmiters, particularly glutamate and aspartate (2). It is licensed as an adjunctive therapy for the treatment of partial and secondary generalized seizures. Lamotrigine (LTG) has several features that make it appropriate for use as monotherapy (3). It has a wide range of efficacy for all types of seizures, seems to be less sedative than other antiepileptic drugs (4) and has an elimination half life longer than 24 hours, so once or twice daily dosing is possible in all patients (5). We report here the results of a randomized trial of LTG in patients with newly diagnosed primary generalized tonic clonic (GTC) seizures. Carbamazepine (CBZ) was chosen for comparison because it is an effective drug for this type of seizure.

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MATERIALS AND METHODS

Seizures were classified according to the international classification of epileptic seizures (6).

The patients (12 years and older) with primary GTC seizures referred to epilepsy clinic of Imam Khomeini hospital from 2001 to 2002 were included in this study. Patients with primary GTC seizures who had two seizures in the previous six months and at least one in previous three months were included in this study.

Patients with other type of seizure, previous treatment with other antiepileptic drugs, abnormalities in laboratory tests, chronic medical disorders, severe mental deficiency or pregnancy were excluded. An informed consent was obtained from all patients or their parents.

Patients were assessed at entry, and necessary diagnostic measures such as EEG and MRI were performed. Patients with primary GTC were randomized according to their file sheet numbers. Those with even numbers received LTG and those with odd ones received CBZ for a 48 weeks treatment period. During this time, they maintained seizure diaries. After randomization, patients received LTG, started with 50 mg/day and increased by 50 mg/week, or CBZ, started with 200 mg/day and increased by 200 mg/week. Hence at the end of the third week, patients were taking 600 mg/day CBZ and at the end of sixth week, 200 mg/day LTG.

Patients were assessed at base line and during treatment every 4 weeks for sixteen weeks and then every 8 weeks for 48 weeks. At each visit the number of seizures and side effects of treatments and compliance of patients were evaluated and recorded. If patients had more than one seizure during the treatment, the daily dosage of CBZ was increased by 100 mg and LTG by 50 mg daily.

Measures of efficacy were the time of the first seizure after eight weeks of treatment and proportions of patients who remained seizure free in last forty weeks of treatment. Mann–Whitney and X^2 tests were used for analysis. The measure of intolerability to treatment was the proportion of patients who withdrew from the study because of adverse events. Fisher exact test for analysis was used and odds ratios and 95% confidence intervals were calculated. Measures of compliance were proportion of patients who completed the course of treatment. X^2 test was used for analysis and differences between two groups were compared.

If there was a severe adverse event or evidence of severe noncompliance, patients could be withdrawn from study. All the statistical analysis was performed by SPSS software.

RESULTS

Ninety one patients entered the study. Demographic details of patients and seizure counts of two groups before treatment are shown in table 1. The median dose of drug in patients who completed the study was 200 mg for LTG and 600 for CBZ. The mean±SD time to first seizure after eight weeks of treatments was 20.2±53 days (with a range of 13-28) in LTG and 18.1±5 days (with a range of 11-23) in CBZ group. The difference was not statistically significant (Mann Whitney test, P= 0.57).

Table 1. Demographic details of patients*

Demographic details	Lamotrigine	Carbamazepine
Total number of patients	46	45
Mean (SD) age (years)	24 (±3)	26 (±4)
Range of age (years)	14 – 50	13 – 45
Mean (SD) weight (kg)	55 (±4.8)	57 (±5.5)
Range of weight (kg)	41 - 69	45–70
Male / Female	21 / 25	21 / 24
Median (range) number of seizure at baseline	3 (2-5)	3 (2-4)
Total number of seizures at baseline	159	138

Abbreviation: SD, standard deviation.

Table 2. Comparison of patients in two groups at different points of treatment*

Group	Lamotrigine	Carbamazepine	*P* Value
Patients at onset of study	46(100)	45(100)	
Patients at eight weeks	44 (95.7%)	40 (88.9%)	0.096
Patients at the end of course	41 (89.1)	33 (73.3)	0.096
Seizure free patients	31 (75.6)	25 (75.8)	0.97
Patients with seizure	10 (24.4%)	8 (24.2%)	0.83

* Data are given as number (percent).

There was no significant difference in proportion of patients who remained seizure free in the last forty weeks of treatment in two groups (75.8% vs. 75.6%) (Mann Whitney, $P = 0.97$, table 2).

Adverse events in two groups are shown in table 3. The only adverse effect for which there was a significant difference in frequency between the treatment groups was sleepiness, which was significantly more frequent with CBZ ($P = 0.039$; odds ratio, 4.1 [95% CI, 1.04–16.04], table 4).

A greater proportion of the patients in LTG group than in CBZ group completed the study (88.9% Vs 73.3% $P= 0.096$, table 2).

There was significant difference between the two groups for the rate of withdrawal because of adverse events (24.5% vs. 6.5%, $P= 0.0216$) in CBZ group versus LTG group (Table 4).

Table 3. Adverse events in two groups*

Adverse event	Lamotrigine	Carbamazepine	*P* Value
Rash	3 (6.5)	4 (8.9)	0.71†
Headache	12 (26.1)	9 (20)	0.66‡
Asthenia	6 (13)	8 (17.8)	0.74‡
Dizziness	5 (10.9)	4 (80.9)	1†
Diplopia	1 (2.2)	3 (6.7)	0.36†
Ataxia	2 (4.3)	4 (8.9)	0.43†
Sleepiness	3 (6.5)	10 (22.2)	0.039†
Cognitive disorders	6 (13)	5 (11.1)	0.78‡
Nausea	8 (17.9)	10 (22.2)	0.75‡
Leukopenia	1 (2.2)	3 (6.7)	0.36†
Raising of hepatic enzymes	1 (2.2)	2 (4.4)	0.62†

*Data are given as number(percent).

† Fisher exact test.

‡X^2 chi square test.

Table 4. Rate of withdrawal because of adverse event*

Causes of withdrawal	Lamotrigine (n = 46)	Carbamazepine(n=45)	*P* Value
Rash	3 (6.5%)	4 (8.9%)	0.71
Sleepiness †		7 (15.6%)	0.0056
Rash or sleepiness ‡	3 (6.5%)	11 (24.5%)	0.0216

*Data are given as number (percent).

DISCUSSION

Epilepsy affects 50 million people worldwide. The mainstay of therapy is antiepileptic drugs. We chose CBZ for comparison because it had identical efficacy as valproate against primary GTC seizures (7).

The two groups were well matched, although the total number of seizures in LTG group was greater than the CBZ group.

Both drugs showed similar efficacy against primary GTC. The proportion of patients who remained seizure free during the last 40 weeks of treatment was similar with both drugs. The main difference between them in this study was the rate of withdrawal because of adverse events, implying that LTG was better tolerated.

Skin rashes developed in 6.5% of patients in LTG and 8.9% of patients in CBZ group, necessitating drug withdrawal. The likelihood of rash with LTG and CBZ can be substantially reduced by a strategy of low dose introduction and slower titration (8, 9). Sleepiness in LTG group was less than in the CBZ group which supports a lower sedative effect previously reported for LTG. The finding in this study was similar to the findings in the randomized multicenter trial carried out in 1996 by Reunanen *et al.* (10).

The only difference between present study and their study was cause of withdrawal in CBZ group which was skin rash in that study and sleepiness in ours.

The lower incidence of rash in our study could be explained by a small number of cases in this study. LTG showed similar efficacy as CBZ against primary GTC seizures but patients receiving LTG had a more likelihood to continue with the treatment. The main reason for this was better tolerability of the newer agent.

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