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A study to Evaluate the Effect of Diltiazem on the Antidepressant Action of Imipramine and Venlafaxine Using Forced Swim Test *In-Vivo* in Rats

Rajesh Komma*, Seema Bhalerao, P.S. Worlikar, Nikhil Vijay, Pavitra Raj Dewda

1. Pd.Dr.D.Y.Patil Medical College,Hospital and Research Centre, Pimpri, Pune-411018.

ABSTRACT

The main objective was to evaluate antidepressant effect of diltiazem in rats**.** Results of numerous pre-clinical studies have demonstrated that calcium channel blockers have an antidepressant activity & a potential for interaction with standard antidepressants. The present study is designed to test this hypothesis in rats .Rats were assigned to six groups, one group is the control group (distilled water) , three groups are ,imipramine (10 mg/kg), venlafaxine (10 mg/kg), and diltiazem (10mg/kg) alone and other two groups are combination of diltiazem with imipramine, and diltiazem with venlafaxine. To know the antidepressant effect, forced swim model had been used, the immobility period of all the groups are compared with each other after giving drugs for 7 days Diltiazem produced significant antidepressant effect either alone or in combination with imipramine. The efficacy of diltiazem (10mg/kg) was comparable to that of imipramine (10mg/kg) and venlafaxine (10mg/kg) results of the present study indicate antidepressant like activity of diltiazem

Keywords: Depression, diltiazem, imipramine, venlafaxine, forced swim test

*Corresponding Author Email: dr.rajeshkomma@gmail.com

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INTRODUCTION

Depression is among the most common psychiatric conditions seen in clinical settings; with up to 25-35% of outpatients meeting criteria for chronic depression.[1] Although there are many drugs for treating depression none of the present drugs would meet the demand without causing troublesome adverse effects. So there is a constant research for the newer antidepressants and also for the drugs as an adjunctive to the present drugs to reduce the doses to overcome the adverse effects.

Calcium channel antagonist have been shown to affect different physiological process particularly neurotransmitter release. It has been suggested that calcium channel blockers may have antidepressant properties, and that calcium may play an important role in affective disorders.[2] Voltage-dependent calcium channel antagonists have been reported to produce antidepressant-like effects in rodents.[3]Interruption of the Ca2+-calmodulin-NOS-guanylyl cyclase subcellular signalling pathway at any point produces antidepressant-like effects.[4]

Diltiazem, a L type calcium channel blocker, used to treat hypertension and supra ventricular tachycardia was found to have antidepressant effects in some animal studies.[5] In a study conducted by Silverstone PH has reported that calcium channel antagonists are useful as adjunctive in the treatment of bipolar disorder in patients who do not respond to standard therapies. All the 8 patients in the study were female, and all of them responded well to diltiazem. This study adds diltiazem to the list of calcium-channel antagonists studied and found useful for this indication.[6] the findings of the study is supported by a previous study carried out on human volunteers. In that study, it was reported that diltiazem partially attenuated the effects of acute dextroamphetamine administration.[7]

So considering the above literature the present study was conducted to evaluate the effect of diltiazem alone and in combination with the standard antidepressants like imipramine and venlafaxine in forced swim test, a model to study antidepressant action of drugs.

Imipramine, the standard tricyclic antidepressant prevents the reuptake of noradrenaline (NA) and 5-hydroxytryptamine (5-HT) at nerve terminals. Venlafaxine is a serotonin and noradrenaline reuptake inhibitor normally given in resistant cases and it is been used effectively by many physicians. These two drugs have shown the antidepressant effect in the animal models based on stress.[8]

MATERIALS AND METHODS

This study was conducted after getting permission from the institutional review board and animal ethics committee. Animals were procured from animal house and after procurement a study gap of one week was given for acclamatization. Sprague dawley rats of 150-200g weight were used and they were kept in separate cages at room temperature (20-25^{o}c).

All the drugs were dissolved in distilled water and given orally for a period of seven days. Imipramine, venlafaxine were given at 10 mg/kg and diltiazem was also given at a dose of 10mg/kg. The dose of diltiazem was from previous studies. Rats were divided into six groups (n=10). One group received distilled water, two groups received doses of antidepressants imipramine (10mg/kg) and venlafaxine (10mg/kg) alone, one group received dose of calcium channel blocker diltiazem (10mg.kg). Two groups each received doses of diltiazem followed by antidepressants (with same doses used either in the previous groups). Drug administration was performed concurrently on the six groups. For all groups, the time of onset of immobility was measured 60 min after drug administration on 7th day.

We used a behavioral model of immobility first postulated by Porsolt.[9,10] And named the behavioral despair model. Rats were forced to swim individually in a jar (25 x 12 x 25^{3}) containing fresh water of 15 cm height and maintained at 25^{o}C. After an initial period of vigorous activity each animal assumed a typical immobile posture. A rat was considered to be immobile when it remained floating in the water without struggling, making only minimum movements of its limbs necessary to keep its head above water.. After screening rats were subjected to 15 minutes test and again after 24 hours they were tested for 6 minutes. The total duration of immobility was recorded in total 6 minutes.

Statistical analysis:

The data were compiled and analysed by using the statistical package, primer of biostatics. Results are expressed as mean ± SD and statistical significance between means was analyzed using one-way analysis of variance (ANOVA) followed by Post Hoc to compare between groups. The comparison between the combination and single drug groups was done by students'' test. Probability value of less than 0.05 was considered as statistically significant.

RESULTS AND DISCUSSION:

Effect of diltiazem on immobility time:

Diltiazem given at a dose of 10mg/kg in rats for 7 days had significantly reduced immobility time compared to the control group.

Effect of diltiazem and imipramine:

Combination group of diltiazem and imipramine at doses of 10mg/kg each had produced significant reduction in immobility time (p=0.008) compared to the imipramine group.

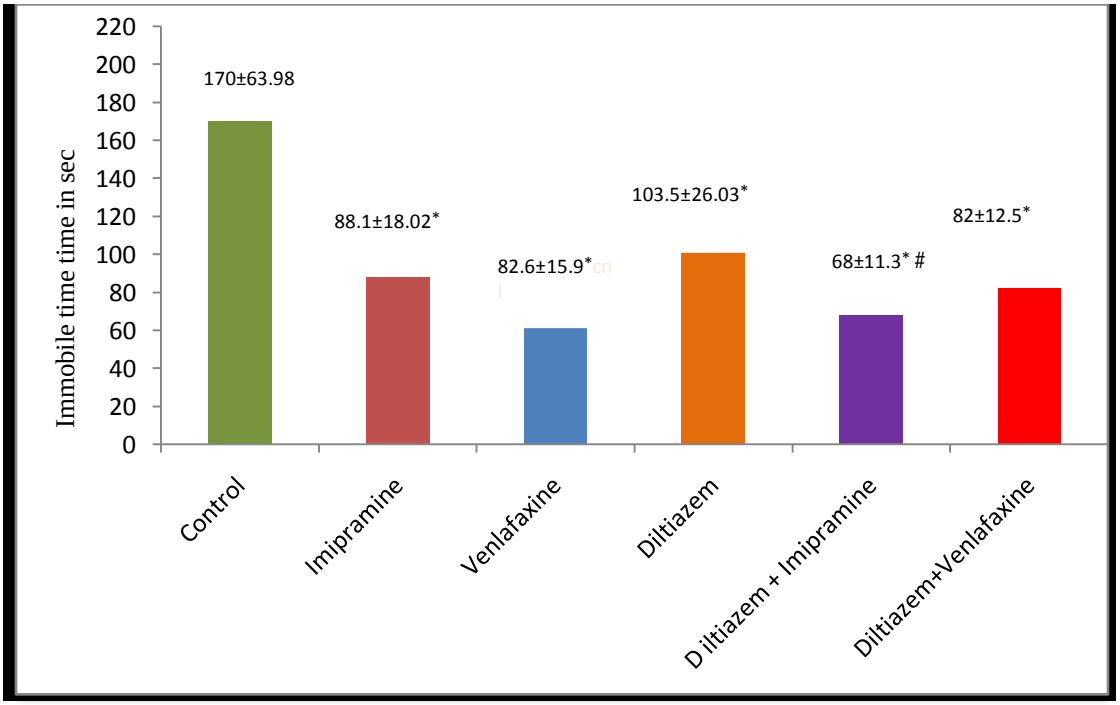
Table: 1 Effect of diltiazem on immobility time in seconds

Sr.no	Groups	Immobility time (sec)
1	control	170 ± 63.98
2	Imipramine	88.1 ± 18.02 *
3	Venlafaxine	82.6 ± 15.9 *
4	Diltiazem	103.5± 26.03 *
5	Diltiazem and Imipramine	68 ± 11.3 *#
6	Diltiazem and Venlafaxine	82± 12.5 *

The results are mentioned as Mean ± SD
* = p < 0.05, compared to the control group
# = p < 0.05, compared to the imipramine group

Administration of imipramine, venlafaxine and diltiazem separately produced a significant reduction in immobility time compared to the control group. The combined administration of imipramine and diltiazem produced a significant reduction in immobility compared to either imipramine treated rat or the control group. The combined administration of venlafaxine and diltiazem did not produce significant effect compared to venlafaxine treated group.

Graph-1:Comparison of groups on immobility time in seconds



The results are mentioned as Mean ± SD
* = p < 0.05, compared to the control group
# = p < 0.05, compared to the imipramine group

It has been suggested that calcium channel inhibitors have antidepressant properties, and that calcium may play an important role in affective disorders. Voltage-dependent calcium channel antagonists have been reported to produce antidepressant-like effects in rodents. Interruption of the Ca2+-calmodulin-NOS-guanylyl cyclase subcellular signalling pathway at any point produces antidepressant-like effects.[4, 11]

Calcium channel blokers produce competitive inhibition of a 5-HT carrier and inhibit Na^+-dependent uptake of 5-HT.[12, 13,14] It facilitates the release of large amounts of K^+ induced 5-HT in the hippocampus synaptosomatic sites. The release is dose dependent and mediated by presynaptic receptors. This increase in endogenous 5-HT is independent of the presence of external calcium. Serotonin activates 5-HT_{1A} receptors to produce an antidepressant effect.[14] It also activates 5-HT3 presynaptic receptors, inducing calcium influx[12, 13,14], which triggers the release of calcium from intracellular stores and leads to increased calcium in both the cytoplasm and nucleus. Activating 5-HT3 postsynaptic receptors induces depolarization.[15] thus both mechanisms would result in an antidepressant action. Diltiazem belonging to the group of calcium channel blockers might possess the same property

In the present study we found diltiazem has an antidepressant affect when given either alone or in combination with imipramine. When combined with imipramine it had potentiated the reduction in immobility time significantly which shows its additive effect on imipramine. When combined with venlafaxine it did not show superiority over venlafaxine treated group. The reason for the additive effect with imipramine could be a pharmacokinetic interaction. The cytochrome enzyme CYP3A4 inactivates the imipramine by increasing its metabolism, diltiazem being a inhibitor of this enzyme might have potentiated the effect of imipramine.

CONCLUSION:

Our study indicated that diltiazem monotherapy has an antidepressant effect and shown additive effect in combination with imipramine.

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