

An experimental study to investigate the effects of venlafaxine and escitalopram on anticonvulsant activity of conventional antiepileptic drugs in mice

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ABSTRACT

Background: Depression is a common psychiatric comorbidity in patients with epilepsy which remains often untreated, due to concern of antidepressant induced seizures. The safety status of selective serotonin reuptake inhibitors (SSRIs) in epileptics is controversial.

Methods: Phase I acute effect of venlafaxine and escitalopram on the seizure threshold was studied. Phase II, the acute effects of test AEDs on the effective dose of AEDs viz valproate, phenobarbitone and phenytoin were studied in maximal electroshock (MES). Phase III- same study design as in phase II except that AEDs and ADDs were administered daily for 28 days.

Results: Venlafaxine raised the electroconvulsive threshold in a dose dependant manner in phase I, however it was significant at a dose of 25mg/kg. In phase II, a significant reduction in ED50 of valproate was observed when it was co-administered with venlafaxine at dose of 12.5 and 25mg/kg, whereas ED50 of phenobarbitone was significantly reduced at a dose of 25mg/kg. Chronic administration of venlafaxine at 12.5mg/kg daily reduced ED50 of valproate. At 25mg/kg daily ED50 of all the three studied AEDs was reduced, Escitalopram 8mg/kg significantly raised the electroconvulsive threshold value in phase I, Escitalopram administered in the dose of 8mg/kg reduced the ed50 value of valproate. Escitalopram given in dose of 4 and 8mg/kg reduced the ED50 value of valproate.

Conclusions: From this finding, it may be concluded that venlafaxine and escitalopram administered either alone or in combination with AEDs acutely or chronically, exhibit anticonvulsant action.

Keywords: Antiepileptics, Antidepressants, Maximal electroshock, Seizures, Seizure threshold

INTRODUCTION

Depression is a common psychiatric comorbidity in patients of epilepsy, manifesting clinically in 66 % of the patients.¹ Co-morbid depression is associated with high rates of suicides, poor quality of life and poor prognosis.² Epilepsy patients who are diagnosed with clinical depression are often untreated, due to concern of antidepressant induced seizures.³⁻⁵ Estimates of the incidence of antidepressant related seizures range from 0.1 to 4.0%.⁵

Tricyclic antidepressants (TCAs) may trigger seizures because of their local anesthetic, antihistaminic, and

antimuscarinic properties.⁴ The safety status of selective serotonin reuptake inhibitors (SSRIs) in epileptics is controversial. Some animal studies had shown enhancement of anticonvulsant action of conventional antiepileptic drugs (AEDs) by fluoxetine on acute and chronic administration.^{6,7} However, another study shows that chronic fluoxetine has no anticonvulsant property.⁸ Atypical antidepressant, mianserin has pro as well as anticonvulsant activity depending on its duration of administration.⁹ In recent studies, venlafaxine which is a serotonin norepinephrine reuptake inhibitor (SNRI) has shown anticonvulsant property in maximal electroshock model in mice and rats.¹⁰⁻¹² However another study shows that high doses of venlafaxine may be proconvulsant in

pentylentetrazole (PTZ) induced seizure model in mice.¹³ There is limited data available on the effect of escitalopram on seizure threshold. In a study escitalopram was found to have proconvulsant property in picrotoxin induced convulsion in mice. Studies on citalopram had shown anticonvulsant property in both animal and human studies.^{14,15}

Aim of the study was to an experimental study to investigate the effects of venlafaxine and escitalopram on anticonvulsant activity of conventional antiepileptic drugs in mice.

METHODS

The experiment complied with the guidelines for animal experimentation of our laboratory and was conducted in Department of Pharmacology.

Animals

Healthy adult Swiss albino male mice weighing 20-30g were used in this study. The mice were fed on standard laboratory diet and water ad libitum. The study was conducted in compliance with Committee for the purpose of Control and Supervision on Experiments on Animals (CPCSEA) guidelines.¹⁶

Drugs and chemicals

Venlafaxine hydrochloride

Venlafaxine hydrochloride was suspended in 1% gum acacia to prepare a suspension of 2mg/ml, and administered orally in doses of 6.25, 12.5 and 25mg/kg.

Escitalopram oxalate

Escitalopram oxalate was suspended in 1 % gum acacia to prepare a suspension of 0.6mg/ml. It was administered orally in doses of 2, 4 and 8mg/kg.

Phenytoin sodium

Phenytoin sodium was suspended in 1% gum acacia to prepare a suspension of 1.5mg/ml and administered orally in doses of 5, 10 and 20mg/kg.

Phenobarbitone sodium

Phenobarbitone sodium was suspended in 1% gum acacia to prepare a suspension of 1.5mg/ml of phenobarbitone. It was administered orally in doses of 5, 10 and 20mg/kg to experimental animals.

Sodium valproate

Sodium valproate was dissolved in distilled water to prepare a solution of 30mg/ml, and administered orally in doses of 100, 200 and 400mg/kg to experimental animals.

Experimental design of the study was carried out in the following three phases.

Phase I

In phase I, acute effect of venlafaxine and escitalopram on the seizure threshold was studied. ADDs were given in three doses once, using 4 groups of 6 mice each per dose of ADD (i.e. total 24 mice per dose of ADD). Venlafaxine was given in the doses of 6.25, 12.5, and 25mg/kg and escitalopram was given in doses of 2, 4, and 8mg/kg to the assigned groups. The control group for both the studied ADDs comprised of 4 groups of 6 mice each and was treated with vehicle (1% gum acacia) alone (Table 1). Each group was exposed to different intensity of electric current i.e. 6, 8, 10 and 12 mA. The number of animals convulsing at each current intensity was noted. CS50 (current strength necessary to induce tonic hind limb extension in 50% of the animals) along with its standard error of mean (SEM) was calculated for control and various treatment groups by the method of Miller and Tainter.¹⁷ Increase/ decrease in the CS50 value of the treatment group were observed and CS50 of various treatment groups were compared with control group.

Table 1: Study design for phase II and phase III studies.

ADDs and their Dose (mg/kg)	Number of animals for various AED groups and AED doses used									
	VPA			PB			PHT			
	100mg/kg	200mg/kg	400mg/kg	5mg/kg	10mg/kg	20mg/kg	5mg/kg	10mg/kg	20mg/kg	
VLF	6.25	6	6	6	6	6	6	6	6	6
	12.5	6	6	6	6	6	6	6	6	6
	25	6	6	6	6	6	6	6	6	6
ESC	2	6	6	6	6	6	6	6	6	6
	4	6	6	6	6	6	6	6	6	6
	8	6	6	6	6	6	6	6	6	6
Control	Vehicle	6	6	6	6	6	6	6	6	6

VPA: sodium valproate, PB: phenobarbitone, PHT: phenytoin, VLF: venlafaxine, ESC: escitalopram, ADD: antidepressant drug

Phase II

In phase II, the acute effects of test ADDs on the effective dose of AEDs viz valproate, phenobarbitone and phenytoin were studied in maximal electroshock (MES). For each ADD and AED combination, total of 9 groups of 6 mice each received both the drugs in various combinations as per Table 1. The controls for each AED were formed by 3 groups of 6 animals each; each control subgroup received different dose of AED only as drug treatment (Table 1). The animals were given MES and the number of animals protected against MES was recorded for each group. The protective efficacy of antiepileptic drugs was expressed as median effective dose (ED50) i.e. dose at which 50% of animals were protected against the maximal electroshock induced tonic hind limb extension. ED50 value along with SEM was calculated for various groups by Miller and Tainter method and ED50 of treatment groups were compared with the control group.¹⁷⁻¹⁹

Phase III

The study was done using the same study design as in phase II except that AEDs and ADDs were administered daily for 28 days as per Table 1.

Instrument used for studying seizure activity.

Electroconvulsimeter (Figure 1) was used to determine electroconvulsive threshold and change in ED50 of various AEDs.

To determine effect on seizure activity following methods were used.

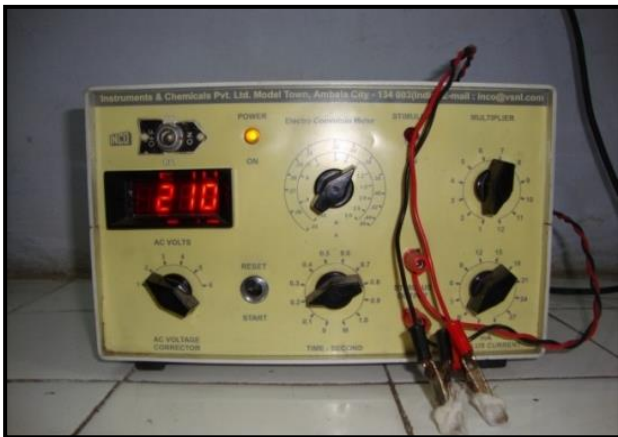


Figure 1: Electroconvulsimeter.

Electroconvulsive threshold method^{7,11,20}

In this test electrical current of various intensity i.e. 6, 8, 10, 12 mA was given to different groups of animals for 0.2 seconds by auricular electrodes using electroconvulsimeter. The minimum current intensity at

which tonic hind limb extension (i.e. hind limb of the animal outstretched to 180 degrees to the plane of body axis) (Figure 2) occurred was taken as the electroconvulsive threshold for that animal.

Maximal electroshock seizure (MES) test^{11,20}

In this test each mouse received an electrical stimulus (48mA) for 0.2 seconds via auricular electrodes to induce tonic hind limb extension.

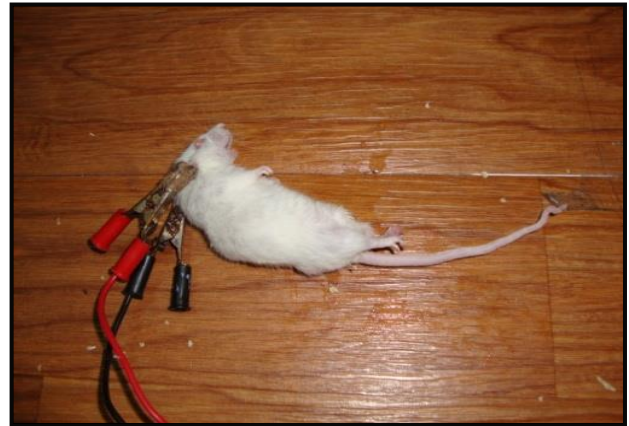


Figure 2: Tonic hind limb extension in mice

Statistical analysis

Graph Pad® Ver. 6, 32 bit for windows was used for statistical analysis. The statistical analysis of respective CS50 and ED50 values vs. control values was performed with student t test. Results were evaluated at a significance value of P value <0.05.

RESULTS

Phase I

Table 2: Effect of the acute treatment with venlafaxine and escitalopram on the electroconvulsive threshold.

Groups	CS 50±SEM (mA)
Vehicle (1% gum acacia)	6.82±1.08
Venlafaxine (6.25mg/kg)	7.3±1.08
Venlafaxine (12.5mg/kg)	8.01±1.04
Venlafaxine (25mg/kg)	9.50±0.90***
Escitalopram (2mg/kg)	6.82±1.08
Escitalopram (4mg/kg)	7.3±1.08
Escitalopram (8mg/kg)	8.85±1.08**

Values are expressed as mean±standard error of mean (SEM).* denotes P<0.05 in comparison to control, ** denotes P<0.01 in comparison to control, *** denotes P<0.001 in comparison to control

Venlafaxine 25mg/kg significantly increased the electroconvulsive threshold from 6.82±1.08 to 9.50±0.85mA. Whereas venlafaxine given at 6.25 and

12.5mg/kg increased the CS50 values from 6.82±1.08 to 7.3±1.08 and 8.01±1.04mA respectively, however these changes were statistically not significant (Table 2). Escitalopram 8 mg/kg significantly raised the electroconvulsive threshold value from 6.82±1.08 to 8.85±1.08mA whereas escitalopram 4 mg/kg increased the CS50 value from 6.82±1.08 to 7.3±1.08mA which was statistically not significant and escitalopram given at 2mg/kg did not alter the CS50 value (Table 2).

Phase II

In phase II, venlafaxine administration at all three doses decreased the ED50 value of valproate in a dose dependent manner. Venlafaxine 6.25, 12.5, 25mg/kg decreased the ED50 of valproate from 237±45.08 to 200±45.08, 162.23±50 and 127±48mg/kg respectively. Reduction in ED50 values of valproate with administration of 12.5 and 25 mg/kg of venlafaxine were statistically significant (Table 3).

Table 3: Effect of the acute treatment with venlafaxine and escitalopram on the anticonvulsant action of valproate.

Treatment	ED 50 value±SEM (mg/kg)
Valproate+Vehicle	237±45.08
Valproate+Venlafaxine (6.25mg/kg)	200±45.08
Valproate+Venlafaxine (12.5mg/kg)	162.23±50*
Valproate+Venlafaxine (25mg/kg)	127±48**
Valproate+Escitalopram (2mg/kg)	237±45.08
Valproate+Escitalopram (4mg/kg)	200±45.08
Valproate+Escitalopram (8mg/kg)	167.93±50*

Values are expressed as mean+standard error of mean (SEM). * denotes P<0.05 in comparison to control, ** denotes P<0.01 in comparison to control, *** denotes P<0.001 in comparison to control.

Venlafaxine administered at 6.25, 12.5 and 25mg/kg reduced the ED50 of phenobarbitone in a dose dependent manner from 13.19±4.2 to 10.0±4.2, 8.82±3.12, 8.09±2.48mg/kg respectively. Reduction in ED50 values was statistically significant at 25mg/kg of venlafaxine (Table 4). Venlafaxine administered at 12.5 and 25mg/kg reduced the ED50 value of phenytoin from 12.74±3.81 to 11.09±4.58 and 10±4.8mg/kg respectively. However the reduction of ED50 value was not statistically significant. Venlafaxine administered at 6.25mg/kg did not affect the ED50 value of phenytoin (Table 5).

Escitalopram administered in the doses of 4 and 8mg/kg reduced the ED50 value of valproate from 237±45.08 to 200±45.08 and 167.93±50mg/kg respectively. Reduction in ED50 value of valproate with co-administration of

8mg/kg escitalopram was statistically significant. Escitalopram given at 2 mg/kg did not affect the ED50 value of valproate (Table 3).

Escitalopram administered in dose of 4mg/kg and 8 mg/kg reduced the ED50 value of phenobarbitone from 13.19±4.2 to 10±3.8 and 8.82±3.12mg/kg respectively, which were statistically not significant. Escitalopram given in dose of 2 mg/kg showed no effect on the ED50 of phenobarbitone (Table 4).

Table 4: Effect of the acute treatment with venlafaxine and escitalopram on the anticonvulsant action of phenobarbitone (PB).

Treatment	ED 50 value±SEM (mg/kg)
Phenobarbitone+Vehicle	13.19±4.2
Phenobarbitone+Venlafaxine (6.25mg/kg)	10.0±4.2
Phenobarbitone+Venlafaxine (12.5mg/kg)	8.82±3.12
Phenobarbitone+Venlafaxine (25mg/kg)	8.09±2.48*
Phenobarbitone+Escitalopram (2mg/kg)	13.19±4.2
Phenobarbitone+Escitalopram (4mg/kg)	10±3.8
Phenobarbitone+Escitalopram (8mg/kg)	8.82±3.12

Values are expressed as mean+standard error of mean (SEM). * denotes P<0.05 in comparison to control, ** denotes P<0.01 in comparison to control, *** denotes P<0.001 in comparison to control.

Table 5: Effect of the acute treatment with venlafaxine and escitalopram on the anticonvulsant action of phenytoin.

Treatment	ED 50 value±SEM (mg/kg)
Phenytoin+Vehicle	12.74±3.81
Phenytoin+Venlafaxine (6.2 mg/kg)	12.74±3.81
Phenytoin+Venlafaxine (12.5 mg/kg)	11.09±4.58
Phenytoin+Venlafaxine (25 mg/kg)	10±4.8
Phenytoin+Escitalopram (2mg/kg)	12.74±3.81
Phenytoin+Escitalopram (4mg/kg)	11.09±4.58
Phenytoin+Escitalopram (8mg/kg)	10±3.11

Values are expressed as mean+standard error of mean (SEM). * denotes P<0.05 in comparison to control, ** denotes P<0.01 in comparison to control, *** denotes P<0.001 in comparison to control.

Escitalopram given in doses of 4 and 8mg/kg reduced the ED50 value of phenytoin from 12.74±3.81 to 11.09±4.58 and 10±3.11mg/kg respectively; however, these reductions in ED50 values were statistically not significant. Escitalopram given in dose of 2 mg/kg had no effect on ED50 value of phenytoin (Table 5).

Phase III

Venlafaxine given in doses of 6.25, 12.5 and 25mg/kg reduced the ED50 Value of valproate in dose dependent manner from 237±45.08 to 200±45.08, 142.94±45.92 and 100±23.30 mg/kg respectively, the reductions in ED50 value of valproate at 12.5 and 25mg/kg was statistically significant (Table 6). Venlafaxine given at dose 6.25, 12.5, and 25 mg/kg reduced the ED 50 value of phenobarbitone from 13.19±4.2mg/kg to 10±4, 8.82±3.12 and 8.01±2.65mg/kg respectively. The reduction in ED50 value with venlafaxine 25mg/kg was found to be statistically significant (Table 7).

Table 6: Effect of the chronic treatment with venlafaxine and escitalopram on the anticonvulsant action of valproic acid.

Treatment	ED 50 value±SEM (mg/kg)
Valproate+Vehicle	237±45.08
Valproate+Venlafaxine (6.25 mg/kg)	200±45.08
Valproate+Venlafaxine (12.5 mg/kg)	142.94±45.92 **
Valproate+Venlafaxine (25 mg/kg)	100±23.30 ***
Valproate+Escitalopram (2mg/kg)	237±45.08
Valproate+Escitalopram (4mg/kg)	200±45.08
Valproate+Escitalopram (8mg/kg)	131.84±51.48 **

Values are expressed as mean + standard error of mean (SEM). * denotes P<0.05 in comparison to control, ** denotes P<0.01 in comparison to control, *** denotes P<0.001 in comparison to control

Venlafaxine administered at dose of 6.25, 12.5 and 25mg/kg reduced the ED50 of phenytoin from 12.74±3.81 to 11.09±3.81, 10±3.11 and 8.09±2.46mg/kg respectively, the reduction in ED50 value of phenytoin with venlafaxine 25 mg/kg was statistically significant (Table 8). Escitalopram given in dose of 4 and 8mg/kg reduced the ED50 value of valproate from 237±45.08 to 200±45.08 and 131.84±51.48mg/kg respectively. The reduction in ED50 value of valproate with 8 mg/kg of escitalopram was statistically significant. Escitalopram given at 2mg/kg had no effect on the ED50 value of valproate (Table 6).

Escitalopram administered chronically in doses of 4 and 8 mg/kg reduced the ED50 values of phenobarbitone from 13.19±4.2 to 10±4.2 and 8.82±3.12 mg/kg respectively,

however these reductions in ED50 values were statistically not significant. Escitalopram given in dose of 2 mg/kg did not influence the ED50 value of phenobarbitone (Table 7).

Table 7: Effect of the chronic treatment with venlafaxine and escitalopram on the anticonvulsant action of phenobarbitone.

Treatment	ED 50 value±SEM (mg/kg)
Phenobarbitone+Vehicle	13.19±4.2
Phenobarbitone+Venlafaxine (6.25mg/kg)	10±4.2
Phenobarbitone+Venlafaxine (12.5mg/kg)	8.82±3.12
Phenobarbitone+Venlafaxine (25mg/kg)	8.01±2.65*
Phenobarbitone+Escitalopram (2mg/kg)	13.19±4.2
Phenobarbitone+Escitalopram (4mg/kg)	10±4.2
Phenobarbitone+Escitalopram (8mg/kg)	8.82±3.12

Values are expressed as mean + standard error of mean (SEM). * denotes P<0.05 in comparison to control, ** denotes P<0.01 in comparison to control, *** denotes P<0.001 in comparison to control.

Escitalopram given in doses of 4 and 8 mg/kg reduced the ED50 values of phenytoin from 12.74±3.81 to 11.09±4.58 and 10±3.11mg/kg respectively. The reduction in both these ED50 value were not significant statistically. Escitalopram given in 2mg/kg did not influence the ED50 value of phenytoin (Table 8).

Table 8: Effect of the chronic treatment with venlafaxine and escitalopram on the anticonvulsant action of phenytoin.

Treatment	ED 50 value±SEM (mg/kg)
Phenytoin+Vehicle	12.74±3.81
Phenytoin+Venlafaxine (6.2 mg/kg)	11.09±3.81
Phenytoin+Venlafaxine (12.5 mg/kg)	10±3.11
Phenytoin+Venlafaxine (25 mg/kg)	8.09±2.46 *
Phenytoin+Escitalopram (2mg/kg)	12.74±3.81
Phenytoin+Escitalopram (4 mg/kg)	11.09±4.58
Phenytoin+Escitalopram (8 mg/kg)	10±3.11

Values are expressed as mean + standard error of mean (SEM). * denotes P<0.05 in comparison to control, ** denotes P<0.01 in comparison to control, *** denotes P<0.001 in comparison to control.

DISCUSSION

Venlafaxine, a SNRI, blocks reuptake of noradrenaline (NA) and serotonin (5-HT) and also has direct action on 5-HT_{1A} and β_2 receptors, without any significant effect on cholinergic and histaminergic receptors. Increase in synaptic concentration of NA and 5-HT has been demonstrated to exert its anticonvulsant and antidepressant activity.²¹

It has been demonstrated that increase in NA levels in brain control GABA, glutamate, and dopamine levels through α and β_2 receptors and is responsible for decrease in seizure activity.^{22,23} Serotonergic transmission has been postulated to modulate seizure activity by decreasing excitatory and increasing the inhibitory activity due to hyperpolarization of glutamatergic neurons by 5-HT_{1A} receptors and depolarization of GABAergic neurons by 5-HT_{2C} receptors, respectively.²⁴ As seen with fluoxetine, chronic administration of venlafaxine has also been shown to elevate brain concentration of inhibitory neurosteroid allopregnanolone which is a potent positive modulator of GABA_A receptors.^{7,11} Elevation in allopregnanolone may also be contributing to anticonvulsant effects of venlafaxine. Thirdly, effect of SSRIs such as inhibition of production of pro-inflammatory cytokines like interleukin 1β , tumor necrosis factor α and interferon γ and increase in anti-inflammatory cytokines such as interleukin-10 may also be another mechanism for anticonvulsant effect of venlafaxine as pro inflammatory cytokines are involved in generating and exacerbating seizures.^{25,26} The contribution of change in levels of venlafaxine or studied AEDs cannot be ruled. In an earlier study, it has been observed that venlafaxine does not change the levels of valproate in brain on acute and chronic administration at the doses administered in this study though these doses have been found to raise the levels of phenobarbitone on acute administration, but lower that of phenytoin on chronic administration in this study.¹¹ The least effect on ED₅₀ of phenytoin with venlafaxine in this study may be explained by lowering of phenytoin concentration in brain.

Escitalopram, S-enantiomer of the citalopram and a SSRI, increased the electroconvulsive threshold in dose dependent manner but significantly at a dose of 8mg/kg. On acute and chronic administration of escitalopram in combination with studied AEDs, significant reduction in ED₅₀ of valproate was observed at 8 mg/kg with no significant change in ED₅₀ of phenobarbitone and phenytoin. The anticonvulsant activity of escitalopram can be explained by the elevation of serotonin concentration in synapses as above. In the present study, it was revealed that venlafaxine and escitalopram administered either alone or in combination with antiepileptics acutely or chronically, exhibit anticonvulsant action.

CONCLUSION

From the above findings, it may be concluded that venlafaxine and escitalopram administered either alone or in combination with AEDs acutely or chronically, exhibit anticonvulsant action. These findings suggest that both of these antidepressants may be given safely in patients of epilepsy suffering from depression. However, the study is experimental in nature and requires further studies.

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Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Animal Ethics Committee

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