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Levetiracetam: Efficacy and Safety in Children in Depth Review

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Abstract:

Levetiracetam (LEV), as an antiseizure medication, is well-known for its unique mechanism of action by modulation of synaptic neurotransmitter release with significant pharmacokinetic advantages. Its efficacy includes both focal and generalized seizures as either add-on therapy or monotherapy with the highest level of tolerability especially in children. However, some studies have reported an unexplained infection like pharyngitis and rhinitis especially after long-term use.

Introduction:

Levetiracetam (Keppra) is a pyrrolidine derivative chemically unrelated to existing antiepileptic drugs. Chemically, it is a racemic mixture of pure S-enantiomer α-ethyl-2-oxo- 1-pyrrolidine acetamide. On November 30, 1999, the drug received accelerated approval by the Food and Drug Administration as adjunctive therapy in the treatment of partial-onset seizures in adults with epilepsy. Levetiracetam was approved within 10 months of submission as a new drug application, the fastest approval of an antiepileptic to date **(1).**

Mechanisms of action:

1. Antiepileptic Mechanism:

The precise mechanisms of action of levetiracetam are still unknown; however, its mechanism of action appears different to that of other antiepileptic drugs (AEDs) and seems to be unrelated to known mechanisms of neuronal transmission. It has no significant affinity for GABAergic or glutamatergic receptors and does not interact directly with the benzodiazepine binding site. Levetiracetam has been shown to selectively inhibit high-voltage activated calcium channels and to reduce calcium release from intraneuronal stores (via ryanodine and inositol trisphosphate receptors). It is known to have a specific binding target in the brain, identified as synaptic vesicle protein 2A (SV2A), an integral membrane glycoprotein expressed ubiquitously in the brain. Although the function of SV2A is not well established, studies performed in knockout mice demonstrate that it is involved in the control of vesicle fusion and exocytosis. SV2A binding provides broad-spectrum antiepileptic activity, with similar potencies in different animal models of partial and generalized epilepsy **(2).**

A recent study has explored the hypothesis that levetiracetam may link α-amino-3-hydroxy-5-methyl-4-isoxazolepro-pionic acid (AMPA) receptor channels in mouse cortical neurons, with a subsequent significant decrease of excitatory postsynaptic currents in cortical neurons **(3).**

2. Neuroprotective Mechanism:

In addition to the indirect neuroprotective effect of LEV, through its anti-ictogenic and anti-epileptogenic mechanisms mentioned above, there are several studies that show a direct neuroprotective effect in different

pathological conditions where the brain has suffered an injury. They found through MRI studies in mice after 2 days from status epilepticus (SE), there was cytotoxic edema developed in the dorsal hippocampus, amygdala and piriform cortex disturbing blood brain barrier (BBB) integrity.

This edema was markedly ameliorated by LEV treatment (30 min after diazepam injection, and thereafter twice a day for 7–10 days; 350 mg/kg). These results were attributed to LEV protective action of the BBB via astrocytes and the inhibition of angiogenesis in the hippocampus; since the drug treatment significantly reduced the mRNA expression of some angiogenic factors (angiopoietin-2, Tie-2, vascular endothelial growth factor-A VEGF and its receptor) increased by SE **(4).**

3. Anti-inflammatory Mechanism:

Regarding neuroinflammation, treatment with LEV (360 mg/kg; for 7–10 days) suppressed the expression of proinflammatory molecules, such as tumor necrosis factor α (TNF- α), interleukin 6 (IL-6) and interleukin 1β (IL-1β) 1 or 3 h after SE. During epileptogenesis, repeated treatment with LEV for 30 days prevented microglial activation, as evidenced by a decrease in morphological changes, phagocytic activity, and cytokine expression. Additionally, in epileptic rats, LEV (30 mg/kg, i.p. for 1 week) reduced reactive gliosis and the expression levels of IL-1β and interleukin 1 receptor type I in the hippocampus and piriform cortex **(5).**

The clinical evidence regarding the anti-inflammatory effect of LEV is limited. The prospective clinical trial of 21 epileptic patients treated with LEV (1464 ± 405 mg/day), showed a decrease in the percentage of T-lymphocytes (CD4+ CD25+) without significant changes in leukocytes, neutrophils, total lymphocytes, and cytokine levels (IL-1β, IL-6, TNF-α and monocyte chemoattractant protein-1(MCP-1)) in the peripheral blood. Similarly, in the serum of children with epilepsy, LEV or valproate treatment for 16 weeks does not change the serum IL-1β levels but decrease levels of the inflammatory marker C–C motif ligand 2 (CCL2). Additionally, both drugs reduced anxiety and improved quality of life in these pediatric patients. In contrast, Gulcebi et al. found a decrease in the IL1-β concentration in patients on monotherapy with LEV for at least one month **(6).**

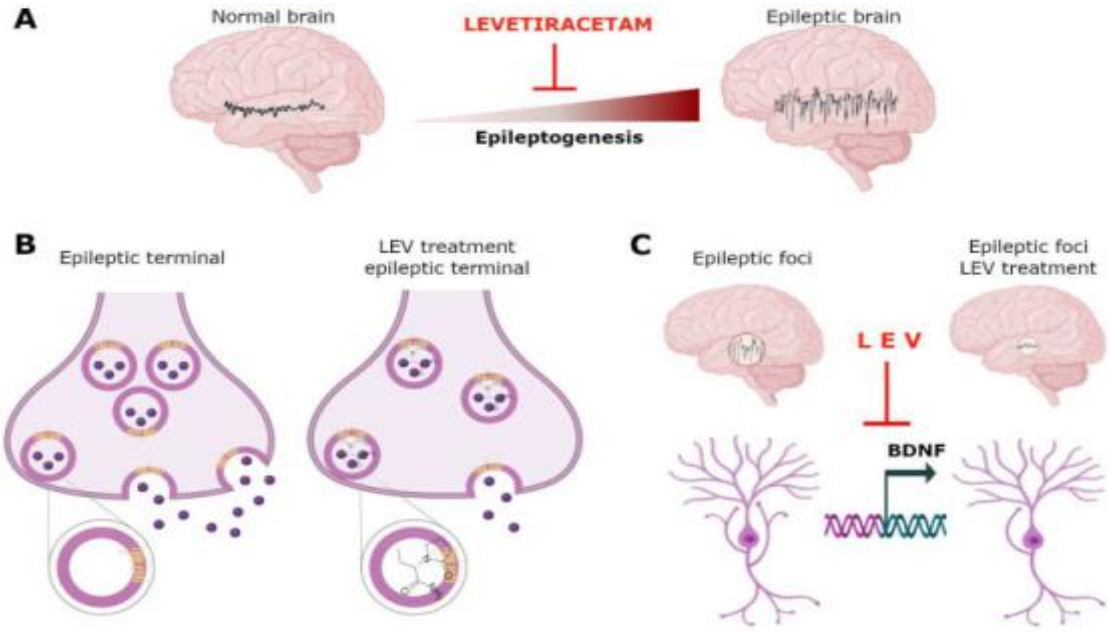

Figure (1): Putative antiepileptogenic levetiracetam (LEV) mechanism. (A) LEV is one of the few antiepileptic drugs (AED) able to retard or inhibit the generation of epileptic neural circuits. The mechanism through which it does is not completely elucidated, but apparently inhibiting the excessive synaptic transmission. (B) The binding LEV-SV2A

improve the SV2A effects, diminishing the hyperexcitability and thus delays epileptogenesis. (C) LEV inhibit epileptic foci formation by suppressing BDNF (Brain-Derived Neurotrophic Factor synthesis) and consequently the mossy fiber sprouting **(4).**

Pharmacokinetics:

Levetiracetam possesses a remarkably favorable pharmacokinetic profile. The terminal elimination half-life of levetiracetam in children is 6.0 – 1.1 (range 4.0–8.2) hours compared with 7.2 – 1.1 (range 6–8) hours in adults. Therefore, while twice-daily administration in adults achieves optimal effects, it is probable that in children three-times-daily dosing could be more appropriate. The body clearance values of levetiracetam in children are 30–40% higher than those seen in adults; peak concentration and area under the plasma concentration- time values are similar in children and adults.

Levetiracetam clearance is via the renal route and is directly dependent on creatinine clearance; because of the faster clearance in children, levetiracetam dosage adjustments are necessary for pediatric patients. Since the metabolism of levetiracetam does not involve enzymes of the cytochrome P450 system, this drug neither induces nor inhibits enzymes involved in hepatic drug metabolism. Levetiracetam is largely not protein bound; therefore, it does not compete with other drugs for binding sites **(7).**

The dosage in pediatric patients is 10 mg/kg/day for the first week, then titrated in increments of 10mg/kg/day every 2 weeks. The usual childhood maintenance dosage is 40–80 mg/kg/day in two to three equally divided doses. However, according to a recent observational study, therapeutic dosing strategies of levetiracetam in children with epilepsy consist of starting levetiracetam therapy at a dosageof 10 mg/kg twice-daily (which provides a plasma concentration similar to that obtained in adults for the recommended 500 mg twice-daily dosage) followed by further dose adjustment according to the clinical outcome **(8).**

LEV has linear kinetics, such that in any individual the serum concentration is proportional to the dose. However, the effective serum level for LEV is not known. One study in 69 patients taking 500–3000 mg/day found that the trough plasma concentration ranged from 1.1 to 33.5 μg/mL. Similar mean concentrations were found in patients experiencing adverse effects and those without adverse effects (11.2 vs 10.9 μg/mL) **(9).**

Approved Indications:

Levetiracetam has been shown to be useful for a wide range of epilepsies in pediatric patients. This drug is initially approved as adjunctive therapy in pediatric patients with partial onset seizures and in primary generalized tonic-clonic seizures. It has also been shown to be effective in patients younger than 2 years of age with a variety of epilepsy syndromes. Lately, this antiseizure medication (ASM) has recently been considered successful as monotherapy **(10).**

Efficacy:

- ✓ **Partial Epilepsy:**

With an initial dosage of levetiracetam (20 mg/kg/day) and then to be titrated every 2 weeks up to 60 mg/kg/day, response rates (>50% seizure reductions) were found 45% among cases. Seizure freedom was achieved successfully after dose titration. Hence, levetiracetam received US FDA approval for the indication of adjunctive treatment in partial epilepsy in children aged 4–16 years **(11).**

In the monotherapy trial, with a median dose of 33 mg/kg/day, there was a 60% seizure reduction. Therefore, Levetiracetam was equally effective for partial and generalized seizures with minor side effects **(12).**

- ✓ **Generalized Epilepsy:**

Using levetiracetam for generalized idiopathic epilepsy, the seizure frequency dropped to 60%. Complete elimination of seizures was documented among 25% with levetiracetam as monotherapy. However, with location-related epilepsy, only 30% of cases showed a 50% reduction in seizure frequency **(13).**

- ✓ **Refractory Epilepsy:**

By the use of LEV as add-on therapy for inadequately controlled partial seizures, a 27% reduction in seizures was noticed **(13).**

On children with different epileptic syndromes. Studies showed that seizure control (50–100% reduction) did not appear to depend upon seizure type. A response rate was attained in 40% patients with focal seizures, 55% patients with generalized seizures, and 61% patients with mixed seizures. In contrast, in some children with treatment-resistant partial-onset seizures, levetiracetam was administrated at a dosage 40 mg/kg/day with only 10% seizure-free percentage **(14).**

- ✓ **Monotherapy:**

Using levetiracetam as monotherapy (either initial monotherapy or conversion to monotherapy) on both partial-onset epilepsy and generalized epilepsy with dose range (14–60 mg/kg), good control (about 61% seizure free and 67% with 50% reduction in seizures) was accomplished. Therefore, levetiracetam appeared to be effective as monotherapy in children with epilepsy **(15).**

- ✓ **Epilepsy Syndromes:**

1. Benign Epilepsy with Centrotemporal Spikes:

The use of levetiracetam in children with benign epilepsy with centrotemporal spikes (BECTS) was reported. In all cases, complete freedom from seizures was observed and no adverse events were reported. In addition, a recent study demonstrated that levetiracetam may have a beneficial effect on language development and may improve auditory comprehension impairments**(15).**

2. Lennox-Gastaut Syndrome (LGS):

Levetiracetam has also been demonstrated to be effective as monotherapy in LGS; the drug was found to be effective against myoclonic seizures and tonic clonic seizures. After administration of LEV as add-on therapy for treatment- resistant LGS by a mean dosage 24 mg/kg/day, complete cessation of tonic-clonic seizures was observed in 40% and cessation of myoclonic seizures was observed in 58% **(16).**

3. Idiopathic generalized epilepsies:

A recent meta-analysis revealed that approximately 60 % of patients with myoclonic seizures had a significant (>50 %) reduction in seizure frequency after the LEV treatment. These results are consistent with previous studies that have reported clinical improvement of myoclonic seizures after LEV monotherapy or combined therapy in a variety of epilepsy syndromes such as juvenile myoclonic epilepsy (JME) and Dravet syndrome (DS). Also, the patients' self-assessments and quality of life regarding the myoclonic seizures have improved due to LEV **(17).**

While comparing the efficacy of valproate (VPA) and LEV as monotherapy in pediatric patients with idiopathic generalized epilepsy with tonic-clonic (GTC) seizures, similar favorable 6-month treatment outcomes popped out with about 80% complete seizure control for both drugs. Age at epilepsy onset, epilepsy syndrome, electroencephalogram (EEG) features and either drug dose were not significant predictors of the 6-month treatment outcomes. None of the patients discontinued VPA or LEV due to treatment-associated adverse effects **(18).**

In a recent study in Italy, it has been concluded that monotherapy with levetiracetam could be effective and well tolerated in patients with childhood absence epilepsy and juvenile absence epilepsy **(19).**

- ✓ **Status epilepticus (SE):**

Benzodiazepines have been used as a first-line treatment for this condition. Interestingly, in meta-analysis studies, LEV was found to be significantly effective for seizure cessation in patients with SE. Based on this kind of evidence, LEV has been considered as a first option for second-line therapy in the treatment of SE with less side effects **(20).**

- ✓ **Neonatal fits:**

A recently-conducted meta-analysis showed that there was no difference in efficacy between LEV and phenobarbital (PB) in the treatment of neonatal seizures. Compared with PB, the incidence of side effects of LEV was lower. The incidence of hypotension and respiratory depression in the LEV group was significantly lower than that in the PB group with no long-term neurodevelopmental outcomes **(21).**

Adverse effects:

In the clinical use of antiepileptic agents, it is often the adverse effect profile, rather than lack of efficacy, that limits use of the drug. Levetiracetam is generally well tolerated and has no serious systemic adverse effects. No routine laboratory monitoring is required.

A) General:

The most common adverse effects reported in placebo-controlled Phase II/III trials that included epilepsy patients were: somnolence 14.8%, asthenia 14.7%, headache 13.7%, dizziness 8.8%, and infection 13.4%. The relationship of common adverse effects to dosage is unclear, but may be related to rate of titration **(22).**

B) Hypersensitivity reactions:

In the Phase II/III placebo-controlled trials, the incidence of hypersensitivity reactions was 0.3. Reports of rash increase with longer duration of treatment **(23).**

C) Psychiatric and behavioral adverse effects:

Both somnolence and asthenia/fatigue may reflect the depressant central nervous system (CNS) effect of LEV. Asthenia and fatigue might also result from decreased excitatory activity. Somnolence and even more serious disturbances of vigilance and alertness are commonly impaired in individuals taking traditional ASMs. A further side effect associated with LEV was nervousness/irritability, which has already been reported in a previous systematic review. Psychiatric effects, such as anxiety, depression and psychosis, were very rarely associated with LEV in randomized controlled trials (RCTs) **(24).**

Pyridoxine at average dose of 7 mg/kg/day has been noted to control behavioral disturbances in children on levetiracetam. Only long-term observational studies provided data about an increased risk of psychiatric disorders in a subset of patients with pre-existing mood disorders, likely due to a genetic predisposition. Dizziness, ataxia and diplopia were commonly observed in individuals treated with LEV **(25).**

D) Hematologic effects:

Laboratory parameters in patients with refractory epilepsy remained fairly stable with LEV therapy, with small percentages of patients developing anemia (4.6%), leukopenia (4.8%) or elevated c-glutamyl-transferase levels (5.3%). White blood cells (WBC) and neutrophil counts were decreased in pediatric patients treated with LEV and ecchymosis occurred in 4% of treated ones versus 1% of placebo-treated patients. No clinically relevant change in bleeding time or difference from placebo was observed **(26).**

Although no bleeding has been reported with LEV in clinical studies, one identified, by platelet aggregometry, that LEV seemed to inhibit thromboxane-dependent platelet activation and aggregation, with total recovery of platelet function observed 3 weeks after treatment substitution with another molecule. The authors suggest that caution should be exercised when this drug is used concomitantly with antithrombotic drugs, especially with antiplatelet agents such as clopidogrel, which do not target the thromboxane A2 pathway, because of an expected additive effect **(23).**

The English Pharmacovigilance Network of Medicines and Healthcare Products Regulatory Agency reports 41 LEV-related blood disorders, none of these cause the death of the patient. The most frequent were neutropenia (12 cases), thrombocytopenia (9 cases), pancytopenia (5cases) and leukopenia (4 cases); the less frequent were aplastic anemia (2 patients), thrombocytopenic purpura (2 patients) and coagulopathy (2patients) **(27).**

E) Bone density:

Statistical analysis demonstrated an increased risk of osteopenia or osteoporosis upon using antiepileptic agents. Of all antiepileptic agents, levetiracetam did not seem to affect bone density **(28).**

F) Infections:

During placebo-controlled trials of levetiracetam, infections, including upper respiratory tract and urinary tract infections, were increased in the levetiracetam group. Post-marketing trials found an incidence of infections in the ranges of 2.6 – 13.2% among levetiracetam-treated patients**(6).**

G) Levetiracetam-induced seizure aggravation (LISA):

In a review of pooled analysis of add-on trials, worsening of seizures occurred only in 14% of cases with no established relationship with dose. Various risk factors for seizure exacerbation following LEV treatment have been reported. Intellectual disability in patients with both focal and generalized epilepsy has been identified as a prominent risk factor in several large cohorts and case series. Another reported risk factor for seizure aggravation was focal epilepsy, and in particular, focal cortical dysplasia (FCD). Interestingly, repetitive spiking on EEG, a prominent electrophysiologic characteristic of FCD, has also been linked to LISA **(29).**

H) Drug–drug interactions:

Combinations of ASMs are often used in patients not responding to a single medication. Antiepileptic medications may also be combined with drugs used to treat associated conditions. Pharmacodynamic interactions involving antiepileptic agents are not well characterized, but are important for a rational approach to combination therapy because neurotoxic effects appear to be more likely with coadministration of ASMs sharing the same primary mechanism of action. Levetiracetam has not been reported to cause, or be a target for, clinically relevant pharmacokinetic drug interactions **(30).**

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