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STUDY OF ANTIDEPRESSANT ACTIVITY OF CHRONIC ADMINISTRATION OF TRAMADOL AND WHEN IT IS CO-ADMINISTERED WITH FLUOXETINE IN LOW DOSES IN SWISS ALBINO MICE USING DESPAIR SWIM TEST

G. Sirisha *, N. S. Usha and B. Santhamma

Department of Pharmacology, Kamineni Institute of Medical Sciences, Narketpally Hyderabad, Telangana- 500007, India

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Correspondence to Author:
Dr Sirisha Goli
H No 9-17/3, St No 8, Ravindranagar colony, Habsiguda, Hyderabad, Telangana- 500007, India.

E-mail:dr.sireesha.g@gmail.com

ABSTRACT: Objective: To evaluate the antidepressant activity of chronic administration of Tramadol alone and when combined with Fluoxetine in low doses in albino mice. **Methods**: The antidepressant effect was determined by recording the immobility time in Despair Swim Test. The mice were randomized into seven groups, with six mice in each group. Group 1 mice were given normal saline (10 ml/kg) which served as control. Mice of groups 2, 3 and 4 received Tramadol in graded doses (10, 20 and 40 mg/kg). Fluoxetine (standard drug) was given to mice of groups 5 and 6. Tramadol and Fluoxetine in low doses (10ml/kg each) were co-administered to mice of group 7. All drugs were given intraperitoneally for 7 days and were subjected to despair swim test on the day 7 of drug administration. **Results**: Tramadol and Fluoxetine have shown significant antidepressant activity when compared to the control. There is dose dependant increase in antidepressant activity of Tramadol. The antidepressant of Tramadol 20 mg/kg was comparable to Fluoxetine 20 mg/kg. Tramadol potentiated the antidepressant effect of Fluoxetine in the low dose combination group. **Conclusion**: The present indicates that Tramadol, a opoid analgesic has anti depressant activity and it can potentiate the antidepressant effect of Fluoxetine when combined in low doses.

INTRODUCTION: Major depressive disorder (MDD) is characterized by depressed mood most of the time for at least 2 weeks and/or loss of interest or pleasure in most activities [1]. In addition, depression is characterized by disturbances in sleep and appetite as well as deficits in cognition and energy. Thoughts of guilt, worthlessness, and suicide are common. An estimated 5.8% of men and 9.5% of women experience depressive episodes in their lifetime. 60% of death toll due to suicides is with depressive illness.[1]

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Approximately two-thirds of the depressed patients respond to the currently available treatments (Tricyclic Antidepressants, Selective Serotonin Reuptake Inhibitors, etc), but the magnitude of improvement is still disappointing. More over these drugs have unusual side effects. So the search for more effective drugs with fewer side effects is on.

Tramadol is a synthetic centrally acting opioid analgesic used mainly for the treatment of moderate-to-severe pain. It produces analgesia because of weak μ opioid receptor agonist and by inhibiting uptake of norepinephrine and serotonin [2]. Tramadol causes activation of both systems mainly involved in inhibition of pain, i.e., the opioid and the descending monoaminergic pain-modulating pathways. There is a large body of evidence to suggest that the analgesic action of Tramadol is mainly related to central monoaminergic

mechanism rather than opioid receptor pathway [3]. It has also been observed that Tramadol-induced analgesia is blocked by α_2 adrenergic receptor antagonist Yohimbine. [4]

Studies have already shown that Tramadol effectively inhibits reuptake of monoamines. It has also been established that Tramadol inhibits reuptake of serotonin in the raphae nucleus [5]. Tricyclic antidepressants mainly act by inhibiting Norepinephrine or Serotonin reuptake; Tramadol by virtue of its property of blocking monoaminergic reuptake may act as an antidepressant. Also, Tramadol bears a close structural similarity to antidepressant Venlafaxine and thus shares a number of its molecular and pharmacological features [6].

So, the present study was taken up to evaluate the antidepressant activity of Tramadol using despair swim test, a simple test to study the effect of learned helplessness and how antidepressant modify this behavior of mice. Antidepressant activity takes time to manifest, so chronic model is taken up for study. Tramadol in graded doses was compared to the standard antidepressant drug Fluoxetine. Also the effect of low dose combination of Tramadol and Fluoxetine was studied for antidepressant activity. This permits dose reduction of either drug, thereby reducing adverse effects, while improving efficacy.

Epidemiological studies confirm frequent appearance of pain symptoms in depressed patients and a marked prevalence of depression in pain conditions. These observations seem to point at a close intertwining between mood regulation and pain perception. In the pathogenesis of both depression and pain symptoms, an important role has been attributed to disturbances of serotonergic and noradrenergic neurotransmission as well as to neuropeptides such as opioids and substance P. Hence this study was undertaken with the objective of studying the antidepressant like activity of Tramadol in animal models of depression and its comparison to Selective Serotonin Reuptake Inhibitor Fluoxetine.

MATERIALS AND METHODS: In the present study, Tramadol was studied in mice to assess its antidepressant activity. It was conducted in Department of Pharmacology, Kamineni Institute of Medical Sciences, Narketpally from October 2010 to September 2012. The study was placebo controlled, Randomized, Laboratory- based comparative study on animals with prior permission of Institutional Animal Ethics Committee (IAEC). Swiss albino mice (25-30 grams) of either sex, were used. Animals were procured from Central Animal House of National Institute of Nutrition, Hyderabad and kept in air conditioned environment in the Central Animal House, KIMS, Narketpally. After procurement, a study gap of one week was given for acclimatization. The animals were housed under standard laboratory conditions, maintained on a 12:12h light dark cycle and had free access to food and water. All the experiments were carried out between 10:00 and 15:00 hr.

Drugs procured from:

1. Tramadol (Zydus Cadila)
2. Fluoxetine (Sigma Aldrich) - Funded by the Management of KIMS, Narketpally.
3. Normal Saline

All the drugs were given to mice, which were randomized into goups as shown in **Fig. 1**.

Despair swim test: (Also called forced swim test or Porsolt test) [7].

This animal model is based on the principle that forcing mice to swim in restricted space from which they cannot escape leads to a characteristic behavior of immobility. This behavior reflects a state of despair, which can be reduced by several agents that are therapeutically effective in human depression. Test drugs were administered intraperitonially for 7 days. On day 7, drugs were administered to mice 40 minutes prior to testing.

Mice were individually forced to swim inside vertical plexiglass cylinder (height, 25 cm; diameter, 10 cm) containing water column of 15 cm height as shown in **Fig. 1**. After an initial 2 minute period of vigorous activity, usually each animal assumes a typical immobile posture. A mouse 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. The total duration of immobility was recorded during the last 4 minutes (240 seconds) of the total 6 minutes of the duration of the test. Duration of immobility period of Tramadol group was compared with that of Control and Fluoxetine group.

TABLE 1: IT SHOWS GROUPING OF MICE AND DOSES OF THE DRUGS ADMINISTERED TO MICE EACH GROUP

Groups n=6	Drug	Status	Dose mg / kg (intraperitoneal)
1	Normal Saline	Control	10 ml / kg
2	Tramadol	Test	10
3	Tramadol	Test	20
4	Tramadol	Test	40
5	Fluoxetine	Standard	10
6	Fluoxetine	Standard	20
7	Tramadol+Fluoxetine	Combination	10+10

FIG. 1: IT SHOWS MICE SUBJECTED TO THE DESPAIR SWIM TEST

RESULTS: Pre- treatment of the mice with drugs (Tramadol, Fluoxetine or Normal saline) was given 40 minutes before the test on day 7. Despair Swim Test performed and the immobility time is noted. Lesser the immobility time, greater is its antidepressant activity. The Mean immobility times were then analyzed by performing one way ANOVA and post hoc least difference method was done using SPSS software.

TABLE 2: IT SHOWS THE IMMOBILITY TIME OF MICE (MEAN ± SE) IN EACH GROUP IN DESPAIR SWIM TEST

Groups	Mean ± SE
Control (NS)	175.50 ± 5.17
Tramadol 10mg/kg (T10)	152.50 ± 3.77
Tramadol 20mg/kg (T20)	80.00 ± 3.21
Tramadol 40mg/kg (T40)	68.83 ± 3.35
Fluoxetine 10mg/kg (F10)	127.17 ± 4.18
Fluoxetine 20mg/kg (F20)	74.00 ± 1.91
Tramadol 10mg/kg+ Fluoxetine 10mg/kg (T10+F10)	79.33 ± 3.61

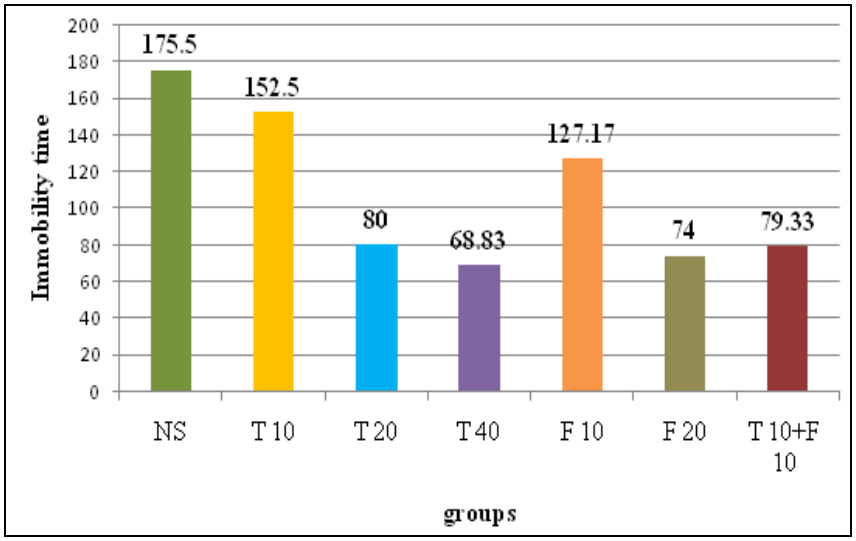

FIG. 2: IT SHOWS COMPARISON OF MEAN IMMOBILITY TIME OF DIFFERENT GROUPS IN DESPAIR SWIM TEST

TABLE 3: IT SHOWS COMPARISON OF MEAN IMMOBILITY TIME BETWEEN THE DIFFERENT GROUPS IN DESPAIR SWIM TEST BY POST HOC LEAST SIGNIFICANT DIFFERENCE METHOD

Comparison of groups	Mean difference	P value	Significance
Control vs T10	23.00	0.0001	***
Control vs T20	95.50	0.0001	***
Control vs T40	106.67	0.0001	***
Control vs F10	48.33	0.0001	***
Control vs F20	101.50	0.0001	***
Control vs T10+F10	96.17	0.0001	***
T10 vs T20	72.50	0.0001	***
T10 vs T40	83.67	0.0001	***
T10 vs F10	25.33	0.0001	***
T10 vs F20	78.50	0.0001	***
T10 vs T10+F10	73.17	0.0001	***
T20 vs T40	11.17	0.054	ns
T20 vs F10	-47.17	0.0001	***
T20 vs F20	6.00	0.261	ns
T20 vs T10+F10	.67	0.900	ns
T40 vs F10	-58.33	.0001	***
T40 vs F20	-5.17	0.332	ns
T40 vs T10+F10	-10.50	0.054	ns
F10 vs F20	53.17	0.0001	***
F10 vs T10+ F10	47.83	0.0001	***
F20 vs T10+ F10	-5.33	0.317	ns

p value <0.001***, <0.01**, <0.05*, ns – not significant

Tramadol in all the three doses (10mg/kg,20 mg/kg and 40mg/kg,i.p.) significantly reduced the immobility time in seconds in comparison to control group suggesting Tramadol produced antidepressant activity in despair swim test in mice. The standard antidepressant drug Fluoxetine, in the doses of 10 and 20 mg/kg i.p. significantly reduced the immobility time in seconds in comparison to control group confirming its antidepressant activity in this test model.

The combination of low doses of Tramadol 10mg/kg + Fluoxetine 10mg/kg significantly reduced the immobility time in seconds in comparison to Tramadol 10mg/kg alone or Fluoxetine 10mg/kg alone suggesting Tramadol

can potentiate antidepressant action of Fluoxetine. Further the immobility time in seconds after Tramadol 20mg/kg is not significantly different than Fluoxetine 20mg/kg suggesting antidepressant activity of Tramadol is comparable to Flouxetine in despair swim test.

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DISCUSSION: The therapeutically used antidepressant drugs like Tricyclic antidepressants, Selective Serotonin Uptake Inhibitors and atypical antidepressants produce effect on brain monoaminergic system. The clinically used analgesic Tramadol apart from having effect on μ type opioid receptors, also have monoaminergic uptake blockade effect [8]. Hence, the present study was carried out to evaluate the antidepressant activity of Tramadol in Despair Swim Test. The results obtained have been compared with the standard antidepressant drug, Fluoxetine [9, 10]. Also, the effect obtained due to combination of low doses of Tramadol 10 mg/kg and Fluoxetine 10 mg/kg determined, so that the toxicity of either drug can be reduced, while increasing their efficacy as antidepressants.

In Despair Swim Test, mice subjected to a non-solvable averse situation alternate between agitation and immobility. The reason of agitation is searching to get out of the situation which is highly energy consuming, while the purpose of immobility is energy conservation. Animals after antidepressant treatment struggle more even in desperate situation, and they spend less time with immobility. These tests are quite sensitive and relatively specific to all major classes of antidepressants like Tricyclic Antidepressants, Selective Serotonin Reuptake Inhibitors (SSRI), MAO Inhibitors and atypical antidepressants.

In this present study, there is significant decrease in immobility time for all groups of Tramadol (10 mg/kg, 20 mg/kg and 40 mg/kg) and Fluoxetine (10 mg/kg and 20 mg/kg) as well as the combination group (Tramadol 10 mg/kg + Fluoxetine 10 mg/kg) in comparison to control group (normal saline) suggesting antidepressant effect in despair swim test. Immobility time in combination group is significantly less than Tramadol 10mg/kg alone and Fluoxetine 10mg/kg alone, suggesting that Tramadol potentiates antidepressant activity of Fluoxetine. There is no significant difference in the immobility time when Tramadol 20mg/kg is compared to Fluoxetine 20mg/kg suggesting antidepressant effect of Tramadol 20mg/kg comparable to Fluoxetine 20mg/kg in despair swim test

The antidepressant-like effect of Tramadol may be explained on its ability to modulate Noradrenaline [11] as indicated by some earlier studies. Few authors even suggested dopaminergic [12] and serotonergic [13, 14] pathways as possible mechanisms of antidepressant activity of Tramadol. Imidazoline receptors as well as opioid receptor may also be involved in the antidepressant- like activity of Tramadol in mice. Jesse et al showed that the acute administration of Tramadol produces antidepressant effect by inhibition of L-arginine-NO- Camp pathway [15].

The same investigators also suggested that oral administration of Tramadol produces antidepressant- like effect in mice by a mechanism that involves the K^+ channels [16]. Berrocosso et al suggested that co-operative opioid and serotonergic mechanisms generate superior antidepressant effects in mice [17]. All these findings need to be confirmed in the future studies to get conclusive evidence regarding the mechanism of antidepressant activity of Tramadol. A few human studies were also done to establish the antidepressant effect of Tramadol, which gave encouraging results [18].

CONCLUSION: This study suggests that Tramadol has significant antidepressant activity, which is further potentiated when combined with Flouxetine in low doses.

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