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A Review on Epileptic Treatment by Levetiracetam

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ABSTRACT

Background: Levetiracetam is a novel antiepileptic drug. It is marketed worldwide since 2000. **Aim**: The paper reviewed the mechanism of action, pharmacokinetics, adverse drug reactions, contraindications and uses of levetiracetam in the treatment of various types of epileptic seizures. Methods: Literature searches were done to identify relevant studies. **Results**: Levetiracetam acts by binding to the synaptic vesicle protein SV2A, thereby modulation of one or more of its actions and ultimately affecting neural excitability. It has less protein binding and lacks hepatic metabolism. In contrast to traditional therapy, it has a wide safety margin and does not require serum drug monitoring. It does not interact with other anti-epileptics. **Conclusion**: The above-mentioned favourable pharmacological benefits of LEV make it an important first-line or adjunctive therapy for epileptic seizures.

KEYWORDS: *Levetiracetam, epilepsy, synaptic vesicle protein, seizures, efficacy, safety*

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INTRODUCTION

Epilepsy is a group of disorder characterized by two or more unprovoked seizures. The estimated average prevalence of epilepsy in US is 6.8 per 1000, Europe is 5.5 per 1000, and Asia is 1.5 to 14 per 1000 people respectively.[1] Epilepsy is classified based on the source of seizure into partial and generalized seizures.[1] About 2/3rd of newly diagnosed epilepsies are partial or secondarily generalized. The treatment of the epilepsy depends on appropriate classification of seizure type and the epileptic syndrome.[2] The older or first generation antiepileptic drugs like phenytoin, carbamazepine and sodium valproate are widely used but they have increased risk of adverse reactions and drug interactions.[3] They also require therapeutic monitoring. Therefore, new or second generation drugs are preferred due to favourable side effect profile and less chance of drug interactions.[4] Levetiracetam (LEV) is a second generationantiepileptic drug. It is chemically unrelated to other antiepileptic drugs and is the α-ethyl analogue of the nootropic agent piracetam.[5] It was discovered in 1992 through screening in audiogenic seizure susceptible mice.[6] It is marketed worldwide since 2000.[7] It has been found to be well tolerated with a favourable pharmacokinetic profile that includes minimal protein binding, lack of hepatic metabolism and twice a day dosing.[5-7] It was initially approved in the US only as adjunctive therapy for partial-onset seizures.[8] However, it is recently approved as an adjunctive therapy for primary generalized tonic- clonic seizures, myoclonic seizures of juvenile myoclonic epilepsy and partial onset seizures with or without secondary generalization.[8] It has also been found to be effective in patients with Lennox-Gastaut syndrome.[8,9] Recently, it is also widely used in the prophylaxis of post operative seizures in neurosurgery.[9]

In contrast to traditional therapy, LEV has a wide safety margin without any requirement for serum drug monitoring, and no interactions with other antiepileptics.[10] This favourable pharmacological profile makes LEV an attractive first-line or adjunctive therapy for epileptic seizures.[10]

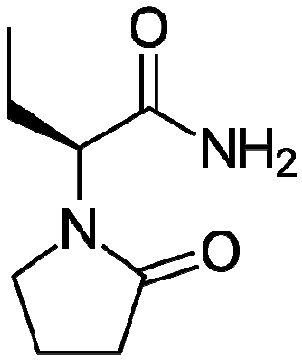

Fig No.1: Structure of Levetiracetam

MECHANISM OF ACTION

The mechanism of action of levetiracetam is different from first-generation and other second-generation anti-epileptic drugs (AEDs).[11] It does not work by the three classic routes of other AEDs: sodium channel modulation, low-voltage-activated (T-type) calcium channel modulation, or direct gamma-aminobutyric acid (GABA) facilitation.[11] It is postulated to act by binding to synaptic vesicle protein 2A (SV2A) and thereby modulation of one or more of its actions, ultimately affecting neural excitability.[12] It is devoid of anticonvulsant activity in the two classic acute seizure models used for AED screening, including the maximal electric shock seizure test and the pentylenetetrazol seizure test.[13] However, it demonstrates anticonvulsive effects in the acute corneal electroshock model and selective chemoconvulsant seizure models, including pilocarpine and kainic acid induced models.[13,14] LEV exerts significant antiepileptic effect, even after discontinuation of therapy, in kindled models and in the double mutant (tm/tm, zi/zi) spontaneously epileptic rat (SER) model.[14] LEV also has been found to selectively inhibit N-type Ca2+ channels,[15] activate GABA current[16] and possess novel desynchronizing effect on neurons that might be involved in the molecular basis of epilepsy.[17]

PHARMACOKINETICS

LEV is readily absorbed following oral administration. The oral bioavailability of LEV is more than 95%. It attains peak plasma concentration approximately one hour after oral administration. [18] It reaches steady state concentration within 48 hours of initiation of therapy. Food reduces the peak plasma concentration of LEV by 20% and delays it by 1.5 hours.[18,19] There is a linear relationship between LEV dose and LEV serum level over a dose range of 500–5000 mg.[18,19] LEV is less than 10% bound to plasma proteins and this protein binding is not clinically relevant.[19,20] Only 27% of LEV is metabolized and metabolism is not dependent on the liver cytochrome P450 enzyme system.[19] The main metabolic pathway is hydrolysis of the acetamide group in the blood to yield an inactive carboxylic derivative. LEV is predominantly excreted unchanged through the kidneys and its plasma half-life is 7 ± 1 hour in adults.[19,20] The half life can be prolonged by an average of 2.5 hours in the elderly, most likely due to decreased creatinine clearance with age.[20] Also, in patients with impaired renal function, a dose adjustment is needed, dependent on the creatinine clearance.[20]

The absence of hepatic metabolism and of protein binding leads to lack of pharmacokinetic interactions.[20] There have no reports of pharmacokinetic interactions with drugs like oral contraceptives, phenytoin, warfarin, digoxin. However, some studies have suggested lower LEV levels or higher clearance in patients taking enzyme-inducing AEDs.[21] Autoinduction probably does not occur with LEV, but one study involving short intensive monitoring suggested a drop in serum levels after the fifth day of administration of the drug.[22]

PUBLISHEDADVERSEDRUG REACTIONS

According to the study by Ben Machen et al., overall incidence of adverse events was comparable between the placebo (53%) and LEV (55%) groups.[23] The commonest adverse reactions seen with LEV therapy were asthenia (13.8%), infection (7.2%), somnolence (6.1%) and headache (3.3%). Around 7.1% patients discontinued the therapy due to the adverse reactions. During the monotherapy phase of LEV, 4 patients developed the serious adverse events, 2 experienced (6.1%) and headache (3.3%). Around 7.1% patients discontinued the therapy due to the adverse reactions. During the monotherapy phase of LEV, 4 patients developed the serious adverse events, 2 experienced convulsions, 3rd patient had oesophagitis related to increase in stress and the fourth patient had an unintended pregnancy. [23] Bootsma et al.[24] reviewed the clinical experience of LEV and mentioned that overall 5% of patients were affected by adverse drug reactions. The most prevalent adverse events at almost each assessment point were mood disorder, tiredness and sleepiness.[24] A remarkable side effect of LEV was positive behavior, reported by about 7% of patients at 3, 6, 9, and 15 months.[24]

According to a review by Lyseng-Williamson, psychiatric and behavioral adverse events were common with LEV.[25] They occurred in >1% and

<10% of patients. Suicidal ideation or behavior was reported in 0.5-0.7% of the patients. Certain subgroups of patients especially children with a past history of psychiatric illness and mental retardation had a greater risk of developing psychiatric adverse events or suicidal behavior and ideation. [25] In

Kossoff et al. and Mula et al. studies, up to 13% of patients experienced the neuropsychiatric symptoms.[26,27] Symptoms were mild, including agitation, hostility, apathy, anxiety, emotional liability and depression.[26,27] In the same studies, about 1% of pediatric or adult patients had experienced serious neuropsychiatric symptoms including hallucinations, suicidal ideations or psychosis.[26] In these cases, there was a significant association between psychiatric adverse events and previous history of febrile convulsions and status epilepticus.[27]

There have been many case reports about the adverse reactions of LEV. In Mahta et al case study,[28] a 45 year old man developed interstitial nephritis after the escalating dose of LEV. The patient was normal after the withdrawal of the drug.[28] In Newsome et al. study,[29] a 9 year old girl developed interstitial lung disease after increasing the dose of LEV. The patient was normal after the withdrawal of the drug. In this case, the girl had a previous history of pneumonia, mental retardation and cerebral palsy.[29] In another case report by Calabro et al,[30] it was reported that two young men experienced loss of libido and anhedonia. In some case studies it has been mentioned that LEV also leads to bleeding disorders and pancytopenia.[30]

LEV has not been found to interfere with cognitive function. It, however, improves the quality of life of patients with epilepsy.[31]

DOSAGE RECOMMENDATIONS

The initial adult dose when used as an adjunct is 1 g on the first day of treatment.[32] The daily dose is then increased in steps of 1 g every 2 to 4 weeks until effective antiepileptic control is achieved.[32] It can be increased to a maximum dose of 3 g daily.[32] The initial dose in children weighing less than 50 kg is 20 mg/kg daily.[32] It is increased in steps of 20 mg/kg every 2 weeks to a maximum of 60 mg/kg daily.[32] Children and adolescents weighing 50 kg or more are given the usual adult dose.[32] When used as monotherapy, the initial dose of LEV is 500 mg daily.[32] It is increased after 2 weeks to 1 g daily.[32] Further increases may be made in steps of 500 mg every 2 weeks up to a maximum of 3 g daily.[32] An injection formulation is also available for LEV.[32]

PRECAUTIONS AND CONTRAINDICATIONS

LEV therapy or transition should be attained gradually to avoid precipitating an increase in the frequency of seizures.[33] LEV should be used with caution in patients with renal impairment, and/or severe hepatic impairment.[33]

REVIEW OF EARLIER STUDIES FOR EFFICACY AND TOLERABILITY

According to SKATE trial by Lambrechts et al.,[34] which was conducted to assess the efficacy safety of LEV as an add on therapy in partial epilepsy in adults≥16 years of age group, 86.9% patients completed the 16 weeks of treatment.[34] The reduction in frequency of partial onset seizures was 62.5%. 19.3% of the patients became seizure free and 56.6% had a reduction in seizures frequency of ≥ 50%.[34] This study concluded that LEV is effective and safe as add on therapy in partial epilepsy.[34]

The efficacy of LEV in pediatric population was studied by Lee et al.[35] It was observed that 48% of the patients showed a seizure reduction of ≥50%, and 22% of the patients became seizure free.[35] Also, there was a reduction of in seizure by ≥50% in 52% of children with partial seizures, and 44% of children with generalized seizures.[35]

According to Berkovic et al.,[36] LEV produced a greater mean reduction of about 56.5% in GTC seizures frequency per week over the treatment period then placebo where it was 28.2%.[36] The percentage of patients who had ≥50% reduction of GTC seizurefrequency per week during the treatment period was 72.2% for LEV and 45.2% for placebo ($p < 0.001$).[36] During the evaluation period the percent of patients free of GTC seizures with of 24.1% for LEV vs 8.3% for placebo with a p-value of 0.009.[36]

In a comparative study of LEV vs carbamazepine (CBZ) in newly diagnosed epilepsy by Brodie et al.,[37] 73.0% of patients randomized to LEV and 72.8% receiving controlled release carbamazepine were seizure free at the last evaluated dose for ≥6 months.[37] The remission rates at the end of 6 month to 1 year were 80.1% of LEV and 85.4% of CBZ.[37] In a multicenter, placebo, controlled study of LEV for myoclonic seizures by Nochtar et al.,[38] a reduction in ≥50% in the number of days per week with myoclonic seizures was seen in 58.3% of patients in the LEV group and 23.3% of patients in the placebo group ($p < 0.001$).[38] LEV treated patients had higher freedom from myoclonic seizures 25.5% vs 5.0% for placebo ($p = 0.004$). [38]

In a double blind, placebo controlled, randomized clinical trial of LEV in partial seizures by Cereghino et al.,[39] a ≥50% reduction in seizure frequency were seen 33.0% patients with 1000mg/day and 39.8% of patients with 3000mg/day.[39] The placebo group had 10.8% reduction in seizure frequency ($p < 0.00$ 1).[39] Also, in the LEV group, 5.52% of patients became completely free of seizures.[39] According to Gurses et al.,[40] which was conducted

to study the efficacy of LEV as on add on therapy in patients with startle epilepsy, it was found that 60% of patients responded to the LEV.[40]

According to KEEPER trial by Morrell et al.,[41] 57.9% patients under LEV experienced at least 50% reduction in frequency of partial onset seizures.[41] Also, 40.1% patients experienced at least 75% reduction, and 20% demonstrated 100% seizure reduction.[41] 74.3% of patients were considered improved with 37% of patients showing marked improvement.[41]

LEV is established as efficacious in adjunctive therapy in partial and generalized seizures. A few studies demonstrated successful conversion to monotherapy in refractory epilepsy.[42,43] Three studies with small number of patients demonstrated its effectiveness as a single agent in partial epilepsy.[42-44] Ben-Menachem et al. conducted a multicenter double blind trial to evaluate the efficacy and tolerability of LEV monotherapy in refractory partial epilepsy.[42] They concluded that in the LEVmonotherapy group, the median percent reduction in partial seizure frequency compared with baseline was 73.8% with a responder rate of 59.2%.[42] In an open study by Alsaadi et al., 82% of patients remained on LEV for atleast 1 year with more than 50% of patients remaining seizure free.[43]

A few studies proved the efficacy of LEV in prophylactic therapy of postoperative seizures and traumatic brain injuries. Milligan TA et al., conducted a study to assess the efficacy and tolerability of levetiracetam versus phenytoin after supratentorial neurosurgery.[44] It was concluded that both LEV and phenytoin (PHT) were associated with a low risk of early postoperative seizures and a moderate risk of later epilepsy.[44] LEV was associated with significantly fewer early adverse reactions than phenytoin.[44] In another comparative study of LEV versus PHT on seizure prophylaxis in severe traumatic brain injury by Jones et al.,[45] the final conclusion was that LEV is as effective as phenytoin in preventing early posttraumatic seizures but is associated with an increased seizure tendency on EEG analysis.[45]

Zachenhofer et al. conducted a study on perioperative LEV for prevention of seizures in supratentorial brain tumor surgery.[46] It was observed that perioperative LEV in supratentorial brain tumor patients was well tolerated.[46] Compared with the literature, it resulted in low (2.6%) seizure frequency in the early postoperative period.[46] Additionally, its advantage of lacking cytochrome P450 enzyme induction allowed early initiation of effective postoperative chemotherapy in malignant glioma patients.[46] A pilot study was conducted by Lim et al. studied the safety and feasibility of switching from phenytoin to LEV monotherapy for glioma-related seizure control following craniotomy.[47] It concluded that it is safe to switch patients from PHT to LEV monotherapy following craniotomy for supratentorial glioma.[47]

Recently, the HELLO trial was conducted by Bahr et al.[48] They assessed the efficacy and tolerability of intravenous and oral LEV in patients with a suspected primary brain tumor and symptomatic seizures undergoing neurosurgery.[48] They concluded that after initiation of therapy with LEV, 100% of the patients were seizure-free in the pre-surgery phase (3 days up to 4 weeks before surgery), 88% in the 48 h post-surgery phase and 84% in the early follow-up phase (48 h to 4 weeks post surgery).[48] Treatment failure occurred in three patients even after dose escalation to 3,000 mg/day.[48]

According to a recent study by Weinstock et al., mild to moderate treatment emergent adverse events occurred in 63% of enrolled subjects.[49] The most frequent of these were pyrexia and dry mouth. Most other treatment emergent adverse events were considered unrelated to intravenous LEV administration. They concluded that intravenous LEV was well tolerated in children 1 month to 16 year.[49] Another study by Ozkale et al., reported that in a patient with multidrug refractory epilepsy and Ohtahara syndrome, accidental administration of LEV in high dose of 300 mg/kg/d for 35 days showed no adverse effects.[50] Another review by Cormier et al., concluded that the current data leading to the approval of LEV for use in infants and children with partial onset seizures is encouraging and more work needs to be done about the efficacy across different pediatric age groups.[51]

ROLE IN THERAPY

LEV has been approved by European medicines agency (EMA) for use as a (i) monotherapy in the treatment of partial onset seizures with or without secondary generalization in patients from 16 years of age with newly diagnosed epilepsy (ii) adjunctive therapy in the treatment of partial onset seizures with or without secondary generalization in adults and children from 1 month of age with epilepsy (iii) treatment of myoclonic seizures in adults and adolescents from 12 years of age with juvenile myoclonic epilepsy and (iv) treatment of primary generalized tonic-clonic seizures in adults and adolescents from 12 years of age with idiopathic generalized epilepsy.[52, 53]

The drug is approved by Food and drug administration for the treatment of (i) adjunctive therapy in the treatment of partial onset seizures in

adults and children 4 years of age[54] and older with epilepsy (ii) adjunctive therapy in the treatment of myoclonic seizures in adults and adolescents 12 years of age and older with juvenile myoclonic epilepsy and

(iii) adjunctive therapy in the treatment of primary generalized tonic clonic seizures in adults and children 6 years of age and older with idiopathic generalized epilepsy.[54,55] The non licensed uses are

(i) mania (ii) neuropathic pain and (iii) status epilepticus.[55]

LEV has also gaining its entry into the prophylaxis therapy for post operative seizures, and traumatic brain injury, duration for the treatment varies according to the individual history, studies has confirmed that prophylactic use of antiepileptic drug can reduce the incidence of post operative seizures.[56]

CONCLUSION

LEV is a novel, second generation antiepileptic drug. It is approved for adjunctive therapy for adults with partial, myoclonic, and generalized tonic clonic seizures. It was proved efficacious as monotherapy in3 mulitcenter studies and adjunctive therapy in 5 multicenter trials. These studies concluded that LEV has similar efficacy as older AED's as in monotherapy. The advantages of LEV are its minimal protein binding, lack of hepatic metabolism and twice daily dosing. The adverse reaction profile of the drug is comparatively better than the older AED's, except the psychiatric manifestations. These manifestations are, however, found to be linked to past psychiatric history of the patients. These features of LEV make it an ideal drug for monothreapy. At present very few studies are available on monotherapy of LEV. Also, all the available monotherapy studies have the drawback of having smaller sample size.

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