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Research Article

Effects of calcium channel blocker, nifedipine, on antidepressant activity of fluvoxamine, venlafaxine and tianeptine in mice

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ABSTRACT

Background: Cardiovascular diseases are commonly associated with depression. Calcium channel blockers (CCBs) form commonly used group of drugs for the treatment of a number of cardiovascular diseases. Nifedipine, a CCB, has been shown to possess antidepressant activity and potentiate antidepressant activity of imipramine and sertraline, however, literature on its interaction with newer antidepressant drugs such as fluvoxamine, venlafaxine and tianeptine is limited. Hence, the present study was undertaken.
Methods: The study was carried out in albino mice in two phases. In Phase I, antidepressant activity of nifedipine, fluvoxamine, venlafaxine and tianeptine were 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 effect of nifedipine on antidepressant activity of fluvoxamine, venlafaxine and tianeptine was studied by orally administering sub-antidepressant doses of these drugs for 28 days. FST and TST were carried out on 1st, 14th and 28th day of the study and change in immobility period was observed.
Results: In Phase I, all the studied drugs exhibited dose dependent antidepressant activity in both FST and TST. Minimal antidepressant dose of nifedipine, fluvoxamine, venlafaxine and tianeptine was observed as 10, 25, 25 and 10 mg/kg respectively. In Phase II, combinations of sub-antidepressant dose of nifedipine (5 mg/kg) with sub-antidepressant doses of fluvoxamine (12.5 mg/kg), venlafaxine (12.5 mg/kg) and tianeptine (5 mg/kg) exhibited enhanced antidepressant activity when compared to the control group and individual drug groups after same duration of treatment.
Conclusions: Nifedipine, fluvoxamine, venlafaxine and tianeptine possess antidepressant activity and nifedipine exhibits synergistic antidepressant activity with fluvoxamine, venlafaxine and tianeptine.

Keywords: Antidepressant, Fluvoxamine, Nifedipine, Tianeptine, Venlafaxine

INTRODUCTION

Cardiovascular diseases such as hypertension, coronary heart disease and congestive heart failure are common globally. Due to chronic nature of these illnesses, such patients may commonly suffer from depression as a co-morbid illness.[1] The prevalence of depression in patients with cardiovascular diseases ranges from 16% to 23%.[2] Depression on the other hand in adults is also associated with risk factors for cardiovascular diseases. Major depression and elevated depressive symptoms are associated with a worse prognosis in patients with coronary heart disease.[2]

Calcium and calcium channels are involved in neurotransmitter release and thus functioning of central nervous system (CNS).[3] Calcium channel blockers (CCBs) like nifedipine are commonly used in the treatment of various cardiovascular diseases.

Although, a number of available effective antidepressant drugs (ADDs) like tricyclic antidepressants, selective serotonin reuptake inhibitors (SSRIs), serotonin nor-epinephrine reuptake inhibitors (SNRIs) and atypical antidepressants exist, however, most of these have frequent adverse effects contributing to reduction in compliance to therapy. Recently, it has been demonstrated in mice that nifedipine, a CCB, possesses antidepressant effects.[4] Antidepressant effects of nifedipine have been shown to be additive with imipramine and sertraline suggesting a reduction in dose requirement of ADD and thus lowering the incidence of their adverse effects and ensuring better compliance to therapy.[5]

However, effects of nifedipine on the antidepressant activity of newer ADDs like fluvoxamine, venlafaxine and tianeptine have not been studied much. In view of above, the present study was planned to investigate the effect of nifedipine on antidepressant activity of fluvoxamine, venlafaxine and tianeptine in mice.

METHODS

Animals

Healthy adult Swiss albino male mice weighing 20-30 g were used in this study. The mice were housed in sterile polypropylene cages containing sterile paddy husk as bedding material. The mice were fed on standard laboratory diet and water *ad libitum*. The animals were acclimatized for 1-week to standardized laboratory conditions (12 hrs dark/light cycle) before the start of the experiment. The study was conducted in compliance with the Committee for the Purpose of Control and Supervision on Experiments on Animals guidelines after approval from Institutional Animal Ethics Committee.[6]

Animal groups and study design

The study was carried out in two phases. In Phase I, minimum antidepressant dose of various test drugs was determined by administering each drug in three different doses orally to three different groups of six animals each – nifedipine 2.5, 5 and 10 mg/kg, fluvoxamine 12.5, 25 and 50 mg/kg, venlafaxine 6.25, 12.5 and 25 mg/kg and tianeptine 5, 10 and 20 mg/kg. The control group consisting of six animals was treated with vehicle alone. Minimum antidepressant dose of individual drug was determined by comparing drug treatment groups with the control group.

In Phase II, the effect of nifedipine on antidepressant action of fluvoxamine, venlafaxine and tianeptine was studied by orally administering sub-antidepressant doses of these drugs for 28 days. Animals were divided into eight groups of six mice each and received following treatments - Group 1: Vehicle alone, Group 2: Nifedipine 5 mg/kg, Group 3: Fluvoxamine 12.5 mg/kg, Group 4: Nifedipine 5 mg/kg and fluvoxamine 12.5 mg/kg, Group 5: Venlafaxine 12.5 mg/kg, Group 6: Nifedipine 5 mg/kg and venlafaxine 12.5 mg/kg, Group 7: Tianeptine 5 mg/kg and Group 8: Nifedipine 5 mg/kg and tianeptine 5 mg/kg. Forced swimming test (FST) and tail suspension test (TST) were carried out on 1st, 14th and 28th day of the study.

Tests used to determine antidepressant activity

FST

Animals were forced to swim in vertical glass cylinder (height: 25 cm, diameter: 10 cm) which was filled upto 15 cm with fresh tap water at 27°C.[5,7] Only one animal at one time was forced to swim in the cylinder for a total of 6 mins. The vigorous activity (escape activity) seen in initial 2 mins of the session was discarded.[8,9] The immobility time during last 4 mins of the session was recorded.[7,8] 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.[7]

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 mins after administering the assigned treatment.[7,10] The time for which animal remained immobile was quantified during the test period of 5 mins.[8] Animal was considered immobile when it hanged passively and motionless.[8,9]

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

Statistical analysis

The data were expressed as the mean±standard error of mean of the parameter measured and they were analyzed by one-way analysis of variance followed by post hoc Tukey test using Statistical Package for the Social Sciences (SPSS) version 20 software. The level of significance was set at $p<0.05$.

RESULTS

Phase I

In this phase, all the test drugs exhibited dose dependent antidepressant activity in FST and TST. In FST, nifedipine exhibited statistically significant antidepressant activity at 10 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 ($p<0.01$) and tianeptine at 10 and 20 mg/kg ($p<0.01$ at both doses) compared to control group (Table 1). In TST, nifedipine exhibited statistically significant antidepressant activity at 10 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 ($p<0.01$) and tianeptine at 10 mg/kg ($p<0.05$) and 20 mg/kg ($p<0.01$) compared to control group (Table 1). Minimal antidepressant dose of nifedipine, fluvoxamine, venlafaxine and tianeptine was observed as 10, 25, 25 and 10 mg/kg respectively.

Phase II

In this phase, combinations of sub-antidepressant dose of nifedipine (5 mg/kg) with sub-antidepressant doses of fluvoxamine (12.5 mg/kg), venlafaxine (12.5 mg/kg) and tianeptine (5 mg/kg) were studied for their antidepressant effects on chronic administration using FST and TST. The results of Phase II are as follows:

Table 1: Effect of nifedipine, fluvoxamine, venlafaxine and tianeptine on single dose administration.

Treatment groups	Dose (mg/kg)	Duration of immobility (seconds)	
		FST	TST
Control	-	142.00±5.06	153.00±8.84
Nifedipine	2.5	133.00±4.02	150.50±11.16
	5	129.50±3.63	132.80±11.69
	10	113.16±7.60*	117.00±11.32*
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±SEM; *p<0.05 and **p<0.01 in comparison to control. FST: Forced swim test, TST: Tail suspension test, SEM: Standard error of mean

Effects of nifedipine and fluvoxamine in FST

Nifedipine and fluvoxamine when administered alone at sub-antidepressant doses (5 and 12.5 mg/kg respectively) exhibited treatment duration dependent antidepressant effect, however, it was statistically significant with nifedipine on day 28 (p<0.05) and with fluvoxamine on day 14 (p<0.05) and day 28 (p<0.01) compared with control group after the same duration of treatment. The combination of sub-antidepressant doses of nifedipine and fluvoxamine also exhibited treatment duration dependent antidepressant effect, which was statistically significant on day 14 (p<0.01) and day 28 (p<0.001) compared with control group and on day 28 (p<0.01) compared with individual drug groups after the same duration of treatment (Table 2).

Effects of nifedipine and fluvoxamine in TST

Nifedipine and fluvoxamine when administered alone at sub-antidepressant doses (5 and 12.5 mg/kg respectively) exhibited treatment duration dependent antidepressant effect, however, it was statistically significant with nifedipine on day 28 (p<0.05) and with fluvoxamine on day 14 (p<0.05) and day 28 (p<0.01) compared to control group after the same duration of treatment. The combination of sub-antidepressant doses of nifedipine and 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 and on day 28 (p<0.05) compared to individual drug groups after the same duration of treatment (Table 3).

Effects of nifedipine and venlafaxine in FST

Nifedipine and venlafaxine when administered alone at sub-antidepressant doses (5 and 12.5 mg/kg respectively) exhibited treatment duration dependent antidepressant effect, however, it was statistically significant with nifedipine on day 28 (p<0.05) and with venlafaxine on day 28 (p<0.05) compared to control group after the same duration of treatment. The combination of sub-antidepressant doses of nifedipine and venlafaxine also exhibited treatment duration dependent antidepressant effect, which was statistically significant on day 28 compared to control group (p<0.001) as well as individual drug groups (p<0.05) after the same duration of treatment (Table 4).

Effects of nifedipine and venlafaxine in TST

Nifedipine and venlafaxine when administered alone at sub-antidepressant doses (5 and 12.5 mg/kg respectively) exhibited treatment duration dependent antidepressant effect, however, it was statistically significant with nifedipine on day 28 (p<0.05) and with venlafaxine on day 14 (p<0.05) and day 28 (p<0.01) compared to control group after the same duration of treatment. The combination of sub-antidepressant doses of nifedipine and venlafaxine 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, but were not statistically different compared to individual drug groups after the same duration of treatment (Table 5).

Effects of nifedipine and tianeptine in FST

Nifedipine and tianeptine when administered alone at sub-antidepressant doses (5 mg/kg of each drug) exhibited treatment duration dependent antidepressant effect, however, it was statistically significant with nifedipine on day 28 (p<0.05) and with tianeptine on day 28 (p<0.001) compared to control group after the same duration of treatment. The combination of sub-antidepressant doses of nifedipine and tianeptine also exhibited treatment duration dependent antidepressant effect which was statistically significant on day 14 (p<0.001) 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 (Table 6).

Effects of nifedipine and tianeptine in TST

Nifedipine and tianeptine when administered alone at sub-antidepressant doses (5 mg/kg of each drug) exhibited treatment duration dependent antidepressant effect, however, it was statistically significant with nifedipine on day 28 (p<0.05) and with tianeptine 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 sub-

Table 2: Effects of sub-antidepressant dose of nifedipine, fluvoxamine and their combination in FST on chronic administration.

Day	Duration of immobility (sec)				One-way ANOVA		
	Control	NFP (5 mg/kg)	FLV (12.5 mg/kg)	NFP (5 mg/kg)+ FLV (12.5 mg/kg)	F	df	p
1	148.17±3.58	141.50±3.51	144.16±5.06	143.66±3.77	0.475	3.20	0.703
14	146.00±4.05	134.50±3.48	128.00±4.16*	123.00±5.10**	5.486	3.20	0.006
28	150.67±3.13	128.00±3.78*	116.17±6.53**	97.66±6.93***,##	17.159	3.20	<0.0001

NFP: Nifedipine, FLV: Fluvoxamine; Values are expressed as mean±SEM. *p<0.05, **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. FST: Forced swim test, SEM: Standard error of mean

Table 3: Effects of sub-antidepressant dose of nifedipine, fluvoxamine and their combination in TST on chronic administration.

Day	Duration of immobility (sec)				One-way ANOVA		
	Control	NFP (5 mg/kg)	FLV (12.5 mg/kg)	NFP (5 mg/kg)+ FLV (12.5 mg/kg)	F	df	p
1	146.50±7.20	143.50±5.16	147.00±6.54	145.16±4.51	0.069	3.20	0.976
14	149.00±5.95	127.16±7.55	122.83±5.60*	111.83±6.18*	5.995	3.20	0.004
28	151.33±4.92	120.83±8.27*	112.33±5.30**	93.83±5.90***,#	14.776	3.20	<0.0001

NFP: Nifedipine, FLV: Fluvoxamine; Values are expressed as mean±SEM. *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. TST: Tail suspension test, SEM: Standard error of mean

Table 4: Effects of sub-antidepressant dose of nifedipine, venlafaxine and their combination in FST on chronic administration.

Day	Duration of immobility (sec)				One-way ANOVA		
	Control	NFP (5 mg/kg)	VNF (12.5 mg/kg)	NFP (5 mg/kg)+ VNF (12.5 mg/kg)	F	df	p
1	148.17±3.58	141.50±3.51	149.00±4.41	143.50±4.64	0.792	3.20	0.513
14	146.00±4.05	134.50±3.48	132.83±6.63	129.00±6.50	1.864	3.20	0.168
28	150.67±3.13	128.00±3.78*	119.50±6.89*	103.50±5.73***,#	14.770	3.20	<0.0001

NFP: Nifedipine, VNF: Venlafaxine; Values are expressed as mean±SEM. *p<0.05 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. FST: Forced swim test, SEM: Standard error of mean

Table 5: Effects of sub-antidepressant dose nifedipine, venlafaxine and their combination in TST on chronic administration.

Day	Duration of immobility (sec)				One-way ANOVA		
	Control	NFP (5 mg/kg)	VNF (12.5 mg/kg)	NFP (5 mg/kg)+ VNF (12.5 mg/kg)	F	df	p
1	146.50±7.20	143.50±5.16	144.83±6.80	144.33±5.04	0.043	3.20	0.988
14	149.00±5.95	127.16±7.55	120.16±7.24*	113.33±5.35**	5.498	3.20	0.006
28	151.33±4.92	120.83±8.27*	116.67±6.66**	98.16±6.43***	10.892	3.20	<0.0001

NFP: Nifedipine, VNF: Venlafaxine; Values are expressed as mean±SEM. *p<0.05, **p<0.01 and ***p<0.001 in comparison to control group after same duration of treatment. TST: Tail suspension test, SEM: Standard error of mean

antidepressant doses of nifedipine and 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 28 (p<0.01) compared to individual drug groups after the same duration of treatment (Table 7).

DISCUSSION

Phase I of the study showed that single dose administration of nifedipine, fluvoxamine, venlafaxine and tianeptine exhibits antidepressant effect in dose-dependent manner and confirms earlier published reports in the literature.[4,5,11-15]

Table 6: Effects of sub-antidepressant dose nifedipine, tianeptine and their combination in FST on chronic administration.

Day	Duration of immobility (sec)				One-way ANOVA		
	Control	NFP (5 mg/kg)	TNP (5 mg/kg)	NFP (5 mg/kg)+ TNP (5 mg/kg)	F	df	p
1	148.17±3.58	141.50±3.51	146.16±3.79	145.66±5.14	0.475	3.20	0.703
14	146.00±4.05	134.50±3.48	128.83±3.27	112.33±7.12***,#	8.721	3.20	0.001
28	150.67±3.13	128.00±3.78*	109.17±3.54***	81.83±4.63***,###	58.42	3.0	<0.0001

NFP: Nifedipine, TNP: Tianeptine; Values are expressed as mean±SEM. *p<0.05 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. FST: Forced swim test, SEM: Standard error of mean

Table 7: Effects of sub-antidepressant dose nifedipine, tianeptine and their combination in TST on chronic administration.

Day	Duration of immobility (sec)				One-way ANOVA		
	Control	NFP (5 mg/kg)	TNP (5 mg/kg)	NFP (5 mg/kg)+ TNP (5 mg/kg)	F	df	p
1	146.50±7.20	143.50±5.16	147.50±6.73	142.83±4.49	0.143	3.20	0.933
14	149.00±5.95	127.16±7.55	122.66±4.46*	113.83±5.46**	6.285	3.20	0.004
28	151.33±4.92	120.83±8.27*	110.50±6.03***	86.16±5.72***,##	18.007	3.20	<0.0001

NFP: Nifedipine, TNP: Tianeptine; Values are expressed as mean±SEM. *p<0.05, **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. TST: Tail suspension test, SEM: Standard error of mean

Fluvoxamine and other SSRIs have been suggested to exert their antidepressant effect 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.[16] Repeated treatments with SSRIs also reduce the expression of the serotonin transporter, resulting in reduced clearance of released 5-HT and increased serotonergic neurotransmission.[16] In addition, down-regulation of post synaptic 5-HT_{2A} receptors may contribute to antidepressant efficacy directly or by influencing the function of noradrenergic and other neurons via serotonergic heteroreceptors.[16] Later-developing effects include sustained increase in adenosine monophosphate (cAMP) signaling and phosphorylation of the nuclear transcription factor (cAMP response element binding), as well as increase in the expression of trophic factors such as brain-derived neurotrophic factor contributing to neural plasticity, resilience, neurogenesis and thereby antidepressant effects.[6,17]

Venlafaxine, a SNRI, has been suggested to block the 5-HT reuptake transporter at low concentrations and noradrenaline (NA) reuptake transporter at high concentrations resulting in various neuroadaptive changes and antidepressant effect.[18]

Tianeptine probably exerts its antidepressant effect due to various CNS changes observed with its administration viz. enhanced uptake of 5-HT in cortex, hippocampus and hypothalamus,[19,20] attenuation of 5-HT induced inwardly rectifying K^+ current resulting in increased excitability of serotoninergic neurons in dorsal raphe,[21] decreased susceptibility of 5-HT to breakdown by central monoamine oxidase type A,[19,22] increase in L-Noradrenaline levels through an unknown mechanism,[19] rise in level of dopamine (DA) in nucleus accumbens,[23] enhancement of functional responsiveness of dopaminergic D_2/D_3 receptors,[24] blockade of 5-HT_{1B} presynaptic heteroreceptors mediated release of acetylcholine independent of its effect on 5-HT availability,[25] 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.[26-28]

Nifedipine has been suggested to exert antidepressant action by interrupting calcium-calmodulin-NOS-guanylyl cyclase signaling pathway, activation of 5-HT_{1A} receptors thereby reducing uptake of 5-HT, increasing intracellular calcium activity by activating 5-HT_{2} and 5-HT_{3} and $GABA_A$ activation on secondary inhibitory interneurons leading to release of NA.[11,29-31]

Antidepressant activity was enhanced when nifedipine in Phase II was combined with fluvoxamine, venlafaxine and tianeptine compared to the effects of individual drugs when administered alone. This enhancement might be due to synergism of their antidepressant effects. The results of our study are similar to the reports of enhanced antidepressant activity of imipramine and sertraline when these were combined with nifedipine.[4,5,11]

This study demonstrates the synergism of antidepressant activity of nifedipine with fluvoxamine, venlafaxine and tianeptine suggesting that in combination their dose

requirement may be reduced and such dose reductions will probably be associated with lower incidence of adverse effects and better compliance to the therapy. However, considering the experimental nature of this study, such combination approach needs to be confirmed and validated through future clinical studies before such approach comes in clinical practice.

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