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Evaluation of isolated and combined effects of riluzole and sodium valproate in genetic absence epilepsy rats

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ABSTRACT

Objective: In epilepsy treatment, drugs that increase GABAergic and decrease glutamatergic activity, like sodium valproate, are used. Riluzole is a neuroprotective drug that blocks glutamatergic neurotransmission and is a potential drug with its anti-seizure effects. This study evaluates the anti-seizure effects of sodium valproate and riluzole on the genetic absence epilepsy rat from Strasbourg (GAERS) model individually and combined.

Materials and Methods: Adult male GAERS rats (n = 22) were used. Rats were administered 5/10 mg/kg riluzole, 150/300 mg/kg sodium valproate, 95% ethanol, and 5 mg/kg riluzole combinations with 150-300 mg/kg sodium valproate intraperitoneally. EEG recordings and locomotor activity tests were conducted. Statistical analysis was performed using GraphPad Prism.

Results: Post-injection of 10 mg/kg riluzole significantly decreased the number of spike-wave-discharges (SWDs) ($p = 0.04$) compared to the control group. A synergistic effect was observed with 5 mg/kg riluzole and 150 mg/kg sodium valproate, reducing total seizure time ($p = 0.03$) and SWDs ($p = 0.03$).

Conclusion: The study demonstrated the anti-seizure effects of 150/300 mg/kg sodium valproate, 10 mg/kg riluzole, and ethanol. A synergistic effect of 5 mg/kg riluzole with 150 mg/kg sodium valproate was noted. As an isolated or combined solution, riluzole shows potential, especially in resistant epilepsy treatment.

Keywords: GAERS, Riluzole, Sodium valproate, Absence epilepsy, Anti-seizure, Ethanol

1. INTRODUCTION

Epilepsy is characterized by spontaneous paroxysmal neuronal electrical discharges [1-3]. In order to diagnose the symptoms as epilepsy, the patients should have at least two unprovoked seizures with intervals lasting more than 24 hours [4]. Different epilepsy subtypes are categorized under three headlines: seizure type, epilepsy type, and syndromes [2].

If the seizure is generalized, non-motor, and characterized by blank staring, it is called an absence seizure. The pathophysiology of absence epilepsy is not yet fully explained [4]. However, cortico-thalamo-cortical structures are considered essential in the absence of epilepsy.

In the absence epilepsy, alterations seen in genes that encode T-type calcium channels and gamma aminobutyric acid (GABA) receptors play a role in etiopathogenesis [4]. Medications that work by suppressing T-type calcium channels, such as ethosuximide and valproate, are effective anti-absence drugs. $GABA_A$ agonist drugs suppress absence seizures by increasing the GABAergic activity of the thalamic nucleus reticularis.

Genetic absence epilepsy rat from Strasbourg (GAERS) is a model to study human absence epilepsy generated from Wistar rats in Strasbourg [5]. In this specific strain, nearly 30% of animals have been observed to have spike-wave-discharges (SWD)s on the cortical electroencephalogram (EEG), some behavioral changes, and a blank stare [5]. SWDs are associated with sudden cessation of activity, and activity continues after the seizure ends [6, 7].

Riluzole is a neuroprotective drug that inhibits glutamatergic neurotransmission, blocking sodium channels and N-methyl

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D-aspartate (NMDA) receptors and enhancing glutamate reuptake [8, 9-13].

Riluzole is known to potentiate the activity of $GABA_A$ receptors, which are the primary mediators of inhibitory neurotransmission in the brain [14]. It has shown anti-seizure properties in various animal models [8, 10, 15, 16]. Sodium valproate, a long-used anti-seizure drug, enhances GABAergic activity and inhibits NMDA receptors.

Uncontrolled epilepsy requires appropriate therapy with the first two monotherapeutical drugs; this is called drug-resistant epilepsy, and 1/3 of patients are drug-resistant [1, 2, 8, 17]. Dealing with epilepsy is much more complicated due to its dynamic nature, with patients differing from manageable to resistant and misdiagnosing [2].

According to all available literature data, riluzole has the potential to be used in anti-seizure therapy. Especially drug-resistant epilepsy patients who need further evaluation and novel pharmacologic modalities might benefit from alternative chemicals such as riluzole.

This study investigates the anti-seizure activity of riluzole compared to valproate and examines their combined effects to provide insight into potential new treatments for epilepsy.

2. MATERIALS and METHODS

Animals

Male adult GAERS rats weighing 200–300 g (8–12 weeks old) were used for all experiments. The animals were obtained from the Experimental Animals Research and Implementation Center, Marmara University, Istanbul, Turkey. Animal experiments were approved by the Animal Experiments Local Ethics Committee of Marmara University [Permit Number: 63.2022mar, Date: 06.12.2022]. The rats were housed in cages until the experiments in groups of four rats under standard laboratory conditions (20±2˚C, natural 12-h light/dark cycle) with food and water available ad libitum. The rats were divided into four groups; each group consisted of 4 animals (Table I).

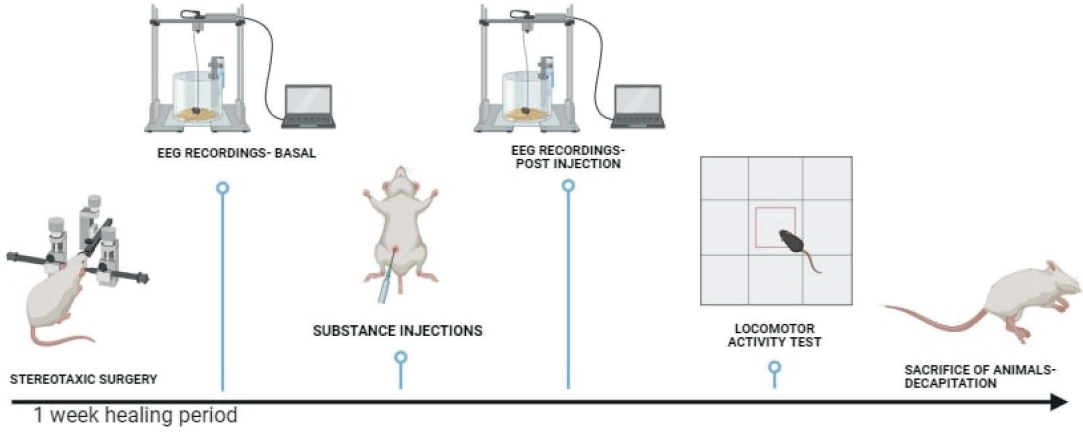

Figure 1. *Timeline of the experiments*

Table I. *Experimental groups and procedures applied to groups*

Group	Number (n)	Procedure
Group 1	4	Stereotaxic surgery + Ethanol (Control Group)
Group 2	4	Stereotaxic surgery + Riluzole 5 mg/kg (RLZ5)
Group 3	4	Stereotaxic surgery + Riluzole 10 mg/kg (RLZ10)
Group 4	4	Stereotaxic surgery + Valproate 150 mg/kg (VPA150)
Group 5	4	Stereotaxic surgery + Valproate 300 mg/kg (VPA300)
Group 6	4	Stereotaxic surgery + Riluzole 5 mg/kg + Valproate 150 mg/kg (COMB1)
Group 7	4	Stereotaxic surgery + Riluzole 5 mg/kg + Valproate 300 mg/kg (COMB2)

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Drugs

Riluzole [2-Amino-6-(trifluoromethoxy) benzothiazole (PHR2499)] was obtained from Sigma-Aldrich® and Depakin was used as sodium valproate. Riluzole (5 mg/ml, 10 mg/ml) (39, 40, 24) and sodium valproate (150 mg/ml, 300 mg/ml) (49, 51) were dissolved in 95% ethanol. Solutions were prepared before EEG recordings and kept in a standard refrigerator at 4˚C, protected from light with aluminum foil. Drugs were injected intraperitoneally at a volume of 1 ml/kg of body weight.

Stereotaxic surgery

The animals were anesthetized with ketamine (100 mg/kg, *ip*) and xylazine (10 mg/kg, *ip*) and placed in a stereotaxic instrument (Stoelting Model 51600, Wood Dale; USA). Recording electrodes were implanted into the frontal cortex (AP: + 2.0 mm and ML: 3.5 mm) and occipital cortex (AP: – 6.00 mm and ML: 4 mm) relative to the bregma. The electrodes were connected to a microconnector for epidural EEG recordings and fixed to the skull with dental acrylic.

EEG Recordings

The animals were individually placed in a plexiglass cage, and the microconnectors were connected by cables to the EEG recordings system (PowerLab 8S, ADI Instruments, England). EEG signals were recorded in a computing environment using Labchart v7 (ADInstruments, Oxford, United Kingdom). The recordings were analyzed using "LabChart for Windows." In the experiments, for each animal, bilateral frontoparietal EEG was recorded for the first 1-hour pre-injection as a basal recording, followed by a 2-hour post-injection recording. SWDs were examined in EEG recordings. In EEG recordings, absence epileptic seizures were evaluated with regard to the cumulative duration of SWDs, the number of SWDs, and the onset time of the first SWD. In the course of analysis, EEG recordings were divided into three sessions: the basal period (0–60 min), the first-hour post-injection (60–120 min), and the second-hour post-injection (120–180 min), and data were evaluated between these sessions.

Locomotor Activity Test

Locomotor activity tests were performed in all animal groups to assess the effects of isolated or combined riluzole and sodium valproate treatment on behavioral changes in animals. For each rat, behavioral experiments were performed, first before the drug injection as a basal and then 1-hour post-injection. In order to assess behavioral changes during tests, 5 mg/kg of riluzole and 150 mg/kg of sodium valproate, a combination of those, and ethanol (control) were administered.

An open-field test evaluated spontaneous locomotor activity as described previously [18]. The test was performed in a transparent plexiglass cage (40 x 40 x 40 cm), and locomotor activity was measured for 15 minutes using a computerized system (Locomotor Activity Cage ACT 508, Commat, Turkey). The total distance traveled is assumed to be the number of positions changes the sensors track.

Statistical Analysis

All EEG recordings and behavioral experiment data were analyzed using GraphPad Prism software version 9.1.2 (GraphPad Software, San Diego, CA, USA). The cumulative duration of SWDs, the number of SWDs, and the onset time of the first SWDs were used in the analysis.

One-way ANOVA and Friedman tests evaluate the cumulative duration and total number of seizures. T-test and Wilcoxon test were used to compare seizure onsets of experimental groups with their basal recordings, and the Mann-Whitney U test and unpaired t-test were used to compare seizure onsets of experimental groups with each other.

All data was presented as mean ± standard error of the mean (SEM) with a 95% confidence interval. A value of $p < 0.05$ was regarded as statistically significant.

3. RESULTS

Examinations based on cumulative duration and the number of SWDs

Comparisons of basal recordings with first and second hours of post-injection in the groups that were injected 5 mg/kg (RLZ5) and 10 mg/kg riluzole (RLZ10), 150 mg/kg (VPA150) and 300 mg/kg sodium valproate (VPA300), 5 mg/kg riluzole+150 mg/kg sodium valproate (COMB1) and 5 mg/kg riluzole+300 mg/kg sodium valproate (COMB2) combined and ethanol (CONT) showed that there was a significant reduction in the cumulative duration in the 1st hour of post-injection in RLZ5 group (p=0.03), 1st and 2nd hours of post-injection in RLZ10 group (p=0.03), in VPA150 group (p=0.02, p=0.04; respectively), in VPA300 group (p=0.001, p=0.003; respectively), in COMB2 group (p=0.003) and CONT group (p=0.001, p=0.005; respectively), 1st hour of post-injection in COMB1 group (p=0.03). It was found that a reduction in cumulative duration in the 1st hour of post-injection was not sustained in the 2nd hour in the RLZ5 and COMB1 groups (p = 0.15) (Figure 1A–1B).

Comparison of VPA150 with COMB1 to see the synergistic effect of the riluzole on sodium valproate showed that the reduction in both cumulative duration (p = 0.03) and the number of SWDs (p = 0.03) was higher in the combined group (Figure 2A-2B).

Analyses of VPA150 and RLZ5 post-injection seizure activities showed that VPA150 significantly reduced cumulative duration (p = 0.03) compared to RLZ5. On the other hand, VPA300 provided a significant reduction in both cumulative duration (p = 0.03) and the number of SWDs (p = 0.008) compared to RLZ5 (Figure 2A-2B).

When post-injection periods of the RLZ5 and RLZ10 groups were compared, it was found that the RLZ10 group showed a more significant decrease both in cumulative duration (p<0.001) and the number of SWDs (p = 0.01) (Figure 2A–2B).

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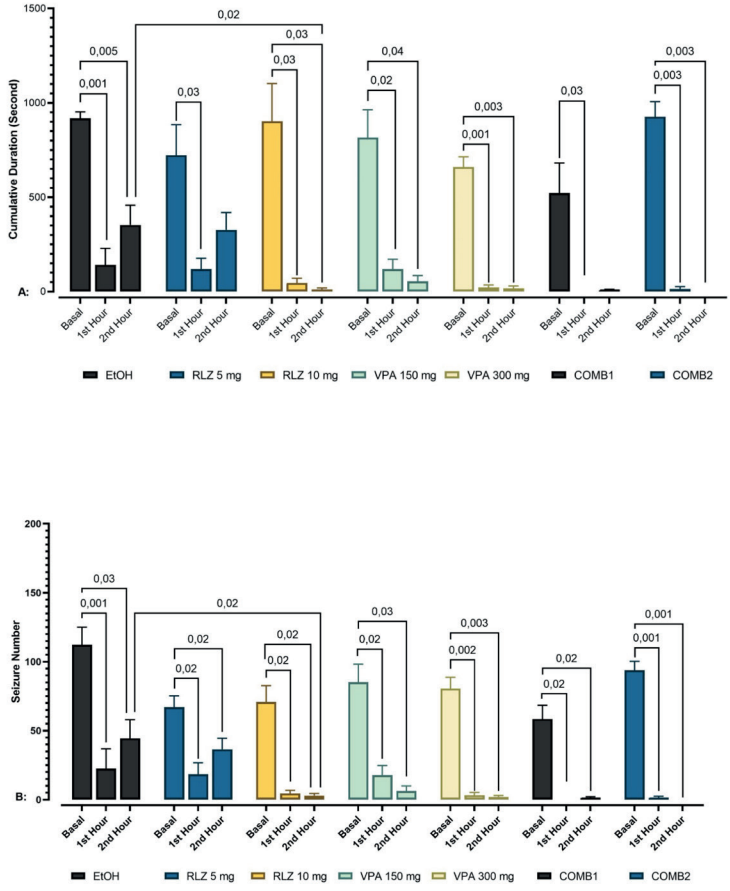

Figure 2. *A) The differences between groups of basal recordings and 1st and 2nd hours after injections on the cumulative duration of spike-wave-discharges (SWDs), B) The differences between groups of basal recordings and 1st and 2nd hours after injections on the number of SWDs, C) The differences between groups of 2 hours post-injection periods on the cumulative duration of SWDs, D) The differences between groups of 2 hours post-injection periods on the number of SWDs*

A significant decrease in cumulative duration and the number of SWDs in the post-injection periods was seen in the VPA300 (p = 0.02, p = 0.02; respectively), COMB1 (p = 0.02, p = 0.02; respectively), and COMB2 (p = 0.02, p = 0.02; respectively) groups compared to the CONT group (Figure 2A-2B).

Effect on seizure onset

When the RLZ10 (p = 0.001) and COMB1 (p = 0.006) groups were examined in terms of delaying the onset of the first seizure after the injection regarding basal recordings, it was observed that they significantly delayed the onset of the seizure. In post-injection comparisons with the control group, it was found that the COMB1 group significantly delayed the onset of seizures (p = 0.01). The first SWD seen in the CONT group was 2070 seconds after the injection; it was seen 758 seconds after the injection in RLZ5 group, 118,5 seconds after the injection in RLZ10 group, 1124,5 seconds after the injection in VPA150 group, 3245,5 seconds after the injection in VPA300 group, 6132 seconds after the injection in COMB1 group and 4353,2 seconds after the injection in COMB2 group (Figure 3).

Locomotor Activity Test

Stereotypical movement

Comparisons of stereotypical activity between the groups were conducted via locomotor activity tests using basal recordings. CONT and VPA150 groups showed a statistically significant decrease in stereotypical movement post-injection (p<0.001, p=0.03, respectively) (Figure 4A).

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Vertical movement

Comparisons of vertical movement between the groups were carried out via locomotor activity tests using their basal recordings. CONT and COMB groups showed a statistically significant decrease in vertical movement post-injection ($p = 0.03$, $p = 0.01$, respectively) (Figure 4B).

The percentage of resting time

Comparisons of the percentage of resting time between the groups were carried out via locomotor activity tests using their basal recordings. CONT and VPA150 groups showed a statistically significant decrease in activity after post-injection ($p = 0.005$, $p = 0.02$, respectively) (Figure 4C).

Total distance traveled

Comparisons of total distance traveled between the groups were conducted via locomotor activity tests using basal recordings. CONT, COMB, and VPA150 groups significantly decreased total movement after post-injection ($p = 0.01$, $p = 0.01$, $p = 0.04$, respectively) (Figure 4D).

The results of the locomotor activity test indicated that VPA150, a combined injection of VPA150+ RLZ5, and ethanol demonstrated a statistically significant sedative effect in most of the parameters. The isolated 5 mg/kg RLZ injection did not cause a statistically significant sedative effect.

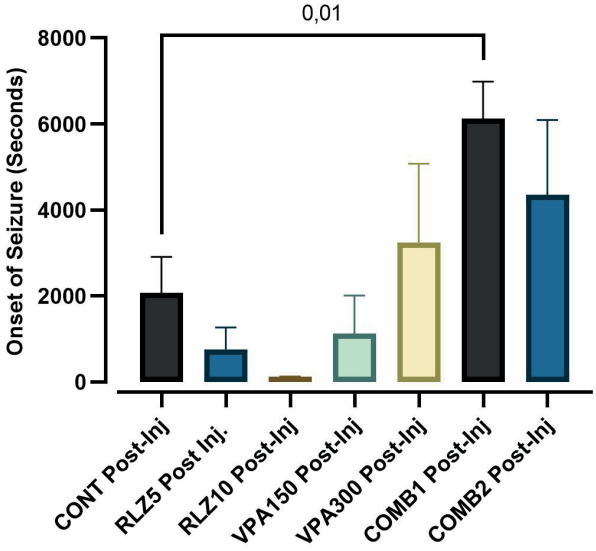

Figure 3. *The differences between groups of post-injection-period on the onset of SWDs*

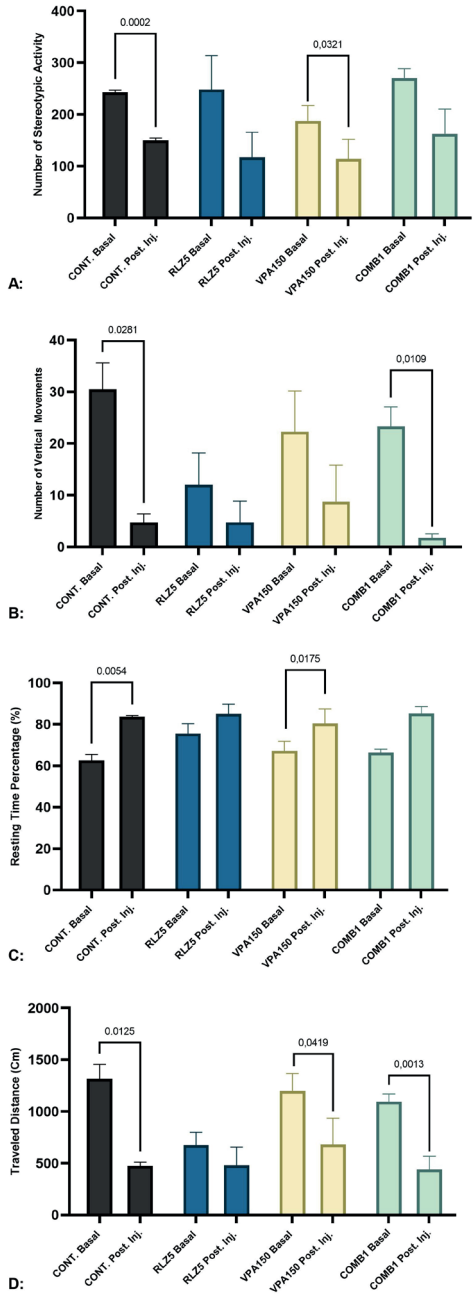

Figure 4. *A) Comparisons of Basal and Post-Injection Recordings in Stereotypic Activity, B) Comparisons of Basal and Post-Injection Recordings in Vertical Activity, C) Comparisons of Basal and Post-Injection Recordings in Resting Time, D) Comparisons of Basal and Post-Injection Recordings in Traveled Distance*

4. DISCUSSION

The existing literature demonstrates that riluzole reduces neuronal activity and possesses anti-seizure properties [8, 10, 19,

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20-22] despite the variations in doses, solvents, animal models, methodologies, and treatment protocols used by researchers. This study corroborates the literature regarding riluzole's anti-seizure properties, focusing on its effects within the GAERS model, a well-established model for human absence epilepsy.

Riluzole's effectiveness diminishes in the second-hour post-injection, consistent with its fast-acting properties [21]. Notably, at a 10 mg/kg dosage, riluzole shows significant reductions in both SWDs and cumulative seizure duration. In contrast, a 5 mg/kg dosage primarily reduces the number of SWDs rather than the total duration of seizures. This finding is important because reducing the number of SWDs may result in fewer interruptions in daily activities, suggesting that riluzole could be particularly useful in clinical settings where minimizing the frequency of seizure events is critical.

The observed efficacy of riluzole at different dosages aligns with previous findings that indicate its potential as a GABAergic augmentative drug. He et al., found that riluzole potentiates the effect of GABA at lower concentrations and directly activates $GABA_A$ receptor channels at higher concentrations [14]. This dual mechanism of action may explain the varied effects observed at different dosages in this study. Moreover, riluzole's ability to act quickly makes it a potential candidate for acute seizure management, provided more comprehensive studies support this application.

Both 150 mg/kg and 300 mg/kg valproate significantly reduced SWDs and cumulative seizure duration post-injection, with the higher dosage showing more pronounced effects. The influence of ethanol, used as a solvent in this study, must be considered. Ethanol has known sedative and anti-seizure properties, which may have contributed to the observed effects [23, 24]. This potential confounding factor underscores the need for future studies to explore alternative solvents to isolate the effects of riuzole and better.

The combination of riluzole and valproate demonstrated a synergistic effect, particularly in reducing total seizure time and the number of SWDs. The low-dose combination of 5 mg/kg riluzole with 150 mg/kg valproate was notably effective without significant side effects, unlike the high-dose combination, which caused considerable sedation and other adverse effects. This finding suggests that combining lower doses of riuzole and valproate could maximize therapeutic benefits while minimizing side effects, making it a promising approach for treating drug-resistant epilepsy.

Behavioral experiments indicated that while riluzole has an anti-seizure effect, it also possesses sedative properties. This dual effect may be advantageous in some clinical scenarios but detrimental in others, mainly where sedation is undesirable. The observed sedative effects align with previous reports in the literature, further supporting the need for careful dosage management. Future studies should evaluate optimal dosages and combinations, considering the influence of solvents like ethanol and the necessity for larger sample sizes to achieve more definitive conclusions.

The study supports the potential of riluzole in anti-seizure therapy, especially for drug-resistant epilepsy, emphasizing its combination with valproate for enhanced efficacy. However, more populated studies with larger sample sizes and varied experimental conditions are necessary to verify these findings. These future studies should consider different dosages, proper inert solvents, and more extended observation periods to understand the clinical applicability of riluzole better.

The observed side effects, such as increased respiratory rate, rotation in the EEG cage, unresponsiveness to stimuli, and excessive sedation in the high-dose combination regimen, highlight the importance of dosage optimization. The appropriate dose identified in this study, 150 mg/kg valproate combined with 5 mg/kg riluzole, offers a balance between efficacy and tolerability, suggesting a potential new therapeutic strategy for epilepsy management.

Furthermore, the behavioral experiments conducted on animals did not reveal any significant results corresponding to the observational outcomes regarding the study's aims. While, riluzole demonstrated an anti-seizure effect, its sedative properties and the influence of ethanol complicate the interpretation of these findings. It is essential to conduct further studies with alternative solvents and larger animal populations to clarify these effects and establish a more accurate understanding of riuzole's clinical potential.

Combining riluzole with other anti-seizure agents, as Borowicz et al., suggested, may enhance therapeutic outcomes [25]. This study examined the combined use of riluzole and valproate, and the anti-seizure effect observed at the combined dose of 150 mg/kg valproate and 5 mg/kg riluzole contributes to the literature. However, the study by Jadhav et al., found that different combinations of riluzole and valproate effectively reduced seizure activity [26]. Therefore, the optimal drug regimen for clinical use may vary, and further research is needed to determine the most effective and safe combinations.

In conclusion, this study suggests that riluzole, particularly when combined with valproate, holds promise as an anti-seizure agent for managing epilepsy, including drug-resistant forms. The findings underscore the need for more extensive research to validate these results and explore the full therapeutic potential of riluzole in various epilepsy models. By addressing the limitations of the current study, such as solvent effects and small sample sizes, future research can provide more robust data to inform clinical practices and improve patient outcomes in epilepsy treatment.

Limitations

The solubility of riluzole and valproate required using 95% ethanol as a solvent, which may have sedative effects that influenced the results. Additionally, the small sample size of four rats per group limits the generalizability of the findings. More extensive studies with larger populations and more extended observation periods are necessary to confirm these results and suggest appropriate clinical dosages.

In this study, only 2 hours of post-injection periods were observed. No further information about long-term drug effects was obtained. Future studies should include longer observation durations and serum drug concentration measurements to provide a more comprehensive understanding of the optimal dosing for clinical applications.

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Compliance with Ethical Standards

Ethical approval: Animal experiments were approved by the Animal Experiments Local Ethics Committee of Marmara University (Approval number: 63.2022mar, date: 06.12.2022).

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