Original paper

Efficacy and Safety of Levetiracetam as Mono and Add on Therapy in Treatment of Epilepsy

Sarwer Jamal Al- Bajalan [1*], Mohammed Tahir Kurmanji [1], Murad W. Kamil[2]

[1]College of medicine, Sulaimani University, Kurdistan Region, Iraq
[2]Khanakin General Hospital, Khanakin, Dyala, Iraq

Abstract

Background: Epilepsy is the second most common chronic neurological disorder after migraine affecting 2% of population with a high incidence of failure to achieve seizure freedom with the usual antiepileptic drugs. Levetiracetam (LEV) is an antiepileptic drug with less drug interactions, minimal side effects, a favorable pharmacokinetic profile and a wide spectrum of anticonvulsant effects in animal models for different types of epileptic seizures.
Objectives: To define the efficacy and safety of LEV in the treatment of epilepsy as add on or monotherapy.
Patients and methods: A random sample of 52 patients with epilepsy, evaluated in a descriptive cross-sectional study for the efficacy and safety of LEV in epilepsy, they were collected among epileptic patients attending the Neurology consultation Clinic in Sulaimani city in the Iraqi Kurdistan Region from May 2012 to May 2013. All the patients were interviewed by using questionnaire forms with comprehensive history, clinical examination, radiological, EEG and laboratory studies done to all patients.
Results: The sample involved female patients 2 folds more than males. Mean patients age was 24.54 ± 13.9 years. Mean duration of treatment; 2.7 years. Mean LEV dosage: 1457 ± 682 mg / day. Seventeen patients received monotherapy and 35 patients received add on therapy. Mean Seizure frequency was 44 attacks / month before treatment and 4 after treatment. Mean percent of seizure reduction was 95.1% in mono therapy and 91.46% in add on therapy.
Conclusion: LEV is a safe, effective, broad spectrum antiepileptic drug that could be used as monotherapy or add on therapy in the treatment of generalized and focal epilepsy.
Key words: Levetiracetam, Epilepsy, Add on therapy & Mono therapy

Introduction

Epilepsy is a common chronic neurological disorder. In which the term 'epilepsy' embraces a constellation of seizures & syndromes, each manifest by recurrent epileptic seizures resulting from abnormal, excessive or hypersynchronous neuronal activity. About 50 million people worldwide have epilepsy, and nearly 80% of epilepsy occurs in developing countries.[1, 2] Epilepsy becomes more common with increasing age.[3] Epilepsy is usually controlled, but not cured, with medication. However, more than 30% of people with epilepsy do not have seizure control even with the best available medications. [4, 5]

Seizures are classified into: partial (focal), generalized & unclassified epileptic seizures. [6]

Levetiracetam (LEV) is an antiepileptic drug (AED) that received FDA approval in November 1999 as adjunctive treatment for adults with partial onset seizures. Its effectiveness was established in three multicentric, well-controlled pivotal drug study trials [7,8,9]. LEV is also approved for use in the European countries. It is a derivative of the nootropic drug piracetam

*for Correspondence E-mail: sarwerjamal@yahoo.com

[10,11] with a wide spectrum of anticonvulsant effects in animal models for different types of epileptic seizure [12,13].
Its efficacy and tolerability have been shown in several studies, mainly as adjunctive treatment for partial epilepsies but also as add-on therapy for generalized epilepsies and as monotherapy for partial epilepsy in both adults and children.[14]
Since LEV is currently available to patients outside of study protocols, it is difficult to perform placebo-controlled trials for treatment of generalized epilepsy. [15]

Aims of the study

To determine the efficacy and safety of LEV in the treatment of epilepsy as add or mono therapy in Sulaimani governorate and its suburbs.

Patients and Method

This is a descriptive cross sectional study carried on 52 patients (aging from 5 to 61 years) with following inclusion criteria:

1. Clinical diagnosis of epilepsy.
2. On continuous treatment of LEV as mono or add on therapy for at least 6 months.
3. All types of epilepsy were included whether focal or generalized.
4. Age; 4 – 65 years.

The drug was administered as a daily dose of 500 to 3000 mg given in 2 equally divided doses per day.
History taken from each case by using special questionnaire forms that included: age, gender, family history, type and duration of treatment, type and frequency of seizures 6 months before and after therapy. The patients divided into: monotherapy & add on group (17: 35 patients).
The variables were entered into a Microsoft office excel data base program and descriptive statistics (numbers and percentages) were calculated for the variables as well as analytic statistics was done to find the relations between variables.

Results

Efficacy

The study enrolled 52 epileptic patients (35 female & 17 male with a ratio of 2: 1).
Patient's ages were 5 – 61 years (with mean age of 24.54 ± 13.9 y).
The duration of epilepsy treatment was from 0.5–15 years (with a mean of 2.75 ± 2.60 y).
LEV dosage ranged from 500 – 3000 mg /day (with a mean of 1457 ± 682 mg).
Forty five of the 52 patients had generalized epilepsy and 7 patients had focal epilepsy. 17 patients were on monotherapy 16 of them had generalized epilepsy and only one had focal epilepsy. 35 patients were on add on therapy 29 of them had generalized epilepsy and 6 patients had focal epilepsy (table -1).
The efficacy of LEV is the percentage of seizure frequency reduction after the treatment period. The drug efficacy was divided into 4 grades:

1. Complete seizure freedom with 100% seizure reduction.
2. Good response with 50-99% seizure reduction.
3. Minimal response with 20-50% reduction.
4. Unmodified response with less than 20% reduction [16].

Mean Seizure frequency was 44 attacks / month before treatment and 4 after treatment. Mean percent of seizure reduction was 95.1% in mono therapy and 91.46% in add on therapy.

Table 1. Shows the number of the patients and type of seizure in each therapy group:

Seizure Type	Monotherapy	Add on Therapy	Total
Generalized	16	29	45
Focal	1	6	7
Total	17	35	52

Twelve (75%) of the 16 patients who were on mono therapy with **generalized epilepsy** had complete seizure freedom (i.e. 100% seizure reduction), while 13 (44.8%) of the 29 patients who were on add therapy with generalized epilepsy had complete seizure freedom. Four (25 %) of the 16 patients on mono therapy with generalized epilepsy had good response to LEV of (50-99%) seizure reduction, while 16 (55.1%) of the 29 patients on add therapy with generalized epilepsy had good response to LEV.

There was no minimal or unmodified response in the two study groups in patients with generalized and focal epilepsy.

In patients with **focal seizures** there was only one patient on mono therapy who made complete recovery and 2 (33.3 %) of the 6 patients who were on add on therapy made complete recovery, while 4 patients (66.6%) made good response (table -2) .

Safety

The mean dose in monotherapy was 1397mg/day and in adds on therapy 1228.5 mg / day with no significant difference.

The most frequently reported side effects were headache, drowsiness, nervousness, weight gain and fatigue. These side effects were observed in more than 10% of patients and in both study groups and were not dose related.

Less common side effects included aggression and weight loss observed in less than 10% of patients. GIT disturbances (nausea, vomiting, and diarrhea) and cough were the least frequent side effects each observed in 1 patient (Table-3).

Non – troublesome side effects observed in 50% of the patients (19 patients with add on therapy and 7 with mono therapy) (Table4).

Discussion

LEV is known to have a broad spectrum antiepileptic effect with a safe profile. All the patients had more than 50% seizure reduction. The effect was significantly higher in the monotherapy group with generalized epilepsy.

Table 2. |Compares the efficacy of LEV between mono and add on therapy

Type of Seizure	Efficacy (mean % reduction of seizure frequency)	Mono-therapy LEV (n=17)	Add on LEV (n=35)	Total population (n=52)	p-value
Mean % reduction of both (focal & generalized seizure)		95.1%	91.46%		= 0.023
Generalized Seizure	**Mean % reduction**	**94.81%**	**91.47%**		
	Seizure Free*	12(75%)	13(44.8%)	25	=0.047
	Good Response**	4(25%)	16(55.1%)	20	=0.046
	Minimal Response***	0	0	0	
	Unmodified Response******	0	0	0	
Focal Seizure	**Mean % reduction**		**91.5%**		
	Seizure Free*	1(100%)	2(33.3%)		=0.288
	Good Response**	0	4(66.6%)		=N/A
	Minimal Response***	0	0		
	Unmodified Response******	0	0		
Total		17	35	52	

*Seizure free (100% seizure reduction), **Good response (50-99% seizure reduction), ***Minimal response (20-50% reduction), ****Unmodified response(less than 20% reduction). N/A; not applicable.

Table 3. The Percentage (%) of Side Effects (SEs) in Epileptic Patients on LEV

Name of the SE	No of Patients (% of SEs)
Headache, Drowsiness, Nervousness, Weight gain Fatigue	13 (≥ 10 %)
Aggression, Weight loss	5 (< 10%)
Nausea vomiting, Diarrhea, Cough	2 (< 5%)

Table 4. Patients with or without side effects in the 2 group

Patients	Mono therapy	Add on therapy	Total
With SEs	7 (41%)	19 (54%)	26
With no SEs	10 (59%)	16 (46%)	26
Total	17 (100%)	35 (100%)	52

The mean percent reduction of seizure frequency in monotherapy group (95.1%) was significantly higher than that in add on therapy group (91.46%).

These results are consistent with that done by Lagae L. et al [16] who found higher numbers of percent seizure reduction in the monotherapy group in children with both generalized and focal epilepsy. Ben-Menachem, et al [17] reported the results of two mono therapy trials in adults, showing a good efficacy and safety profile. In Cohen J. et al [18] study, 3 patients with refractory generalized epilepsy became seizure free on LEV monotherapy.

The responder rates, however, must be viewed cautiously. Lifestyle changes such as avoidance of sleep deprivation and other treatment factors might have reduced the frequency of seizures.

The high efficacy and seizure freedom rate of LEV monotherapy is due to the broad antiepileptic spectrum activity of the drug in patients with non- refractory epilepsy taking the drug for the first time with effective daily dosage , good safety profile and drug compliance.

The female gender predominance of the patients is referred to the trend of the neurologists to prescribe LEV for young females during child bearing ages because of its least teratogenicity [19]. Both in the add on and monotherapy groups, LEV was effective in focal and generalized seizures.

High dosage of LEV was not necessary in most of our patients for effective control of seizure activity. More than 50% of our patients controlled with doses less than 1500 mg per day and more than 90% controlled with doses less than 2250 mg per day.

We found significantly fewer side effects than in the previous studies, and the patients were compliant with treatment. Side effects appeared in both study groups and were not dose related.

In our study nervousness or irritability was one of the most common side effects. This is consistent with other studies like those done by Grosso S. et al [20] who found that irritability was the most common side effect and the same results were found by Goldberg-Stern H. et al. [21]. The difference is that in our study side effects, such as irritability were recorded in high percent (21%) of patients, while in other studies like that done by S. Grosso, et al the incidence of irritability was (14%).

Patients who stopped the treatment because of severe side effects were within the exclusion criteria of our cross-sectional study because we only include patients on LEV for more than 6 months.

Conclusions

LEV is a safe and effective broad spectrum antiepileptic drug that could be used as mono therapy and add on therapy in the treatment of generalized and focal epilepsy.

Acknowledgments

Great thanks to all our colleagues in Sulaimani Neurology Consultation Clinic for their kind help & referal of patients.
Special thanks to all our patients for their cooperation.
Great thanks to our staff in the EEG, Laboratory and Neuroimaging department.

Disclosure

No disclosure

References

1. Zhu F, Lang SY, Wang XQ, Shi XB, Ma YF, Zhang X, et al. Long-term Effectiveness of Antiepileptic Drug Monotherapy in Partial Epileptic Patients: A 7-year Study in an Epilepsy Center in China. Chinese Medical Journal 2015 Nov 20; 128:3015-22.
2. Rashid S, Hussain Z, Imam H, Waris AA, Ibrahim Z, Farooq M, et al. Efficacy and Tolerabilityof Leviteracetum and Topiramate in Patients with Epilepsy. Annals of King Edward Medical University. 2012 Apr;18:143-46
3. Brodie MJ, Elder AT, Kwan P. Epilepsy in later life. Lancet neurology 2009; 8 11: 1019-30.
4. Cascino GD. Epilepsy: contemporary perspectives on evaluation and teatment. Mayo Clinic Proc 1994; 69:1199–1211.
5. Engel J Jr. Surgery for seizures. NEJM 1996 334: 647–652.
6. Proposal for revised clinical and electroencephalographic classification of epileptic seizures. From the Commission on Classification and Terminology of the International League Against Epilepsy. Epilepsia 1981; 22: 489–501.
7. Cereghino, J J, Biton V, Abou-Khalil B. et al. Levetiracetam for partial seizures: results of a double blind randomized clinical trial. Neurology 2000; 35: 236–242.
8. Shorvon SD, Löwenthal A, Janz D, Bielen E, Loiseau P. Multicenter double-blind, randomized, placebo-controlled trial of Levetiracetam as add-on therapy in patients with refractory partial seizures. Epilepsia 2000; 41: 1179–1186.
9. Ben-Menachem E, Falter U. Efficacy and tolerability of Levetiracetam 3000 mg in patients with refractory partial seizures: a multicenter, double-blind, responder-selected study evaluating monotherapy. Epilepsia 2000; 41: 1276–1283.
10. Genton P, Van Vleymen B. Piracetam and LEV: close structural similarities but different pharmacological and clinical profiles. Epileptic Disord 2000; 2: 99–105.
11. Loscher W, Richter A. Piracetam and LEV. Two pyrrolidone derivatives, exert antidystonic activity in a hamster model of paroxysmal dystonia. Eur J Pharmacol 2000; 391 3:251-254.
12. Loscher W, Reissmuller E, Ebert U. Anticonvulsant efficacy of gabapentin and LEV in phenytoin-resistant kindled rats. Epilepsy Res 2000; 40: 63–77.
13. Klitgaard H, Matagne A, Gobert J, Wülfert E. Evidence for a unique profile of LEV in rodent models of seizures and epilepsy. Eur J Pharmaco 1998; 353: 191–206.
14. Anne Hagemann, Theodor W. May, Esther Nieder et al. Quality of life, anxiety and depression in adult patients after add-on of Levetiracetam and conversion to Levetiracetam monotherapy. Epilepsy res 2012; 4814, 2.
15. Andermann F, Berkovic SF. Idiopathic generalized epilepsy with generalized and other seizures in adolescence. Epilepsia 2001; 42: 317–320.
16. Lagae L, Buyse G, Ceulemans B. Clinical experience with Levetiracetam in childhood epilepsy: an add- on and mono-therapy trial. Seizure 2005; 14: 66-71.
17. Ben-Menachem E. Preliminary efficacy of levetiracetam in monotherapy. Epileptic Disord 2003; 5:S51- 5.
18. Cohen J. Levetiracetam monotherapy for primary generalized epilepsy. Seizure 2003;12:150-3.
19. Tomson T, Battino D, Bonizzoni E, Craig J, Lindhout D, Sabers A, Perucca E. et al. Dose-dependend risk of malformations with antiepileptic drugs: an analysis of data from the EURAP epilepsy and pregnancy registry, Lancet Neurol. 2011 Jul; 10:609-17.
20. Grosso S, Franzoni E, Coppola G, Iannetti P, Verrotti A, Cordelli DM. et al. Efficacy and safety of levetiracetam: An add-on trial in children with refractory epilepsy. Seizure 2005 14, 248-253.
21. Goldberg-Stern H, Feldman L, Eidlitz-Markus T, Kramer U, Perez S, Pollak L. et al. Levetiracetam in children, adolescents and young adults with intractable epilepsy: Efficacy, tolerability and effect on electroencephalogram. Eur J Paediatr Neurol. 2013 May; 17:248-53.