European Journal of Molecular & Clinical Medicine

ISSN 2515-8260 Volume 07, Issue 06, 2020

Assessment of Levetiracetam for the Treatment of Epilepsy

Ms. Samera Ali Siddique, Department of Pharmacy,

Glocal University, Saharanpur, Uttar Pradesh

Email Id- sameera.ali@theglocaluniversity.in

ABSTRACT: ***Epilepsy is a disease related to central nervous system disorder where brain activity become unusual, thereby a patient experience a seizures or periods of strange behaviour, vibrations, and sometimes loss of consciousness. It might be due to genetic disorder or some sort of brain injury, such as shock or stroke. It requires a long duration treatment of drug therapy for getting cured. As per various researches half of patients do not pass the initial antiepileptic treatment and around 35 per cent are highly resistant to medical treatment, demonstrating the rising requirement for more effectual and improved tolerated medicines. Levetiracetam is an adjunctive management of seizures in victims with epilepsy, the fourth most general neurological chaos distressing individuals of different age groups. Its pharmacokinetic compensation comprise fast and approximately full absorption, limited irrelevant binding with plasma protein, no activation of enzymes, no connections with other products, and unfair metabolism external the liver.Yet another advantage is the provision of an intravenous injection. This has been shown to be efficient as adjunctive treatment for partial-onset refractory seizures, primary widespread tonic-conic seizures, and juvenile myoclonic seizure. In addition, controlled release of carbamazepine was found to be similar to first-line treatment for partial-onset seizure, together in effectiveness and acceptability.***

KEYWORDS: ***Adjunctive therapy, Antiepileptic drug therapy, Carbamazepine Central nervous system, Epilepsy, Intravenous injection, Levetiracetam.***

INTRODUCTION

Epilepsy is a major medical urgent situation associated with high humanity and morbidity. It is considered by recurrent senseless epileptic. The scientific causes of epileptic seizures consist of symptoms as well as indication of an unbalanced, prolonged, and hypersynchronous release of neurons within the brain of an individual. Epilepsy is a state; it may not be regarded a disease, since many medical situation may cause it. Epilepsy might be inherited or may be the result of a number of brain injuries, counting head upset, stroke, congenital brain malformations. Since seizures and epilepsy are very diverse they must be categorized accordingly. The generally frequently used categorization is the one presented in 1981 by the International League toward Epilepsy which divides psychotic episodes into temporary and generalised seizures. Partial seizures would be those suggested by the first diagnostic and electrographic changes in which original stimulation is restricted to a part of a brain cortex. Partial seizures are further segmented into a specific generalisation of partial, complex partial, and generalised partial seizures. Temporal lobe seizures are those that retain memory and responsiveness entirely. Electrical activity in the brain seizures warrants, at

ISSN 2515-8260 Volume 07, Issue 06, 2020

least, a shift in receptiveness or interpretation. Moreover generalised seizures may begin as temporal lobe or complex partial seizures, but then extend to the visual cortex and most typically manifest with generalised tonic behaviour and then clonic activity in their graduation rate. symptoms generally are the ones that indicate the initial involvement of both sides of the brain in the first impact patient. Conscious experience is frequently impaired at the onset, except for paroxysmal hallucinations which are too concise for distorted states of awareness to recognise. If motor signs occur then they are bilateral. Typical absence, generalised myoclonics, generalised tonics, generalised clonics, and generalised atonic seizures are generalised types of seizures.

Intravenous lorazepam is regarded the drug of preference in clinics and its cost - effectiveness have been documented in various settings. However, the Rapid Anticonvulsant Medication Prior to Arrival Trial (RAMPART) magnificently showed that subcutaneous access delays the induction of medication and the time for inject able lorazepam SE surveillance in relation to inject able use. in view of the fact that this applicator is at present not obtainable in many country, alternative non-intravenous routes of application in clinical practice should be considered. an assortment of meta-analyses complete that benzodiazepine intramuscular, buccal or intranasal application are efficient and secure alternatives in the behaviour of sensitive seizures and may be superior to rectal and intravenous applications. In recent times, the Food and Drug Administration of united state has approved a 5 mg/0.5 mL midazolam nasal spray for the acute behaviour of sporadic, stereotypic episodes of repeated seizure activity (e.g., seizure bursts, acute recurrent seizures) that are distinct from the normal example of seizure in persons with epilepsy 12 years of age or older.

The International League for Epilepsy has suggested a categorization of epilepsy and epileptic syndrome in adding together to the categorization of epileptic seizures. Because the majority of patients have either prejudiced types of seizures or widespread types of seizures, component (focal, or localization-related) epilepsy and generalized epilepsy are the two major subdivisions in the classification. Of these main groups is sub-classified into those epilepsy linked to a brain attack which is idiopathic and assumed hereditary or symptomatic / cryptogenic (probably symptomatic).Generally, idiopathic epilepsy responds differently to medication than symptomatic epilepsy. Under this definition of epilepsy are epileptic syndromes, marked at the onset by a particular age group, different forms of seizures, particular natural history or path, and specific treatment response [1].The electroencephalogram (EEG) in this syndrome reveals generalized spike-and-wave discharges

ISSN 2515-8260 Volume 07, Issue 06, 2020

of 4–6 Hz between seizures. Although, most epilepsies are chronic requires long-term therapy for its proper cure.

The treatment plan of epilepsy could also rely on the strict description of the type of invasion for epileptic cardiomyopathy, then the alternative of the most appropriate antiepileptic drug(AED) for the type of convulsion and epileptic disorder, and thus the most secure and perhaps one of the most suitable for the individual's particular health information. As one half of the over seventeen antiepileptic drugs offered, older products were launched before 1980, while others were introduced after 1990 (Table1). The grown-up AEDs were typically accepted for advertising, and were utilized with front-line agents before going through all the extensive clinical trials now needed by the new antipsychotic medication.Approval process for new AEDs is limited to the existing groups of patients with seizures in whom the drug has established its efficacy and the precise mode of use in the medical study involved. For example, a novel AED would only obtain first-line monotherapy approval if proved successful as monotherapy in a sound clinical examination If the new AED is not introduced as a first-line combination therapy but an immunotherapy is accomplished after the elimination of an established AED, then the approval process is only for transformation to immunotherapy. Initially, the large proportion of newer AEDs were reviewed and accepted for use as adjunctive treatment. Immunotherapy trials typically occurred later. These trials have gained approval from several AEDs for combination therapy use. That being said, regulatory bodies are not consistent in their approval requirements for suggestion AED: in Europe several agents have been approved for combination therapy.

ISSN 2515-8260 Volume 07, Issue 06, 2020

Table 1: Spectrum of efficacy of standard (A) and new AEDs (B). The new AEDs are listed in the order of their marketing in the US, following approval by the US Food and Drug Administration.

		Partial	lary GTC	G myoclonic	G absence
A	Phenytoin	+	+	-	-
	Carbamazepine	+	+	-	-
	Valproate	+	+	+	+
	Phenobarbital	+	+	-	-
	Primidone	+	+	+	-
	Ethosuximide	-	-	-	+
	Methsuximide	+	?	?	+
	Clonazepam	+	+	+	+
B	Felbamate	+[b]	+	?	?
	Gabapentin[a]	+[b]	-	-	-
	Lamotrigine[a]	+[b]	+[b]	?	+[b]
	Topiramate[a]	+[b]	+[b]	?	?
	Tiagabine	+[b]	?	-	-
	Oxcarbazepine[a]	+[b]	+?	-	-
	Levetiracetam[a]	+[*]	+[b]	+[b]	?
	Zonisamide	+[b]	+	+	?
	Pregabalin	+[b]	?	-	-

where; ‘a’ represents new AED with optimistic original monotherapy trials,‘b’ represents new AED effectiveness suggestion backed by blinded examination.

A change in therapy may be recommended when seizures occur after completely accepted first doses of AEDs. Even though an experimental monotherapy is more often than not prescribed , there is almost no systematic confirmation to hold up traditional monotherapy over adjunctive treatment. In general, widespread knowledeg would suggest that in case of failure of primary drug or if it is entirely unsuccessful the best choice would be alternative monotherapy. It could be deemed an adjunctive therapy when the very first drug was well accepted but it was at least partially successful. The alternative of first substitute combination therapy or additional treatment dependent on a variety of considerations, including safety, immunogenicity, clinical trial efficacy, user-friendliness, rapid titration performance, pharmacokinetic reactions, co-morbidity efficacy and less common mechanisms involved.

Patients who are not responding to AED are not very much prone to get seizure-free for the next AED than someone who has attempted first AED. After three to four AEDs failure,

ISSN 2515-8260 Volume 07, Issue 06, 2020

which is extremely successful in some "surgically resolvable" epileptic disorders such as schizoaffective disorder with neuronal sclerosis or primary epilepsy, sufferers with temporary epilepsy should be suggested for surgery. Patients who are not outstanding applicants for diagnosis and treatment may initiate more AED testing, which include AED configurations. In particular, the prospect of conversations and additive negative impacts makes it great to prevent configurations of even more than three AEDs. No pharmacologic treatments such as vagus stimulus and keto diets or customised Atkins diet may also be prescribed for patients who are being refused to adhere to or not able to accept antiepileptic medicines. Nonetheless, vagus nerve stimulus is impossible to deliver seizure freedom so complying with Atkins diet may be a significant obstacle.

LEVETIRACETAM

Levetiracetam (LEV) is known as most recent AEDs sold all over world since 2000. This was originally only accepted as an adjunctive treatment for partial in the US. More current trials, however, received support as an adjunctive treatment for most important comprehensive tonic-clonic seizure and myoclonic seizure in adolescent epilepsy[2], and a new monotherapy study won endorsement for use as an first monotherapy in the European countries .Additionally, the current agreement and launch of an intravenous treatment has contributed to that AED's flexibility.

1. *Levetiracetam pharmacology*:

LEV is control the frequency and approximately entirely after oral ingestion, with increasing doses just about 1 hour after orally administered. Food reduces the peak plasma attentiveness by 22 percent, delaying them by 1.4 hours, but that will not increase LEV bioavailability. There is a systematic association between the LEV dosage and the LEV serum level over a dose range of 500 mg. LEV drug absorption is not clinically pertinent. LEV processing is not a part of the liver cytochrome enzymes network P450 at less than 10 per cent. LEV is mainly excreted unchanged in the kidneys, metabolising just about 28 per cent. Acetamide enhance hydrolysis in the blood is the primary metabolic pathway[3]. The resulting created metabolite is inactive.Half-life of LEV plasma in adults is 8 ± 1 hours, but might be extended by an regular of 2.5 hours in the aged people, most probable due to reduced creatinine permission[4]. For patients with renal impairment a dose change is required, depending on the creatinine permission.

2. *Intravenous levetiracetam*:

ISSN 2515-8260 Volume 07, Issue 06, 2020

The intravenous LEV formulation has been shown to be bioequivalent to oral formulation. In the original analysis 1,500 mg LEV have been inject for 16 minutes. The mixture was well tolerate, and unfavourable effects were comparable to those with oral LEV, although the intravenous administration was more severe in somnolence. The most serious adverse effects, dizziness and drowsiness, were not specifically linked to the rate of dose or infusion. The plasma peak was reached at 6 or 16 minutes as predicted, equivalent to the end of the combination. The 15-minute LEV mixture has been shown to be a safe solution in patients who cannot obtain the oral prescription.

3. *Mechanism of Action of levetiracetam*:

LEV, in fact, is quite different from AEDs and reason is that LEV is not shown any effective measure in standard animal prototype used to test for anticonvulsant action, whereas it is effective in chronic model. The SV2A binding similarity of LEV derivative was closely associated with their binding tendancy within the brain as well as brain's ability to defend alongside seizures in the autogenic mouse model. Similar findings have been reported in the corneal incandescent model of the mouse and the generalise epilepsy of GAERS rat model [5]. The special result of LEV required to SV2A seems to be a decrease in the vesicle release rate. LEV has some other mechanisms of accomplishment which are likely to play a relatively lesser role: the reversal of the suppression of neuronal GABA-and glycine-gated current by the unconstructive allosteric modulators, and the partial depression of N calcium[6].

4. *Efficacy of Levetiracetam*:

Across 3 landmark placebo-controlled randomised blinded clinical trials, LEV was shown to be successful across adults with partial refractory epilepsy[7]. Two doses, 1000, and 2000 mg / day were tested in those trials. All three doses have been reported as being effective.The US study compared placebo with 1000 or 3000 mg / day (in two separated doses). The research randomized 293 patients; of which 268 completed therapy for the 14 weeks.LEV had been titrated over 4 weeks after a single-blind baseline of 12 weeks. The mean proportion lessening over baseline in seizures was 29.5% for LEV of 1000 mg per day and 36.5% for LEV 3000 mg per day in comparison to 6.7% for gesture. Seizure control has been observed in the 1000 mg in 5 percent of patients and in the 3000 mg in 8 percent. Several patients in the placebo group had been seizure-free. Maximum efficacy was already present 2 weeks after initiation of the titration during the first visit. For the 2000 mg per day, there was a 26.7 percent median seizure lessening from baseline, for the 1000 mg per day 18.8 percent and for the placebo group 6.1 percent. The 55 percent response pace for the 2000 mg / day was 32.5

per cent, for the 1000 mg / day 24.7 per cent and for the placebo group 10.4 per cent. Two percent of patients with 2000 mg, 5 percent of patients with 1000 mg, and 2 percent of patients with 121 mg placebo are seizure-free.

A one more trial has been conducted in Europe, contrasted a placebo to just 3000 mg per day. Patients randomised to LEV using 1000 mg per day for 3 weeks after the reference condition, then 2000 mg per day for 3 weeks prior to actually receiving 3000 mg per day for the rest of the study. The average significant decrease in the occurrence of baseline seizures was 38.8% for LEV versus 7.1% for placebo. LEV response rate was 55 percent, compared to placebo sample size of 16.6 per cent. Seizure autonomy has been reported in 7.1% of LEV patients compare to 1.5% of gesture healthcare professionals[8].

The results from the studies were replicated in a lesser blind study (95 people) conduct in Taiwan, compared to placebo with an adjunctive 2000 mg per day of LEV. In the LEV group the response rate was 53.4 percent compare to 11.5 percent in the placebo group. Seizure independence was found in 9.5 percent of person with LEV but no one diagnostic person with placebo[9].

5. *Levetiracetam tolerability*:

The initial placebo-controlled adjunctive trials in one-sided epilepsy indicated so as to diagnosis with emerging unfavourable effects with a advanced LEV incidence is somnolence, faintness and contagion .In the US, during the pivotal partial seizure trial, somnolence was the most frequent explanation for discontinuation of LEV. The number of adult pivotal trials ranged from 5 to 20 per cent and 23 per cent in paediatric trial. The most common adverse effects in the studies that tested more than one dose of LEV did not appear to be dose dependent. In general, adverse effects occurred within the first month of diagnosis[10]. During LEV up-titration, somnolence was documented in one trial in 10 per cent of patients but not during the evaluation period.

CONCLUSION

LEV is regarded as an original or near the beginning supplemental therapy for temporary epilepsy, original or near the beginning supplemental therapy for myoclonic symptoms in children with myoclonic young offenders epilepsy, and thus as a supplemental treatment. people with generalised tonic-clonic seizure activity in the generalised idiopathic epilepsy ecosystem. The pharmaco-EEG-dependent study established that LEV is successful as well as

ISSN 2515-8260 Volume 07, Issue 06, 2020

well-tolerated for the acute treatment of Epileptic seizures. The clinical effects of LEV administration in patients occurs within the 04:08 and 05:06 on average. Intranasal LEV is considered to be the most effective and rapidly as well as easily applicable therapy for the buccal or intramuscular relevance as if the intravenous way is not accessible in case.

REFERENCES

[1] L. Mantoan and M. Walker, "Treatment options in juvenile myoclonic epilepsy," *Curr. Treat. Options Neurol.*, 2011.

[2] K. A. Lyseng-Williamson, "Levetiracetam: A review of its use in epilepsy," *Drugs*, 2011.

[3] R. M. A. Packer, G. Nye, S. E. Porter, and H. A. Volk, "Assessment into the usage of levetiracetam in a canine epilepsy clinic," *BMC Vet. Res.*, 2015.

[4] D. Schmidt and S. C. Schachter, "Drug treatment of epilepsy in adults," *BMJ*, 2014.

[5] L. S. Deshpande and R. J. DeLorenzo, "Mechanisms of levetiracetam in the control of status epilepticus and epilepsy," *Frontiers in Neurology*. 2014.

[6] M. Charalambous, D. Brodbelt, and H. A. Volk, "Treatment in canine epilepsy - A systematic review," *BMC Vet. Res.*, 2014.

[7] J. J. Shih, J. B. Whitlock, N. Chimato, E. Vargas, S. C. Karceski, and R. D. Frank, "Epilepsy treatment in adults and adolescents: Expert opinion, 2016," *Epilepsy and Behavior*. 2017.

[8] J. Kapur *et al.*, "Randomized trial of three anticonvulsant medications for status epilepticus," *N. Engl. J. Med.*, 2019.

[9] C. Wright *et al.*, "Clinical pharmacology and pharmacokinetics of levetiracetam," *Frontiers in Neurology*. 2013.

[10] K. A. Lyseng-Williamson, "Spotlight on levetiracetam in epilepsy," *CNS Drugs*, 2011.