RESEARCH ARTICLE

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Interaction of Verapamil, a calcium channel blocker, with Fluvoxamine, Venlafaxine and Tianeptine on their antidepressant activity in mice

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ABSTRACT

Introduction:
Depression is a common co-morbid illness with a prevalence of 16-23% in patients suffering from cardiovascular diseases. Verapamil, a calcium channel blocker, is widely used in the treatment of various cardiovascular diseases and has been shown to possess antidepressant effects, however, information on its interaction with antidepressant drugs like fluvoxamine, venlafaxine and tianeptine is limited. Hence, the present study was conducted.

Method:
The study was carried out in albino mice in two phases. In phase I, antidepressant activity of verapamil, fluvoxamine, venlafaxine and tianeptine was confirmed after their single dose administration using forced swim test (FST) and tail suspension test (TST) and their minimum antidepressant doses were determined. In phase II, the interaction of verapamil with fluvoxamine, venlafaxine and tianeptine for antidepressant activity was studied by administering these drugs orally on daily basis for 28 days and performing FST & TST on 1st, 14th and 28th day.

Results:
In phase I, all the studied drugs demonstrated antidepressant activity in dose dependent manner in both FST and TST. Minimal antidepressant dose of verapamil, fluvoxamine, venlafaxine and tianeptine was observed as 40, 25, 25 and 10 mg/kg respectively. In phase II, combinations of sub-antidepressant dose of verapamil (20 mg/kg) with sub-antidepressant doses of fluvoxamine (12.5 mg/kg), venlafaxine (12.5 mg/kg) and tianeptine (5 mg/kg) demonstrated additive antidepressant activity when compared to the control group and individual drug groups after same duration of treatment.

Conclusion:
Verapamil exerts dose dependent as well as treatment duration dependent antidepressant activity which is additive to antidepressant activity of fluvoxamine, venlafaxine and tianeptine.

Keywords:
Antidepressant, Fluvoxamine, Verapamil, Tianeptine, Venlafaxine.

INTRODUCTION

Depression is a common co-morbid illness with a prevalence of 16-23% in patients suffering from cardiovascular diseases due to chronic nature of these illnesses [1,2]. The association of major depression and elevated depressive symptoms with coronary heart disease has been shown to worsen the prognosis[3].

Antidepressant drugs (ADDs) like tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin nor-epinephrine reuptake inhibitors (SNRIs) and atypical antidepressants are commonly used for the treatment of depression but compliance to therapy remains low due to frequent adverse effects.

Calcium channel blockers (CCBs) affect neurotransmitter release and thus functioning of the central nervous system (CNS). Verapamil, a CCB, is widely used in the treatment of various cardiovascular diseases and has been shown to possess antidepressant effects which are also additive to antidepressant effects of imipramine and sertraline [4,5]. However, information about interaction of verapamil with ADDs like fluvoxamine, venlafaxine and tianeptine is limited in existing literature. Hence, the present study was undertaken to investigate the

antidepressant effect of verapamil and its interaction with fluvoxamine, venlafaxine and tianeptine for antidepressant activity.

MATERIALS AND METHODS

Albino mice, weighing 20-30g, housed in sterile polypropylene cages containing sterile paddy husk as bedding material in the standard laboratory conditions with free access to food and water were used in this study after obtaining Institutional Animal Ethical Committee (IAEC)clearance.

The study was conducted in two phases. In phase I, the animals were divided into one control group of six animals which received vehicle orally and four drug treatment groups of eighteen animals each. Each drug treatment group was further subdivided into three sub groups of six animals each which received different doses of the study drug orally viz. Group A: Verapamil 10, 20 and 40 mg/kg, Group B: Fluvoxamine 12.5, 25 and 50 mg/kg, Group C: Venlafaxine 6.25, 12.5 and 25 mg/kg and Group D: Tianeptine 5, 10 and 20 mg/kg. Minimum antidepressant dose of individual drug was determined by comparing drug treatment groups with control group using forced swim test (FST) & tail suspension test (TST).

In phase II, the animals were divided into eight groups of six mice each and received following daily drug treatments orally for 28 days - Group A: Vehicle alone, Group B: Verapamil 20 mg/kg, Group C: Fluvoxamine 12.5 mg/kg, Group D: Verapamil 20 mg/kg & Fluvoxamine 12.5 mg/kg, Group E: Venlafaxine 12.5 mg/kg, Group F: Verapamil 20 mg/kg & Venlafaxine 12.5 mg/kg, Group G: Tianeptine 5 mg/kg and Group H: Verapamil 20 mg/kg & Tianeptine 5 mg/kg. The effect of verapamil on antidepressant action of fluvoxamine, venlafaxine and tianeptine was studied using FST & TST on 1st, 14th and 28th day of study.

Forced swimming test (FST):

Animals were forced to swim in vertical glass cylinder (height: 25 cm, diameter: 10 cm) which was filled upto 15cm with fresh tap water at 27^{o}C [5]. Only one animal at one time was forced to swim in the cylinder for 6 min. The vigorous activity (escape activity) seen in initial 2 min of session was discarded [6]. The immobility time during last 4 min of the session was recorded. Animal was considered immobile when it remained floating in the water without struggling, making only minimum movements of its limbs necessary to keep its head above water [6].

Tail suspension test (TST):

Animals were hanged upside down at the edge of the table by using adhesive tape approximately 1 cm from the tip of the tail for 5 min after administering the assigned treatment [6]. The time for which animal remained immobile was quantified during the test period of 5 min. Animal was considered immobile when it hanged passively and motionless [7].

The decrease in the period of immobility in the above tests was considered as suggestive of antidepressant activity.

Statistical analysis

Data were statistically analyzed by one way ANOVA followed by post hoc Tukey test using Statistical Package for the Social Sciences (SPSS) version 20 software. Results were expressed as mean ± standard error of mean (SEM). 'P' value <0.05 was considered statistically significant.

RESULTS

In phase I, all the studied drugs demonstrated antidepressant activity in dose dependent manner in both FST and TST. Verapamil exhibited statistically significant antidepressant activity at 40 mg/kg ($P < 0.05$), fluvoxamine at 25 mg/kg ($P < 0.05$) and 50 mg/kg ($P < 0.01$), venlafaxine at 25 mg/kg ($P < 0.01$),tianeptine at 10 and 20 mg/kg ($P < 0.01$ for both doses) compared to control group (Table 1).

Treatment groups	Dose (mg/kg)	Duration of immobility (seconds)	
		FST	TST
Control	-	142.00 ± 5.06	153.00 ± 8.84
Verapamil	10	138.16 ± 4.96	148.50 ± 8.54
	20	132.16 ± 3.72	136.33 ± 9.22
	40	122.00 ± 4.06*	123.00 ± 6.74*
Fluvoxamine	12.5	133.16 ± 3.95	145.66 ± 5.32
	25	124.00 ± 4.00*	129.50 ± 9.04*
	50	107.00 ± 6.46**	112.50 ± 5.56**
Venlafaxine	6.25	137.83 ± 6.54	152.83 ± 8.43
	12.5	128.83 ± 4.67	145.00 ± 9.07
	25	111.33 ± 6.83**	115.50 ± 5.08**
Tianeptine	5	130.50 ± 4.27	136.83 ± 6.22
	10	107.16 ± 8.70**	119.66 ± 7.14*
	20	95.50 ± 7.72**	92.50 ± 5.35**

Values are expressed as mean ± standard error of mean (SEM)

*: $P < 0.05$ and **: $P < 0.01$ in comparison to control

Table 1: Effect of verapamil, fluvoxamine, venlafaxine and tianeptine in FST & TST on single dose administration

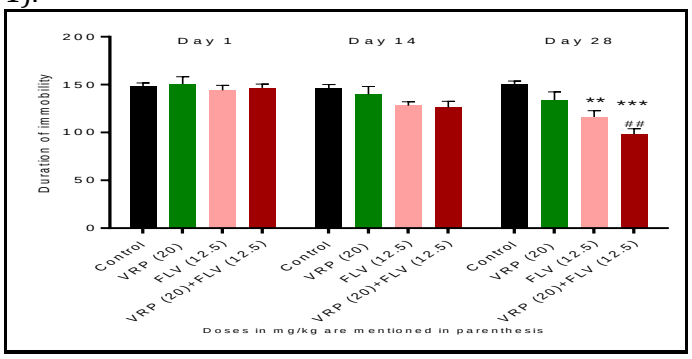
Minimal antidepressant dose of verapamil, fluvoxamine, venlafaxine and tianeptine was observed as 40, 25, 25 and 10 mg/kg respectively.

In phase II, sub-antidepressant doses of test drugs and their combinations were studied for their antidepressant effects on chronic administration using FST and TST. The results of phase II of this study are as follows:

Effects of verapamil and fluvoxamine in FST:

Sub-antidepressant doses of verapamil (20 mg/kg) & fluvoxamine (12.5 mg/kg) individually exhibited treatment duration dependent antidepressant effect, however, it was statistically significant only with fluvoxamine on day 28 ($P < 0.01$) compared to control group after the same duration of treatment. The

combinations of sub-antidepressant dose of verapamil (20 mg/kg) with sub-antidepressant dose of fluvoxamine (12.5 mg/kg) also showed treatment duration dependent antidepressant effect which was statistically significant on day 28 compared to both control group (P < 0.001) and individual drug groups (P < 0.01) after the same duration of treatment (Fig 1).



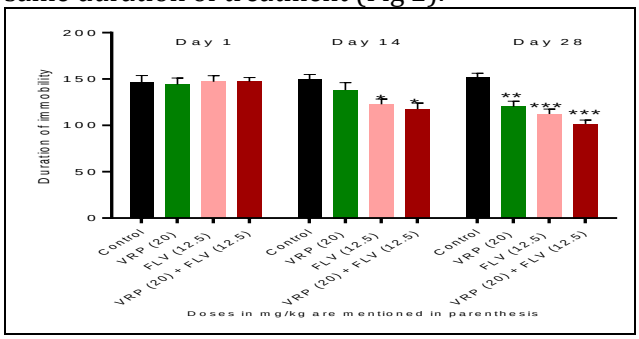
**: P < 0.01 and ***: P < 0.001 in comparison to control group after same duration of treatment

#: P < 0.01 in comparison to individual drug groups after same duration of treatment

Fig 1: Effects of sub-antidepressant dose of verapamil (VRP), fluvoxamine (FLV) and their combination in FST on chronic administration

Effects of verapamil and fluvoxamine in TST:

Sub-antidepressant doses of verapamil (20 mg/kg)& fluvoxamine (12.5 mg/kg) individually exhibited treatment duration dependent antidepressant effect, however, it was statistically significant with verapamil on day 28 (P < 0.01) and fluvoxamine on day 14 (P < 0.05) and day 28 (P < 0.001) compared to control group after the same duration of treatment. The combination of verapamil & fluvoxamine also exhibited treatment duration dependent antidepressant effect which was statistically significant on day 14 (P < 0.05) and day 28 (P < 0.001) compared to control group but was not statistically different compared to individual drug group after the same duration of treatment (Fig 2).

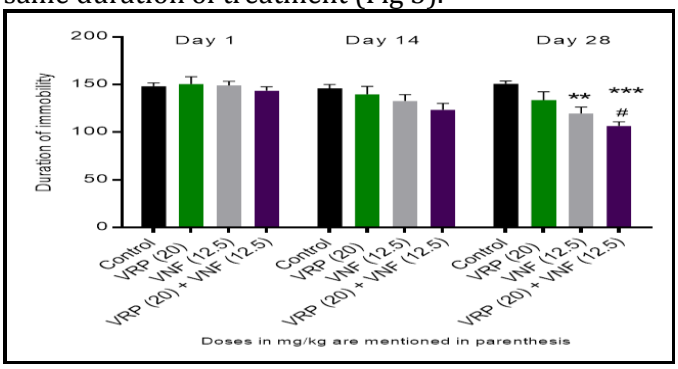


*: P < 0.05, **: P < 0.01 and ***: P < 0.001 in comparison to control group after same duration of treatment

Fig 2: Effects of sub-antidepressant doses of verapamil (VRP), fluvoxamine (FLV) and their combination in TST on chronic administration

Effects of verapamil and venlafaxine in FST:

Sub-antidepressant doses of verapamil (20 mg/kg) & venlafaxine (12.5 mg/kg) individually exhibited treatment duration dependent antidepressant effect, however, it was statistically significant only in venlafaxine group on day 28 (P< 0.01) compared to control group after the same duration of treatment. The combination of verapamil & venlafaxine also exhibited treatment duration dependent antidepressant effect which was statistically significant on day 28 compared to control group (P < 0.001) and individual drug groups (P< 0.05) after the same duration of treatment (Fig 3).

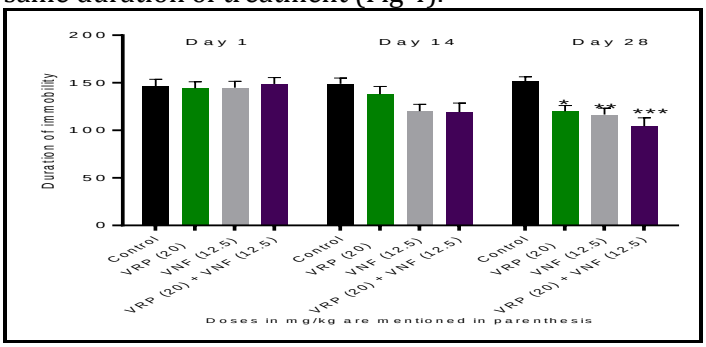


**: P < 0.01 and ***: P < 0.001 in comparison to control group after same duration of treatment, #: P < 0.05 in comparison to individual drug groups after same duration of treatment

Fig 3: Effects of sub-antidepressant doses of verapamil (VRP), venlafaxine (VNF) and their combination in FST on chronic administration

Effects of verapamil and venlafaxine in TST:

Sub-antidepressant doses of verapamil (20 mg/kg) & venlafaxine (12.5 mg/kg) individually exhibited treatment duration dependent antidepressant effect, however, it was statistically significant only on day 28 with both verapamil (P < 0.05) as well as venlafaxine (P < 0.01) compared to control group after the same duration of treatment. The combination of verapamil & venlafaxine also exhibited treatment duration dependent antidepressant effect which was statistically significant on day 28 (P < 0.001) compared to control group but was not statistically different compared to individual drug groups after the same duration of treatment (Fig 4).



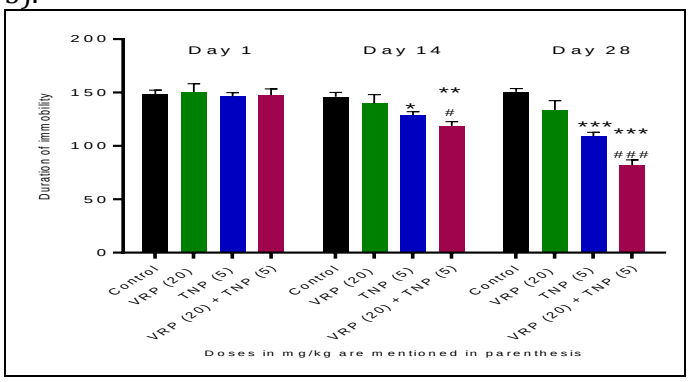
*: P < 0.05, **: P < 0.01 and ***: P < 0.001 in comparison to control group after same duration of treatment

Fig 4: Effects of sub-antidepressant doses of verapamil (VRP), venlafaxine (VNF) and their combination in TST on chronic administration

Effects of verapamil and tianeptine in FST:

Sub-antidepressant doses of verapamil (20 mg/kg) & tianeptine (5 mg/kg) individually exhibited treatment duration dependent antidepressant effect, however, it was statistically significant only with tianeptine on day 14 (P < 0.05) and on day 28 (P < 0.001) compared to control group after the same duration of treatment. The combination of verapamil & tianeptine also exhibited treatment duration dependent antidepressant effect which was statistically significant on day 14 (P < 0.01) and day 28 (P < 0.001) compared to control group and on day 14 (P < 0.05)

and on day 28 (P < 0.001) compared to individual drug groups after the same duration of treatment (Fig 5).



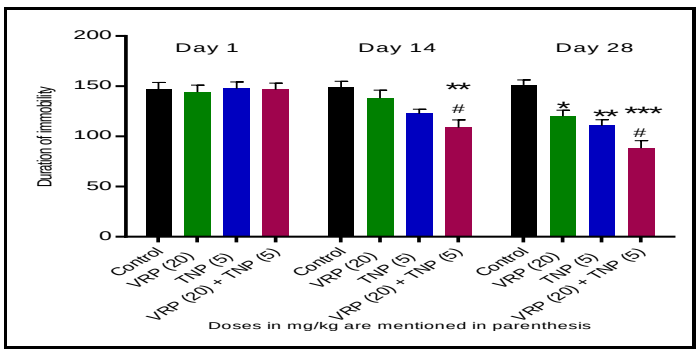
*: P < 0.05, **: P < 0.01 and ***: P < 0.001 in comparison to control group after same duration of treatment

#: P < 0.05 and # # #: P < 0.001 in comparison to individual drug groups after same duration of treatment

Fig 5: Effects of sub-antidepressant doses of verapamil (VRP), tianeptine (TNP) and their combination in FST on chronic administration

Effects of verapamil and tianeptine in TST:

Sub-antidepressant doses of verapamil (20 mg/kg) & tianeptine (5 mg/kg) individually exhibited treatment duration dependent antidepressant effect, however, it was statistically significant on day 28 with both verapamil (P < 0.05) and tianeptine (P <0.001) compared to control group after the same duration of treatment. The combination of verapamil & tianeptine also exhibited treatment duration dependent antidepressant effect which was statistically significant on day 14 (P < 0.01) and day 28 (P < 0.001) compared to control group and on day 14 and 28 (P < 0.05 on both days) compared to individual drug groups after the same duration of treatment (Fig 6).



* P < 0.05, **: P < 0.01 and ***: P < 0.001 in comparison to control group after same duration of treatment

#: P < 0.05 in comparison to individual drug groups after same duration of treatment

Fig 6: Effects of sub-antidepressant doses of verapamil (VRP), tianeptine (TNP) and their combination in TST on chronic administration

DISCUSSION

The single dose administration of verapamil, fluvoxamine, venlafaxine and tianeptine showed antidepressant effect in dose dependent manner and supports the findings published in the existing literature [5, 8-11].

Fluvoxamine and other SSRIs exert their antidepressant by blocking serotonin (5-Hydroxytryptamine, 5-HT) uptake which gradually results in down-regulation and desensitization of 5-HT_{1A}, 5-HT_{1D} and 5-HT_7 autoreceptors with enhanced and prolonged serotonergic neurotransmission [12]. Repeated treatments with SSRIs also reduce the expression of serotonin transporter (SERT), resulting in reduced clearance of released 5-HT and increased serotonergic neurotransmission [12]. In addition, down-regulation of post synaptic 5-HT2A receptors may contribute to antidepressant efficacy directly or by influencing the function of noradrenergic and other neurons via serotonergic heteroreceptors [12]. Later-developing effects include sustained increase in cyclic AMP signaling and phosphorylation of the nuclear transcription factor as well as increase in the expression of trophic factors such as brain-derived neurotrophic factor (BDNF) contributing to neural plasticity, resilience, neurogenesis and thereby antidepressant effects [6]. Venlafaxine, a SNRI, blocks the serotonin transporter (SERT) at low concentrations and noradrenaline (NA) reuptake transporter at high concentrations resulting in various neuroadaptive changes and antidepressant effect[13]. The antidepressant effect of tianeptine is due to various CNS changes observed with its administration viz. enhanced uptake of 5-HT in cortex, hippocampus and hypothalamus [14, 15], attenuation of 5-HT induced inwardly rectifying K^+ current resulting in increased excitability of serotoninergic neurons in dorsal raphe [16], decreased susceptibility of 5-HT to breakdown by central monoamine oxidase type A [16, 17], increase in L-Noradrenaline levels through an unknown mechanism [14], rise in level of dopamine (DA) in nucleus accumbens [18], enhancement of functional responsiveness of dopaminergic D_2/D_3 receptors [19], blockade of 5-HT_{1B} presynaptic heteroreceptors mediated release of acetylcholine independent of its effect on 5-HT availability [20], decrease in elevation of nitric oxide (NO, a neurotoxin) levels by inhibiting activity of NO synthase (NOS) probably due to crosstalk between 5-HT-glutamate-NO pathways [21-22].

Verapamil has been suggested to exert antidepressant effect by inhibiting 5-HT uptake by a mechanism that does not involve alteration in calcium fluxes [8, 23], increasing the NA release from sympathetic neurons directly as well as by blocking pre-junctional α_2 receptors [8, 24] and interacting with catecholamine storage vesicles so as to reduce taking up and storing of catecholamines in them [8].

Antidepressant activity was enhanced when verapamil was combined with fluvoxamine, venlafaxine and tianeptine compared to the effects of individual drugs when administered alone. The pattern of results of phase II of this study is similar to the reports of enhanced antidepressant activity of imipramine when it was combined with verapamil or nifedipine[5 8,25].This enhancement might be due to synergism of the antidepressant effects of the studied drugs.

CONCLUSION

Verapamil exerts dose dependent as well as treatment duration dependent antidepressant activity which is additive to antidepressant activity of fluvoxamine, venlafaxine and tianeptine suggesting that in combination the dose requirement of these drugs may be reduced and such dose reductions will probably be associated with lower incidence of adverse effects and better compliance to the therapy. Since the study is experimental in nature, the findings need to be confirmed in clinical studies before such approach is applied in clinical practice.

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