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EFFICACY AND SAFETY OF LEVETIRACETAM AS MONO AND ADD ON THERAPY IN TREATMENT OF EPILEPSY

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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 a new novel 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 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 years. Mean duration of treatment; 2.7 years. Mean LEV dosage: 1475.9 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:** Levetiracetam (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.

KEYWORDS: Levetiracetam Epilepsy Add on therapy Mono therapy.

INTRODUCTION

Epilepsy: Epilepsy is a common and diverse set of chronic neurological disorders characterized by seizures.[1,2] Some definitions of epilepsy require that seizures should be recurrent and unprovoked,[1,3,4] but others require only a single seizure combined with brain alterations which increase the chance of future seizures.[5] In many cases a cause can not be identified; however, factors that are associated include brain trauma, strokes, brain cancer, drugs and alcohol misuse among others.[1]

Epileptic seizures result from abnormal, excessive or hyper synchronous neuronal activity in the brain.[5] About 50 million people worldwide have epilepsy, and nearly 80% of epilepsy occurs in developing countries.[3]Epilepsy becomes more common with increasing age.[6,7] Onset of new cases occurs most frequently in infants and the elderly.[8]

About 4% of all people will have an unprovoked seizure by the age of 80 and the chance of experiencing a second seizure is between 30% and 50%.[9][10] Treatment may reduce the chance of a second one by as much as half.[10]

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. Surgery may be considered in difficult cases.[11,12] Not all epilepsy syndromes are lifelong – some forms are confined to particular stages of childhood. Epilepsy should not be understood as a single disorder, but rather as syndromic with vastly divergent symptoms, all involving episodic abnormal electrical activity in the brain and numerous seizures.[1]

Signs and Symptoms

Epilepsy is characterized by a long term risk of recurrent seizures.[13] The signs and symptoms of seizures vary depending on the type.[14] Seizures may cause involuntary changes in body movement or function, sensation, awareness, or behavior. Seizures are often associated with a sudden and involuntary contraction of a group of muscles and disturbed level of consciousness. However, a seizure can also be as subtle as a fleeting numbness of a part of the body, a brief or long term loss of memory, visual changes, sensing/discharging of an unpleasant odour, a strange epigastric sensation, or a sensation of fear and total state of confusion. A seizure can last from a few seconds to status epilepticus, a continuous group of seizures that is often life-threatening without immediate intervention. Therefore seizures are typically classified as motor, sensory, autonomic, emotional or cognitive (table 1-1). After the

active portion of a seizure, there is typically a period referred to as postictal state before a normal level of consciousness returns.[14]

In some cases, the full onset of a seizure event is preceded by some of the sensations described above. These sensations can serve as a warning to that a generalized tonic–clonic seizure is about to occur. These warning sensations are cumulatively called an aura and are due to a focal seizure.[14]

Some patients can tell when a seizure is about to happen. Some symptoms experienced by the person before the seizure and they may include dizziness, lightheadedness, tightening of the chest, and some experience things in slow-motion just prior to the seizure. Symptoms experienced by a person during a seizure depend on where in the brain the disturbance in electrical activity occurs. Parietal and frontal seizures and focal epileptic discharges tend to happen more during sleep than during awakefulness. In contrast, psychogenic nonepileptic seizures are rare between midnight and 6 am and never occur during sleep.[15] Generalized epilepsy but not focal epilepsy is higher in the morning probably reflecting a diurnal variation in cortical excitability.[16]

Table (1-1) International classification of seizure types (1981).[17]

<table>
<tr><th colspan="3">International classification of seizure types (1981)</th></tr>
<tr><th>1. Partial seizures(focal seizures)</th><th>2.Generalized seizures</th><th>3.Unclsssified epileptic seizures</th></tr>
<tr><td>A.Simple partial seizures(consciousness not impaired)
1.with motor signs
2.with sensory symptoms
3.with autonomic symptoms or signs
4.with psychic symptoms</td><td rowspan="3">A.abscense seizure(petitmal)
1. Typical absence seizures
2.Atypical absence seizures
B.Myoclonic seizures
C.Clonic seizure
D.Tonic seizures
E.Tonic-clonic Seizure(grandmal)
F.Atonic seizure</td><td rowspan="3"></td></tr>
<tr><td>B.Complex partial seizures(consciousness is impaired)
1.Simple partial onset,followed by impairment of consciousness.
2.with impairment of consciousness at onset</td></tr>
<tr><td>C. Partial seizures evolving to secondary generalized seizures.
1. Simple partial seizures evolving to generalized seizures
2.complex partial seizures evolving to generalized seizures</td></tr>
</table>

Pathophysiology: Mutations in several genes have been linked to several types of epilepsy. Some genes that code for protein sub units of voltage-gated and ligand-gated ion channels have been associated with forms of generalized epilepsy and infantile seizure syndromes.[18]

Causes

The diagnosis of epilepsy usually requires that the seizures occur spontaneously. Nevertheless, certain epilepsy syndromes require particular precipitants or triggers for seizures to occur.These are termed **reflex epilepsy**. For example: 1.patients with primary reading epilepsy have seizures triggered by reading.[19] 2.Photosensitive epilepsy can be limited to seizures triggered by flashing lights.

Other precipitants can trigger an epileptic seizure in patients who otherwise would be susceptible to spontaneous seizures. For example: 3.children with childhood absence epilepsy may be susceptible to hyperventilation. In fact, flashing lights and hyperventilation are activating procedures used in clinical EEG to help trigger seizures to aid diagnosis. Finally, other precipitants can facilitate, rather than obligatory trigger, seizures in susceptible individuals: 4.Emotional stress 5.sleep deprivation 6.sleep itself 7.heat 8.stress 9.alcohol 10.febrile illness are examples of precipitants cited by patients with epilepsy. Notably, the influence of various precipitants varies with the epilepsy syndrome.[20] 11.Likewise, the menstrual cycle in women with epilepsy can influence patterns of seizure recurrence. Catamenial epilepsy is the term denoting seizures linked to the menstrual cycle.[21]

Different **causes** of epilepsy are common in certain age groups

1. During the neonatal period and early infancy the most common causes include hypoxic ischemic encephalopathy, central nervous system infections, trauma, congenital CNS abnormalities and metabolic disorders.
2. During late infancy and early childhood, febrile seizures are fairly common. These may be caused by many different things, some thought to be things such as CNS infections and trauma.
3. During childhood, well-defined epilepsy syndromes are generally seen.
4. During adolescence and adulthood, the causes are more likely to be secondary to any CNS lesion. Further, idiopathic epilepsy is less common. Other causes associated with these age groups are stress, trauma, CNS infections, brain tumors, illicit drug use and alcohol withdrawal.
5. In older adults, cerebrovascular disease is a very common cause. Other causes are CNS tumors, head trauma, and other degenerative diseases that are common in the older age group, such as dementia.[22]

Levetiracetam (LEV)

In recent years, several new drugs have been introduced to treat seizures in adults and children. In the majority of patients, these drugs suppress epileptic seizures without causing unacceptable side effects.[23] Levetiracetam (LEV) is a novel 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 multicentre, well-controlled pivotal drug study trials.[24-26] LEV is recently approved for use in the European countries. It has been available since April 2000 in the USA and available for compassionate use in Sweden since August 2000 and as a commercial drug since January 2001. It is a derivative of the nootropic drug piracetam[27,28] with a wide spectrum of anticonvulsant effects in animal models for different types of epileptic seizure.[29,30] Since LEV is currently available to patients outside of study protocols, it is difficult to perform placebo-controlled trials for treatment of generalized epilepsy.[31]

LEV is a new AED with favourable pharmacological and pharmacokinetic characteristics; about 100% bioavailability, less than 48 hours to steady state, linear kinetics, twice-daily dosing, protein binding less than 10%, no hepatic metabolism, minimal metabolism in blood, no significant interactions with other AEDs. 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.[32]

Recently, the binding site of LEV was discovered[33]: the synaptic vesicle protein V2A is the brain-binding site of LEV. Probably, LEV acts by modulating the function of SV2A, supporting previous indications that LEV possesses a mechanism of action that is different from other AEDs. There are reports of other effects of LEV, including the partial inhibition of N-type high voltage-gated Ca 2+ channels and the reduction of inhibition of GABA and glycine-gated currents.[34] Furthermore, LEV has been shown to delay the development of kindling, indicating that it may have disease-modifying properties to the development that results in reduced seizure threshold.[35]

The aim of our study is to define the efficacy and safety of Levetiracetam in the treatment of epilepsy as add on or mono therapy in Sulaimani governorate and its suburbs.

Patients and Methods: This is a unicentric, descriptive cross sectional study which was carried on 52 patients attending the Neurology consultation Clinic in Sulaimani city in a period of one year from May 2012 to May 2013. The patients included were recruited consecutively with the clinical diagnosis of epilepsy by senior neurologists. The patients were on continuous treatment of LEV as mono or add on therapy for at least 6 months aging from 5 to 61 years. All types of epilepsy were included whether focal or generalized, from any cause (symptomatic, cryptogenic) or idiopathic.

Patients who discontinued therapy or of short duration (less than 6 months) were excluded from the study. The drug was administered as a daily dose of 500 to 4000mg given in 2 equally divided doses per day. Patients were interviewed, history taken for each case by using special questionnaire forms. Thorough investigations were done to all patients including EEG, brain imaging, liver function test, thyroid function test and complete blood count. Suitable protocols have been prepared, including queries and investigations, namely name of the patients, age, gender, family history, type and duration of treatment, type and frequency of seizures before and after therapy.

The way of analysis: 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 were done to find the relations between variables.

RESULTS

The sample enrolled 52 patients with epilepsy diagnosed by senior neurologists. 17 (30.76%) patients were males. And 35 patients (69.23%) were females with female to male ratio of about 2:1 as shown in Figure (3-1).

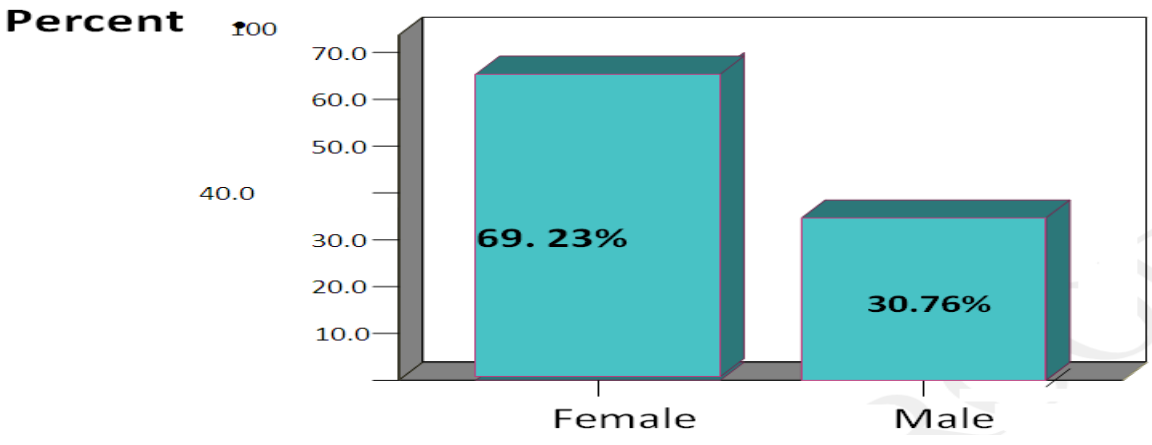

Figure. (3-1) Sex distribution in epilepsy.

Patient's ages were from 5 to 61 years with mean age of 24.54 years and standard deviation 13.97.The duration of treatment was from 0.5 to 15 years with a mean of 2.75 years and standard deviation of 2.60. LEV dosage ranged from 500 to 4000mg /day with a mean of 1475.962 mg and standard deviation 738.074 mg as shown in table (3-1). 17 (34%) had monotherapy and 35 patients (66%) had add on therapy. The number of AEDs administered ranged from 1 to 3 drugs. 17 patients (34%) received 1 AED. 19 patients received 2 AEDs (38%) and 16 patients (32%) received 3 AEDs. Drugs received included Tegretol (carbamazepine), Depakine (Na valproate), Rivotril (clonazepam), and Luminal (phenobarbital).

The mean seizure frequency before treatment was 44.32 attack/ month and 4.20 attack / month after treatment. Epilepsy was focal in (7) patients (13.46 %) and generalized in (45) patients (86.52 %). Seizure frequencies were taken as an estimation of average number of seizures per month related by the patient or his / her relatives they were aware of.

Table. (3-1) shows descriptive analysis of age, duration of epilepsy and dosage of Levetiracetam.

Variable		**(mean ± standard deviation)**
Age / year		(24.54 ± 13.97)
Duration of epilepsy / year		(2.75 ± 2.60)
Levetiracetam dosage Range (mg/day)	**500 - 4000**	1475.962 ±738.074

LEV side effects were taken in the two study groups. 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. The LEV dosage was between 500-4000mg/day. Less common side effects included aggression and weight loss observed in less than 10% of patients. GIT disturbances (nausea, vomiting, diarrhea) and cough were the least frequent side effects each observed in 1 patient as shown in table below.

Table (3-2) describes the percentage of SEs in epileptic patients on LEV.

Name of the SE	**Percentage (%) of SE**	**No of Patients**
Head Headache, drowsiness, nervousness, weight gain fatigue	≥ 10 % SEs	13
Aggression, weight loss	< 10% SEs	5
Nausea vomiting, diarrhea, cough	< 5% SEs	2

Twenty six patients were free of side effects; 16 of them were on add on therapy and 10 on mono therapy, while 26 patients complained of side effects (19 patients with add on therapy and 7 with mono therapy).

Table (3-3) shows the No. of patients with and without SEs in the two types of therapy.

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

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 3-4).

Table (3-4) 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

In table (3– 5) we compared the efficacy of LEV between the two study groups of mono therapy and add on therapy with regard to the type of seizure whether it is generalized or focal. 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 frequency reduction.
2. Good response with 50-99% seizure reduction.
3. Minimal response with 20-50% reduction.

Unmodified response with less than 20% reduction.[36]

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 on 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 on 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 3-5) .

Table (3-5) compares the efficacy of LEV between mono and add on therapy

Type of seizure	Efficacy(median percent reduction of seizure frequency)	Mono-therapy levetiracetam(n=17)	Add on levetiracetam(n=35)	Total population(n=52)	P value
Mean percent reduction(in focal and generalized seizure)		95.1%	91.46%		P value =0.023
Generalized seizures	Mean percent reduction(generalized seizure)	94.81%	91.47%		
	1.Seizure free(100% reduction)	12(75%)	13(44.8%)	25	P value =0.047
	2.good response(50-99%reduction)	4(25%)	16(55.1%)	20	P value =0.046
	3.minimal response(20-50%reduction)	0	0	0	
	4.unmodified(<20%reduction)	0	0	0	
Focal seizure	Mean percent reduction		91.5%		
	1.Seizure free(100% reduction)	1(100%)	2(33.3%)	3	P value =0.288
	2.good response(50-99%reduction	0	4(66.6%)	4	P value =NOT
	3.minimal response(20-50%reduction)	0	0	0	
	4.unmodified(<20%reduction)	0	0	0	
Total		17	35	52	

We found statistically significant effect of LEV on reduction of seizure frequency in generalized epilepsy in the add on group. Although the difference in reduction of seizure frequency in the mono therapy group was not significant statistically but the percentage of reduction was very high; this may reflect the small sample size of our sample as shown in table (3-6).

Table (3-6) shows the difference of seizure frequency before and after treatment

		Focal epilepsy		Generalized epilepsy	
		Add on therapy	**Monotherapy**	**Add on therapy**	**Monotherapy**
Mean frequency of attack/month	**Before treatment**	44	`1	49	16.87
	After treatment	6	0	5.99	2.75
P- value		0.083	NA	**0.005**	0.064

Note: NA means not applicable

Table (3– 7) compares LEV daily dose between monotherapy and add on therapy. The median dose in both types of therapy was 1000 mg / day. The mean dose in monotherapy was 1397mg / day and in adds on therapy 1228.5 mg / day with no significant difference between the two values.

Table. (3 – 7) compares the dose of LEV with the type of therapy.

Dose	**Type of therapy**	
	No. of patients on Monotherapy	**No. of patients on Add on therapy**
500	0	3
750	1	0
1000	9	15
1500	2	5
2000	4	8
3000	1	3
4000	0	1
Mean of the dose (mg / day)	1397	1228.5

DISCUSSION

LEV is known to have a broad spectrum antiepileptic effect with a safe profile. All the patients in our study had more than 50% seizure reduction. The reduction was significantly higher in the add on group with generalized epilepsy. Although the difference in reduction of seizure frequency in the monotherapy group was not significant statistically but the percentage of reduction was very high in generalized epilepsy. This may reflect the small size of our sample rather than poor effect of LEV in this group. We found statistically significant freedom from seizure in the monotherapy group rather than the add on therapy group (p-value 0.047). The mean percent reduction of seizure frequency in monotherapy (95.1%) group was significantly higher than that in add on therapy (91.46%) group when we analyze the data of the patients with focal and generalized seizure together (p- value 0.023).

These results are consistent with that done by L. Lagae, et al [36] who found higher numbers of percent seizure reduction in the monotherapy group in children with both generalized and focal epilepsy. Ben-Menachem, et al [37] reported the results of two mono therapy trials in adults, showing a good efficacy and safety profile. In Cohen, et al [38] 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 tratogenecity.[39] Both in the add on and monotherapy groups, LEV was effective in focal and generalized seizures.

High dosage of LEVwas 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 S. Grosso, et al [40] who found that irritability was the most common side effect and the same results were found by Hadassa Goldberg-Stern et al.[41] 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.

Our study had several limitations including the followings

1. It was a single center study.
2. Small sample size because the drug amount was limited and not always available.
3. It was a cross-sectional uncontrolled study, because it was difficult and not ethical to follow patients on a placebo AED for a long period of time in the presence of approved drugs.
4. The drug is costly.

CONCLUSIONS

We concluded from our study that Levetiracetam 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.

RECOMMENDATIONS

We recommend that additional information is needed considering the treatment of **LEV** in generalized epilepsy. Our preliminary findings need to be confirmed in controlled studies, but provide preliminary evidence that **LEV** may be effective for treating the generalized epilepsies in addition to the partial onset epilepsy. A larger sample monotherapy study is needed to confirm our findings.

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