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Original Article

Evaluation of Antidepressant Activity of Tramadol in Swiss Albino Mice Compared to Desipramine

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ABSTRACT

Objectives: To evaluate the antidepressant activity of tramadol compared to desipramine in swiss albino mice. **Methods:** Total of 30 male swiss albino mice (N=30) were divided into 5 treatment group (n=6) and were injected with normal saline 5 ml/kg (control), desipramine 30 mg/kg(standard), tramadol 10 mg/kg ,20 mg/kg and 40 mg/kg (test drug) intraperitoneally to each group respectively. Duration of immobility was observed for 6 minutes in tail suspension test and for 6 minutes in forced swimming test on same set of animals after giving a sufficient wash out period of 4 weeks. Results were compared among the different groups using (ANOVA) followed by post hoc Tukey's test**. Results:** In the forced swimming model the mean (± Standard Deviation) immobility time was 196.3 ± 18.8 sec, 12.8 ± 5.7 sec, 40.7 ± 9.5 sec, 31.3 ± 8 sec, 13.3 ± 3.1 sec in the control, standard, tramadol at 10 mg/Kg, 20 mg/Kg and 40 mg/Kg respectively. In the tail suspension test the mean (± Standard Deviation) immobility time was 166.2 ± 42.8 sec, 152.2 ± 11.9 sec, 73.5 ± 5.6 sec, 64.5 ± 4.8 sec, 30.8 ± 4.2 sec in the control, standard, tramadol at 10 mg/Kg, 20 mg/Kg and 40 mg/Kg respectively. Tramadol at a concentration of 40 mg/Kg significantly reduced the immobility time in both the models compared to standard ($p < 0.001$). **Conclusion:** Tramadol has significant antidepressant activity in animal models.

Keywords: Tramadol, Desipramine, Antidepressant, Forced Swimming model, Tail Suspension method.

1. INTRODUCTION

A disorder characterized by depressed mood most of the time for at least 2 weeks and/or loss of interest or pleasure in most activities is called Major Depression. In addition, depression is characterized by disturbances

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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. [1]

Depression is a heterogenous disorder that affects a person's mood, physical health and behaviour. Patients with major depression have symptoms that reflect changes in brain monoamine transmitter specifically nor-epinephrine, serotonine and dopamine like reduced monoamine signaling and monoamine metabolite levels in CSF of depressed patients and increased level of monoamine oxidase enzyme in brain which in turn reduces levels of monoamines. [2, 3, 4] The current modalities of treatment for depression include tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and selective serotonin reuptake inhibitors (SSRIs).TCAs and MAOIs are not preferred these days because of their adverse effect profile. SSRIs are presently the most widely used antidepressants because of their safety profile. [5]

Depression is a co-morbid condition coexisting with a lot of chronic illnesses including cancer. Depression affects 15 – 25% of patients with cancer worldwide and both the genders are affected equally. Sadness and grief are normal reactions when patients are diagnosed with cancer. A critical part of cancer care is recognizing and diagnosing the levels of depression and to intervene appropriately to improve the quality of life of the patient. The treatment modalities are psychotherapy and if necessary pharmacotherapy. [6]

Another factor that can severely affect the quality of life of a cancer patient is cancer pain. In various studies, regardless of the type and site of cancer, pain was experienced by 52 – 77% of patients. Opioids are the mainstay of managing cancer pain. In the WHO analgesic ladder of managing cancer pain, from stage 2, the management of cancer involves opioids. One of the opioids used for pain relief in stage 2 is tramadol. [7, 8]

Tramadol, being a synthetic centrally acting opioid analgesic, is used mainly for the treatment of moderate-to-severe pain. Analgesia by tramadol is because of weak μ opioid receptor agonism and also by inhibiting uptake of norepinephrine and serotonin. [9] It causes activation of both systems mainly involved in inhibition of pain, i.e., the opioid and the descending monoaminergic pain-modulating pathways. There is also evidence that the analgesic action of tramadol can be related to central monoaminergic mechanism more than opioid receptor pathway. [10] It has also been observed that Tramadol-induced analgesia is blocked by α 2 adrenergic receptor antagonist Yohimbine. [11]

There are studies to that show tramadol inhibits reuptake of monoamines and serotonin reuptake is inhibited in the raphae nucleus. [12] Tricyclic antidepressants' main mechanism of action is inhibiting norepinephrine or serotonin reuptake and as tramadol too has this property it may act as an antidepressant. Also structurally, tramadol is similar to antidepressant Venlafaxine and thus shares a number of its molecular and pharmacological features. [13]

There is a 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. [14]

In this present study, the antidepressant activity of tramadol is compared against the standard tricyclic antidepressant, desipramine.

2. MATERIALS AND METHODS

2.1 Animals: Male swiss albino mice weighing 20-30g aged between 3-4 months which are healthy with normal behaviour and activity were procured from central animal house of Department of Pharmacology, JJM Medical College, Davangere. Mice were kept under suitable conditions of housing, temperature (26-28˚C), ventilation and nutrition . However food was withdrawn 1hr before and 2hr after the administration of the drugs. The animals were housed in an animal house with alternatively light-dark cycle of 12 hr each.

The animals were acclimatized to the laboratory conditions for at least five days prior to the behavioral experiments. The experiments were carried out between 0900 h and 1800 h. The Institutional Animal Ethics Committee (IAEC) approved the experimental protocol. Care of laboratory animals was in adherence with the guidelines specified by the CPCSEA, Ministry of Forests and Environment, Government of India (Registration number 0436).

A total of 30 animals (N=30) were divided into 5 groups of 6 each (n=6). Each group were housed in different cages.

2.2 Drugs and Chemicals

Normal saline was used as control in the dose of 0.1ml/10g of mouse. Desipramine in the dose of 30 mg/Kg was the standard drug in our study. The test drug tramadol was used in doses of 10mg/Kg, 20mg/Kg and 40mg/Kg. Both the test drug and standard drugs were dissolved in 0.9% saline to make them suitable for administration through intra-peritoneal route.

2.3 Forced Swim Test

Forced swim test was proposed as models to test antidepressant activity by Porsolt et al. [17] Mice were forced to swim individually in glass jar (25 x 12 x 25 cm^3) containing fresh water up to 15 cm height and maintained at 25^0C). After an initial 2 min period of vigorous activity, each animal assumed a typical immobile posture.

A mouse 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 the water. The total duration of immobility was recorded during the next 4 min of the total test duration of six minutes. The changes in immobility duration were studied after administrating the drugs in separate groups of animals. Each animal was used only once.

2.4 Tail suspension test

This test was done according to the model described by Steru et al. [18] The total duration of immobility induced by tail suspension was measured according to the method described as a means of evaluating potential antidepressants. Mice were suspended on the edge of a table, 50 cm above the floor, with the help of an adhesive tape placed approximately 1 cm from the tip of the tail. Immobility time was recorded during a 6 min period. The animal was considered to be immobile when it did not show any movement of the body and hanged passively.

2.5 Grouping

Total of 30 male swiss albino mice (N=30) were divided into 5 treatment groups (n=6) and were injected with normal saline 5ml/kg (control), desipramine 30mg/kg(standard), tramadol 10 mg/kg, 20 mg/kg and 40 mg/kg(test drug) intraperitoneally to each group respectively. Duration of immobility was observed for 6 mins in tail suspension test and for 4 mins in forced swimming test on same set of animals after giving a sufficient wash out period of 4 weeks. Results were compared among the different groups.

3. RESULTS AND DISCUSSION

The mean duration of immobility after tramadol administration intraperitoneally in both the models was compared to the control and standard. The summarized

results are given in **Table 1**. ANOVA was done to check if there was any significance in the group followed by post-hoc tukey's test to know the inter-group significance.

3.1 Forced Swim model

In our study, there was a highly significant reduction in immobility period with standard, desipramine (12.8 ± 5.7 sec) when compared to control (196.3 ± 18.8 sec) ($p<0.001$). All the three groups of test drug i.e., tramadol 10mg/kg group (40.7 ± 9.5 sec), tramadol 20 mg/kg group (31.3 ± 8.0 sec), tramadol 40 mg/kg group(13.3 ± 3.1 sec), showed significant reduction in the time of immobility compared to control ($p < 0.001$). The immobility period seen in the test groups was comparable to desipramine group. Tramadol 40 mg/kg group showed mean values closer to the standard group and is better than 10 mg/kg and 20 mg/kg group **(Figure 1)**.

3.2 Tail suspension model

In this model, there was no significant reduction in immobility period with standard drug, desipramine (152.2 ± 11.9 sec) when compared to control (166.2 ± 42.8 sec) ($p=0.75$). With tramadol 10 mg/kg, the duration of immobility was 73.5 ± 5.6 sec, with a dose of 20 mg/kg it was 64.5 ± 4.8 sec and with 40 mg/kg it was 30.8 ± 4.2 sec. Compared to control the 'p' values of all test groups were <0.05. The mean reduction in immobility period was higher in all the test groups than the standard with a p value of <0.001 in all groups **(Figure 2)**.

The present study evaluated the possible antidepressant activity of tramadol by using the forced swimming model and tail suspension test. Both of these models are widely used to screen newer and potential antidepressant drugs. There is also a very good correlation between the results seen in these tests and the clinical activity of the drugs. [17] These tests are quite sensitive and relatively specific to all major classes of antidepressants like tricyclics, selective serotonin reuptake inhibitors, monoamine oxidase inhibitors and atypical antidepressants. [15, 16] The antidepressant activity is indicated by the reduction in the duration immobility ie., lesser the duration more the potency. The results have been expressed mean duration of immobility in seconds ± standard deviation.

Table 1: The results of both the models summarized

Groups		Forced swimming model (in seconds ± SD)	Tail suspension model (in seconds± SD)
1. Control		196.3 ± 18.8	166.2 ± 42.8
2. Standard 30 mg/kg		12.8 ± 5.7	152.2 ± 11.9
3. 10 mg/kg		40.7 ± 9.5	73.5 ± 5.6
4. 20 mg/kg		31.3 ± 8.0	64.5 ± 4.8
5. 40 mg/kg		13.3 ± 3.1	30.8 ± 4.2
ANOVA	F	328.97	50.68
	p	0.00**	0.00**
Difference between groups (p value)	1 and 2	0.00**	0.75, NS
	1 and 3	0.00**	0.00**
	1 and 4	0.00**	0.001*
	1 and 5	0.00**	0.001*
	2 and 3	0.001*	0.00**
	2 and 4	0.039*	0.00**
	2 and 5	1.00, NS	0.00**
	3 and 4	0.55, NS	0.94, NS
	3 and 5	0.001*	0.010*
	4 and 5	0.047*	0.05*

The p value of < 0.05 was considered significant (*) and a p < 0.001 (**) was considered highly significant; a value of p >0.05 (NS) was considered not significant.

From the **Table 1** it is clear that tramadol has antidepressant activity. In the forced swimming model, the antidepressant activity of tramadol in a dose of 40mg/Kg is comparable to that of standard drug. In the tail suspension model, tramadol in all the doses is expressing better antidepressant activity than the standard. Tramadol therefore is an effective antidepressant.

Martin P et al and Desmeules JA et al in their studies have shown that tramadol, apart from μ receptor agonism, causes inhibition of reuptake of norepinephrine and serotonin. Its antidepressant like effects are mediated by noradrenergic system mainly by its action on β_2 receptors. Tramadol increases the

levels of 3-methoxy-4-hydroxy phenyl glycol and noradrenaline in locus coreleus, hypothalamus, hippocampus and cerebellum in stressed mice. [10, 18]

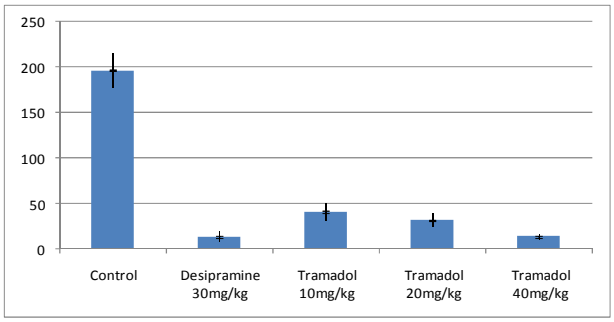

Fig 1: Results of Forced Swimming Model

Each histogram represents mean duration of immobility in seconds(n=6). Vertical line on top represents SD. Tramadol in the dose of 40 mg/Kg is showing almost similar reduction in immobility as the standard, desipramine

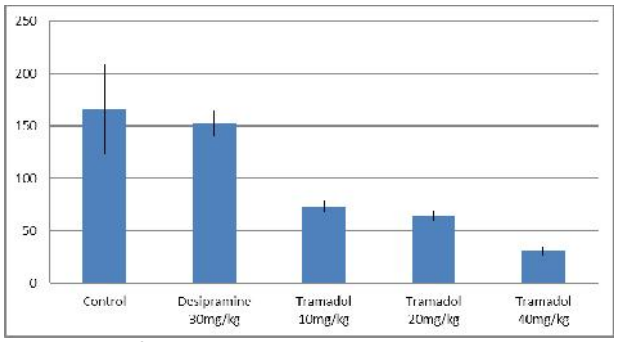

Fig 2: Results of Tail Suspension Model

Each histogram represents mean duration of immobility in seconds(n=6). Vertical line on top represents SD. All the doses of test are showing better reduction of immobility time compared to control and standard.

Rojas-Corrales MO et al showed the dual mechanism of action of tramadol which exists as racemers. The + enantiomer is opioid agonist and inhibits serotonin uptake and the – enantiomer inhibits noradrenaline uptake. He also showed that the abuse potential of tramadol is very low ie., one in one lakh patients. [19]

Tramadol is widely used to manage chronic pain. In the WHO step ladder pattern of management of cancer pain management, the step 2 involves managing the pain with weak opioids like codeine, dihydrocodeine and tramadol. Wojciech Leppert in his review he has noted that tramadol has completely replaced codeine for managing step 2 cancer pains in few countries like Poland where its efficacy was proven. Another important advantage of tramadol over other drugs in the step 2 is lesser incidence of constipation. It also can be combined in a fixed dose combination with paracetamol to improve analgesia without increasing toxicity and can also be prescribed without any limit on the number of prescriptions or refills as the abuse potential is very low. Its noradrenaline reuptake inhibition can be utilized to manage pains that have neuropathic component too. All these advantages make tramadol a very effective analgesic to manage mild to moderate cancer pains. [8]

Pain in cancer patients is very common and many of them suffer from co-existent depression. Though these patients are primarily treated by psychotherapy, pharmacotherapy is sometimes necessary. [6] Whenever drugs are necessary for the management of moderate cancer pain and depression, tramadol can be a monotherapy. Sirisha G et al in their animal study of chronic administration of tramadol, have also proven that tramadol potentiates other antidepressants like fluoxetine. [14] So if the depression is not adequately treated by antidepressants, tramadol could be a suitable adjuvant drug. Further evaluation of tramadol as an antidepressant has to be done in humans. After confirming the antidepressant action of tramadol in humans, it can also be promoted as an antidepressant which will go a long way in benefitting cancer patients.

4. CONCLUSION

Tramadol has a very good antidepressant action comparable to the tricyclic antidepressant, desipramine as seen in these animal models. It can be very effective in managing patients who are experiencing mild to moderate pains due to cancer and are also diagnosed to have co-morbid depression.

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