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Vilazodone as a Novel Anticonvulsant: A Preclinical Evaluation in Experimental Seizure Models

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Abstract

Background: Epilepsy is one of the most common neurological abnormalities worldwide. Current antiepileptic drugs have limitations in efficacy and safety. Studies have shown decreased serotonin level can induce epileptic seizures in animal models. Vilazodone possess dual mechanism on serotonin by inhibit its reuptake and partial agonistic action on 5-HT1A receptors, it enhances the extracellular serotonin levels in brain. ***Objective:*** To evaluate the anticonvulsant effect of vilazodone in acute seizure models and compare it with sodium valproate. Methods: A preclinical experimental study was conducted on 36 Swiss albino mice divided into six groups (n=6). Vilazodone (1, 2, 5, 10 mg/kg), sodium valproate (40 mg/kg), and control were administered orally. Seizures were induced using maximal electroshock (MES) and pentylenetetrazole (PTZ) models. Outcomes included duration of tonic hind limb extension, seizure duration and latency. ***Results:*** All doses of Vilazodone significantly reduced tonic hind limb extension in MES and decreased seizure duration in PTZ models. Vilazodone showed increased seizure latency in PTZ model at all doses with maximum increase seen in higher doses (5mg/kg and 10mg/kg). ***Conclusion:*** Vilazodone demonstrates dose-dependent anticonvulsant activity, suggesting potential as an adjunct therapy in epilepsy.

Keywords: Vilazodone, Epilepsy, Anticonvulsant, MES model, PTZ model

INTRODUCTION

Epilepsy is one of the most common neurological abnormalities affecting about 1% of the world population1. An ideal anti-epileptic drug has the following features of wide spectrum of action, rapidly acting, well absorbed orally with minimal side effects and relatively inexpensive. Contemporary anticonvulsant therapy, however, is neither universally effective nor invariably safe as they are associated with adverse effects like ataxia, CNS depression, megaloblastic anemia, cardiac arrhythmias, teratogenicity and hepatic dysfunction. Although most people with epilepsy become seizure free with proper antiepileptic therapy, 30-40% of patients having seizures despite the use of antiepileptic medications either alone or in combination2. The wide distribution and various actions of 5-HT receptors are in both central and peripheral nervous system. Recently, various subtypes of 5-HT receptors were involved in seizure disorders has been described in several animal studies3. For example, Decreased serotonin level can induce epileptic seizures while some antiepileptic drugs produce antiepileptic effects by increasing extracellular serotonin level4. Endogenous serotonin inhibits epileptiform activity in rat hippocampal neurons via 5HT1A receptor activation. Furthermore, several 5-HT receptor subtypes may be relevant to epilepsy, such as 5-HT1A, 5-HT1B and 5-HT35. Vilazodone is a newer FDA approved drug for the treatment of major depressive disorder. Due to its novel chemical structure and dual mechanism on serotonin by inhibit its reuptake and partial agonistic action on 5-HT1A receptors, it enhances the extracellular serotonin levels in brain. There were no previous studies to evaluate the anticonvulsant activity of vilazodone in animal models. This is the first study to evaluate the anticonvulsant effect of Vilazodone in mice models of epilepsy for acute models by using maximal electroshock (MES) and pentylenetetrazole methods (PTZ).

MATERIALS AND METHODS

This pre-clinical experimental study was carried out in the Department of Pharmacology, Karpagam faculty of Medical Sciences and Research, Coimbatore. The study was conducted for a period of 6 months from August 2019 to January 2020. 36 Swiss albino mice of both sex weighing about 25 – 30grams procured from central animal house, Karpagam University, Coimbatore. As per CCSEA guidelines, animals were acclimatized for 1 week in department of pharmacology, Karpagam faculty of medical sciences and research. They were housed properly within clean cages and fed with standard pellet diet and water ad libitum throughout the study. Animals were maintained at 22 – 240 c temperature and 12/12 dark-light cycle. Ethical clearance was obtained from the Institute of animal ethical committee, Karpagam faculty of medical sciences and research, Coimbatore (IAEC No.: KFMSR/MD(PC)/05/2018 dated 11.12.2018).

Drugs and Chemicals:

Vilazodone (1mg/kg, 2mg/kg, 5mg/kg and 10mg/kg BW*)6

1. Sodium valproate (40mg/kg BW)7
2. Distilled water (10ml/kg BW)
3. Pentylenetetrazole (70mg/kg BW)

Animal Groups:

36 Swiss albino mice were divided into 6 groups (n=6 in each group)8

GROUPS	DRUG & DOSE	ROUTE
I (CONTROL)	Distilled water 10 ml/kg BW	Oral
II (STANDARD)	Sodium valproate 40mg/kg BW	Oral
III	Vilazodone 1mg/kg BW	Oral
IV	Vilazodone 2mg/kg BW	Oral
V	Vilazodone 5mg/kg BW	Oral
VI	Vilazodone 10mg/kg BW	Oral

***BW – Body Weight**

Animals from the above mentioned six groups were subjected to Maximal Electroshock (MES) model (electrically induced seizures) and 2 weeks after the wash out period, all same groups were used for pentylenetetrazole (PTZ) model (chemically induced seizures).

Maximal Electroshock (MES) model:

In this method, an electroconvulsiometer is used to induce the seizure by delivering electrical shock of 50 mA current through a pair of ear clip electrodes for 0.2 seconds in mice. Drugs were administered orally 60 minutes before the seizure induction in mice. Duration of tonic hind limb extension in seconds was noted for each animal.9

Pentylenetetrazol (PTZ) model:

In this method, seizure is induced by administering 70mg/kg BW of pentylenetetrazole is injected intraperitoneally. Drugs were administered orally 60 minutes before the seizure induction in mice. Duration of seizures and seizure latency in seconds were noted for each animal 10,11.

Statistical analysis

Results were expressed as Mean + Standard deviation(S.D). Student-t-test were used for statistical analysis using SPSS 23.0. P value less than 0.05 were taken as statistically significant.

RESULTS

Acute MES model:

Results showed groups II, III, IV, V, VI have significant reduction ($P < 0.05$) in mean duration of tonic hind limb extension in seconds (Table 1) in comparison to group I (control).Similarly, all groups showed a reduction in mean duration of tonic hind limb extension with maximum reduction in group VI (10mg/kg Vilazodone).

Figure 1: Acute MES model - Mean duration of Tonic hind limb extension in seconds

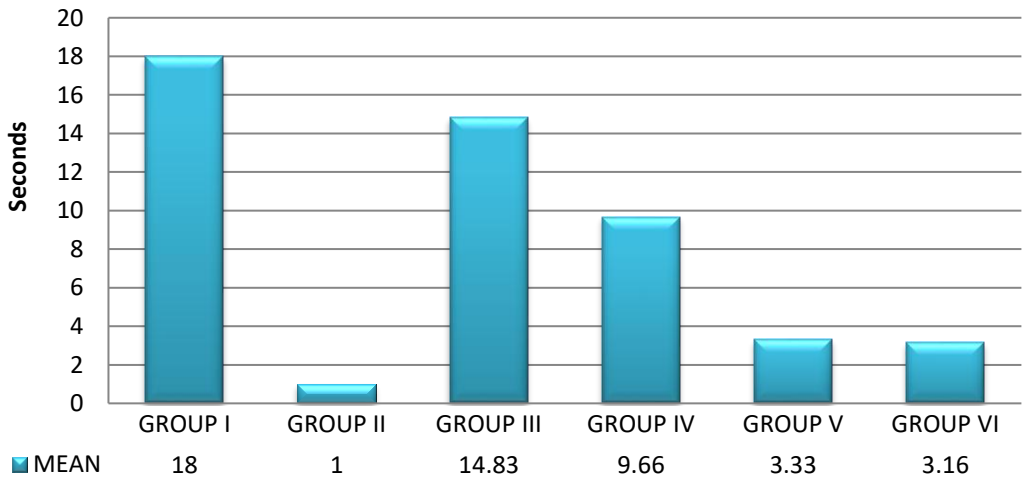

Table 1: Acute MES model – Statistical analysis of Mean duration of Tonic hind limb extension in seconds

Groups	Control (p value)
Group I	-
Group II	0.0001
Group III	0.0001
Group IV	0.0001
Group V	0.0001
Group VI	0.0001

Acute Pentylenetetrazole (PTZ) model (Mean duration of seizures):

Results showed groups II, III, IV, V, VI have significant reduction ($P < 0.05$) in mean duration of seizures in seconds (Table 2) in comparison to group I (control). All doses (1mg/kg, 2mg/kg, 5 mg/kg, 10mg/kg) of Vilazodone showed a reduction in seizure duration with maximum reduction occurred at highest dose (Figure 2).

Figure 2: Acute PTZ model - Mean duration of seizures in seconds

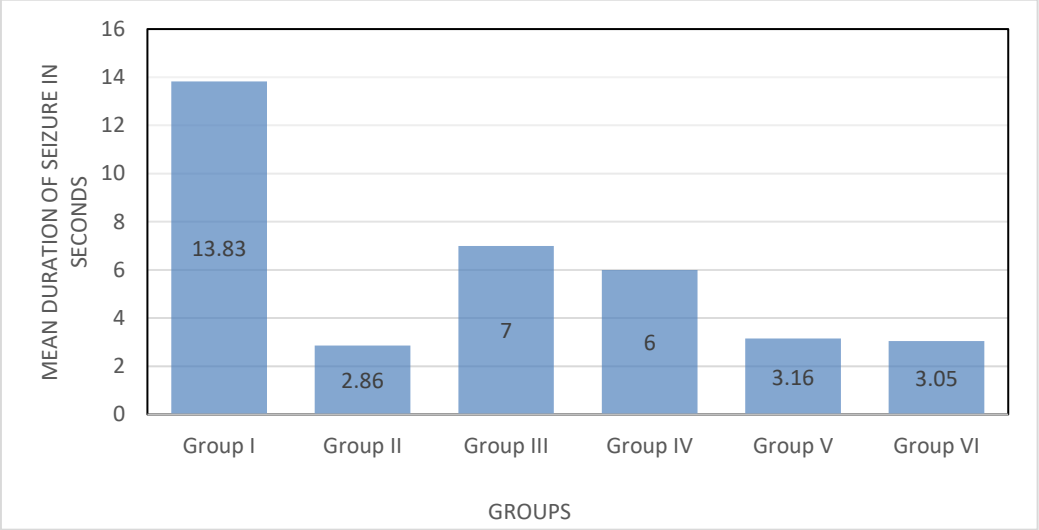

Table 2: Acute PTZ model – Statistical analysis of mean duration of seizures in seconds

Groups	Control (p value)
Group I	-
Group II	0.0001
Group III	0.0001
Group IV	0.0001
Group V	0.0001
Group VI	0.0001

Acute PTZ model - Mean duration of seizure latency

Results showed groups II, V, VI have significant increase ($P < 0.05$) in mean duration of seizure latency in seconds (Table 3) in comparison to group I (control). All doses (1mg/kg, 2mg/kg, 5 mg/kg, 10mg/kg) of Vilazodone showed a increase in seizure latency with maximum seen at higher doses (5mg/kg, 10mg/kg) (Figure 3).

Figure 3: Acute PTZ model - Mean duration of seizure latency in seconds

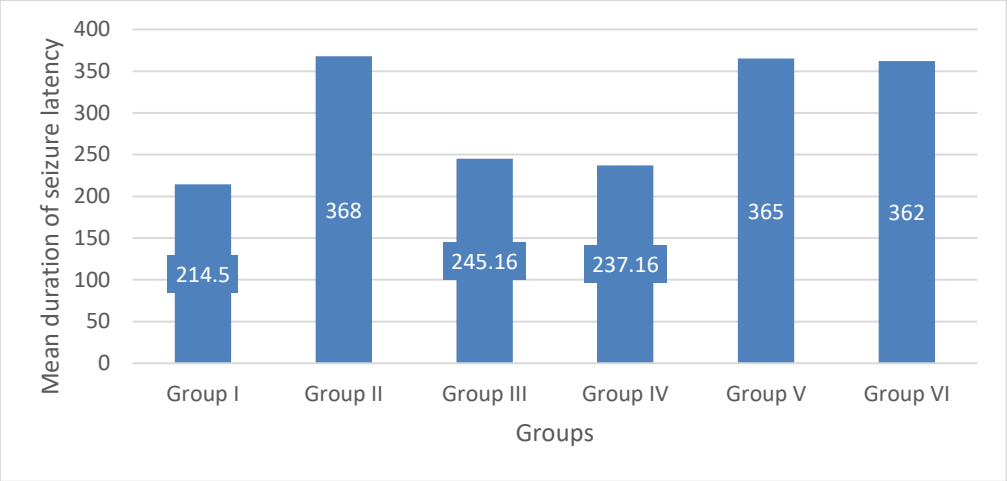

Table 3: Acute PTZ model – Statistical analysis of mean duration of seizure latency in seconds

Groups	Control (p value)
GROUP I	-
GROUP II	0.0001
GROUP III	0.07
GROUP IV	0.1
GROUP V	0.0001
GROUP VI	0.0001

DISCUSSION

This study was conducted as per CPCSEA guidelines, and all precautions were taken to reduce errors due to gender related and diurnal variations. A total of 36 Swiss albino mice were used in this study to evaluate the anticonvulsant property of vilazodone and compared with sodium valproate. Vilazodone was used at various doses of 1mg/kg, 2mg/kg, 5mg/kg and 10mg/kg of mice body weight. To screen the anticonvulsant activity, there are large number of models are available. But maximal electroshock model and pentylenetetrazole model remains the gold standard models for antiepileptic drug screening. The observations emanated in this study indicated that duration of tonic hind limb extension phase was significantly decreased in test groups (vilazodone 1mg/kg, 2 mg/kg,5mg/kg and 10mg/kg) when compared to control group. The decreased duration of these components may be due to the anticonvulsant activities of vilazodone. In acute MES model, study results show that vilazodone 1mg/kg, 2mg/kg, 5mg/kg and 10mg/kg has dose dependent suppression of tonic hind limb extension. In acute PTZ model, similarly there is a dose dependent reduction in duration of seizures and marked increase in seizure latency at all given doses of vilazodone. zarnes et al (1999) proposed serotonergic ascending pathway regulates the cortical and subcortical excitatory / inhibitory balance and these modulations contribute the control of epileptic activity3. Lu KT et al study supports barnes et al proposals that agents that increases the extracellular serotonin levels, which include 5-HT and 5-HT reuptake blockers, inhibit each focal (limbic) and generalized seizures4. Jakus et al also report that selective inhibition of 5-HT1A receptors reduces the seizure activity12. We already know that vilazodone has both of these actions such as 5-HT reuptake blocking and 5-HT1A partial agonism. So Vilazodone has the ability to reduce the seizure activity. Our study results also support the same as Vilazodone 1mg/kg, 2mg/kg and 5mg/kg having an anti-epileptic action.Wang et al (2013) study showed that acute administration of SSRI like anti depressant drugs increase the extra neuronal levels of serotonin. However, this increase of serotonin is immediately counteracted by pre synaptic 5-HT1A auto receptor mediated negative feedback inhibition13.Ashby et al (2013) study showed that chronic stimulation of 5HT1A receptors (via continuous administration) may produce pre-synaptic auto receptor desensitization but this is not happened in postsynaptic receptors. Therefore, the autoreceptor-mediated negative feedback action will be reduced and the serotonin release is normalized and the postsynaptic serotonergic receptors are activated enormously that results in increased serotonin levels in synaptic region14.Novelty of this study is, this is the first study to assess the acute effects of vilazodone 1mg/kg, 2mg/kg, 5mg/kg and 10mg/kg in MES model and PTZ model in swiss albino mice. Previous studies states that other SSRIs like citalopram, venlafaxine has significant anti-epileptic activity in pre clinical studies. Fluoxetine, a

SSRI drug proves its anti-epileptic property in humans8. Drevets et al (1999) found that reduction in 5-HT1A receptors and its binding is seen in depressed patients and Savic et al strengthens the hypothesis and Bagdy G et al confirms that anti-epileptic agents has reduce the seizure focus, and patients with both epilepsy and depression had lower activity than those with epilepsy alone [15,16,17].

CONCLUSION

Vilazodone possess faster onset of anticonvulsant activity at various doses of 1mg/kg, 2mg/kg, 5mg/kg and 10mg/kg BW by acute MES and PTZ models in swiss albino mice. In acute study, Vilazodone 1mg/kg, 2mg/kg, 5mg/kg and 10mg/kg showed reduction in the tonic hind limb extension in MES model and reduction in seizure duration and increase in seizure latency in PTZ model. Further studies are required to confirm the anticonvulsant activity of vilazodone. If the anti-epileptic activity of vilazodone is once proved, it may be used as add-on therapy with first line anti-epileptic drugs in patients with depression.

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