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Original Article

Lacosamide Increases Absence Seizures and Anxiety-Like Behavior in WAG/Rij Rat Model

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Abstract

Objective: The aim of the present study was to evaluate the effects of antiepileptic drug lacosamide on spontaneous absence seizures and anxiety in genetic absence-epilepsy WAG/Rij rats.

Methods: Tripolar electrodes were placed in the cortex of WAG/Rij rats in each group using a stereotaxic instrument. Saline (4 mL/kg) was administered to the rats in the control group, while 5, 10, 25, and 50 mg/kg lacosamide was administered intraperitoneally to the rats in lacosamide groups. After lacosamide injections, electroencephalography recording was taken for 180 minutes. Then, the open field test was performed for 5 minutes.

Results: The total number and duration of spikes and wave discharges increased significantly in a dose-dependent manner after lacosamide injection in all lacosamide groups compared to the control group ($P < .001$). In addition, the seizure activity of rats in all groups began to increase 10 minutes after lacosamide injections ($P < 0.001$). Intermittent loss of clinical righting reflex was observed after absence seizures and convulsions also developed. Epileptic seizure activity with simultaneous sharp spikes was observed in the electroencephalography recording, and a dose-dependent seizure activity increase was observed ($P < .001$). All lacosamide groups had significantly lower values for the number of squares crossed, number of rearing, and duration of grooming in the open field test compared to the control group.

Conclusion: It was found in the present study that absence seizures in WAG/Rij rats increased in a dose-dependent manner after lacosamide treatment. Anxiety-like behaviors were also increased by lacosamide treatment.

Keywords: Absence epilepsy, anxiety, lacosamide, WAG/Rij rat

INTRODUCTION

Epilepsy is a common neurological condition characterized by a predisposition to form epileptic seizures and affects around 70 million people throughout the world.[1] Childhood epilepsy is associated with a high risk for adjustment reactions, attention-deficit hyperactivity disorder, concomitant anxiety, depression, and social difficulties.[2-4] Absence epilepsy is more common among children, and typical absence epilepsy was reported to account for approximately 10% of pediatric epilepsy seizures.[5] Absence epilepsy presents with seizures associated with a short consciousness loss which begins and ends suddenly accompanied by short (5-10 seconds) generalized bilateral spikes and wave discharges (SWDs) on electroencephalography (EEG).[6,7]

Lacosamide (LCM) was approved by the U.S. Food and Drug Administration in 2008 as an adjunct agent for the treatment of resistant focal-onset seizures in children and adolescents 17 years of age and older. Recently, LCM approval was expanded to include 4-year-old children and adolescents. In a recent study, LCM has been administered to patients whose ages ranged from a month to 18 years to determine the effective doses in status epilepticus.[8] Lacosamide was investigated in different experimental epilepsy models. It was shown to reduce seizures in the kainic acid-induced experimental epilepsy model,[9] in amygdala kindling epilepsy model,[10] and in focal epilepsy model.[11] However, the effectiveness of LCM in the absence epilepsy, which is most common type of childhood epilepsy, remains unclear.

Wistar Albino Glaxo/Rijswijk rat model (WAG/Rij), produced by inbreeding of Wistar albino rats, is a widely used genetic absence epilepsy model.[7,12,13] Clinical, electrophysiological, and pharmacological characteristics of this rat breed have similarities to human absence epilepsy.[14] WAG/Rij may have hundreds of daily SWDs. They have consistent absence seizure development.[7] Conventional antiepileptic drugs which effectively remedy absence seizures in humans may suppress SWDs in WAG/Rij rats.[12] Furthermore, WAG/Rij rats undergo behavioral changes related to anxiety and depression, which are commonly observed in patients with epilepsy.[15,16]

In the present study, the efficacy of LCM on absence epilepsy was investigated electrophysiologically, while its effect on anxiety was studied using open field test in genetic absence epilepsy model WAG/Rij rats.

EXPERIMENTAL PROCEDURES

Animals

In the present study, 6-month-old male WAG/Rij rats of 260-280 g were used. The rats were kept in cages under 55 ± 5% humidity, 23 ± 1 °C temperature, and 12/12 hours reversed dark/light cycle in which lights were on at 7.00 AM. The animals had free access to standard laboratory food and tap water during the experiment. The animal procedures were carried out in accordance with the European Union Directive 2010/63/EU. The local ethics committee of Tokat Gaziosmanpaşa University approved the study protocol (2019 HAYDEK-49/ Date: January 22, 2020).

Five groups of 7 rats each were established by random allocation of rats: control, (saline 2 mL/kg), LCM (5 mg/kg), LCM (10 mg/kg), LCM (25 mg/kg), and LCM (50 mg/kg) groups.

Animal Surgery

First, a ketamine (100 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.) combination was used to anesthetize WAG/Rij rats. The anesthesia status of the rats was clinically evaluated by pedal reflex. Then, tripolar electrodes were placed in the rats under anesthesia using a stereotaxic instrument. The skin and subcutaneous tissues were separated from the bone and folded back in rats, which were put in a stereotaxic instrument. Small holes were drilled in the skull with the help of a micro drill. Permanent bipolar electrodes of 0.22 mm diameter (Plastic One, Roanoke, USA) were placed in the cortex: one in the anterior region (AP = 2 mm; L = 3.5 mm) and the other in the parietal region (AP = 6 mm; L = 4 mm) based on the atlas coordinates described by Paxinos and Watson. The ground electrode was connected to the cerebellum. Two stainless steel screws and cold dental acrylic were used to fix the electrodes to the skull. During the surgery, the rectal temperature of the rats was kept at 37.5°C using a heating blanket with thermostatic control. After the operation, the animals were housed separately and kept for a 7-day recovery period.

Electroencephalogram Recording

After their recovery period, the rats were accustomed to the recording cage (50 × 50 × 40 cm) by attaching it to the recording wires for at least 2 days. Basal electroencephalogram (EEG) recording was obtained for 3 hours with EEG and a data evaluation and MP150 multichannel physiological analysis device (BioPac Systems Inc., California, USA). The EEG recording was performed at a bandwidth of 0.16-150 Hz. A basal recording was performed at a sampling rate of 1 kHz. After basal EEG recordings, 5, 10, 25, or 50 mg/kg LCM was injected (i.p.) and EEG recording was made for 3 hours. Electroencephalogram recording was realized between 9.00 and 12.00 AM hours only to prevent possible within-group circadian variations. In the EEG recordings of each rat, SWD number and its duration and amplitude were evaluated at 10-minute intervals (periods). For WAG/Rij rats, 180 minutes basal recording was averaged and this value was used as the control for each individual animal. The calculated value was taken as the initial value for that animal. Percent variations in electrophysiological recordings were calculated at 10-minute intervals using the control value. This calculation was conducted separately for each animal:

$$\frac{\text{The number and duration of SWDs after LCM administration}}{\text{Control value, 0th minute}} \times 100$$

Behavioral Tests

Open Field Test

The test was administered to WAG/Rij rats as explained previously.[13] In short, the open space was a square surrounded by a wall of 40 cm in height and divided into 64 squares (100 × 100). During the experiment, the rats were put in the middle of the field. The test was performed for 5 minutes and recorded with a video camera. The test apparatus was cleaned using 5% ethanol after open field test of the previous rat. In the evaluation of the open field test, the number of squares crossed representing movement activity, the number of rearing representing explorative activity, and the duration of grooming (seconds) were measured. In the open field test, the percentage calculation was made according to the control group.

Statistical Analyses

First, the Kolmogorov–Smirnov test was used to check the normal distribution of the data. Post hoc Tukey test was used to detect differences among the groups for the data with normal distribution (one-way analysis of variance (ANOVA) post hoc Tukey). For the analysis of non-normally distributed data, the differences among the groups were compared using the Kruskal–Wallis analysis of variance, and then, Mann–Whitney *U* test was employed for 2-way comparisons. Since the number and duration of SWDs were measured in the same animals, inter-group differences were analyzed using 2-way ANOVA and then post hoc Bonferroni test within time factor for treatments or 1-way ANOVA and followed by post hoc Tukey test. Statistical analyses were performed using GraphPad Prism 7.0 software (GraphPad Software Inc, California, USA). *P* values <.05 were considered significant.

RESULTS

First, basal EEG recording was taken for 180 minutes. Then, saline was administered (2 mL/kg, i.p.) and another recording for 180 minutes was carried out. Saline injection did not cause any change in absence seizure parameters. All LCM groups (5, 10, 25, or 50 mg/kg) had significantly higher count, duration, and percentage of SWDs compared to the control group ($P < .001$). In 5 mg/kg LCM group, the increase in SWD number and duration ended after 40 minutes and there was no significant difference compared to the control group ($P > .05$). However, in 10, 25, and 50 mg/kg LCM groups, the increase in SWD count and duration continued for 180 minutes ($P < .001$, Figure 1).

The total number and duration of SWDs during the 180-minute recording increased significantly in 5, 10, 25, or 50 mg/kg LCM groups ($P < .001$, Figure 2). No significant difference was observed between 5 and 10 mg/kg LCM groups for the total number and duration of

MAIN POINTS

- Lacosamide (LCM) administration at 5, 10, 25, and 50 mg/kg rates increased the absence seizures in WAG/Rij rats.
- It was observed that after LCM injections, convulsions accompanied the loss of clinical righting reflex, and simultaneous sharp spike waves were observed on the electroencephalography.
- In the open field test, the number of squares crossed, duration of grooming, and number of rearing activities of the rats decreased.
- This is the first study to evaluate the efficacy of LCM on both seizure activity and behavior in WAG/Rij rats.

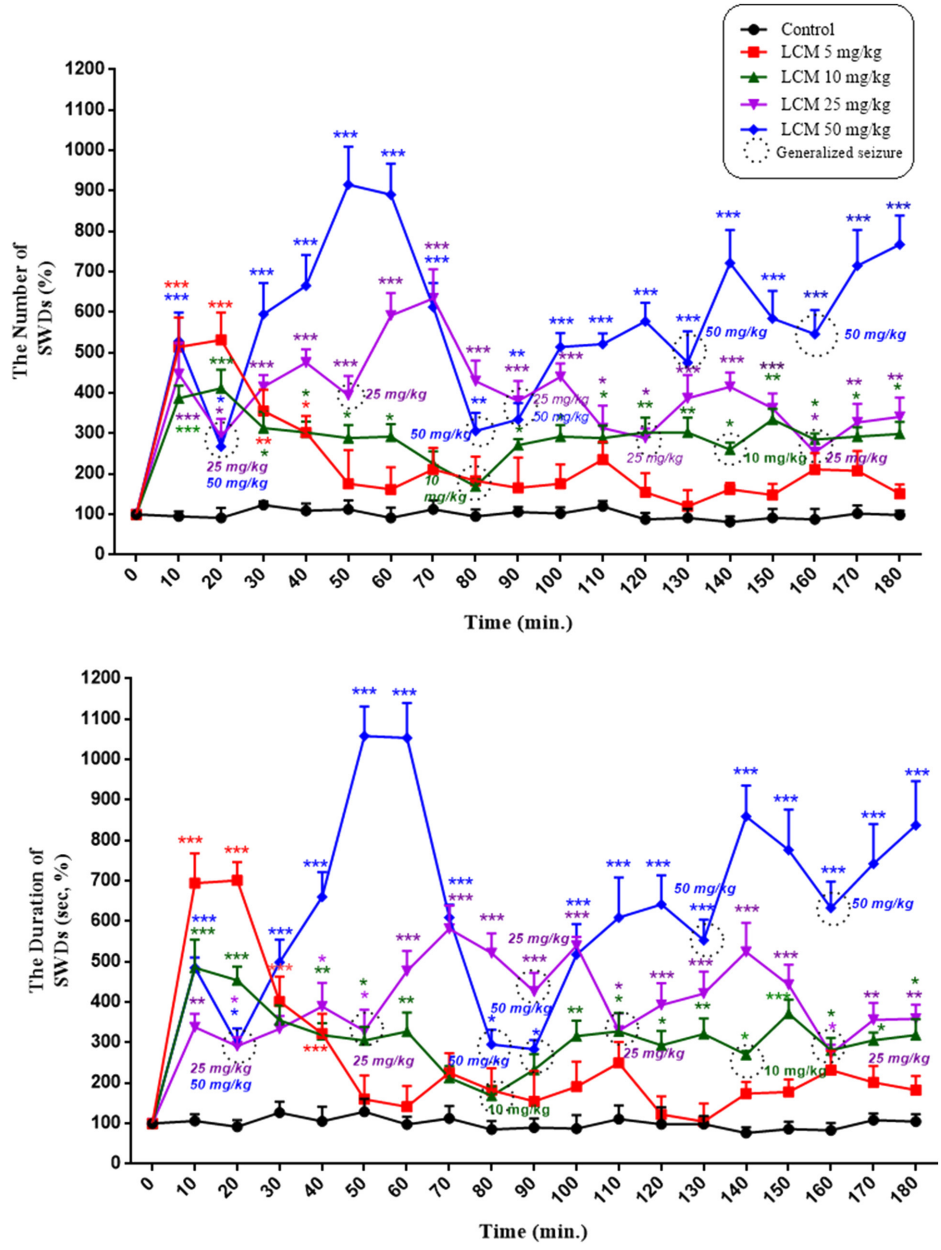

Figure 1. All lacosamide groups were compared with the control group (*$P < .05$; **$P < .01$, and ***$P < .001$). ◯ Shows the status.

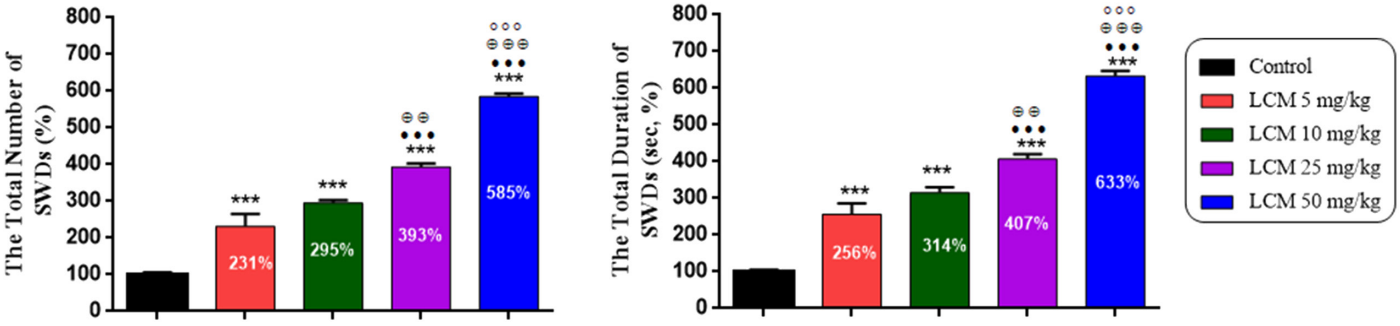

Figure 2. *$P < .05$; **$P < .01$; and ***$P < .001$; 5, 10, 25, and 50 LCM mg/kg group compared to the control group. ‴$P < .001$; 5 mg/kg lacosamide group compared to the 25 and 50 mg/kg LCM groups. ⊖⊖$P < .01$; ⊖⊖⊖$P < .001$; 10 mg/kg lacosamide group compared to the 25 and 50 mg/kg LCM group. °°°$P < .001$; 25 mg/kg lacosamide group compared to the 50 mg/kg LCM group.

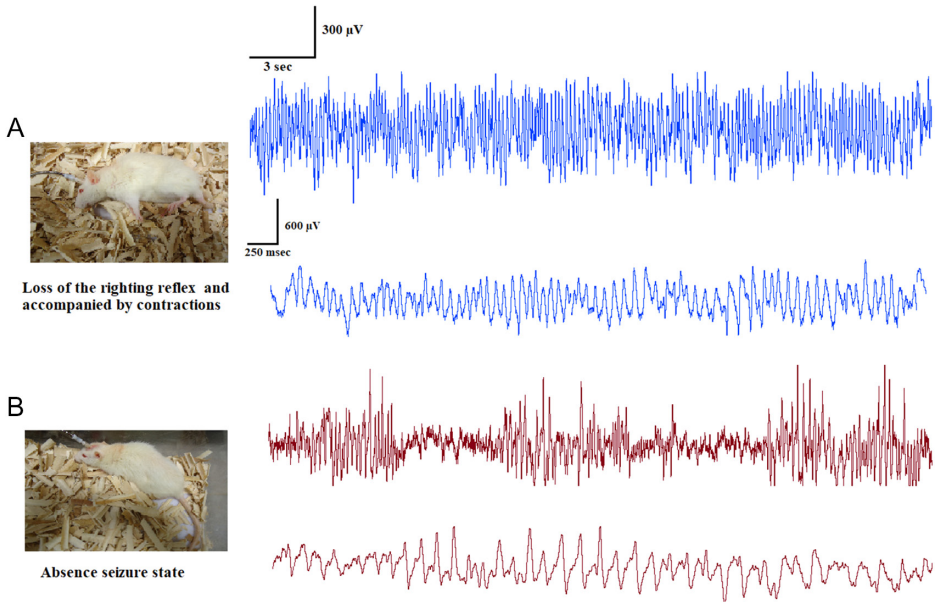

Figure 3. A representative clinical EEG recording image of WAG/Rij rats during seizure. (A) Epileptic seizure activity in which the righting reflex is lost and sharp spikes are observed after LCM injections on the EEG simultaneously with clinical seizure activity accompanied by convulsions. (B) The representative recording image during the absence seizure where rats remain dull.

SWDs ($P > .05$). However, both the number and the duration of SWDs increased significantly in 25 and 50 mg/kg LCM groups compared to 5 and 10 mg/kg LCM groups ($P < .001$ and .01, respectively). In addition, total number and duration of SWDs in LCM 50 mg/kg group were significantly higher than in those of 25 mg/kg LCM group ($P < .001$, Figure 2).

It was found that after LCM administration, clinical righting reflex was intermittently lost, convulsions accompanied, and epileptic seizure activity accompanied by sharp spike activity was observed in EEG recording of WAG/Rij rats. The frequency of this epileptic seizure activity increased in a dose-dependent manner (LCM 10 mg/kg [130 minutes]; LCM 10 mg/kg [80 and 140 minutes]; LCM 25 mg/kg [20; 50, 90, 120, and 160 minutes]; LCM 50 mg/kg [20, 80, 90, 130, and 160 minutes]). This was shown by a circle in the graph and illustrated in Figures 3 and 4. Scoring of righting reflex loss and occurrence of sharp spikes were evaluated and no difference was observed in 5 mg/kg LCM group compared to the control group ($P > .05$), while in the 10, 25, and 50 mg/kg LCM groups, there were significant

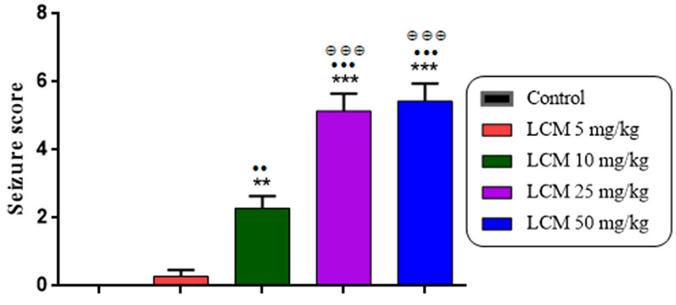

Figure 4. $^{**}P < .01$ and $^{***}P < .001$; 5, 10, 25, and 50 mg/kg LCM groups compared to the control group. $^{\bullet\bullet\bullet}P < .001$; 5 mg/kg lacosamide group compared to the 25 and 50 mg/kg LCM groups. $^{\ominus\ominus\ominus}P < .001$; 10 mg/kg lacosamide group compared to the 25 and 50 mg/kg LCM groups.

increases in these scores compared to the control and 5 mg/kg LCM groups ($P < .001$ and .01, respectively). In addition, the increase was significant in 25 and 50 mg/kg groups compared to 10 mg/kg group ($P < .001$). The difference between the 25 and 50 mg/kg groups, however, was not significant ($P > .05$).

Open Field Test

Rats in 5, 10, 25, and 50 mg/kg LCM groups crossed significantly fewer squares and had fewer rearing and shorter duration of grooming compared to control group ($P < .001$). On the other hand, differences between 5 and 10 mg LCM groups were not significant for any open-field test parameters. The number of squares crossed was significantly lower in 25 and 50 mg/kg LCM groups compared to 5 mg/kg LCM group ($P < .01$), while the differences between these groups for the duration of grooming ($P > .05$) or number of rearings were not significant ($P > .05$, Figure 5).

DISCUSSION

Lacosamide administration at 5, 10, 25, and 50 mg/kg rates resulted in increased absence seizures in WAG/Rij rats. In addition, it was observed that after LCM injections, convulsions accompanied the loss of clinical righting reflex, and simultaneous sharp spike waves were observed on the EEG. In the open field test, the rats crossed fewer squares and had fewer rearings and shorter duration of grooming. This is the first study to evaluate the efficacy of LCM on both seizure activity and behavior in WAG/Rij rats.

Lacosamide was tested in various animal models of chemo-convulsant-induced seizures. In the kainic acid-induced limbic status epilepticus model, LCM was found to elevate the level of brain-derived neurotrophic factor (BDNF) in the cortex and to decrease seizure activity.[9] In temporal lobe animal epilepsy models, LCM administration was shown to delay the occurrence of kindling-induced epileptic seizures and to raise the seizure threshold.[10,17,18] In the 6 Hz psychomotor seizure model, a model for treatment-resistant seizures, LCM was shown to

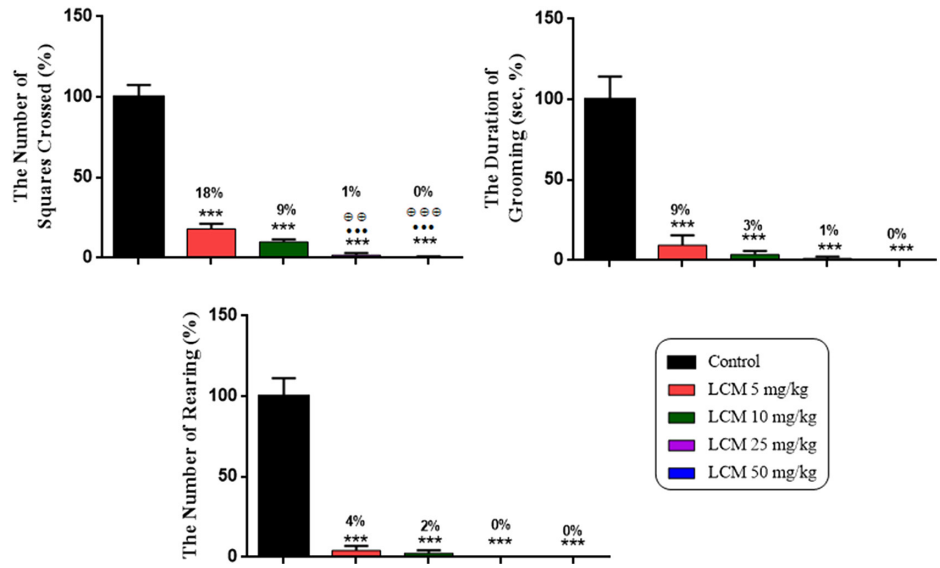

Figure 5. *$P < .05$; **$P < .01$; and ***$P < .001$; 5, 10, 25, and 50 mg/kg lacosamide compared to control. ¨$P < .01$; ¨¨$P < .001$; 5 mg/kg lacosamide compared to 25 and 50 mg/kg LCM. ⊕⊕$P < .01$; ⊕⊕⊕$P < .001$; 10 mg/kg lacosamide compared to the 25 and 50 mg/kg LCM.

suppress seizure activity.[19] In a recent study conducted by our team on a focal epilepsy model, LCM treatment was found to suppress epileptiform activity.[11] A literature evaluation revealed that LCM significantly reduced seizure activity in convulsive type experimental epilepsy models. Unlike convulsive-type epileptic seizures, the effect of LCM on genetic absence seizures has not been well-studied. Only a few clinical case reports and an experimental study are available regarding the effect of LCM on absence-type epileptic seizures. One of the case reports dealt with a patient who had generalized genetic epilepsy which was considered to be status epilepticus with recurrent absence-type seizures during video EEG monitoring.[20] The patient was treated with LCM after failures of first- and second-line treatments with antiepileptic drugs. Absence status epilepticus was reported to end within 30 minutes of intravenous administration of 400 mg of LCM. However, in another case report, increased absence seizures were reported after LCM administration in 7 patients.[21] Lacosamide therapy was added to the treatment plan of a patient with juvenile myoclonic epilepsy who previously had absence and resistant generalized tonic-clonic seizures. It was observed that after 8 months of follow-up, SWDs appeared on EEG, which disappeared after discontinuation of LCM treatment.[22] Thus, based on clinical findings, therapeutic effect of LCM in patients with absence epilepsy remains unclear.

Sodium channel blockers such as carbamazepine, oxcarbazepine, and phenytoin were shown to augment absence seizures in epilepsy patients and in absence epilepsy experimental models.[23-28] WAG/Rij rats represent the well-known absence epilepsy models. In particular, Russo et al[24] observed dose-dependent SWD increases after carbamazepine administration in WAG/Rij rats. In the present study, a dose-dependent increase was observed in absence seizures after LCM injection in WAG/Rij rats. In addition, generalized seizure activity accompanied by simultaneous sharp wave discharges and convulsions with intermittent loss of clinical righting reflex between absence seizures were observed on EEG.

Recently, a study on another genetic absence epilepsy model, GAERS rats, evaluated the efficacy of LCM and showed that LCM administration exhibited an anti-epileptogenic potential with a 50% decrease in spontaneous absence seizures. Interestingly, acute systemic administration of 10 mg/kg LCM was shown to increase the formation of SWDs within 80 minutes after injection, but 30 mg/kg dose had no effect on SWD number.[29] In the present study, on the other hand, acute LCM administration increased the absence seizures starting from the first 10 minutes. At 5 mg/kg LCM dose, increase of seizures ended after the 40th minute, while at 10, 25, and 50 mg/kg LCM doses, the absence seizure increases continued through the 180th minute.

Neuronal excitability depends on voltage-gated sodium channel (VGSC) activity.[30,31] There are at least 2 different classes of kinetic inactivation, that is, fast and slow. Actions of anti-epileptic drugs are closely associated with the inactivation of sodium channels. While other VGSC-blocking anti-epileptic drugs (carbamazepine [CBZ], phenytoin, lamotrigine, oxcarbazepine) act on rapidly inactivating VGSC channels, LCM acts by increasing the slow inactivation of VGSC.[32,33] In the present study, LCM administration increased seizure activity within 10 minutes. This different mechanism of LCM on VGSCs may be responsible for its rapid action.

The most common psychiatric disorders associated with epilepsy are depression and anxiety. Open field test is extensively used to evaluate anxiety-like behavior in rodent models. In the present study, the number of squares crossed and duration of grooming and rearing decreased after treatment with LCM. Decreased locomotor activity indicates elevated anxiety-like behavior.[15,34] Lower rearing activity, on the other hand, may show behaviors suggestive of anxiety and depressive disorder, such as a decrease in motivation to seek novelty and loss of interest in new situations. Decreased grooming responses, on the other hand, mimic loss of interest and lack of pleasure, a typical key symptom of depression.[35-39]

Studies with WAG/Rij rats showed an upward trend in anxiety and depression-like situations parallel to increased seizures.[40] Sarkisova et al[40] found that ethosuximide administration had a preventive effect on absence seizures and alleviated depressive status. In another study,

aripiprazole was reported to not only reduce absence-like seizures but also inhibit depression- and anxiety-like behaviors.[41] Increased absence seizures may have led to increased anxiety-like behaviors in the open field test in the present study. Besides, in the present study, loss of righting reflex was observed in WAG/Rij rats along with epileptic seizures in the anterior and posterior extremities accompanied by convulsion. It was observed that the rats could not move after the seizure and it was thought that the inactivity and fatigue after the seizures may have resulted in decreases in the open field test behavior parameters.

CONCLUSION

Acute LCM administration increased absence seizure activity in a dose-dependent manner and decreased open field test parameter values. In addition, the seizure-promoting effect was observed within 10 minutes of LCM administration. The effect of LCM on absence epilepsy needs to be explained by further studies.

Ethics Committee Approval: Ethical committee approval was received from the Local Ethics Committee of Tokat Gaziosmanpaşa University (Date: January 22, 2020, Decision No: 2019 HAYDEK-49).

Informed Consent: Written informed consent was obtained from all participants who participated in this study.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – H.A.; Design – O.S., H.A., R.K.; Supervision – H.A.,O.S.; Funding – O.S., R.K.; Materials – O.S.; Data Collection and/or Processing – O.S., R.K.; Analysis and/or Interpretation – O.S., H.A., R.K.; Literature Review – O.S.; Writing –O.S.; Critical Review – H.A., R.K..

Declaration of Interests: The authors declare that they have no conflict of interest.

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