LOSARTAN AND PROPRANOLOL POTENTIATE ANTIDEPRESSANT AND ANXIOLYTIC ACTIVITY OF VENLAFAXINE IN EXPERIMENTAL ANIMALS WITHOUT ALTERING THE SYSTOLIC BLOOD PRESSURE.

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Summary

The comorbid condition involving depression or anxiety with hypertension is very common. The antidepressant/ anxiolytic, venlafaxine is also known to rise blood pressure and thus might worsen hypertension. Also the anti-hypertensives like prazosin, propranolol and losartan are reported to alter psychotropic activity. So, a month long study was planned to elicit the effect of antihypertensive prazosin, propranolol and losartan treatment with venlafaxine on psychotropic activity as well as blood pressure. Depression paradigms; Forced swim test and tail suspension test while anxiety paradigms; elevated plus maze and light dark arena were used. Systolic blood pressure was monitored using tail-cuff method. Propranolol and losartan potentiated antidepressant and anxiolytic activity of venlafaxine, while prazosin potentiated only anxiolytic activity, without altering the systolic blood pressure significantly. Whereas venlafaxine rised systolic blood pressure significantly and showed significant antidepressant as well as anxiolytic activity. Thus losartan or propranolol could be co administered with venlafaxine to annul its hypertensive adversity by reducing the dose requirement, without compromising its psychotropic action.

Keywords: Anxiety; Depression; Prazosin; Propranolol; Losartan; Venlafaxine.

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Introduction

The clinically used antidepressants like SSRIs, TCAs have been shown to possess various adverse effects.[1] The new class of atypical antidepressants like venlafaxine is reported to possess greater efficacy than SSRIs[2] and seems to have one of the most favorable drug-interaction profiles[3]. Venlafaxine has been shown to be helpful in improving symptoms of generalized anxiety disorder, in addition to its antidepressant activity.[4]

As secondary manifestations anxiety and depression have been implied with a number of physical disorders like hypertension, myocardial infarction, stroke, dementia, epilepsy, endocrinal disorders like diabetes, hyperthyroidism (anxiety) and hypothyroidism (depression) etc.[5,6] Prevalence of comorbidity of hypertension with depression has been reported to be as high as 18-37% of the hypertensive population[7]. On the contrary major depressive disorder could be an independent risk factor for hypertension[8]. These reports strongly indicate the need for inclusion of an antidepressant to treat the various physical disorders as mentioned above. Therefore it is imperative to consider the potential interactions of various drugs with commonly used antidepressant or anxiolytic.

The commonly prescribed anti-hypertensives like ramipril[9], propranolol and losartan have been shown to possess antidepressant and anxiolytic activity, while prazosin has been shown to possess anxiolytic activity and induce depression in animal models[10]. Their acute interaction with antidepressants amitriptyline, venlafaxine has also been reported[10].

Venlafaxine, a commonly prescribed antidepressant has been reported to rise systolic blood pressure[11], which depends on dose and duration of its administration, compelling the substitution with other antidepressant or use of an anti-hypertensive to annul the same. In case of venlafaxine treatment for comorbid condition with hypertension losartan and propranolol could be better anti-hypertensives as they have been reported to possess anti-depressant and anxiolytic activity also in experimental animals.[10]

Both hypertension and depression need chronic treatment and the results of acute study may not be relevant. The present study was therefore planned to explore the potential interaction of prazosin, propranolol and losartan with venlafaxine over a month long treatment.

Materials and methods

Animals

Healthy male adult Wistar rats weighing 150 ± 25 g and Swiss albino mice weighing 25 ± 5g were used for the study. The animals were obtained from the central animal house of the Institute and were kept in the laboratory for about 10 days in 12: 12 hour light and dark cycle. Throughout the experiment the animals were fed with laboratory chow (Amrut Brand) and water *ad libitum*.

The study was approved by Institutional Animal Ethics Committee constituted as per the CPCSEA guidelines, New Delhi.

Psychotropic studies: The anti-depressant paradigms employed in the present study were; forced swim test in rats[12] and tail suspension test in mice[13] as described earlier, the mean immobility time in seconds were compared with that of control. The anxiolytic activities were studied using paradigms; elevated plus maze[14] and light dark arena[15]. The mean number of rears, time spent (in seconds), percentage of entries into open arm were studied in elevated plus maze, while rearing, number of entries and percentage of time spent in light arena were observed for comparison in light dark arena.

Sub effective dose (SED) for each drug was determined in separate set of experiments. The maximum dose which just failed to reduce immobility time in FST paradigm significantly as compared to that of control was considered as sub effective dose. The SEDs in mg/kg of prazosin, propranolol, losartan and venlafaxine were determined to be 0.2, 8, 5 and 6.6 respectively for rats and the corresponding mice doses were calculated with the help of conversion table devised by Paget and Barnes.[16]

Antidepressant activity using FST paradigm was studied in 5 groups (n=6, in each) of rats, similar groups of mice were used for TST. Two groups of rats and mice were subjected for treatment with either saline or therapeutic equivalent dose of venlafaxine (20mg/kg for rat and 29mg/kg for mice). Remaining three groups of rats and mice received SED of venlafaxine with SED of prazosin or propranolol or losartan. Similarly treated separate 5 groups of rats were subjected for elevated plus maze and light dark arena to study anxiolytic activity. All the drugs were administered intra peritonially (i.p). In combination treatment venlafaxine was administered 30 min prior to the study, while others were administered one hour priorly and the treatment was continued once every 24hrs for 30 days. Various treated groups were also subjected for locomotor activity studies for 5min (using photoactometer, INCO, Ambala, India) and systolic blood pressure (SBP) recording.

Systolic Blood Pressure[17]: Rats were acclimatized for about 5-6 hr in lab at room temperature (30 ^{0}C). SBP was measured with a tail-cuff sphygmomanometer (Harvard apparatus, USA) between 15:30 and 16:30 h.[18] The equipment used included a restrainer, a tail cuff containing latex tube and a dual – channel recorder. Rats were allowed to acclimatize in restrainer before measuring SBP and then tail –cuff was placed on the rat tail and moved towards base till the sensors detects pulses. Then pressure was applied and systolic blood pressure was determined at least 8 times in each animal using Biopac system inc. (MP100A-CE 111A4306, Santa Barbara, California) to calculate group mean. The mean of eight consecutive readings was used for statistical comparisons.

The antidepressant, anxiolytic and locomotor activity was assessed on day 15 and 30, while SBP was recorded on day 0, 15 and 30.

Statistical analysis

All the results of the various experiments carried out in the present study were analyzed by ANOVA followed by Dunnet's posthoc test. The 'p' value ≤ 0.05 was considered as significant.

Results

Forced swim test

As expected venlafaxine treatment significantly ($p<0.01$, $p<0.001$) decreased immobility time. Similarly venlafaxine combination with propranolol or with losartan significantly ($p<0.05$, $p<0.01$) decreased immobility time. Combination treatment with venlafaxine and prazosin did not significantly alter the immobility time as compared to that of control.(Table 1)

Tail suspension test

The mean immobility time in venlafaxine treated mice was significantly ($p<0.001$) decreased throughout the study and venlafaxine combination with propranolol or losartan also showed significant ($p<0.05$, $p<0.01$) decrease as compared to that of control. Whereas in venlafaxine with prazosin treated group no significant difference in immobility time was observed as compared to control. (Table 1)

Table 1. Effect of various treatments on depression paradigms.

	15th day		30th day	
	FST	**TST**	**FST**	**TST**
Control	176.3 ± 5.28	218.7 ± 12.60	177.2 ± 4.25	214.2 ± 10.33
VNL	118.7± 12.64**	142.2± 7.63***	98.3± 4.13***	118.3± 3.88***
VNL+PRZ	172.7± 4.89	204.8± 11.63	174.8± 7.60	213.7± 12.67
VNL+PRP	149.7± 7.23*	178.0± 5.87*	143.3± 5.40**	171.0± 5.17**
VNL+LTN	129.0± 2.84***	149.2± 6.86***	110.8± 5.13***	139.7± 4.75***

*p<0.05, ** p<0.01, ***p<0.001

Elevated plus maze

Rearing behavior (number of rears), Open arm entry (percentage of entry) and percentage of time spent in open arm of elevated plus maze were significantly (p< 0.05; 0.001) increased throughout the study in groups treated with therapeutic equivalent dose of venlafaxine or SED of venlafaxine with SED of prazosin/ propranolol/ losartan as compared to that of control.(Table 2)

Light dark arena

Similar to the observations in EPM experiments rearing behavior (number of rears), number of entries and percentage of time spent in light arena were significantly (p< 0.05; 0.001) increased in animals treated with venlafaxine alone or its combination with prazosin/ propranolol/ losartan as compared to those of control.(Table 3)

Locomotor Activity

Locomotor activity in venlafaxine treated group with mean values of 21.67±0.88 and 20.67±0.88 on day 15 and 30 respectively were not significantly differing from control value of 20.67±0.88. Similarly the venlafaxine co administered with prazosin or propranolol or losartan with mean values 20.50±0.72, 22.67±0.80, 22.67±0.76 respectively on day 15 and 20.33±0.76, 22.33±0.80, 23.17±0.70 respectively on day 30, were not significantly differing from that of control.

Table 2. Effect of various treatments on elevated plus maze (anxiety paradigm).

	15th day			30th day		
	Rears	**% Time Spent (Open Arm)**	**% Entry in open arm**	**Rears**	**% Time spent (Open arm)**	**% Entry in open arm**
Control	2.33± 0.33	9.17 ± 3.17	24.79 ± 4.57	2.50 ± 0.34	9.17 ± 2.16	23.39 ± 4.49
VNL	3.83± 0.40*	21.55± 1.56**	49.34± 4.46**	5.17± 0.60**	21.72± 1.28**	49.89± 5.38**
VNL+PRZ	4.16± 0.65*	18.72± 0.99*	46.05± 5.00*	4.5± 0.43**	20.5± 1.61*	48.06± 3.79**
VNL+PRP	4.17± 0.48*	18.94± 1.12*	49.69± 4.51**	4.5± 0.34**	20.0± 1.25*	49.44± 2.69***
VNL+LTN	4.33±0.49**	21.39± 1.50**	47.56± 2.05***	4.83± 0.31***	21.5± 1.29**	49.5± 4.46**

*p<0.05, ** p<0.01, ***p<0.001

Table 3. Effect of various treatments on light dark arena (anxiety paradigm)

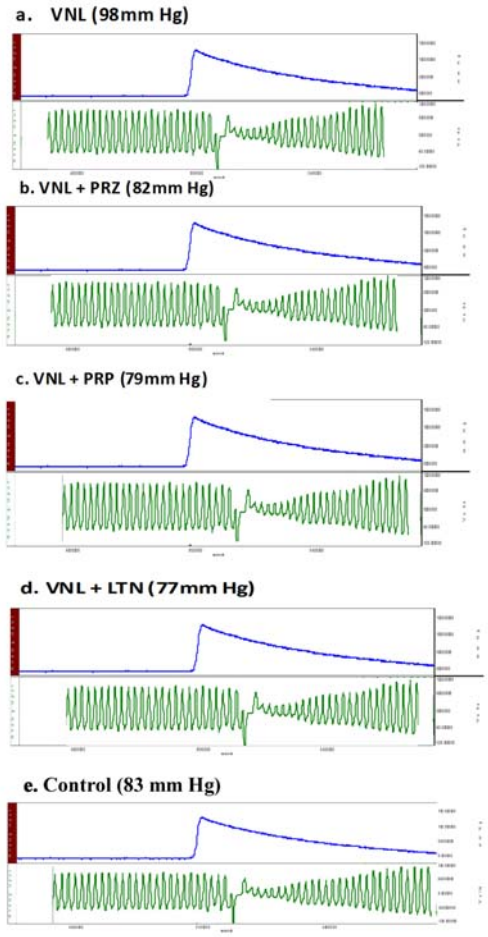
	15th day			30th day		
	Rears	**% Time spent (light arena)**	**Entry in light arena**	**Rears**	**% Time spent (light arena)**	**Entry in light arena**
Control	3.17 ± 0.31	9.22 ± 2.11	1.67 ± 0.21	3.33 ± 0.33	9.72 ± 1.57	1.83 ± 0.31
VNL	5.5± 0.43**	16.53± 1.04**	3.33± 0.42**	6.0± 0.37***	17.94± 0.75**	4.33± 0.21***
VNL+PRZ	4.5± 0.43*	15.89± 0.81*	3.5± 0.22***	4.83± 0.31**	17.39± 1.01**	3.67± 0.21***
VNL+PRP	4.83± 0.40*	15.89± 0.81**	3.83± 0.40***	5.0± 0.26**	17.33± 1.12**	4.0± 0.37***
VNL+LTN	5.0± 0.26**	15.89± 1.04*	3.67± 0.49**	5.67± 0.42**	17.61± 1.29**	4.17± 0.31***

*p<0.05, ** p<0.01, ***p<0.001

Systolic blood pressure

The mean systolic blood pressure (in mm Hg) recordings for each animal was noted and the mean for each group was calculated. In venlafaxine treated group mean SBP 90.17±1.83 and 99.5±3.4 on day 15 and 30 indicating significant ($p<0.05$, $p<0.01$) increase as compared to basal mean SBP of 84.67±1.23. In venlafaxine combination with prazosin the mean SBP 81.5±1.29 and 82.0±1.59 on days 15 and 30 were comparable to the basal SBP of 82.5±1.67. In venlafaxine and propranolol combination treated group the mean SBP was 84.5±1.89 and 86.33±2.09 which were comparable to their respective basal SBP of 83.0±1.69. Similarly, in venlafaxine combination with losartan treated animals the mean SBP were 81.33±2.51 and 82.83±1.70 were not significantly differing from the basal SBP of 87.5±2.05. Basal SBP in all the treated group did not significantly differ from mean SBP of control animals (83.5± 2.32) calculated from the three recordings of day 0, 15 and 30. (Figure 1)

Figure 1. Effect of various treatments on systolic blood pressure (using Biopac software) on day 30.



VNL: Venlafaxine, PRZ: Prazosin, PRP:Propranolol, LTN: Losartan

Discussion

The study was carried out mainly to elicit the interaction of venlafaxine with prazosin, propranolol as well as losartan. The venlafaxine alone treated group received therapeutic equivalent dose (ED), while its SED was co administered with SED of prazosin or propranolol or losartan. During month long treatment BP and behavioural studies were carried out on day 0, 15 and 30.

As expected, in venlafaxine (ED) treated group significant rise in systolic BP, anxiolytic and anti-depressant behaviour were observed throughout the study and these observations corroborate the findings of earlier report[10].

In interaction studies, as observed in earlier acute experiments[10] prazosin failed to modify anti- depressant activity of venlafaxine, while it potentiated the anxiolytic activity both on day 15 and 30. However systolic blood pressure remained at the basal level. Reports regarding such interactions are scanty.

Co administration of propranolol in SED with that of venlafaxine potentiated anti-depressant and anxiolytic activities of the latter, but annulled the hypertensive potential of venlafaxine throughout the study. Reports regarding such interactions could not be traced in the available literature. Similarly losartan also potentiated the anti-depressant and anxiolytic activities of venlafaxine without altering the systolic BP throughout the study. There are no reports about such interactions.

The mechanism of action of various anti-depressant and anxiolytic agents is not clearly understood. The explanations proposed in the literature often based on conflicting observations, involve several types of receptors such as adrenergic (α and β), serotonin, dopamine, *etc.* in mediating psychotropic activity. The crosstalk among these receptors have lead to proposal of confounding hypotheses making the task challenging. Venlafaxine has been reported[19] to act by inhibiting reuptake of both serotonin and norepinephrine. Obviously, this proposed mechanism is over simplification of the facts.

Based on the findings of the present investigation, it could be hypothesized that, anti-depressant activity involving adrenergic mechanisms appears to be mediated through α-adrenoceptors at least in part, since prazosin failed to potentiate and propranolol potentiated the anti-depressant activity of venlafaxine.

Prazosin being a selective α_1- adrenoceptor blocker, probably α_1^- adrenoceptors could be involved in mediating anti-depressant activity and this mechanism is supported by earlier studies where in phenylephrine, a selective α_1-adrenoceptor agonist has been reported to possess anti-depressant activity[20]. However, α_2-adrenoceptors also have been implicated with anti-depressant activity.[20]

Antidepressant activity of losartan is mainly attributed to restoration of dysregulated HPA axis through blockade of AT_1 receptors in anterior pituitary[21], preservation of enkephalins and increasing cortical as well as hippocampal BDNF.[22]

The anxiolytic activity of venlafaxine though not clearly understood the mechanisms involved appear to be due to reduced norepinephrine (NE) output in the prefrontal cortex. [23] However involvement of GABA mechanisms appear to be unlikely since there was no significant change in the locomotor activity in all the treated groups except prazosin. Decreased locomotor activity in prazosin treated animals indicate involvement of GABA mechanisms mediating its anxiolytic activity.

Anxiolytic mechanism of losartan as proposed in the literature could be through blockade of AT_1 (anxiogenic) receptors and thus permitting increased angiotensin II to act on AT_2 (anxiolytic) receptors. These receptors are involved in regulating negative feedback mechanism on adrenergic neurons, thereby leading to suppressed NE release and anxiolytic action.[24]

As alluded in introduction, the main objective of the interaction studies was to identify a suitable anti-hypertensive to co-administer with venlafaxine either to annul its hypertensive effect or to treat co-morbid conditions. The findings of the present study clearly indicate that both propranolol and losartan can overcome hypertensive adversity of venlafaxine without compromising its anti-depressant or anxiolytic activity, on the contrary they have synergistic psychotropic activity with venlafaxine.

It is not clear from the present study whether these two (propranolol and losartan) drugs maintain normal systolic BP by their anti-hypertensive action or through their synergistic antidepressant activity with venlafaxine leading to decreased dosage of the latter. However it is more likely that the observed beneficial effect is through the reduction in the dose of venlafaxine, since its hypertensive adverse effect is said to be dose dependent.[11]

It is very difficult to pinpoint the nature of the interactions observed in the present investigation as plasma drug levels were not monitored. The probable nature of interaction appears to be of pharmacodynamic rather than pharmacokinetic, since kinetic interactions of these anti-hypertensives with venlafaxine are poorly documented in the available literature.

If the findings of the present study could be extrapolated to human situation and if venlafaxine has to be used to treat isolated depression or associated with hypertension, losartan or propranolol appears to be choice of anti-hypertensives to be co-administered with the former.

The observations of the study also indicate that use of lower doses of losartan or propranolol could not only decrease the venlafaxine dose requirement but also could prevent the predictable hypertensive adversity of the latter. However these experimental findings need to be confirmed clinically.

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