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Antidepressant Effect of Tramadol on *balb-c mice* in Animal Models of Depression

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ABSTRACT

Depression is a multifactorial disease, commonly occurring due to deficit of norepinephrine and serotonin. Tramadol, a weak μ opioid agonist, is used in treatment of chronic pain. Tramadol also inhibits the reuptake of norepinephrine and serotonin in the synaptic cleft. This study was done to explore the antidepressant activity of tramadol in male *balb c mice* by forced swim test and also to evaluate its mechanism through the serotonergic pathway. Thirty six male mice were grouped randomly of 6 mice in each group. Twenty four hours following the pretest session, they were given distilled water, escitalopram 5 mg/kg, tramadol 10, 20, 30 mg/kg and ondansetron 4 mg/kg plus tramadol 30 mg/kg intraperitoneally. After 30 minutes of drug administration, they were made to swim individually in the cylindrical transparent jar with a water column of 15 cm for 6 minutes. Tramadol showed significant ($p < 0.05$) reduction in immobility time with increase in dosage. Tramadol 30 mg/kg showed significant antidepressant activity compared to escitalopram . On combination of tramadol with ondansetron(a serotonin antagonist), there was increase in the immobility time. Tramadol could be helpful in patients with both depression and chronic pain.

Key words: Tramadol, antidepressant, forced swim test,ondansetron

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INTRODUCTION

Depression is a disorder of mood, affecting 10-15 percent of people at some part of their lives [1]. It is defined as depressed mood on daily basis for a minimum duration of 2 weeks. It can affect people of any age, but the incidence increases with age. It is twice more common in females than in males [2]. It could occur due to genetic predisposition, neurotransmitter dysfunction or due to chronic illness [3]. In about 15 percent of people with depression suicidal thoughts are more common [4]. It has gained importance due to its high prevalence and its capacity to derail the quality of life. Depression is found to be the most common mental disturbance in almost half of patients with chronic pain, affecting their day to day activities [5]. Hence it is important to treat depression to have a better living.

The commonly involved neurotransmitters in depression are noradrenaline and serotonin. The management of depression is a multistep process and antidepressant drugs are the treatment of choice. Common among them are the TCA (Tricyclic Antidepressants) and SSRI (Selective Serotonin Reuptake Inhibitor) which will inhibit the reuptake and increases the availability of the neurotransmitters in the synaptic cleft. Thus they enhance the synaptic transmission and afford relief from depression. The TCA's produce more side effects such as anticholinergic symptoms, drowsiness, restlessness, weight gain, sedation and sexual dysfunction, due to which the SSRI's are preferred now [3].

Escitalopram, an enantiomer of citalopram is an SSRI, commonly used for depressive disorders. It has got advantages of improved tolerability and increased potency than that of citalopram. Tramadol is a centrally acting opioid analgesic. It is a synthetic opioid binding weakly to μ opioid receptor. It also interferes with reuptake and release of Noradrenaline and Serotonin, thus increasing their extra neuronal concentration [6]. Hence, the present study was done to know the role of tramadol as an antidepressant in animal models of depression.

The Antidepressant effect was studied in mice as an experimental animal model. The forced swim test of mice is one of the models, whose predictive validity is well established. In this the mice were made to swim individually in a cylindrical tank (25cm X 10 cm) containing water of 15 cm height for a period of 6 minutes. The mice were observed for immobility in that 6 minute session. The duration of immobility reflects the state of depression in the animal. Drugs which cause reduction in the immobility time are said to possess anti depressant property [7].

Ondansetron, a $5HT_3$ antagonist is a conventionally used antiemetic for chemotherapy induced vomiting. This was used in combination with tramadol in mice Forced Swim Test. This combination was observed for any change in the immobility time. If this combination causes increase in the immobility time, then it suggests that tramadol may have a role through the serotonergic pathway, which is counteracted by Ondansetron, a serotonin antagonist.

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Thus this study was done to evaluate the effect of tramadol as an antidepressant compared to escitalopram, a SSRI and hence to treat both depression and pain simultaneously. It also evaluates the role of tramadol on the serotonergic pathway.

MATERIALS AND METHODS:

Subjects:

Male Balb/c mice were used in our study. All mice were 14-20 weeks old and weighed around 20-30 g. They were housed in groups of 6 mice in a cage. Food and water were provided ad libitum. The test was done during 11 a.m. to 2 p.m. Each experimental group consisted of six randomly grouped mice, which were used for 2 sessions (pretest and test session). All testing were conducted within the guidelines of CPSCEA.

Apparatus:

The experiment was carried out in a cylindrical transparent jar of height 25 cm and diameter 10 cm, which contained water to a height of 15 cm at 250C [16]. The water was changed after each 6 minute session, and the activity was recorded by a video camera for further analysis.

Drugs:

The drugs used in this study were, Escitalopram Oxalate, Tramadol Hydrochloride, Ondansetron Hydrochloride (A to Z Pharmaceuticals, Chennai). They were all dissolved in distilled water and given intraperitoneally. Control group received only distilled water i.p.

Study Design:

It was a randomized, controlled experimental study, conducted in the Department of Pharmacology, SMVMCH.

Table 1: Design of the study

Group	Treatment	Dosage
Control Group	Distilled water	0.25 ml i.p.
Standard Group	Escitalopram Oxalate	5mg/kg i.p.
Test group 1	Tramadol Hydrochloride	10mg/kg i.p.
Test group 2	Tramadol Hydrochloride	20mg/kg i.p.
Test group 3	Tramadol Hydrochloride	30mg/kg i.p.
Test group 4	Tramadol Hydrochloride+ Ondansetron	30mg/kg i.p.+ 4 mg/kg i.p.

The animals were divided in 6 groups, each comprised of 6 mice as given in Table 1. (Design of the study)

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EVALUATION OF ANTIDEPRESSANT ACTIVITY USING FORCED SWIM TEST

Each animal was subjected for two sessions of treatment, i.e. pretest and test session [17]. In the pretest session, the mice were made to swim inside the cylinder for a period of 6 minutes, without administration of any drug. After 24 hours, the same mice were given the respective drug and after 30 minutes of drug administration they were made to swim again in the tank for 6 minutes. In this test session, the swimming activity of each mouse was observed and recorded with a video camera [6]. Following the swimming session, the animals were removed out of the beaker, dried with towel and placed in a dry cage for 1 hour, before returning to their home cage. The water in the beaker was changed after each session.

The activity of the mice in the initial 2 minutes was discarded and period of immobility in the last 4 minutes was measured. The observation of immobility is made in such a way that there can be little and finer movements, for the mouse to keep its head above the surface of water. This state of immobility provides the state of depression of the animal [5]. The drugs with antidepressant property, decreases the duration of immobility and vice versa. The test results obtained from the standard and test groups are then compared and analyzed.

RESULTS AND DISCUSSION

The results are summarised in Table.2 (Duration of immobility in FST). The mean duration of immobility in the control group was observed to be 170.33 seconds, whereas it was 111.16 seconds in the standard group treated with escitalopram 5 mg/kg. In the groups treated with tramadol 10, 20 and 30 mg/kg, the immobility time was 153.5, 120.83, 88.5 seconds respectively. Tramadol at 30 mg/kg significantly ($p<0.05$) decreased the immobility time compared to escitalopram. There was no significant immobility in other doses of tramadol, and it shows that there is increase in antidepressant activity with increase in dosage.

Table 2: Duration of immobility in FST

Sr.No.	Drug Treatment	No. of animals	Dose (mg/kg)	Immobility time (seconds)(mean± S.D)
1	Distilled water	6	-	170.333 ± 24.12
2	Escitalopram	6	5	111.166 ± 26.4*
3	Tramadol	6	10	153.5 ± 53.25
4	Tramadol	6	20	120.83 ± 61.59
5	Tramadol	6	30	88.5 ± 52.45*
6	Tramadol + Ondansetron	6	30+4	170.33 ± 43.94

indicate the significant reduction in immobility time compared to other groups ($p<0.05$)

In the group of Tramadol 30 mg/kg, pretreated with ondansetron, there is decrease in the antidepressant activity of tramadol. This combination produced immobility time same as that of the control group receiving distilled water.

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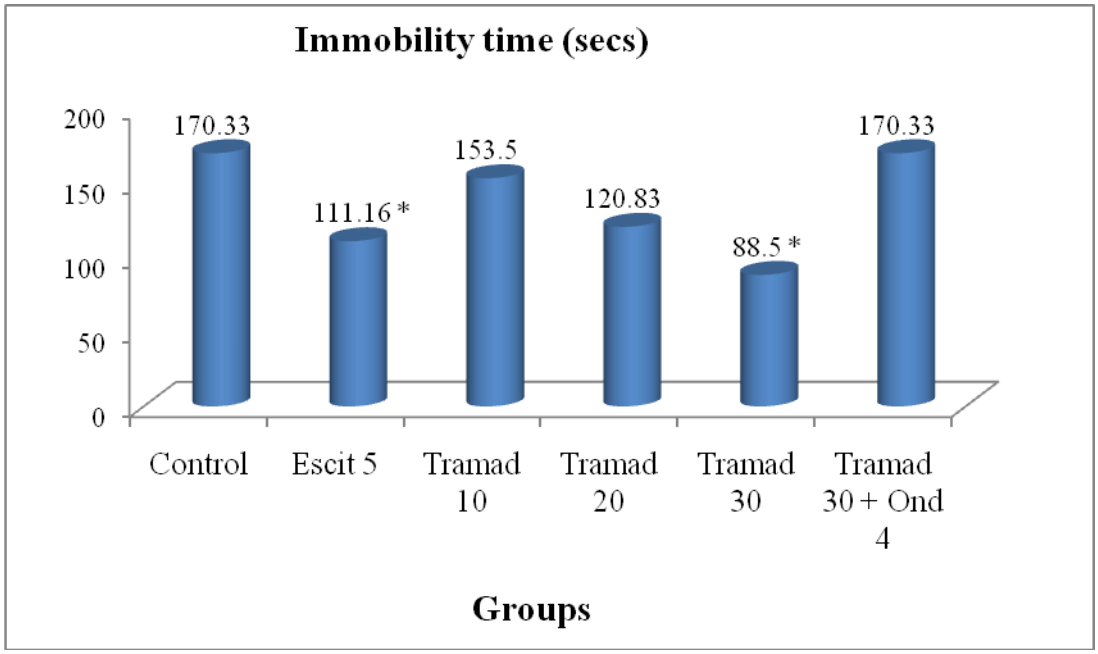
Major depression is a pervasive mood disorder affecting people of all ages. It exhibits not only depressed mood, but also sleep/psychomotor disturbances, low self-esteem, anhedonia, loss of appetite, lack of concentration, etc. In spite of the availability of various antidepressant drugs, depression continues to be a major medical problem.

Fig1: Effect of administration of various drugs in Mice Forced Swim Test.



n= 6 per value. * indicate a significant decrease in the immobility time.
*p<0.05 (one-way ANOVA)

Antidepressant effect of Tramadol:

In our present study, the antidepressant effect of Tramadol was compared with escitalopram, a commonly used SSRI in depression. The study was done with the Forced Swim Test of mice, a standard animal model predictive of antidepressant activity. In this, when the mice were forced to swim in a water beaker from which they cannot escape, they will adopt a characteristic immobile posture after an initial period of vigorous activity. In such posture they remain floating in water making only finer movements to keep their head above the water column. It has been suggested that this immobility posture may serve as a screening model for antidepressants [17].

Similar studies were done to evaluate the antidepressant effect of Tramadol [12, 13].In our study, Tramadol (30 mg/kg) produced immobility duration for 88.5 seconds, which is comparatively less than the other groups. We found significant increase in the antidepressant activity with increase in dosage of Tramadol. This significant antidepressant activity ($p < 0.05$) was observed in higher dose (30 mg/kg) of tramadol as compared to escitalopram.

Tramadol in combination with ondansetron:

When this dose of Tramadol is combined with Ondansetron which is a serotonin ($5HT_3$) antagonist, there was a significant decrease in the Antidepressant effect of Tramadol. This combination produced immobility time more than the group receiving only tramadol. The immobility time of this combination was same that of the group receiving distilled water (170.33 seconds). It infers that Ondansetron dampens the anti-depressant effect of tramadol. Since serotonin is a major neurotransmitter involved in this, it gives an impression that the antidepressant effect of tramadol is mainly by increasing the availability of serotonin.

This mechanism of action is very similar to that of SSRI which also increases the duration of action of serotonin on the synapse by blocking its reuptake. Antidepressants (SSRI) by virtue of their property of mood elevation and increasing the levels of 5HT, they consequently causes inhibition of release of transmitters carrying pain sensation from nerve endings; thus they are efficacious as an adjunctive in chronic pain treatment [11].

Similarly, from our study, it could be implied that Tramadol acting through similar mechanism might add a mood elevation property to its analgesic effect. Hence it can be used as an adjunctive in patients suffering from chronic pain and depression simultaneously.

To confirm the SSRI like action of Tramadol further molecular level studies have to be done. Also other extensive studies to find out other mechanism of actions of Tramadol should be done.

CONCLUSION

From our study, we conclude that Tramadol has significant Antidepressant property compared to Escitalopram. This effect of tramadol was reduced with pretreatment of Ondansetron, hence there lies some role of tramadol through the Serotenergic pathway.

It is evaluated that tramadol could be used simultaneously in patients with depression and chronic pain.

The limitations of our study were, it is an experimental animal study with small number of subjects. Hence more studies with large number of subjects should be carried out to potentiate the results of this study. The authors would like to acknowledge ICMR for having funded this study.

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