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Original Article

Comparative Effectiveness of 100 mg/kg Levetiracetam Injection in Two Different Epilepsy Models: Temporal Lobe Epilepsy and Genetic Absence Epilepsy

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Abstract

Objective: Levetiracetam (LEV) is a broad-spectrum anti-seizure drug primarily prescribed for partial seizures. We aimed to compare the effects of LEV in two epilepsy models: the kindling model for temporal lobe epilepsy and the genetic absence epilepsy rats from Strasbourg (GAERS) model for absence epilepsy.

Methods: GAERS and Wistar rats underwent stereotaxic surgery for cortical recording electrodes implantation, while bipolar stimulation electrodes were implanted in the right basolateral amygdala of Wistar rats for kindling stimulations. For the kindling procedure, Wistar rats were stimulated at after discharge (AD) threshold twice daily. After three consecutive stage five seizures, the animals were considered kindled and randomly divided into two groups. Kindled animals received intraperitoneal injection of either saline or 100 mg/kg LEV 1 hour before stimulation. Seizure stage, amygdala AD, and total seizure duration were evaluated. GAERS rats were randomly divided into two groups, and spike-and-wave discharges (SWDs) were recorded for 2 hours after intraperitoneally injecting 100 mg/kg LEV or saline. Cumulative SWD duration, number of SWDs, and mean duration of an individual SWD were compared with the saline-treated control group.

Results: LEV significantly reduced the seizure severity and AD duration compared to controls. The mean seizure stage was 1.42±0.29 in the LEV group ($p<0.0001$) while all saline-treated kindled animals reached stage 5 seizure. LEV also lowered the total seizure duration (13.14±1.11 s) significantly compared to vehicle (86.76±12.59 s; $p<0.005$). In GAERS group, LEV suppressed the SWDs around 40 min after injection, and this anti-seizure effect lasted until the end of a 2-hour electroencephalography recording.

Conclusion: LEV, at a dose, 100 mg/kg, effectively reduced convulsive and non-convulsive seizures in two different epilepsy models. These results underscore the efficacy of LEV in mitigating seizure severity and duration across different epilepsy types, suggesting its potential as a promising therapeutic agent for managing both focal and absence seizures.

Keywords: Levetiracetam, temporal lobe epilepsy, absence epilepsy, kindling, genetic absence epilepsy rats from Strasbourg

INTRODUCTION

Levetiracetam (LEV), approved as a single agent in the early 2000s, is a widely used broad-spectrum second-generation anti-seizure drug (ASD) in the treatment of focal-onset seizures and focal to bilateral tonic-clonic seizures [previously known as partial seizures and partial seizures with secondary generalization, such as temporal lobe epilepsy (TLE)].[1] LEV is also prescribed for children with epilepsy characterized primarily by typical absence seizures. It is approved for adjunctive therapy for the treatment of myoclonic seizures in adults and juvenile myoclonic epilepsy in adolescents over the age of 12 years, and primary generalized tonic-clonic seizures in adults and children over five years old with idiopathic generalized epilepsy.[2-4] In a randomized, placebo-controlled trial of LEV in children and adolescents with newly diagnosed childhood or juvenile absence epilepsy, 23.7% of patients responded to LEV monotherapy.[5] In a short-term randomized, placebo-controlled study to determine whether LEV is efficacious in controlling typical absence seizures in patients with newly diagnosed childhood or juvenile absence epilepsy, LEV treatment caused an aggravation of childhood absence epilepsy patients and increased the daily number of absence seizures.[6] The progressive decrease of LEV dose was followed by a corresponding reduction in absence seizures in these patients.

The primary mechanism of action is through the interaction with the synaptic vesicle protein 2A (SV2A), which is involved in vesicle trafficking and exocytosis and appears to exert a role in epilepsy pathophysiology.[7,8] Additional mechanisms are thought to include the gamma-aminobutyric acid (GABA)-mediated GABAergic system, modulation of targets related to cellular calcium (Ca^{2+}), a key modulator of neuronal excitability and synaptic transmission, direct or indirect interaction with noradrenaline, adenosine, serotonin receptors, and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors, among others. The integration of these mechanisms into a single mechanism of action explains the antiepileptogenic, anti-inflammatory, neuroprotective, and antioxidant properties of LEV.[8]

Animal models are used to study epilepsy/seizures, the mechanisms underlying these conditions, and to develop ASDs. As an animal model of secondary generalized convulsive seizures, the amygdala kindling model is an established experimental model of human TLE. This is because the amygdala possesses the lowest threshold for the induction of kindling, in which daily electrical stimulation results in a gradual progression and intensification of limbic motor seizures.[9,10] Potent protection has been observed with LEV in genetic and chronic epilepsy animal models, such as the amygdala-kindling model of TLE.[11-13]

Genetic absence epilepsy rats from Strasbourg (GAERS) have emerged as an animal model highly reminiscent of a specific form of genetic/idiopathic generalized epilepsy.[14] Both its electrophysiological [spike-and-wave discharges, (SWDs)] and behavioral features fit well with those observed in humans with typical childhood absence epilepsy. The sensitivity to anti-seizure medications match the clinic, making this model one of the most predictive and validated.[15]

This study aimed to provide insights into the therapeutic potential of LEV across different types of seizures (focal seizures vs generalized absence seizures) in both TLE and absence epilepsy rat models. For this purpose, we aimed to compare the effect of a 100 mg/kg dose of LEV on seizure activity and severity in experimental rat models representing these two distinct epileptic conditions: electrical kindling for secondary generalized convulsive TLE and the GAERS model for non-convulsive absence epilepsy.

METHODS

Animals

Adult (3-4 months old) 250-350 g male GAERS and Wistar rats were used in the experiments. Animals were obtained from Acıbadem Mehmet Ali Aydınlar University, Laboratory Animal Application and Research Center, and the experiments were performed there. Animals were kept on a 12 h light-dark cycle, in 21-24 °C room temperature, and were provided with standard food and water ad libitum. After stereotaxic surgery, each animal was placed in a separate cage. All procedures performed on rats were approved by the Ethical Committee for Experimental Animals of Acıbadem University (approval no: 2024/43, date: 24.07.2024), in accordance with the European Parliament and Council Directive 2010/63/EU for animal experiments and ARRIVE guidelines. A detailed representation of the experimental plan can be seen in Figure 1.

MAIN POINTS

- Levetiracetam (LEV) demonstrates efficacy in both temporal lobe epilepsy (TLE) and absence epilepsy model, effectively targeting different seizure types focal seizures in TLE and generalized absence seizures.
- While synaptic vesicle protein 2A binding plays a central role in LEV's mechanism of action in both models, additional mechanisms may differentially contribute to its anti-seizure effects in TLE and absence epilepsy.
- LEV has the potential to be effective across various epilepsy types; however, optimal dosing and tailored therapeutic strategies may be required for different conditions.

Stereotaxic Surgery

Wistar rats (n=14) were anesthetized with isoflurane (2.5-3%, oxygen's flow rate was 0.8 L/min) inhalation anesthesia and placed in a stereotaxic instrument (Stoelting Model 51600, Stoelting Co. Illinois, USA), and the scalp was shaved, and the skull exposed. For the kindling procedure, a bipolar twisted 2 channel electrode (MS303/1-B; Plastics One, Roanoke, VA, USA) targeting the right basolateral amygdala (BLA) was implanted according to the coordinates obtained from the rat brain in stereotaxic coordinates atlas [anteroposterior (AP)=-2.6 mm; mediolateral (ML)=-4.8 mm; dorsoventral=-8.5 mm from bregma].[16] Stainless steel screws, used for extradural ground and recording electrodes, were placed bilaterally over the fronto-parietal cortices (for frontal cortex AP=2.0 mm, ML=±1.7 mm; for parietal cortex AP=-6.3 mm, ML=±4.0 mm). Electrodes were connected by insulated wires to a micro connector for electroencephalography (EEG) recordings. Dental acrylic was used to protect each implant on the skull.

GAERS (n=16) were anesthetized with isoflurane (2.5-3%, oxygen's flow rate was 0.8 L/min) inhalation anesthesia and placed in a stereotaxic instrument (Stoelting Model 51600, Stoelting Co. Illinois, USA); the scalp was shaved, and the skull was exposed. For cortical EEG recordings from somatosensorial cortex, four cortical recording electrodes were placed bilaterally over the fronto-parietal cortices (for frontal cortex AP=2.0 mm, ML=±1.7 mm; for parietal cortex AP=-6.3 mm, ML=±4.0 mm) and two ground electrodes were implanted. Electrodes were connected by insulated wires to a micro connector for EEG recordings. Then all the implants were fixed to the skull with dental acrylic. After the surgeries, 100 mg/kg paracetamol was administered by intramuscular injection.

The animals were allowed to recover from surgery for ≥7 days before the first day of the experiment. Post-operative care was given for 3 days after surgery. Paracetamol (100 mg/kg, intramuscular) was injected. Their nutrition was checked by daily weight monitoring, and a saline injection (100 mL/kg, subcutaneous) was given if necessary.

Amygdala Kindling and Levetiracetam Treatment

After a 1-week recovery period, the animals were placed in plexiglas cages, and a baseline EEG was recorded for 20 minutes from the right and left cortex. To determine the after discharge (AD) threshold, a 2 s, 80-Hz monophasic square-wave stimulus of 1 ms per pulse was used, and the BLA of rats was stimulated with the stimulus intensity beginning at 50 μA. This intensity was subsequently increased in 50 μA steps until a first AD was obtained using the A310 Stimulator and A365 Stimulus Isolator (World Precision Instruments, Florida, USA). The animals were

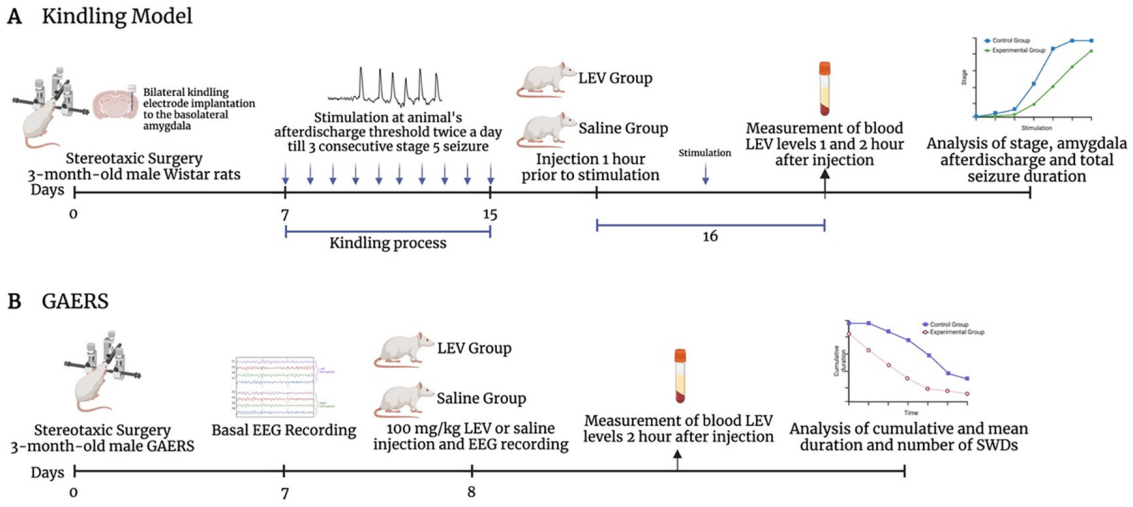

Figure 1. Experimental plan. **A.** levetiracetam's effect on kindling model and **B.** genetic absence epilepsy rats Strasbourg
LEV: Levetiracetam, GAERS: Genetic absence epilepsy rats Strasbourg, SWDs: Spike-and-wave discharges, EEG: Electroencephalography

then stimulated twice a day at the current AD threshold. Seizure stages observed after each stimulation were classified using Racine's scale: stage 1; facial movements; stage 2; rhythmic head movements, head nodding; stage 3; unilateral forelimb clonus; stage 4; bilateral forelimb clonus and rearing; and stage 5; falling and clonic convulsion. EEG was recorded before and after each stimulation. EEG was amplified, through a BioAmp ML 136 amplifier, with band pass filter settings at 1-40 Hz, recorded using Chart v.8.1 program (PowerLab8S ADInstruments, Oxfordshire, UK).

Once animals reached stage 5 seizures three consecutive times, they were considered "kindled". Subsequently, kindled animals were randomly divided into two groups. The following day, the LEV group received 100 mg/kg LEV via intraperitoneal (i.p.) injection and was stimulated one hour later. The control group received an equivalent volume of i.p. saline injection. Seizure stage, amygdala AD duration, motor seizure duration, and total seizure duration were then calculated for each group.

Genetic Absence Epilepsy Rats from Strasbourg and Levetiracetam Treatment

GAERS rats implanted with EEG electrodes were placed in a Plexiglas recording chamber and habituated for 20 minutes after the recovery period. Then, a 2-hour baseline EEG (from 9 a.m. to 11 a.m.) was recorded to confirm typical SWD occurrence after surgery. The next day after a 20-minute baseline EEG recording, GAERS rats were randomly divided into two groups and received either 100 mg/mL/kg LEV or an equivalent volume of i.p. saline injection. EEG was recorded for 120 min after i.p. injection. EEG was amplified through a BioAmp ML 136 amplifier, with band pass filter settings at 1-40 Hz, recorded using Chart v.8.1 program (PowerLab8S ADInstruments, Oxfordshire, UK).

Serum Concentrations of Levetiracetam

To monitor the serum levels of LEV in the blood, under light isoflurane anesthesia (% isoflurane), 1 mL of blood was collected from the jugular vein of amygdala-kindled Wistar rats at 1 and 2 hours after LEV injection, and from GAERS rats 2 hours after LEV injection. Serum was separated by centrifugation at 5000 rpm for 5 minutes, and sent to Acıbadem Labmed for measurement of LEV concentrations in blood. Blood LEV levels were measured with Shimadzu 8040 LC-MS/MS triple quadrupole mass spectrometer (Japan).

Statistical Analysis

For the TLE group, amygdala AD duration, total seizure duration and stages were calculated for each animal and analyzed with GraphPad Prism version 10.4.1 (Boston, Massachusetts, USA). For statistical analysis, two-way analysis of variance and uncorrected Fisher's LSD test were used.

In the GAERS group, only SWD complexes with a train of SWD (7-11 Hz) and an amplitude at least twice that of the background EEG were found at periods longer than 1 second and were assessed during both the baseline recording and the post-administration recording. The cumulative SWD duration, number of SWDs, and the mean duration of an individual SWD were analyzed with two-way ANOVA and post-hoc Benferroni's multiple comparisons test. Data were expressed as mean±standard error of the mean.

RESULTS

Amygdala Kindling

The mean number of stimulations needed for a rat to reach a stage 5 seizure was 12.6±1.1 stimulations; whereas the mean number of stimulations needed to reach the first stage 5 seizure was 10.4±1.2 stimulations. The mean amygdala AD duration on the last day of kindling for stage 5 was 76.4±8.3.

The Effect of Levetiracetam on Kindling Model

We tested the effects of LEV on the amygdala kindling model of TLE after animals experienced 3 consecutive stage 5 seizures and were considered to be kindled. The kindled animals were then randomly

divided into two groups. The next day, animals were treated with either saline (control group) or LEV (LEV group) one hour before receiving the next stimulation. All animals in the control group remained at stage 5; however, following the stimulation, seizure stage was significantly decreased to a non-convulsive stage (stage 1.42±0.29; p<0.0001) in LEV group (Figure 2A).

Amygdala AD duration (6.4±1.29 s; p<0.0001) and the total seizure duration (13.14±1.11 s; p<0.0001) in the LEV group were significantly decreased compared to the control group (amygdala AD duration: 62.37±8.92 s; total seizure duration: 86.76±12.59 s) and the last day of the kindling (amygdala AD duration: 75.84±8.48 s; p<0.05; total seizure duration: 89.01±7.02 s; p<0.0001) (Figure 2A and B). Supporting this, serum LEV concentrations were within the therapeutic range 140±10.6 µg/mL and 76.5±10.9 µg/mL in blood samples taken 1 hour and 2 hours post-injection, respectively (Figure 3).

The Effect of Levetiracetam on Spike-and-wave Discharges

In GAERS, LEV significantly reduced the cumulative duration of SWDs within the 40 min post injection period (115.8±40.8, p<0.001) compared to the saline-treated vehicle group (406.3±33.7). The number of SWDs was also significantly reduced after the LEV injection (12.8±3.5, p<0.05) compared to saline (30.8±2.4) (Figure 4A and B). There was a statistically significant difference in the mean duration of an individual SWD only during the 20-40 min post-injection period. This seizure suppression effect on the SWDs correlated with the serum LEV concentrations measured at 2 h (98.15±8.0 ug/mL) post injection within the therapeutic range.

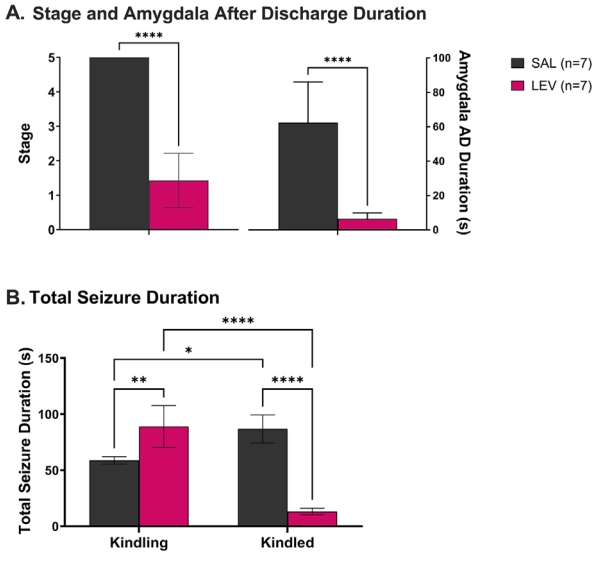

Figure 2. The effect of intraperitoneal 100 mg/kg LEV or saline injection in kindling model of convulsive seizures with secondary generalization on seizure stage and amygdala AD duration **(A)**, and total seizure duration **(B)**. Data expressed as mean±SEM
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, LEV: Levetiracetam, AD: After discharge, SEM: Standard error of the mean

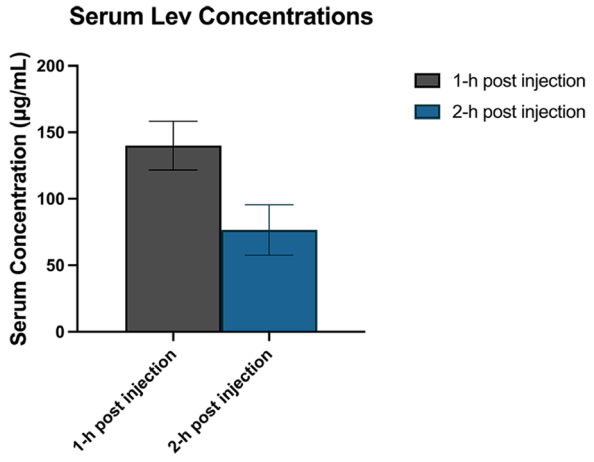

Figure 3. Serum levels of LEV 1 hour and 2 hours after intraperitoneal injection in kindling model. Data expressed as mean±SEM
LEV: Levetiracetam, SEM: Standard error of the mean

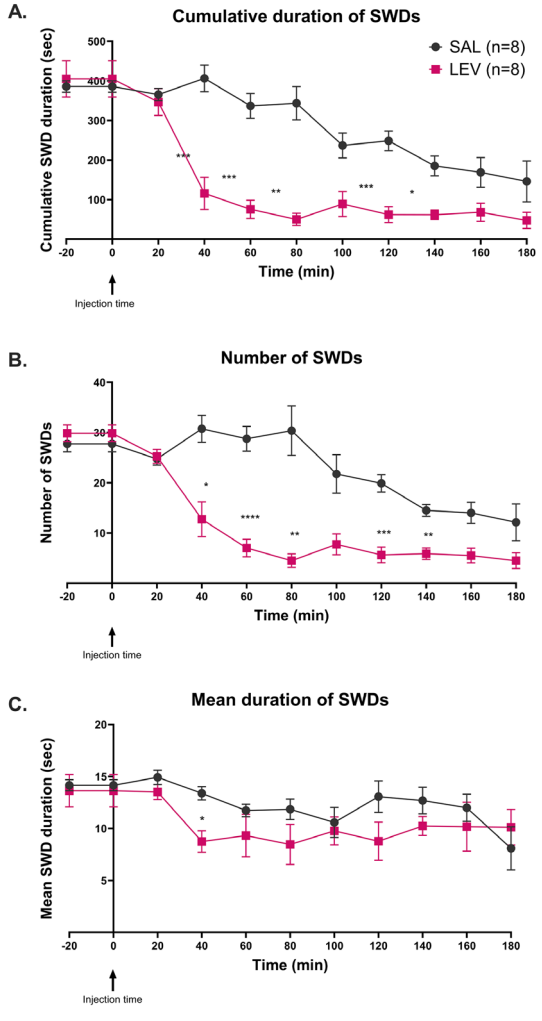

Figure 4. The effect of intraperitoneal 100 mg/kg LEV injection compared to saline injected control group on cumulative duration of SWDs **(A)**, number of SWDs **(B)**, mean duration of an individual SWDs **(C)**. Data expressed as mean±SEM
*p<0.05, **p<0.01, ***p<0.001, ****p<0.0001, LEV: Levetiracetam, SEM: Standard error of the mean, SWDs: Spike-and-wave discharges

DISCUSSION

The findings from our study highlight the significant anti-seizure effects of LEV in two distinct animal models of epilepsy, providing valuable insights into its therapeutic potential. In amygdala-kindled rats, LEV administration led to a marked reduction in seizure severity and seizure duration compared to saline-treated animals. Specifically, the mean seizure stage of the LEV group was significantly lower than that of saline-treated kindled rats. Moreover, LEV significantly decreased the total seizure duration, which contrasts sharply with the control group.

In the GAERS model, administration of LEV, resulted in a substantial suppression of SWDs beginning approximately 40 minutes post-injection, with this anti-seizure effect persisting throughout the 2-hour EEG recording period. These results underscore LEV's efficacy in mitigating seizure severity and duration across different epilepsy types, suggesting its potential as a promising therapeutic agent for managing both focal and absence seizures.

The efficacy and safety of LEV have been studied in different animal models for different epilepsy types, with the kindling model being one of the first. The amygdala-kindling model, first characterized by Goddard et al.[9] includes most, if not all, of these characteristics of human TLE.[17] LEV exerts potent anticonvulsant effects in fully kindled rats and it also has potent antiepileptogenic effects during kindling development.[12,13] In our study, we showed that a single injection of 100 mg/kg LEV reversed the effects of kindling stimulation. No motor seizures were observed in the experimental group, while all the animals in the control group had stage 5 seizures according to Racine's scale. Additionally, LEV injection caused a statistically significant decrease in amygdala AD duration and total seizure duration compared to the control group. These observations correlated with the high plasma LEV levels measured at 1 h, and 2 h post-injection.

We also showed the anti-absence properties of LEV in adult GAERS in accordance with the study of Gower et al.[18] This previous study has shown that an i.p. injection of LEV at doses ranging from 5.4 to 170 mg/kg markedly reduced SWDs from 15 to 30% in a non-dose-dependent manner. Furthermore, SWD suppression exceeded 95% in one or two rats per group, at doses of 5.4-96.0 mg/kg, in a 2-hour EEG recording. The effect of LEV in absence epilepsy was investigated in another animal model of absence epilepsy, Wistar-Albino-Glaxo from Rijswijk rats, by Bouwman et al.[19] where they showed that both 50 mg/kg and 100 mg/kg LEV decreased the mean and cumulative duration of SWDs. They also showed LEV decreased the peak frequency of SWDs, like the GABA transaminase inhibitor vigabatrin, suggesting the same anti-absence mechanism for LEV. In our study, suppression in terms of cumulative SWD duration and number of SWDs started to be observed in all animals around 40 minutes after LEV injection, and continued until the end of the 2-hour EEG recording. In parallel, the LEV concentrations remained high in blood samples taken two hours after injection.

The options for the treatment of absence epilepsy are limited; ethosuximide, lamotrigine, and valproic acid alone or in combination are the first choice. However, pharmaco-resistant seizures are observed in 20% of patients.[20,21] The main mechanism of action of ethosuximide is the blockade of transient, low-threshold Ca^{2+} currents produced by T-type Ca^{2+} channels in thalamic neurons. Lamotrigine is a voltage-dependent sodium (Na^{+}) channel blocker. Unlike other Na^{+} channel-blocking agents, it must have additional mechanisms that explain its efficacy in generalized epilepsies; however, these mechanisms are not yet characterized. Valproic acid is a broad-spectrum anti-seizure medication that has multiple mechanisms of action, including raising GABA levels in the brain, blocking voltage-sensitive Na^{+} channels, and activating Ca^{2+} dependent potassium (K^{+}) conductance, but the specific mechanism of preventing absence seizures is unknown. Valproic acid is as effective as lamotrigine and ethosuximide in controlling absence seizures, but its use is limited due to the side effects.[22] It has been reported that many anti-seizure medications, such as carbamazepine and phenytoin, can exacerbate absence seizures. The mechanism of seizure aggravation is uncertain, but it is known that these drugs act on Na^{+} channels. There is an urgent need for more effective and well-tolerated treatments to be developed for absence epilepsy to prevent or reverse the epilepsy-related comorbidities.

In a multicenter, prospective, long-term, open-label treatment study evaluating efficacy, tolerability, and safety of LEV in 21 patients with absence epilepsy, at the 6-month evaluation, 11 patients became seizure free and one showed 'decreased' seizures (more than 50% reduction in seizures).[23] At the 12-month evaluation, 10 patients were completely seizure free and two were seizure free with some anomalies in EEG. In contrast to these findings, there are studies showing seizure aggravation with LEV treatment in patients with absence epilepsy. The decrease in LEV dose caused a gradual decrease in seizure aggravation in these patients, and they recovered after stopping LEV treatment.[6] In another study, LEV treatment was only effective in 2 absence epilepsy patients out of 11; the treatment failed in 9 patients.[24]

Here, we are not only demonstrating the anticonvulsive effect of LEV in the amygdala kindling model of TLE but also the possible anti-absence properties of LEV in the animal model of absence epilepsy, GAERS.

Study Limitations

Female GAERS and Wistar rats were not included in this study to minimize response variability caused by hormonal and metabolic factors.

CONCLUSION

This is the first study to demonstrate the comparative effectiveness of LEV in two different types of epilepsy at the same time, TLE and absence epilepsy, to determine whether LEV is effective in both convulsive and non-convulsive types of seizures. This was tested using the amygdala kindling model of TLE and the GAERS model for absence epilepsy, simultaneously. In the light of these findings, it is evident that a single and efficacious dose of LEV not only reversed the effects of amygdala-kindling in fully kindled Wistar rats, but also exhibited anti-absence features in adult GAERS. At the dose of 100 mg/kg, LEV decreased both the time spent in seizure and the number of seizures in GAERS, during a 2-hour EEG recording compared to control.

Since the main mechanism of LEV is thought to be through its interaction with the SV2A, additional mechanisms through the GABAergic system and the modulation of Ca^{2+} channels, may

contribute differently to its anti-seizure effects in TLE and absence epilepsy. Further studies exploring the drug's mechanisms of action, optimal dosing regimens, long-term effects, and safety profiles in each epilepsy type are warranted to fully elucidate its clinical implications and optimize its therapeutic use in epilepsy management.

Ethics

Ethics Committee Approval: The study was approved by the Acıbadem Mehmet Ali Aydınlar University Ethical Committee for Experimental Animals (approval no: 2024/43, date: 24.07.2024).

Informed Consent: Animal experiment.

Footnotes

Authorship Contributions

Surgical and Medical Practices: E.T.E., Concept: F.O., N.Ç., Design: F.O., N.Ç., Data Collection or Processing: E.T.E., Analysis or Interpretation: E.T.E., F.O., N.Ç., Literature Search: E.T.E., F.O., N.Ç., Writing: E.T.E., F.O., N.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

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