Levetiracetam

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Abstract

Levetiracetam (LEV) is a novel antiepileptic drug (AED) which was discovered in early 1980s and soon, in 1999 FDA approved LEV for the management of partial onset seizure. In India, LEV tablet was approved in April 2005. It acts by binding to the synaptic vesicle protein SV2A, which is present on synaptic vesicles and some neuroendocrine cells. Pharmacokinetics of LEV such as, less protein binding and lack of hepatic metabolism makes LEV less susceptible to drug interactions with other anticonvulsants. Evidence also suggests that LEV is much better than other AEDs in the way of broad therapeutic window, convenient dosing and less adverse effect. Besides the pharmacological effects, pharmacoeconomically also, LEV is a beneficial drug. All these valuable pharmacological and pharmacoeconomic aspect makes LEV an important option in management of various types of epilepsy.

Levetiracetam (LEV) is an antiepileptic drug (AED) with favourable pharmacologic characteristics and demonstrated activity in improving seizure control. It was synthesized in the early 1980s during a follow-up chemical program aimed at identifying a second-generation nootropic drug, and initial pharmacologic studies with LEV explored its ability to facilitate cholinergic neurotransmission. In 1991, pivotal clinical studies were initiated in epilepsy patients as adjunctive therapy in refractory partial onset seizures. In November 1999, the FDA approved LEV as a new AED.[1] LEV tablet was approved in India in April 2005 as adjunctive therapy in treatment of partial onset seizures in adults with epilepsy.[2]

There has been increasing evidence that besides partial seizures in adults and paediatric patients, LEV may also be useful in patients with generalized absence or myoclonic seizures, in patients with Lennox-Gastaut syndrome. It has become one of the most frequently prescribed new drugs for the treatment of partial seizures. In contrast to traditional therapy, LEV has a convenient twice daily dosing, wide margin of safety, no requirement for serum drug monitoring and no interactions with other anticonvulsants. This advantageous pharmacological profile makes LEV an attractive first-line or adjunctive therapy for epileptic seizures.[1]

Mechanism of Action

The chemical name of LEV, a single enantiomer, is (s)-alpha-ethyl-2-oxo-1-pyrrolidine acetamide). Its molecular formula is $C_8H_{14}N_2O_2$ and molecular weight is 170.21. The molecular structure is given in fig.1. It is a soluble ethyl analogue of the widely used nootropic agent piracetam. LEV possesses antiepileptic, anxiolytic, and cognitive enhancing properties. Only the S-enantiomer of LEV has anticonvulsant activity.

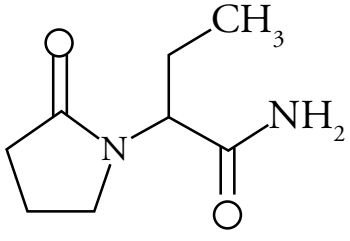

Fig. 1 : Levetiracetam: Chemical Structure

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In vitro studies revealed that LEV has no significant affinity for gamma-aminobutyric acid (GABA) or benzodiazepine receptors. LEV appears to act via an unknown specific binding site in the brain. This novel binding site is the synaptic vesicle protein, SV2A, which is an integral membrane protein present on synaptic vesicles and some neuroendocrine cells.[3]

There are reports of other effects of LEV, including the partial inhibition of N-type voltage gated Ca^{2+} channels and the reduction of inhibition of γ-aminobutyric acid (GABA) - and glycine-gated currents, induced by Zn^{2+} and β-carbolines. Currently, it is unclear whether these effects are mediated by the observed interaction with SV2A, or by alternate mechanisms. It is believed that the correlation between SV2A binding and drug potency suggests that LEV is modulating one or more of the functions of SV2A, and correspondingly contributing to its efficacy in treating epilepsy.[4]

Pharmacokinetics

LEV is rapidly and almost completely absorbed after oral administration. Peak plasma concentration is reached ~1 h after administration to fasting subjects. Time to peak plasma concentration is unaffected by the dose. Food does not affect the extent of bioavailability of LEV. The absorption of LEV was unaffected by the coadministration of calcium- or aluminum-containing antacids. The peak concentration (Cmax) is ~2.4 mg/ml after repeated dosing at 1 mg/kg. The half-life of oral levetiracetam is 7 ± 1 h. Twice-daily dosing was established in early pharmacodynamic and phase III controlled studies. The drug is < 10% protein bound. Steady-state plasma levels are achieved after ~2 days of twice-daily dosing. The major route of LEV elimination is renal excretion, approximately 66% of the administered dose is excreted unchanged in the urine. The total body clearance of LEV is ~0.96 ml/min/kg, and the renal clearance is 0.6 ml/min/kg. Less than 1% was excreted in the feces in the 48 h after dosing.[5]

In the elderly, elimination half-life is between 10 – 11 hours, regardless of dosage or frequency of administration. The prolonged elimination half-life of LEV in the elderly is likely

Table 1 : Formulations of Levetiracetam

Formulation	Strength
Tablet	250 mg 500 mg 750 mg 1000 mg
Film coated tablet	250 mg 500 mg
Extended release tablet	500 mg 750 mg
Oral solution	100 mg/ml
Injection	100 mg/ml

attributable to the age related decline in the renal function. So in patients with renal impairment and elderly patients, care should be taken in appropriate dosage reduction and regular monitoring of renal function.[1] Metabolism of LEV does not occur through the hepatic P450 cytochrome system. The major metabolic pathway is enzymatic hydrolysis of the acetamide group. Because of the lack of hepatic metabolism and low protein binding, the risk of interaction with other drugs is considered low.[5]

Drug Interactions

In pharmacokinetic and clinical studies, concurrent administration of carbamazepine and LEV did not affect serum levels of either drug. However, in post-marketing experience, coadministration of these agents resulted in symptoms consistent with carbamazepine toxicity in 4 individuals with severe refractory epilepsy. While the exact mechanism for this interaction is unknown, it is postulated to be pharmacodynamic, and not pharmacokinetic, in origin. Caution is advised when these agents are prescribed together. Patients may need to be monitored closely for symptoms of carbamazepine toxicity (nystagmus, ataxia, dizziness, double vision). Reduction of carbamazepine dosage may be necessary to resolve the symptoms.[6] No significant interaction was reported with co-administration of other antiepileptic drugs, oral contraceptives, digoxin, warfarin or probenecid.[7]

Indications

- It is used as an adjunct in the treatment of partial seizures with or without secondary generalizations in adults and children aged 4 years and over.
- In addition, levetiracetam is licensed for adjunctive use in the treatment of myoclonic seizures in adults and children aged 12 years and over with juvenile myoclonic epilepsy.
- It is also licensed for use as an adjunct in the treatment of primary generalized tonic-clonic seizures in adults and children with idiopathic generalized epilepsy.[8]

Precautions and Contraindications

Precautions

As with other antiepileptics, withdrawal of LEV therapy or transition to or from another type of antiepileptic therapy should be made gradually to avoid precipitating an increase in the frequency of seizures.[8]

Contraindications

LEV should be used with caution in patients with renal impairment, and/or severe hepatic impairment.[8]

Side Effects

It may cause somnolence, weakness, and dizziness. Anorexia, diarrhoea, dyspepsia, nausea, weight gain or loss, myalgia, ataxia, headache, amnesia, depression, emotional lability, insomnia, nervousness, tremor, vertigo, diplopia, and rash may occur less frequently. Other adverse effects include paraesthesia, pancreatitis, hepatic failure, and hepatitis. Alopecia may also develop; in some cases, stopping levetiracetam has resulted in regrowth of hair.

Dosage Recommendations

The initial adult dose when used as an adjunct is 1 g on the first day of treatment; thereafter, the daily dose may be increased in steps of 1 g every 2 to 4 weeks until effective antiepileptic control is achieved, up to a maximum dose of 3 g daily.

The initial dose in children weighing less than 50 kg is 20 mg/kg daily which may be 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 should be given the usual adult dose.

When used as monotherapy, the initial dose of LEV is 500 mg daily, 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.[7] More recently, the intravenous formulation has been approved in the United States when oral administration of LEV is temporarily not feasible.[9]

The available formulations are given in table 1. Pharmacoeconomic data show that the incremental cost of treating patients with LEV is low when compared with the benefits of seizure freedom.[10] Another cost-effective and economic analysis of LEV inferred that with use of LEV, there was a reduction in other direct medical costs as a consequence of an increase in number of seizure free days. There is also a reduction in number of candidates for surgical evaluation and surgery through a reduction of seizure frequency.[11]

Place in Therapy

LEV is effective as adjunctive therapy for generalized tonic-clonic seizures and as adjunctive or monotherapy in reducing partial seizures in patients with epilepsy. It may also be useful in the treatment of photosensitive epilepsy, and in the treatment of post-encephalitic/post-hypoxic myoclonus. Several studies have evaluated the potential efficacy of Levetiracetam as monotherapy, using the withdrawal trial model.[12] A randomized double-blind trial involving 579 patients comparing LEV with controlled-release carbamazepine illustrated that both AEDs produced equivalent seizure freedom rates in newly diagnosed epilepsy. Importantly no other newer AED has been shown to be equivalent to an older generation AED.[1] Monotherapy will further make the treatment more cost-effective. Potential advantages of levetiracetam include a high therapeutic index, a desirable pharmacokinetic profile (i.e. rapid and complete oral absorption, low protein binding, lack of active or toxic metabolites), minor adverse effects, and a lack of effect on serum levels of other antiepileptic agents (although levetiracetam can increase phenytoin serum levels).

Meta-analysis results for add-on LEV compared with placebo and estimation of its efficacy and tolerability compared with other new AEDs (gabapentin, lamotrigine, oxcarbazepine, tiagabine, topiramate and zonisamide) has been presented. LEV was more effective in terms of responder rate than gabapentin

and lamotrigine and equally well tolerated. It had significantly lower withdrawal rate than topiramate and oxcarbazepine. The indirect comparisons suggest that add-on therapy with LEV has a favourable responder and/or withdrawal rate relative to several AEDs in patients with partial epilepsy with doses used in clinical trials. Safety of parenteral LEV at high doses has important implications in treatment of seizure emergencies and sets the stage for the drug to be evaluated in the treatment of status epilepticus.[13]

To conclude, with the discovery and approval of LEV and other new AEDs, in the recent years has greatly increased the treatment options available to patients with refractory epilepsy. Moreover, monotherapy with LEV may be a safe, rational and effective treatment of choice for new-onset and refractory epilepsy, given the lower risk of adverse events and drug interactions.[11] Also, safety of parenteral LEV at high doses has important implications in treatment of seizure emergencies and sets the stage for the drug to be evaluated in the treatment of status epilepticus. [9]

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