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RESEARCH ARTICLE

Is escitalopram safe to use as an antidepressant in epilepsy patients?

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ABSTRACT

Objective: Epilepsy is a devastating neurological disorder with several cognitive or psychiatric comorbidities, including anxiety, autism spectrum disorder, and depressive disorder. It is known that long-term drug treatment in epileptic patients increases the incidence of depression. Thus, patients with epilepsy who later developed depressive symptoms usually require to use of antidepressant medication throughout their epilepsy treatment. However, selective serotonin reuptake inhibitors (SSRIs) derived from antidepressant drugs could have bidirectional effects on seizure activity. This experimental study was designed to determine the impact on the epileptiform activity of escitalopram in a penicillin-induced seizure model.

Method: Administration of penicillin (500 IU, 2.5 µL, intracortical) into the somatomotor cortex of Wistar albino male rats triggered epileptiform activity. Electrocorticography of seizure activity was recorded for 180 min. Escitalopram, at doses of 5, 10, and 20 mg/kg, was administered 30 min after the penicillin injection.

Results: While escitalopram, at doses of 5 and 10 mg/kg, increased the mean spike frequency for 180 min compared with the penicillin group, the 20 mg/kg dose caused a marked increase in the mean spike frequency and amplitude of seizure activity.

Conclusion: The electrophysiological data propose that escitalopram, used for treating depression, has proconvulsant effects in penicillin-induced seizure activity. Therefore, other SSRIs, especially escitalopram, must be used with great care. The mechanism of action needs to be clarified in further detailed studies.

Keywords: ECoG recording, escitalopram, penicillin-induced epilepsy model, seizure, SSRI

INTRODUCTION

Epilepsy is the most common nervous system disease, affecting approximately 70 million people worldwide (1). Epilepsy is closely related to several psychiatric or cognitive comorbidities, such as depressive disorder, anxiety, and autism spectrum disorders (ASD) (2). In most epileptic patients, seizures can be successfully controlled by antiseizure medications (ASMs) or surgery, and seizures are pharmaco-resistant in at least 30%–40% of patients (3). Therefore, developing effectual ASMs behaves a thorough comprehension of the mechanisms that cause seizures.

Evidence from clinical and experimental studies indicates the link between epilepsy and depression (4,5). In a clinical study, depressive symptoms and suicidal ideation were higher in people with epilepsy (4). Also, this study revealed that suicidal ideation was higher in focal epilepsy than in generalized genetic epilepsy. The prevalence of depression in epileptic patients is thought to be approximately 15%–50%, and depression risk is almost twofold as high in

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epilepsy patients (6). Epilepsy is related to limited employment opportunities and mobility, lower income, and social marginalization. Many epilepsy patients suffer from reduced quality of life. Depending on these factors and the ASMs treatment, the risk of depression increases in epilepsy patients. Therefore, patients with epilepsy who later developed depressive symptoms usually require to use of antidepressant medication throughout their epilepsy treatment (7).

However, epilepsy and depressive disorder are pathophysiological resembling in some cases and might be affected by altered neurotransmitter release (8). For instance, ASMs that increase gamma-aminobutyric acid (GABA) levels, such as benzodiazepines and barbiturates, are particularly closely related to depression (2). On the other hand, while antidepressants, including various selective serotonin reuptake inhibitors (SSRIs), are successful in treating depression, they are also directly related to an increased risk of seizures (9). A previous study demonstrated that an SSRI, fluoxetine, increased seizure activity in the kindling model (10). Also, another study revealed that high doses of fluoxetine increased the epileptic bursts in the penicillin-induced seizure model (11). In addition to the proconvulsant properties of SSRIs, studies show that drugs such as sertraline and vortioxetine are anticonvulsants against seizures (12,13).

Major SSRIs, including fluoxetine, citalopram, escitalopram, paroxetine, sertraline, and fluvoxamine, have a similar mechanism on serotonin reuptake. Nevertheless, each SSRI has unrivaled pharmacodynamics, pharmacokinetics, and adverse effect profile. One of them, escitalopram (escitalopram oxalate; Cipralex®, Lexapro®), is an SSRI that selectively binds to the serotonin transporter. It prevents serotonin reuptake and enhances serotonin's level in synaptic clefts, ending in antidepressant action (14). In addition to the antidepressant effects of SSRIs, it is known that drugs increasing synaptic serotonin levels have beneficial effects on epileptic seizures (15). SSRIs are mostly reported to increase the seizure threshold and have protective effects against seizures (16). However, widely used SSRIs such as fluoxetine and trazodone are also known to trigger seizures in various experimental epilepsy models (11,17).

Experimental rodent models are very valuable in understanding the mechanism and drug development studies. The epileptiform activity could be induced through various techniques. Various epilepsy and seizure models are created using proconvulsant agents, one of these techniques, in rodents. The experimental penicillin-induced seizure model is a widely used focal model for inducing seizure activity (18). When penicillin is administered to the cerebral cortex of rodents, seizure activity begins locally and then turns generalized.

Considering the possible side effects of antidepressants, determining which antidepressant is safe for epilepsy patients is crucial. As mentioned above, experimental and clinical studies have revealed that antidepressants, especially in epilepsy, have both detrimental and beneficial effects. Therefore, the present research aims to determine the impact on seizure activity of escitalopram in a penicillin-induced seizure model.

METHOD

Animals

Twenty-eight Wistar albino rats (175–250 g, 8 weeks old) were housed in 12-h light/dark cycle (22 °C) laboratory conditions. The animals were obtained from Erciyes University Experimental Research and Application Center. The Ethics Committee approved this study for animal experiments at Erciyes University (approval number: 22/003). Experimental groups were determined as follows:

Group 1: Control group; penicillin G potassium (500 IU, 2.5 µL, intracortical [i.c.]) + saline (1 mL, i.p.) (n=7)

Group 2: penicillin G potassium + escitalopram (5 mg/kg, i.p.) (n=7)

Group 3: penicillin G potassium + escitalopram (10 mg/kg, i.p.) (n=7)

Group 4: penicillin G potassium + escitalopram (20 mg/kg, i.p.) (n=7)

Experimental Protocol

Penicillin G potassium (retail pharmacy) was prepared in distilled water and injected i.c. Cipralex® (escitalopram) tablets obtained from a retail pharmacy were prepared in saline and administered at 5, 10, and 20 mg/kg 30 min after penicillin injection (Fig. 1).

The implantation of stainless steel screw electrodes in rats was defined in previous papers (15). The stereotactic surgery was performed under anesthesia with urethane (1.25 g/kg, i.p.). Following the small scalp incision from the midline, two holes were drilled with a hand drill for the electrodes over the left somatomotor cortex (first AP: +4.0 mm, LL: 3.0 mm;

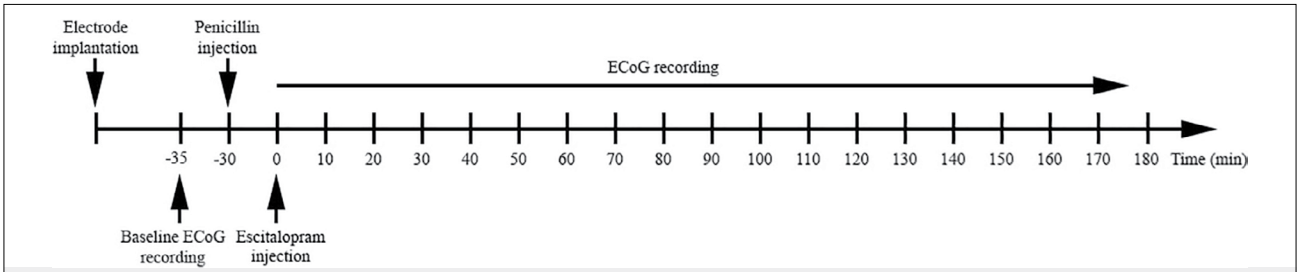

Figure 1. Timeline of electrocorticography (ECoG) recording before and after the administration of penicillin G and escitalopram.

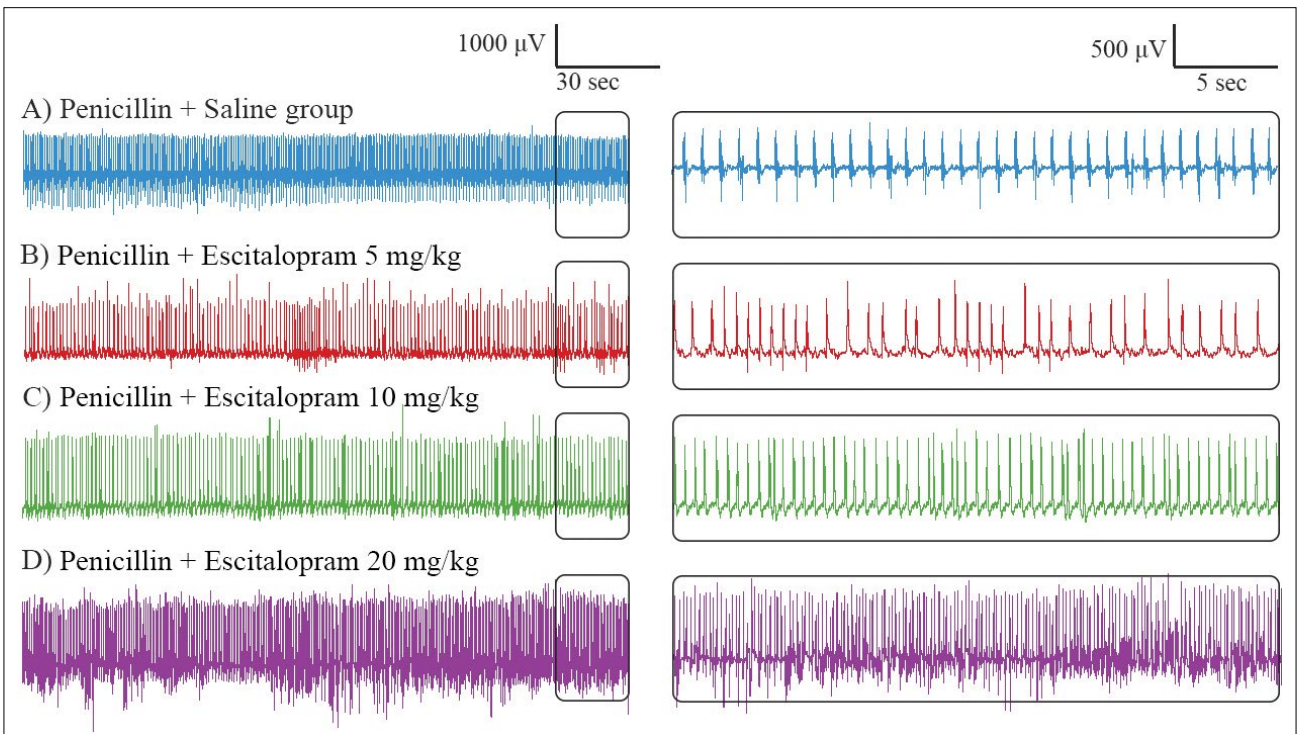

Figure 2. ECoG recordings of the groups in 120 min.

second AP: -4.0 mm, LL: 3.0 mm). A third hole was opened (1.5 mm lateral and 2 mm caudal to bregma) to induce epileptiform activity, and penicillin G potassium (500 IU; 2.5 µL) was administered at an infusion rate of 0.5 mL/min (1 mm beneath the brain surface by a Hamilton microsyringe type 701N) to produce epileptiform activity (19). Electrocorticography (ECoG) activity was recorded with a sampling frequency of 1024 Hz as bipolar by a PowerLab 16/SP (AD Instruments, Australia) for 3 h. Filter settings were set as follows: 0.3–100 Hz low and high pass filter, 50 Hz notch filter. ECoG recordings were analyzed using a software program (LabChart v8).

Statistical Analyses

All statistical analyses were carried out using GraphPad Prism 8 software. After applying drugs, the electrophysiological data were estimated in 10 min periods for 3 h. Values are expressed as means±SEM. The data were analyzed using a one-way ANOVA followed by Tukey's post hoc test for multiple comparisons. The results were considered significant at confidence limits of $p<0.05$.

RESULTS

Penicillin G potassium (500 IU/2.5 µL, i.c.) triggered epileptiform activity. Penicillin-induced seizure activity began within 3–4 min after injection, and the seizure activity reached a constant level after about 30 min. This activity lasted approximately 5–6 h. The means of spike and amplitude of the epileptiform activity were 30.37±2.48 spike/min and 1.193±0.259 mV, respectively (Fig. 2a, Tables 1 and 2).

Table 1: Mean spike frequency of groups

Groups	Time (min)			
	60	90	120	180
Saline	34.98±2.87	33.06±2.62	34.38±2.81	33.68±2.42
Escitalopram 5 mg/kg	35.93±3.11	34.8±2.79	31.5±3.43	29.2*±2.15
Escitalopram 10 mg/kg	35.55±3.32	34.8±3.38	36.85±3.5	34.56±3.86
Escitalopram 20 mg/kg	38.55*±1.71	39.22**±2.67	41.80*±3.57	44.80*±3.58

Statistical comparisons were made with the saline group for each time period. *: P<0.05; **: P<0.01 indicate significant differences compared to saline group and escitalopram groups. Statistical analyses were performed using one-way ANOVA, followed by Tukey's post hoc test. The data are presented as mean±SEM.

Table 2: Mean amplitude of groups

Groups	Time (min)			
	60	90	120	180
Saline	1.32±0.29	1.36±0.29	1.23±0.38	1.07±0.24
Escitalopram 5 mg/kg	1.24±0.25	1.09±0.20	0.97±0.27	0.99*±0.25
Escitalopram 10 mg/kg	1.16±0.18	1.37±0.24	1.19±0.22	1.20±0.16
Escitalopram 20 mg/kg	1.53**±0.46	1.42±0.37	1.34±0.35*	1.31**±0.30

Statistical comparisons were made with the saline group for each time period. *: P<0.05; **: P<0.01 indicate significant differences compared to saline group and escitalopram groups. Statistical analyses were performed using one-way ANOVA, followed by Tukey's post hoc test. The data are presented as mean±SEM.

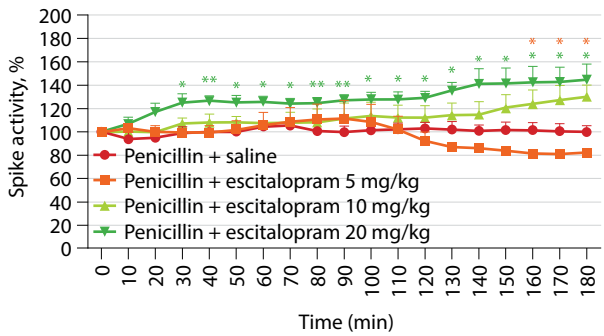

Figure 3. Effects of escitalopram on the mean spike frequency of penicillin-induced epileptiform activity. Data comparison among multiple groups was analyzed by one-way ANOVA. The data are expressed as mean±SEM.

n=7 in each group; *: P<0.05; **: P<0.01 show significant differences compared with the penicillin + saline group.

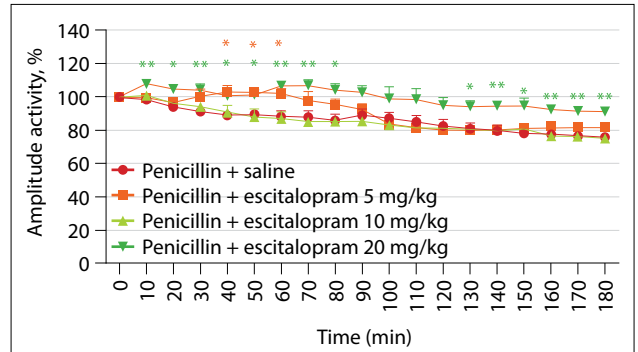

Figure 4. Effects of escitalopram in the mean spike amplitude of penicillin-induced epileptiform activity. Data comparison among multiple groups was analyzed by one-way ANOVA. The data are expressed as mean±SEM.

n=7 in each group; *: P<0.05; **: P<0.01 show significant differences compared with the penicillin + saline group.

Three doses of escitalopram (5, 10, and 20 mg/kg, i.p.) were administered 30 min after the penicillin injection. The mean spike frequency and amplitude of escitalopram 5 mg/kg were 30.05±1.45 spike/min and 0.946±0.167 mV, respectively (Fig. 2b, Tables 1 and 2). The 5 mg/kg escitalopram dose increased the mean spike frequency to the 100th minute (Fig. 3 and 4). Later, this activity decreased toward the end of the experiment (p=0.9383). At a 5 mg/kg dose, escitalopram did not change the mean amplitude of epileptiform activity (p=0.9435).

At a 10 mg/kg dose, escitalopram's mean spike frequency and amplitude were 32.95±2.77 spike/min and 1.077±0.104 mV, respectively (Fig. 2c, Tables 1 and 2). The 10 mg/kg dose increased the mean spike frequency compared with penicillin and 5 mg/kg dose; however, it was not statistically significant (Figs. 3 and 4) (p=0.8519). The percentage amplitude value of the 10 mg/kg dose remained at the same level as the penicillin group until the end of the experiment.

The presence of escitalopram 20 mg/kg significantly increased the mean spike frequency of

epileptiform activity in 30 min (p=0.0022). The mean spike frequency and amplitude of escitalopram 20 mg/kg were 34.35±2.35 spike/min and 1.138±0.201 mV, respectively (Fig. 2d, Tables 1 and 2). Although there was a slight decrease in amplitude, the amplitude was significant compared with the penicillin group throughout the experiment (Figs. 3 and 4).

DISCUSSION

Determining the effects of escitalopram on epilepsy is crucial for long-term drug treatment in patients who suffer from seizures and depression. Because of the uncertain impact of SSRIs and ignorance about the effect of escitalopram on penicillin-induced seizure activity, escitalopram was selected as the experimental drug in the present study. The study results proclaimed the proconvulsant activity of escitalopram, at doses of 5, 10, and 20 mg/kg, for treating depression. To the best of our knowledge, this is the first study to determine the effects of escitalopram on the penicillin-induced seizure model.

The administration of penicillin to the rat's brain gives rise to the synchronous discharge of neurons, like human epileptic discharges (20,21). Therefore, a penicillin-induced acute model of experimental epilepsy was used to reveal the role of escitalopram. The results show that single administration of penicillin (500 IU/2.5 µL, i.c.) caused increased spike frequency and amplitude on ECoG. Arslan et al. (19) showed that administration of penicillin (2.5 µL, 500 units, i.c.) induced epileptiform activity. Similarly, Han et al. (22) induced epileptiform activity using penicillin G potassium (400 IU, i.c.). These findings are also concordant with those from previous studies (18,23). While escitalopram, at doses of 5 and 10 mg/kg, increased the mean spike frequency, the dose of 20 mg/kg escitalopram caused a marked increase in the mean spike frequency and amplitude of penicillin-induced epileptiform.

It is known that epilepsy is related to several psychiatric comorbidities, such as depression, anxiety, and ASD. Antiepileptic drugs which enhance GABA levels are particularly relevant to harmful psychotropic properties such as depression (2). With long-term drug treatment, the incidence of depression in epileptic patients is relatively high. Therefore, epileptic patients with depression may need antidepressant drugs throughout their epilepsy treatment (7).

SSRIs are a widely used type of antidepressant in the treatment of depression. Most studies have reported that SSRIs and antidepressants have antiepileptic effects on various experimental epilepsy models (24,25). For instance, in our published article, vortioxetine (5 and 10 mg/kg), a novel SSRI, suppressed epileptiform activity in the pentylenetetrazole (PTZ)-induced kindling model (15). Ogun et al. (12) also reported that vortioxetine, at a dose of 10 mg/kg, decreased spike frequencies of epileptiform activity in penicillin-induced epilepsy. Similarly, sertraline (5 mg/kg), an SSRI drug, exhibited protective effects in the PTZ-induced kindling model (13). Alhaj et al. (26) reported that recurring injection of fluvoxamine (20 mg/kg) decreased seizure severity scores and protected against neuronal death in PTZ-kindled mice. The protective effects of fluoxetine were also reported in various experimental epilepsy models (27,28).

There is no experimental study in the literature showing the effects of escitalopram on epilepsy; clinical trials of escitalopram and citalopram (the therapeutically active S-enantiomer of citalopram) are limited. On the other hand, while antidepressants, including various SSRIs, are successful in treating depression, it is known that they are also directly related to an increased risk of seizures (9). The present study confirms these effects, and seizure activity gradually increased with increasing doses of escitalopram. A clinical study reported that an overdose of escitalopram gives rise to fewer seizures than citalopram in humans (29). In another clinical study, lamotrigine and oxcarbazepine combined with escitalopram separately displayed good efficacy against epilepsy and depression in patients (7). The present study results are not in agreement with the results of these two clinical studies. Li et al. (10) showed that chronic treatment of fluoxetine (10 mg/kg/day) accelerated kindling epileptogenesis in mice. Aygun (11) showed that fluoxetine, at low and moderate doses, exhibits an anticonvulsant effect while high doses exhibit a proconvulsant effect on a penicillin-induced experimental model. A current study reported that vortioxetine augments absence seizures in WAG/Rij rats but reduces penicillin and PTZ-induced seizures in rats (18). In another study, the same authors reported that trazodone, an SSRI antidepressant drug, increased absence seizures in WAG/Rij rats while reducing them in a penicillin-induced model (17). As mentioned above,

SSRIs may have different effects on seizure activity depending on the experimental epilepsy model, type of SSRIs, and the dose of SSRIs.

The mechanism of action of SSRIs on epilepsy could be complicated. Increased serotonergic neurotransmission could exhibit antidepressant and anticonvulsant effects. Anticonvulsant effects of SSRIs and 5-hydroxytryptophan (5-HT) in seizures are well known. Similarly, various studies of 5-HT receptor agonists and 5-HTP were reported to suppress seizure activity (30). In this mechanism, it was reported that the activation of the 5-HT receptor increased GABA-mediated synaptic inhibition and inhibited seizure activity (31). Thus, it shows that increased serotonin levels may be beneficial in epilepsy with its anticonvulsant effects. However, in studies where SSRIs are proconvulsant, a different mechanism of action could be mentioned. Related to this, Nakatani and Amano (32) stated that escitalopram might inhibit Nav1.2 voltage-gated sodium channels (VGSCs) current and affects both activation and inactivation states of Nav1.2 VGSCs. Therefore, it is believed that one possible explanation for the proconvulsant effect of escitalopram might occur through Nav1.2 VGSCs. Finally, the experimental and clinical doses of a drug are different. Therefore, dose conversion is required prior to the preclinical or clinical use of the experimentally preferred dose. In a clinical study, escitalopram at a dose of 1860 mg triggered seizure formation, while in another study, escitalopram at a dose of 300 mg induced this activity (29,33). This study calculated the human equivalent dose values to be 4.56–18.24 mg for the 5–20 mg/kg dose range (34). Therefore, the equivalent dose determined in our study is quite different from these two studies.

CONCLUSION

As mentioned above, SSRI doses are critical criteria for being proconvulsant or anticonvulsant. The Food and Drug Administration approves only fluoxetine and escitalopram in treating pediatric depression though citalopram and sertraline are preferred. Thus, it is crucial to specify which type of SSRIs regulates seizure activity and which exhibits proconvulsant or anticonvulsant effects for safe use in epilepsy and depression. Although this study is an experimental animal study, it is suggested that escitalopram should be preferred in various epilepsy types. Further studies with varied experimental models and clinical trials are required to determine the effect of escitalopram.

Contribution Categories		Author Initials
Category 1	Concept/Design	M.T., S.Y.T
	Literature review	M.T., S.Y.T
	Data analysis/Interpretation	M.T.
Category 2	Drafting manuscript	M.T., S.Y.T
	Critical revision of manuscript	M.T.
Category 3	Final approval and accountability	M.T., S.Y.T

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Conflict of Interest: The authors declare that they have no conflict of interest.

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