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REVIEW

Levetiracetam Extended Release as Adjuvant Therapy for the Control of Partial-onset Seizures

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Abstract: Extended release (XR) formulation of levetiracetam (LEV) is approved by the Food and Drug Administration as an add-on to other antiepileptic drugs (AEDs) for adults with partial onset seizures. This is based on class-I evidence demonstrating significant seizure reduction in once daily dosing. Keppra-XR is marketed with the brand name of Keppra XR since 2008 (UCB Pharma). Its original immediate release (IR) formulation has been in the market since 2000. LEV has a unique molecular structure which is chemically unrelated to existing AEDs. The precise mechanism of action is unknown. Animal studies showed binding to synaptic vesicle protein SV2A, thought to be involved in modulating synaptic neurotransmitter release. LEV-IR is proven effective as adjunctive therapy for partial-onset seizures, primary generalized tonic-clonic seizures and myoclonic seizures. It was shown to be equivalent to carbamazepine as first-line treatment for partial-onset seizures. The extended release formulation added advantages such as better tolerance and increased compliance.

Keywords: levetiracetam, extended release, partial-onset seizures

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Introduction

Epilepsy is a chronic condition characterized by recurrent unprovoked epileptic seizures.[1] It affects 0.5%–1% of the population and at least 50% of patients with epilepsy have partial seizures. About 30%–70% of partial seizures are controllable with antiepileptic drugs (AEDs). The majority of these patients will need lifelong AED therapy. Strict AED compliance is often related to better tolerability and is a key factor in achieving better seizure control. An inverse relationship between the number of daily doses and compliance has been reported. Every increase in dosing frequency (from one to four doses per day) resulted in progressively worsening compliance and increased missed doses.[2–4] Conceptually, the stable plasma concentration profile of extended release AED formulations is expected to minimize peak concentration–related adverse events and improve compliance and seizure control.[5,6] Extended release formulations may contribute to better tolerability and improved efficacy.[6] Extended release levetiracetam (LEV-XR) was developed to provide patients with the convenience of once-daily dosing, potentially improving compliance and the efficacy–tolerability ratio. It is shown that the pharmacokinetic profile for LEV-XR is comparable to immediate release levetiracetam (LEV-IR).[6,7] While both LEV-XR and LEV-IR formulations may cause similar side effects that are generally well-tolerated, LEV-XR is usually preferred for its ease of use and more stable serum drug levels, both increasing patient compliance. The ease of conversion between LEV formulations also makes LEV-XR an attractive option.[8]

Mechanism of Action, Metabolism and Pharmacokinetic Profile

Mechanism of action

LEV-XR and LEV-IR have the same mechanism of action since the active molecule in these two formulations is the same. Despite much progress, the precise mechanism of action of LEV is still unknown. So far, the evidence supports a unique mechanism of action unlike any other known AED.[1,9,10] LEV does not have a known effect in common animal models of epilepsy, except in the chronic kindling models.[1,11,12] LEV doesn't act through the three classic routes of other AEDs being sodium channel modulation, low-voltage-activated (T-type) calcium channel modulation, or direct gamma-aminobutyric acid (GABA) facilitation.[8] It also does not share a high affinity to several known targets for existing AEDs including phenytoin, carbamazepine, sodium valproate, phenobarbital, dimethadione or benzodiazepines.[8,9] Lynch et al showed a saturable and stereoselective neuronal binding site for LEV in rat brain tissue. The experimental data indicated that this binding site is a synaptic vesicle protein SV2A, thought to be involved in the regulation of vesicle exocytosis and neurotransmitter release.[10] Although the molecular significance of LEV binding to synaptic vesicle protein SV2A is not completely understood, LEV and related analogs showed a rank order of affinity for SV2A which correlated with the potency of their anti-seizure activity in audiogenic seizure-prone mice.[10] Similar findings were noted in the mouse corneal kindling model and the GAERS rat model of generalized absence epilepsy.[1,13] SV2A protein was shown to have a size of about 90 kDa and to be ubiquitous throughout the central nervous system.[8,10] SV2A is thought to be involved in the physiologic functioning of the vesicle.[10] Crowder et al demonstrated seizures in SV2A knockout mice soon after birth which resulted in death of the mice at three weeks of age.[14] In vitro and in vivo recordings of epileptiform activity from the hippocampus have shown that LEV inhibits burst firing without affecting normal neuronal excitability, suggesting that LEV may selectively prevent hypersynchronization of epileptiform burst firing and propagation of seizure activity.[15]

Metabolism and pharmacokinetics

The package insert drug information for Keppra XR UCB Pharma, Inc, described LEV-XR as 500 mg and 750 mg (white) extended-release tablets for oral administration. The chemical name of LEV, a single enantiomer, is (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide, its molecular formula is C8H14N2O2 and its molecular weight is 170.21. LEV is a white to off-white crystalline powder with a faint odor and a bitter taste. It is very soluble in water (104.0 g/100 mL). LEV-XR tablets contain the labeled amount of LEV. Inactive ingredients include: colloidal anhydrous silica, hypromellose, magnesium stearate, polyethylene glycol 6000, polyvinyl alcohol-partially hydrolyzed, titanium dioxide and talc.

Bioavailability of LEV-XR tablets is similar to that of the LEV-IR tablets.[7] Its pharmacokinetics were shown to be dose proportional after single dose administration of 1000 mg, 2000 mg, and 3000 mgs.[7] LEV-XR is almost completely absorbed after oral administration. The pharmacokinetics of LEV-XR are linear and time-invariant, with low intra- and inter-subject variability.[7] LEV is not significantly protein-bound (<10% bound) and its volume of distribution is close to the volume of intracellular and extracellular water.[16,17] Sixty-six percent of the dose is renally excreted unchanged. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. The major metabolic pathway of LEV (24% of dose) is through an enzymatic hydrolysis of its acetamide group. Its metabolism is not through the cytochrome P450 system of liver.[6] The metabolites have no known pharmacological activity and are renally excreted.[6] Plasma half-life of LEV across studies is approximately 6–8 hours. This half-life is increased in the elderly (primarily due to impaired renal clearance) and in subjects with renal impairment.[18,19] LEV-XR peak plasma concentrations occur in about 4 hours. The time to peak plasma concentrations is about 3 hours longer with LEV-XR than with LEV-IR.[7] Compared to 500 mg LEV-IR tablet twice daily, single administration of two 500 mg LEV-XR tablets once daily produced comparable maximal plasma concentrations.[7] Cmax and Cmin were lower by 17% and 26% after multiple dose LEV-XR tablets intake in comparison to multiple dose LEV-IR tablets intake.[7] Intake of a high fat or high calorie breakfast before the administration of LEV-XR tablets resulted in a higher peak concentration, and longer median time to peak. The median time to peak (Tmax) was 2 hours longer in the fed state.[16,17] Single administrations of two 750 mg LEV-XR tablets and three 500 mg LEV-XR tablets were equivalent to each other.[7] In vitro data on metabolic interactions indicate that LEV is unlikely to produce, or be subject to, pharmacokinetic interactions.[16,17] LEV and its major metabolite, at concentrations well above Cmax levels achieved within the therapeutic dose range, are not inhibitors and do not exhibit high affinity to human liver cytochrome P450 isoforms, epoxide hydrolase or UDP-glucuronidation enzymes.[16,17] In addition, LEV does not affect the in vitro glucuronidation of valproic acid. LEV and its major metabolite are less than 10% bound to plasma proteins; rendering interactions with other drugs through competition for protein binding sites unlikely.[16,17] The potential for drug interactions for LEV-XR is expected to be similar to that with LEV-IR.

Clinical Studies

Pivotal studies for LEV-IR

Three major randomized placebo-controlled blinded clinical trials were conducted for LEV-IR efficacy in adults with refractory partial epilepsy. One of these trials was conducted in the US[20] and the remaining two studies were conducted in Europe.[21,22] LEV-IR was found to be efficacious in all three of these studies.[1] Three doses of 1000, 2000, and 3000 mg/day were studied and all were found to be efficacious.[1,20–22]

The US trial by Cereghino et al compared LEV-IR 1000 mg/day (500 mg bid) and 3000 mg/day (1500 mg bid) with placebo[20] in adult patients 16 to 70 years of age with drug resistant partial onset seizures (refractory to at least 2 AEDs). A total of 294 patients were randomized, of whom 268 completed the 14 weeks of treatment. After an initial 12-week single-blind baseline, LEV-IR was titrated over four weeks. Patients in the 1000 mg/day group first received 333 mg/day for 2 weeks then 666 mg/day for 2 weeks. Patients in the 3000 mg/day group received 1000 mg/day for 2 weeks and then 2000 mg/day for 2 weeks. The median percentage reduction in seizures over baseline was 32.5% for LEV-IR 1000 mg/day and 37.1% with LEV-IR 3000 mg/day, and 6.8% with placebo ($P < 0.001$). The median percent reduction in seizure frequency over placebo was 20.9% with LEV-IR 1000 mg/day ($P < 0.001$) and 27.7% with LEV-IR 3000 mg/day ($P < 0.001$). The responder rate was 33% with LEV-IR 1000 mg/day, 39.8% with LEV-IR 3000 mg/day, and 10.8% with placebo ($P < 0.001$). Eight patients in the LEV-IR 3000 mg/day group were seizure-free during the entire 14-week evaluation period compared to none in the placebo group ($P = 0.01$).

One of the European trials by Shorvon et al evaluated the efficacy and tolerability of LEV-IR 1000 mg/day (500 mg bid) and 2000 mg/day (1000 mg bid) and placebo as add-on therapy in adult patients with drug-resistant partial-onset seizures (refractory

to 1 to 2 AEDs).[21] The study consisted of an 8-week baseline period followed by 4-week titration period. The LEV-IR 1000 mg/day group received placebo for 2 weeks followed by 500 mg bid of LEV-IR. The LEV-IR 2000 mg/day group received 500 mg bid for 2 weeks followed by 1000 mg bid. The 4-week titration period was followed by a 12-week maintenance period. A total of 324 patients were randomized and 278 completed the study. There were 112 patients in the placebo group, 106 in the LEV-IR 1000 mg/day group, and 106 in the LEV-IR 2000 mg/day group. There was a 26.5% median seizure reduction from baseline for the LEV-IR 2000 mg/day group ($P < 0.001$), 17.7% median seizure reduction for the LEV-IR 1000 mg/day group ($P < 0.001$) and 10.4% median seizure reduction for the placebo group. Two percent of the LEV-IR 2000 mg/day group, 5% of the LEV-IR 1000 mg/day group and 1% of the placebo group were seizure free. The responder rate was 22.8% with LEV-IR 1000 mg/day ($P < 0.02$), 31.6% with LEV-IR 2000 mg/day ($P < 0.001$), and 10.4% with placebo.

Another European trial by Ben-Menachem and Falter, compared LEV-IR 3000 mg/day and placebo as add-on therapy in patients 16 to 70 years of age with drug-resistant partial-onset seizures.[22] The study consisted of 12-week baseline period followed by a 4-week titration and 14-week maintenance period for add-on part of the study. This was followed by a 12-week monotherapy phase after a 12-week taper period of additional AEDs. Patients initially received LEV-IR 1000 mg/day for 2 weeks, then 2000 mg/day for 2 weeks and then 3000 mg/day for the remainder of the trial. The monotherapy phase included patients who responded very well to LEV-IR and who received 3000 mg/day. A total of 286 patients were randomized, 181 to LEV-IR and 105 to placebo. Of this intention-to-treat population, 19.9% of patients in the LEV-IR group completed the study in comparison to 9.5% in the placebo group ($P = 0.029$). In reference to the add-on phase, the median percent reduction in seizure frequency from baseline was 39.9% with LEV-IR and 7.2% with placebo ($P < 0.001$). The responder rate was 42.1% with LEV-IR and 16.7% with placebo ($P < 0.001$). Fourteen patients in the LEV-IR group (8.2%) remained seizure-free during the add-on evaluation period and one in the placebo group ($P = 0.012$). Eighty-six patients out of 239 were continued into the monotherapy phase (69 patients on LEV-IR, and 17 patients on placebo). Out of the 69 LEV-IR treated patients, 49 were successfully tapered to monotherapy and 36 (19.9%) completed the study. Only 10 patients in the placebo group completed the study and 4 of them switched to LEV-IR but remained in the placebo group. In the LEV-IR group the median percent seizure reduction from baseline during the monotherapy phase was 73.8%, responder rate was 59.2% and 9 patients out of 49 became seizure free.

Other LEV-IR studies

Brodie et al compared LEV-IR to controlled-release carbamazepine (CBZ-CR) in adult patients with newly diagnosed epilepsy.[23] This was a large multicenter, double-blind trial which compared the efficacy and tolerability of these two AEDs. To enter the study, patients had to have two or more partial or generalized tonic-clonic seizures in the previous year. After randomization, patients were randomized to either LEV-IR 500 mg bid (n = 285) or CBZ-CR 200 mg bid (n = 291). The doses could be titrated up to 1500 mg bid for LEV-IR and 600 mg bid for CBZ-CR if patients had further seizures. At six months, 73% of LEV-IR and 72.8% of CBZ-CR patients were seizure free. At one year 56.6% of LEV-IR and 58.5% of CBZ-CR patients were seizure free. There was a trend towards higher withdrawal rates due to adverse events in the CBZ-CR group (19.2%) when compared to the LEV group (14.4%); however, this was not statistically significant. This study demonstrated that LEV-IR had similar efficacy as CBZ-CR but lower adverse effects. This trial formed the basis of granting LEV-IR an indication for monotherapy in newly diagnosed epilepsy patients in the European Union. LEV-IR does not have FDA approval for the same indication in the US.

LEV-IR received FDA approval as an add-on therapy for refractory partial-onset seizures in pediatric patients (4 to 16 years of age) based on a double-blind, placebo controlled, multicenter trial.[24] In this study, 216 patients were randomized and 198 patients provided sufficient data. The goal dose was 60 mg/kg/day in two divided doses. This dose was reached in three steps. The initial dose was 20 mg/kg/day for two weeks then 40 mg/kg/day for two weeks and then 60 mg/kg/day. The goal dose

could be reduced back to 40 mg/kg/day if poor tolerability occured. For the whole treatment period, the median seizure reduction was 43.3% in LEV-IR group and 16.3% in the placebo group. The 50% responder rate was 44.6% for the LEV-IR group and 19.6% for the placebo group. Seizure freedom was reported in 6.9% for the LEV-IR group and 1% of for the placebo group. Additional smaller studies have confirmed the efficacy and safety of add-on LEV in children with refractory partial-onset seizures.[8,25–28]

Berkovic et al compared LEV-IR to placebo in the treatment of idiopathic generalized epilepsies.[29] This was a randomized double blind study using LEV-IR as add-on therapy in patients aged 4 to 65 years (10% of patients were under 16 years of age). The inclusion criteria included having at least 3 generalized tonic-clonic seizures during an 8-week baseline period. These were patients with uncontrolled seizures taking at least one or two AEDs. The target dose for LEV-IR was 3000 mg/day or 60 mg/kg/day in patients younger than 16 years and weighing less than 50 kgs. The primary efficacy parameter was reduction in generalized tonic-clonic seizure frequency from baseline. A total of 164 patients were randomized, 80 patients to the LEV-IR group and 84 patients to the placebo group. Seventy patients from each group completed the study. The mean percentage reduction in weekly seizure frequency was 56.5% for LEV-IR and 28.2% for placebo ($P = 0.004$) and the median percentage seizure reduction was 77.6% for LEV-IR and 44.6% for placebo ($P < 0.001$). The 50% responder rate was 72.2% for LEV-IR and 45.2% for placebo ($P < 0.001$).

Noachtar et al conducted a recent randomized, double-blind, placebo-controlled, multicenter trial comparing LEV-IR as add on therapy (3000 mg/day) to placebo in 120 patients ≥12 years of age with myoclonic seizures associated with idiopathic generalized epilepsies.[30] There was a reduction of ≥50% in the number of days/week with myoclonic seizures in 58.3% of patients in the LEV-IR group and in 23.3% of patients in the placebo group ($P < 0.001$). Freedom from myoclonic seizures was seen in 25% of patients in the LEV-IR group and 5% of patients in the placebo group ($P = 0.004$). Freedom from all seizure types occurred in 21.7% of LEV-IR treated patients and in 1.7% of placebo treated patients ($P < 0.001$).

Intravenous LEV (LEV-IV) in status epilepticus

In a recent observational study by Aiguabella et al the efficacy of LEV-IV in status epilepticus was evaluated by retrospective review from multiple centers. Efficacy was defined as cessation of seizures within 24 hours subsequent to starting LEV-IV, with no need of any further AED. All patients were treated following the standard protocol (IV benzodiazepines plus IV phenytoin/fosphenytoin or IV valproate). LEV-IV was used as add-on therapy, except in those cases with contraindication for the standard protocol, when it was administered earlier. Forty patients were included, 57% men, with a mean age of 63 years. The most common type of status epilepticus was partial convulsive status epilepticus (90%). LEV-IV was effective in aborting seizures in more than half of the patients (57.5%), with a mean time of 14.4 hours. LEV-IV was used as add-on treatment in 26 patients (after IV benzodiazepines plus IV phenytoin/fosphenytoin, IV valproate or the combination) with an efficacy of 46.1%. In 14 patients (after IV benzodiazepines or nothing) the efficacy was 78.5% (P = 0.048). Adverse events were observed in 15% of patients.[31]

In another study by Ramantani et al the efficacy and safety of LEV-IV was evaluated in neonatal patients. This was a prospective feasibility study. LEV-IV was used as first-line treatment in 38 newborns with EEG-confirmed seizures, after ruling out hypoglycemia, hypocalcaemia, hypomagnesaemia and pyridoxin dependency. Initial intravenous doses of 10 mg/kg LEV-IV were gradually increased to 30 mg/kg over 3 days with a further titration to 45–60 mg/kg at the end of the week. Acute intervention with up to two IV doses of phenobarbital 20 mg/kg were tolerated during LEV-IV titration. LEV-IV was switched to LEV-IR (oral dosing) as soon as the infant condition allowed. Based on clinical observation, EEG tracings and laboratory data, drug safety and AED efficacy were assessed over 12 months. In 19 newborns, a single phenobarbital dose of 20 mg/kg was administered, while three newborns received two phenobarbital doses. Thirty infants were seizure free with LEV at the end of the first week and 27 remained seizure free at four weeks and EEGs markedly improved in 24 patients at 4 weeks. In 19 infants, LEV was discontinued after 2–4 weeks, while seven infants received LEV up to 3 months. No

severe adverse effects were observed. The conclusion was that LEV-IV was an effective and safe AED for status epilepticus, but its efficacy depended on the timing of its administration, being more effective when used early, and less effective as add-on treatment.[32]

Szaflarski et al compared LEV-IV to intravenous phenytoin (PHT-IV) for seizure prophylaxis after CNS injury in a prospective randomized single-blinded trial. A total of 52 patients were randomized (LEV-IV = 34; PHT-IV = 18), 89% of them with traumatic brain injury (TBI). Controlling for baseline severity, LEV patients experienced better long-term outcomes than those on PHT; the Disability Rating Scale score was lower at 3 months ($P = 0.042$) and the Glasgow Outcomes Scale score was higher at 6 months ($P = 0.039$). There were no differences between groups in seizure occurrence during continuous-EEG ($P = 1.0$) or at 6 months EEG follow-up ($P = 1.0$). There was also no differences in mortality ($P = 0.227$). There were no differences in side effects between groups (all $P > 0.15$) except for a lower frequency of worsened neurological status ($P = 0.024$), and gastrointestinal problems ($P = 0.043$) in LEV-IV treated patients.[33]

Pivotal trial for LEV-XR

This was a double-blind, randomized, placebo-controlled, multicenter, multinational trial of LEV-XR as adjunctive treatment of partial-onset seizures with or without secondary generalization in patients between 12 and 70 years of age.[34] The trial provided class-1 evidence that LEV-XR 1000 mg once daily dosing was effective and well tolerated as add-on therapy in patients with partial-onset seizures who were already on one to three AEDs. The trial started with an 8-week prospective baseline period and eligible patients were randomized to either LEV-XR 1,000 mg once daily (n = 79) or placebo (n = 79) for the 12 weeks. Of 188 patients screened, 158 were randomized (intention-to-treat population). Seventy-one (89.9%) patients on LEV-XR and 72 (91.1%) patients on placebo completed the trial. Median partial-onset seizure frequency/week reduction was 46.1% on LEV-XR and 33.4% on placebo. Estimated reduction with LEV-XR over placebo was 14.4% ($P = 0.038$). Thirty-four (43%) patients on LEV-XR and 23 (29.1%) patients on placebo experienced 50% reduction in partial-onset seizure-frequency/week. Eight (10.1%) patients receiving LEV-XR and one (1.3%) patient receiving placebo became seizure free during the 12-week treatment period. Forty-one (53.2%) LEV-XR patients and 43 (54.4%) placebo patients reported more than one adverse event. Somnolence, influenza, irritability, nasopharyngitis, dizziness, and nausea were the commonest adverse effects observed in the LEV-XR group.

Efficacy, safety and tolerability of LEV-XR in adults

In its pivotal study by Peltola et al, LEV-XR was generally well tolerated. Safety analyses were performed on all patients who received at least one dose trial of the medication. The evaluation was based on changes in laboratory values, physical and neurologic examination results, vital signs, ECGs, body weight, and assessment of treatment-emergent adverse events.[34] Overall, the incidence of adverse events did not significantly differ between the placebo and treatment groups. A treatment-emergent adverse event was defined as any untoward medical occurrence in a patient with an onset date on or after first study drug intake. Treatment-emergent adverse reactions that had a higher incidence with LEV-XR compared with placebo were somnolence, irritability, dizziness, nausea, influenza and nasopharyngitis. Headache was reported more frequently in the placebo arm. Five patients in the LEV-XR group discontinued due to adverse events such as mouth ulceration, skin rash, asthenia and seizures. Two patients in the placebo arm discontinued treatment due to adverse events. An adverse drug event was considered drug-related when the relationship to study drug was assessed by the investigator as possible, probable, or highly probable. There were no clinically relevant changes from baseline in vital signs, body weight, laboratory values, electrocardiograms or physical examination findings. Furthermore, in the original pivotal trials that led to LEV-IR FDA approval, treatment-emergent adverse reactions that were more often reported with LEV-IR than placebo were somnolence, asthenia, dizziness, headache, infection, rhinitis, and flu syndrome. Infections consisted mostly of common colds and upper respiratory infections that were not associated with low or elevated white blood cell counts.[8,34]

In a systematic review by French et al, the safety profile of LEV-IR among studies showed similar

pattern of adverse effects and included somnolence, asthenia, and dizziness that occurred most frequently during the first month of therapy. Changes in laboratory test values from placebo-controlled trials that were statistically significant remained in the normal range. Reports of the coding term "infection" (common cold, upper respiratory infection) were not preceded by low neutrophile counts that might suggest impaired immunological status. LEV-IR was well tolerated and safe for patients with cognitive and anxiety disorders. Overall incidence of adverse effects in the LEV groups was little higher than reported from the placebo groups.[18]

In a recent study by Kwan et al the safety and efficacy of LEV-IR was evaluated as adjunctive therapy for partial seizures in everyday clinical practice in Asian populations.[35] Patients aged ≥16 years (n=251) with inadequately controlled partial epilepsy were recruited from 29 centers across Asia. LEV-IR was added to existing AEDs for 16 weeks at a starting dose of 500 or 1000 mg/day and titrated to a maximum of 3000 mg/day according to clinical response. The study completion rate was 86.9%. Adverse events were reported by 73.3% of patients and were generally mild, leading to treatment withdrawal in only 7.2%. The most common adverse events were somnolence (30.3%) and dizziness (14.7%). Compared with pretreatment baseline, 44% of patients had a ≥50% reduction in seizure frequency, with a median reduction of 46.4%, and 17.7% became seizure free during the treatment period. The conclusion was that LEV-IR was well tolerated and efficacious as adjunctive therapy for partial epilepsy in clinical practice among Asian populations.[35]

Efficacy, safety and tolerability of LEV-XR in children

There is not enough data demonstrating efficacy, safety and tolerability of LEV-XR in pediatric populations. However conclusions can be driven from the data available for LEV-IR. The efficacy of LEV-IR as an adjunctive therapy or monotherapy for generalized and partial childhood epilepsies and for some types of specific epileptic syndromes of infancy and childhood (such as juvenile myoclonic epilepsy, benign rolandic epilepsy, and Jeavon syndrome) has been demonstrated in several studies.[36] The reported tolerability of LEV-IR and its safety profile were favorable. Among the side effects reported, behavioral changes and psychotic reactions seemed to occur more frequently in younger patients (under 4 years of age). The onset of signs/symptoms usually occurs early, during the titration phase, and in many cases at a low doses (<20 mg/kg/day). Adverse events were always reversible after discontinuation of LEV.[36]

Psychiatric symptoms and LEV-XR

The adverse events reported by ≥5% of patients in the pivotal trial for LEV-XR did not include psychiatric symptoms. However, behavioral adverse events were noted in open-label studies and post-marketing analyses of LEV-IR. The systematic review by French et al on safety and tolerability of LEV-IR reported the incidence of behavioral problems (agitation, antisocial reaction, anxiety, apathy, depersonalization, depression, euphoria, hostility, nervousness, neurosis, and personality disorder) in 13.5% of patients on LEV-IR compared to 6% in the placebo group.[18] Behavioral adverse events did not appear to be dose-related, and there was no correlation to seizure reduction. Further logistic regression analyses also revealed that patients with a previous pregnancy and lactation related psychiatric disorders were more likely to report behavioral adverse events.[18] In another study by Mula et al out of 517 patients on LEV-IR, 10.1% developed psychiatric adverse effects (3.5% aggressive behavior, 2.5% affective disorder, 2.3% emotional lability, 1.2% psychosis, and 0.6% other behavioral abnormalities). A significant association was found in patients with a history of status epilepticus, febrile convulsions, or previous psychiatric disorders. Concomitant use of lamotrigine appeared to have a protective effect.[37] Interestingly, the incidence of affective symptoms was significantly higher among patients taking LEV as an AED than those taking it for other off-label conditions such as anxiety. This raises the possibility that epilepsy itself predispose to higher behavioral adverse events.[8,38]

Tolerability in elderly

The efficacy and tolerability of LEV as add-on therapy for partial-onset seizures was evaluated in 78 patients ≥65 years of age.[39] Somnolence was the most common reported adverse event, occurring in 16.7% of patients, followed by dizziness in 9%. Discontinuation of treatment due to an adverse event

occurred in 19.2% of patients. Cramer et al compared treatment-emergent side effects in LEV trials of young and elderly patients with anxiety and cognitive disorders versus young patients with epilepsy. The results showed overall well tolerance of LEV-IR in both groups of patients. Elderly with anxiety disorders, headaches or tremors appeared to have poorer tolerability compared to the younger patients with similar problems.[40]

Lactation and pregnancy

Longo et al recently reported that the clearance of LEV increases during pregnancy, particularly during the third trimester, which subsequently leads to decreased serum LEV concentrations.[41] The increase in clearance is most likely due to an increase in renal blood flow. The teratogenic studies included a total of 147 patients. Of these patients, 2% experienced major congenital malformations (MCM) and 4.8% experienced a minor anomaly. All of the patients who had either an MCM or a minor anomaly were receiving AED polytherapy. It was unknown whether 10.9% of the 147 patients discussed were receiving LEV-IR monotherapy or AED polytherapy. None of the published literature assessed adherence to AED therapy. Folic acid supplementation was addressed in only one of the case series without clear evidence supporting its benefit in pregnant woman taking LEV-IR.[42] When LEV-IR or LEV-XR are used during pregnancy, women should receive adequate amounts of folic acid (0.4–5 mg/day) and serum concentrations of LEV should be determined before conception if possible and during each trimester, especially during the middle of the third trimester, to assess therapeutic concentrations.[41] The dose may need to be increased during the third trimester to provide concentrations consistent with those before conception. Patients should be informed that there appears to be a small chance of malformations with LEV, but that the data are limited.

Conclusions

LEV-XR is demonstrated to be safe and effective add-on treatment for partial onset seizures in adult patients. Although there are not many clinical trials evaluating LEV-XR in epilepsy, the extensive data available for LEV-IR can help us derive conclusions. More clinical studies may be required to elucidate all possible indications for LEV-XR use. Overall, LEV-XR has favorable pharmacokinetic properties, no significant drug—drug interactions and excellent safety and tolerability profile. Its once daily dosing provides further advantages. The straightforward conversion dose between LEV-IR and LEV-XR makes its use practical and easy. The simplified dosing regimen of LEV-XR enhances patient compliance. The steadier serum concentrations of LEV-XR reduce peak plasma concentrations resulting in lower adverse events.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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