

Second Generation Novel Antiepileptic- Levetiracetam

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Abstract: Epilepsy is a very common neurological disorder with high prevalence and incidence. The administration of antiepileptic drugs is the first treatment of epilepsy. Several conventional antiepileptic drugs are being used for the treatment of various types of epilepsies. Conventional/ first generation antiepileptic drugs like phenytoin, carbamazepine and sodium valproate are widely used but they have increased risk of adverse reactions and drug interactions (Table No.1 & 2). Over the last two decades, there has been a rapid expansion in the number and types of available antiepileptic drugs (AED). Newer AEDs are now available for the treatment of various forms of epilepsies. Many other newer AEDs are under investing. These newer drugs are quite effective and safer than conventional antiepileptic drugs. About 2/3rd of newly diagnosed epilepsies are partial or secondarily generalized.¹ The treatment of the epilepsy depends on appropriate classification of seizure type and the epileptic syndrome.

Keywords: AEDs- antiepileptic drug, SV2A- synaptic vesicular protein, TBI –traumatic brain injury

1. Introduction

Levetiracetam is a Second generation antiepileptic drug with novel mechanism of action.² It is approved as an add-on treatment for partial-onset seizures, myoclonic, primary generalized, and with or without secondary generalization. Its pharmacokinetic attributes (Table No.1 & 2) have facilitated its wide clinical use.

Table 1: Problems with the conventional Anti-epileptics

| |
|--|
| Narrow spectrum - |
| Drug interactions - Effect on hepatic CytP450 enzyme & High plasma protein binding |
| Increased risk of adverse reactions |
| Low margin of safety - Requires TDM |
| High risk of teratogenicity |

Labelled Indications of Levetiracetam

It was approved by the US-FDA

November 1999 for use in adult patients -Myoclonic seizures, Juvenile myoclonic epilepsy, Primary generalized tonic-clonic seizures.

In 2012 for use in paediatric patients with age of 1 month & older - As adjunctive therapy for partial onset seizures in.

In 2013- It has gained indications as monotherapy in adult, In partial onset seizures, adult tonic-clonic seizures, and children with benign childhood epilepsy with centro-temporal spikes.

Table 2: Beneficial aspects of Levetiracetam

| |
|---|
| Linear pharmacokinetics - Safely increase dose |
| No significant drug interactions |
| No effect on hepatic cytochrome P450 enzymes & low protein binding fewer than 10% |
| Favourable adverse effect profile - |
| Broad spectrum antiepileptic effect –All age antiepileptic |
| Relatively safer in pregnant patient –Still not significant data available |

Pharmacokinetics of levetiracetam

LEV has a favourable pharmacokinetic profile. It is well tolerated, safe and efficacious in several phase-III LEV studies of adult patients. LEV is almost completely absorbed after oral administration and its bioavailability is approximately 100%.³ Levetiracetam metabolizes minimally and does not undergo hepatic metabolism. Renal excretion is the major elimination route for levetiracetam. Children also has same pharmacokinetic profile as that of adult, although clearance is approximately 30% - 40% higher.^{4,5}

Mechanism of action- Although the exact mechanism of action is still unknown, it was suggested that LEV might modulate SV2 protein interactions which may lead to reduce seizures. It is suggested that LEV partially inhibits N-type high-voltage-activated Ca²⁺ currents and reduces the release of Ca²⁺ from intra-neuronal stores.^{6,7}

Dose & duration of levetiracetam:

The initial adult dose when used as an adjunct is 1 g on the first day of treatment. The daily dose is then increased in steps of 1 g every 2 to 4 weeks until effective antiepileptic control is achieved. It can be increased to a maximum dose of 3 g daily. The initial dose in children weighing less than 50 kg is 20 mg/kg daily. It is increased in steps of 20 mg/kg every 2 weeks to a maximum of 60 mg/kg daily. Children and adolescents weighing 50 kg or more are given the usual adult dose.

As monotherapy -The initial dose of LEV is 500 mg daily. It is increased after 2 weeks to 1 g daily. Further increases may be made in steps of 500 mg every 2 weeks up to a maximum of 3 g daily. An injection formulation is also available for LEV.

Levetiracetam in Pregnancy

While treating pregnant women with antiepileptic drugs (AEDs), clinicians have to balance potential fetal adverse effects against the risks of uncontrolled maternal disease. Potential harm of seizure on mother and foetus is greater than the teratogenicity of AED. Various standard guidelines for Epilepsy management has recommended the

continuation of AEDs during pregnancy, as seizure frequency is increased in 30% cases.⁸ As per the recommendations the AEDs should be given as monotherapy and in minimum effective dose under proper USG and serum α fetal protein monitoring for screening of foetal malformation.

It is observed that prenatal exposure to first-generation antiepileptic drugs has been shown to increase the risk of congenital malformations and cognitive deficits in the foetus (Table 3). The risk of major congenital malformations with antiepileptic exposure is estimated to be between 4 and 9 percent, compared with the background risk of 1 to 2 percent (2). It is recommended that folic acid supplementation 4 mg/day must be given within the first 25 days post-conception to protect against NTDs.

Table 3: Teratogenic effects with antiepileptic drugs⁹

| Antiepileptic drug | Congenital malformation |
|--------------------|---|
| Valproic acid | Neural tube defects ,Autism, hypospadias |
| Carbamazepine | Figure hypoplasia, cardiac defect, orofacial clefts |
| Phenytoin | Hydantoin syndrome – epicanthal fold, flat nasal bridge, finger hypoplasia, wide & prominent lips ,Mental retardation |
| Phenobarbitone | Cardiac malformation |
| Gabapentine | Unilateral renal agenesis |
| Lamotrigine | Craniofacial defects |
| Topiramate | Hypospadias & oral cleft |

Second generation antiepileptics

Lamotrigine is relatively well studied amongst the newer AEDs. Less data is available with levetiracetam and oxcarbazepine. Safety issues appear to be favorable for lamotrigine and preliminary results are also promising for levetiracetam and oxcarbazepine.

Levetiracetam - As per the results from the UK and Ireland Epilepsy and Pregnancy Registers in a meaningful number of exposed pregnancies, confirms a low risk for major congenital malformation with levetiracetam mono therapy use in pregnancy. MCM risk is higher when levetiracetam is taken as part of a polytherapy regimen, although further work is required to determine the risks of particular combinations. With respect to MCM, Levetiracetam taken in monotherapy can be considered a safer alternative to valproate for women with epilepsy of childbearing age.¹⁰

Clinical trial evidence with Levetiracetam -Drug has proved its safety, efficacy & tolerability in various studies

Newly diagnosed partial epilepsy patients by swaroop et al in 2015¹¹

Compared safety efficacy and tolerability of levetiracetam mono therapy with carbamazepine. It was a randomized, prospective and open labelled study. Results showed that the overall seizure freedom rate at the end of 6 months was 71.42% in CBZ group compared to 78.57% in LEV group. Both LEV and CBZ reported a similar incidence of adverse reactions. It showed better QOL compared to the CBZ group. LEV monotherapy demonstrated similar efficacy for treatment of partial epilepsy and were found to be well tolerated (Fig-1).

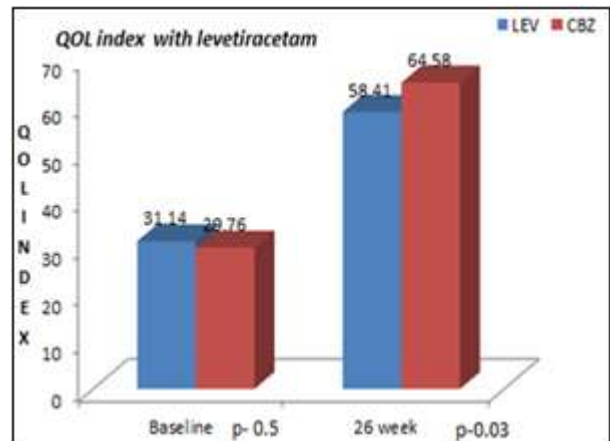


Figure 1: QOLI with levetiracetam

Refractory partial-onset seizures conducted by Beran et al in 2005¹²

compared the Efficacy and safety of levetiracetam 1000-3000 mg/day in patients. It was a multicentric open-labelled single-arm study. A total of 42.4% of patients were responders (> or = 50% reduction from baseline in weekly seizure frequency) over the treatment period (fig-2). The most frequent drug-related adverse events were fatigue (27.3% of patients), somnolence (11.1%), headache (8.1%), and dizziness (8.1%).

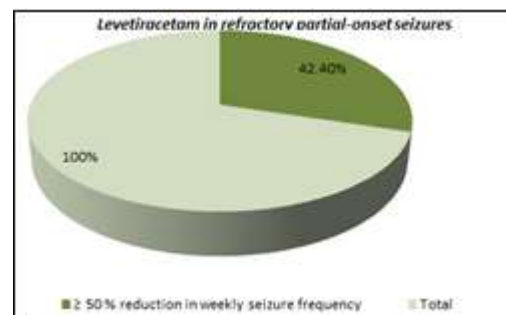


Figure 2: Levetiracetam in refractory partial seizure

Adjunct in Idiopathic Generalized Epilepsy by Berkovic in 2007.¹³

It was a Placebo-Controlled Study of Levetiracetam. seizure frequency by 56.5%, proportion of patients with 50% reduction in seizure frequency -72.2% and that of patients free of GTC seizures -34.2% (Fig.3). Hence showed that levetiracetam is effective and well-tolerated antiepileptic drug for treating generalized tonic-clonic seizures in patients with idiopathic generalized epilepsies.

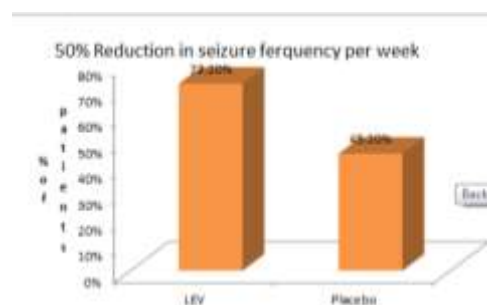


Figure 3: levetiracetam in idiopathic generalised epilepsy

Levetiracetam in Provoked seizure

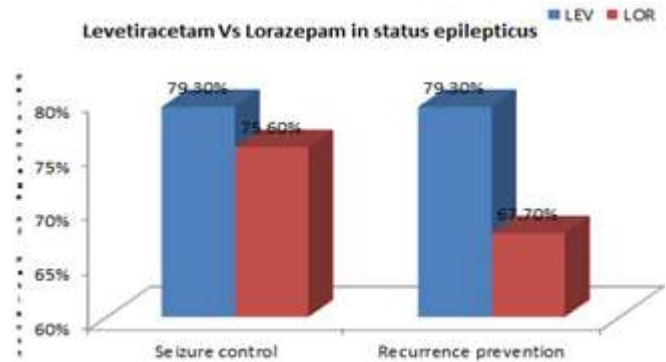
Provoked seizures are those seizures occurring within 7 days of acute brain insult. It may be due to structural damage & traumatic Brain Injury. Structural damage - traumatic brain injury (tbi), brain tumor, stroke, tuberculosis, or neurocysticercosis. Metabolic abnormalities - alcohol withdrawal and renal or hepatic failure

Traditionally, phenytoin has been used for seizure prophylaxis due to its availability in an intravenous formulation and nonsedating properties. Guidelines recommend that patients with severe TBI should receive intravenous PHT to prevent posttraumatic seizure within 7 days; PHT should not be continued after 7 days. In mild TBI, antiepileptic prophylaxis is not recommended. Prophylactic anticonvulsants are not indicated in mild TBI. Use of fosphenytoin has recently declined in favor of levetiracetam as the initial drug choice for seizure prophylaxis. It was found to be more effective than fosphenytoin in preventing early seizures.¹⁴ Incidence of refractory cases was also lower with levetiracetam. Phenytoin has been linked to worse cognitive outcomes when administered to adults with subarachnoid hemorrhage. Taylor et al. demonstrated that levetiracetam is associated with greater retention of cognitive function while providing better seizure prophylaxis when compared with phenytoin in adults with acute ICH.¹⁵

Brain tumour- Seizures are common complications for patients with brain tumors. No clear evidence exists regarding the use of antiepileptic agents for prophylactic use yet newer agents are being favoured in many clinical settings. Studies show that levetiracetam is effective for reducing seizures in patients with brain tumors and may be considered a first-line agent. It decreased seizure frequency in brain tumor patients with or without craniotomy. Safety outcomes were also favourable. The efficacy of prophylaxis with levetiracetam was shown to be superior to that with phenytoin and valproate.¹⁶

Levetiracetam in status epilepticus

Status epilepticus is a common & emergency in neurological disease. It is characterised by seizure activity for >30 min, or two or more seizures occur without recovery of consciousness. Fits have to be controlled as quickly as possible to prevent death and permanent brain damage with high disability and mortality rates. Various treatment options for emergency control of seizure include intravenous lorazepam is the first choice and Phenytoin & Fosphenytoin as the second choice. Both these drugs have significant toxicity. As per the various clinical trials lorazepam was associated with significantly higher need of artificial ventilation and insignificantly higher frequency of hypotension. Levetiracetam, a new broad-spectrum anti-epileptic drug, can be used to rapidly and effectively control SE episodes with few side effects. It has proved its safety, efficacy in various clinical trials (17). It is available in the intravenous formulation. These data suggest that IV LEV may be an effective/safe option for status epilepticus (fig-4).



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