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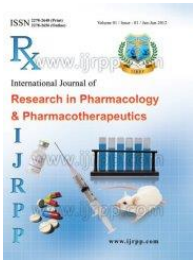

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Comparative evaluation of antidepressant activity of tramadol and tapentadol in swiss albino mice

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ABSTRACT

The study was done after obtaining approval from the institutional animal ethical committee of JJM Medical College, Davangere and CPCSEA. A total of 60 Swiss albino mice inbred in the Central Animal House of J.J.M.M.C of either sex and of weight between 20-40g and aged 3-4 months were taken for the study. They were divided into 10 groups of 6 animals each. The antidepressant activity of tramadol and tapentadol was evaluated in mice using forced swim test model and tail suspension test model.

In both the experimental models, Group i received normal saline- 10ml/kg(control group), group ii,iii,iv,v were given tramadol 20mg/kg, tramadol 40mg/kg, tapentadol 20mg/kg and tapentadol 40mg/kg respectively, once a day for 7 days. The drugs were given intraperitoneally.

On day 7, the drugs were given 1 hour before conducting the experiment. The duration of immobility was noted and compared amongst the 5 groups in both the models. The observations were analyzed using ANOVA (one way) and post hoc Tukey's test. The test drugs tramadol and tapentadol showed significant reduction in duration of immobility in both the models. In FST model, tapentadol showed significant reduction in duration of immobility at the dose of 20mg/kg (34.67sec) when compared to 40mg/kg (67.5sec); ($P < 0.003$) and was comparable to tramadol at a dose of 20mg/kg (36sec). In TST model, tapentadol at 20mg/kg has shown a greater reduction in duration of immobility (54.8sec) as compared to tramadol at 20mg/kg (106.17sec). Tapentadol showed a greater antidepressant activity compared to tramadol in TST model ($P<0.001$) and showed similar activity but was statistically insignificant.

Both tramadol and tapentadol have shown significant antidepressant activity in comparison with control group in both the test models. Tapentadol has shown better antidepressant activity than tramadol in TST model. Hence further animal studies with different model for depression and clinical studies should be conducted to confirm these findings and in choosing the better drug for treatment of chronic painful conditions like cancer which is often associated with depression.

Keywords: Antidepressant, Tapentadol, Tramadol

INTRODUCTION

Depression is a mental disorder that presents with depressed mood, loss of interest or pleasure, feelings of guilt or low self-esteem, disturbed sleep or appetite, low energy and poor concentration lasting for at least 2 weeks. [1]

Patients may lose their interest in several common activities which were pleasurable to them. They experience loss of concentration, problem in remembering details or making decisions and may think or attempt to suicide. [2] Patients with major depression have symptoms that reflect changes in brain monoamine neurotransmitters, specifically nor epinephrine and serotonin. [3]

Chronic pain is also called 'disease of pain'. The cause can be malignant or non malignant. People presenting with chronic pain provide the health practitioner with a therapeutic challenge since depression is a common comorbidity, which often goes unrecognized in these patients [4] Hence it becomes important to not only relieve the symptoms of pain but also to treat depression in order to improve the overall quality of life.

Neurotransmitter systems that are used to control pain overlap with those which are considered to be the main pathophysiological mechanisms in depressive disorders, i.e., serotonergic, noradrenergic, and glutamatergic systems. [5] Hence drugs altering these neurotransmitter systems could have potential anti depressant and analgesic activity.

Tramadol is a synthetic centrally acting opioid analgesic used mainly for the treatment of moderate to severe pain. It is a weak μ opioid receptor agonist and also produces analgesia by inhibiting uptake of norepinephrine and serotonin. [6]

Tapentadol is a centrally acting analgesic for the treatment of moderate to severe acute pain with a dual mode of action: agonist at the μ-opioid receptor (analgesic effect) and as a norepinephrine & 5-HT reuptake inhibitor (antidepressant effect). [7] Unlike tramadol, which inhibits reuptake of both norepinephrine and serotonin, tapentadol has limited interaction with serotonin transporter proteins and minimal effect upon serotonin reuptake. Therefore, the risk of serotonin syndrome is less with tapentadol. [8]

Previous studies conducted in mice using an experimental model, it was seen that tramadol exhibits antidepressant activity. [6] Very few animal studies have been conducted to evaluate the antidepressant property of tapentadol and none comparing the two. Hence this study is undertaken with the aim to evaluate and compare the antidepressant effect of tramadol and tapentadol in mice.

METHODOLOGY

The study was conducted after taking the necessary approval from the Institutional Animal Ethical Committee (IAEC) of J.J.M. Medical College, Davangere, in accordance with the CPCSEA guidelines.

Chemicals and drugs

Tramadol 20mg/kg, 40mg/kg
Tapentadol 20mg/kg, 40mg/kg
Normal saline

Selection of animals

A total of 60 Swiss albino mice inbred in the Central Animal House of J.J.M.M.C, Davangere, Karnataka, of either sex and of weight between 20-40g and aged 3-4 months were procured.

The animals were fed with freely accessible standard pellet diet and with water *ad libitum*. They were maintained under standard ambient conditions of temperature, humidity, and light (12 h light/12 h dark cycle). Experiments were carried out between 9 a.m. and 5 p.m.

Inclusion criteria

- → Swiss albino mice of either sex weighing between 20-40grams.
- → Age 3-4 months.
- → Healthy with normal behaviour and activity.

Exclusion criteria

- → Pregnant and diseased animals were not included in the study.
- → The mice previously used for any experiments.

Duration of study: 2 months

Instruments

Two, of the most commonly used animal screening methods for the evaluation of antidepressant activity of potential drugs, were used. These two are Despair-based tests.

1. Forced swimming method apparatus
2. Tail suspension model apparatus

PROCEDURE

A total of 60 animals (n=60), 30 for each model were used in the study. They were divided into 5 groups of 6 animals each for each model. They were evaluated for antidepressant activity using two models. Animals were randomly housed at an ambient temperature and humidity, with a 12 hour light: 12 hour dark cycle. The animals have free access to standard pellet and water. Test drug was administered intraperitoneally for 7 days after dissolving it in the Normal Saline. On day 7, drugs were administered to the mice 40 min before conducting the study. After completing the experiment, the animals were dried with the cloth and returned to the home cage.

Model i: forced swimming test (FST)

The animals were divided as follows.
Group i: Received 0.1ml/10g of Normal saline intra peritoneal. (i.p) – CONTROL (C)
Group ii: Received 20 mg/kg of Tramadol i.p. – TEST 1 (T1)
Group iii: Received 40 mg/kg of Tramadol i.p. – TEST 2 (T2)
Group iv: Received 20mg/kg of Tapentadol i.p -- TEST 3 (T3)
Group v: Received 40mg/kg of Tapentadol i.p -- TEST 4 (T4)

Figure 1: Forced Swimming Test

Mice were individually forced to swim inside vertical plexi glass cylinder (25×10×25 cm3) filled with a water to a height of 15 cm.(Figure 1). After an initial 2 min period of vigorous activity, each animal assumes a typical immobile posture. The total duration of immobility will be recorded after 2 min, for 4 min in a total of 6 min test. Duration of immobility period will be compared with those of control group. Following swimming sessions, the mice were dried with towel and placed in a cylinder under 60 W bulb for 15 min before returning to home cages.

MODEL II: Tail Suspension Test (TST)

The animals were divided as follows.
Group i: Received 0.1ml/10g of Normal saline intra peritoneal. (i.p) – CONTROL (C)
Group ii: Received 20 mg/kg of Tramadol i.p. – TEST 1 (T1)
Group iii: Received 40 mg/kg of Tramadol i.p. – TEST 2 (T2)
Group iv: Received 20mg/kg of Tapentadol i.p -- TEST 3 (T3)
Group v: Received 40mg/kg of Tapentadol i.p -- TEST 4 (T4)

Figure 2: Tail Suspension Test apparatus

On the day of test, mice were hung/ suspended individually on a horizontal metal bar in upside down position, 58 cm above a table top, after giving the drug, using the adhesive tape placed approximately one cm from the tip of the tail [10] (Figure 2).After an initial vigorous movements, the mouse assumes an immobile posture and the period of immobility be recorded after 2 minutes, for 4 minutes in a total of 6 minutes test. Duration of immobility period were compared with those of control group.

Parameters observed

Duration of immobility were observed after 2 min, for 4 min in a total of 6 min in both the experiments. The immobility displayed by rodents, when subjected to an unavoidable and inescapable stress, has been hypothesized to reflect behavioral despair, which in turn may reflect depressive disorders in humans. Clinically effective antidepressants reduce the immobility that mice display after active and unsuccessful attempts to escape when suspended by the tail/ made float on the surface of water.

STATISTICAL ANALYSIS

Mean and Standard Deviation were used for Continuous variables. Comparison of all the five groups (Intra-Group) for each experimental model was done with One Way Analysis of Variance (ANOVA). Multiple Inter-Group comparisons were done with Turkey's Post Hoc analysis for group wise comparison within each experimental model. Inter model comparison of groups were done with Student's t test unpaired as the data passes normality test.

Probability (P) value < 0.05 is considered as the level of statistical significance and P < 0.01 is considered highly significant. Statistical analysis was carried out with IBM SPSS version 20 for Windows.

RESULTS

Table 1: Mean Duration of immobility observed in Forced Swim Test model

Groups	Group1 (control)	Group 2 tramadol 20mg/kg	Group 3 tramadol 40 mg/kg	Group 4 tapentadol 20mg/kg	Group 5 tapentadol 40mg/kg
Mean Duration of immobility (seconds)	102.33	36	14.83	34.67	67.5

In forced swim test model, there was a significant reduction in the mean duration of immobility in all the four test groups when compared with control group. The reduction is maximum with tramadol 40mg/kg. The reduction with tramadol 20mg/kg and tapentadol 20mg/kg was moderate and comparable. (Table1, figure 3)

Table 2: Mean Duration of immobility observed in Tail suspension test model

Groups	Group1 (control)	Group 2 tramadol 20mg/kg	Group 3 tramadol 40 mg/kg	Group 4 tapentadol 20mg/kg	Group 5 tapentadol 40mg/kg
Mean Duration of immobility (seconds)	141	106.17	123.67	54.8	126.17

In tail suspension test model, there was a significant reduction in the mean duration of immobility in all the four test groups when compared with control group. And tapentadol at 20mg/kg showedmaximum reduction when compared with control and other test groups. (Table 2, figure 4)

Table 3: **Effect of test drug on immobility period in FST model for antidepressant activity**

MODEL-FORCED SWIM TEST

IMMOBILITY TIME (Sec)	Mean	Std Deviation	ANOVA	P Value
GRP1-CONTROL,NORMAL SALINE	102.33	14.81	36.67	P<0.000
GRP2-TRAMADOL 20mg/kg	36	14.87		
GRP3-TRAMADOL 40mg/kg	14.83	7.81		
GRP4-TAPENTADOL20mg/kg	34.67	10.46		
GRP5-TAPENTADOL40mg/kg	67.5	18.75		

In the FST model of antidepressant activity assessment, there is significant reduction in the mean duration of immobility with the tramadol 40mg/kg. On inter group assessment, it is found to be of high statistical significance, with 'P' value <0.0. It is observed that the change in the mean value of duration of immobility is not dose dependent. (Table3)

Table 4: **Effect of test drug on immobility period in the TST model for antidepressant activity.**

MODEL-TAIL SUSPENSION TEST

IMMOBILITY TIME (Sec)	Mean	Std Deviation	ANOVA	P Value
GRP1-CONTROL,NORMAL SALINE	141	27.04		
GRP2-TRAMADOL 20mg/kg	106.17	5.85		
GRP3-TRAMADOL 40mg/kg	123.67	36.2	10.69	P<0.000
GRP4-TAPENTADOL20mg/kg	54.8	25.14		
GRP5-TAPENTADOL40mg/kg	126.17	20.54		

In the TST model of antidepressant activity assessment, compared to Control group, there is reduction in the mean duration of immobility with the Tapentadol 20 mg/kg treated group with a statistical significance with a P < 0.00. Also, it is observed that the change in the mean value of duration of immobility is not dose dependent. (Table 4)

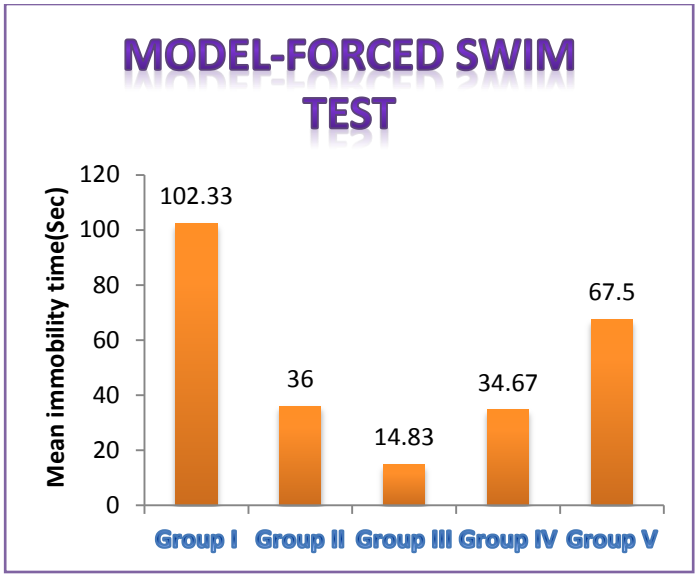

Fig 3: Bar diagram representing mean duration of immobility in Forced swim test.

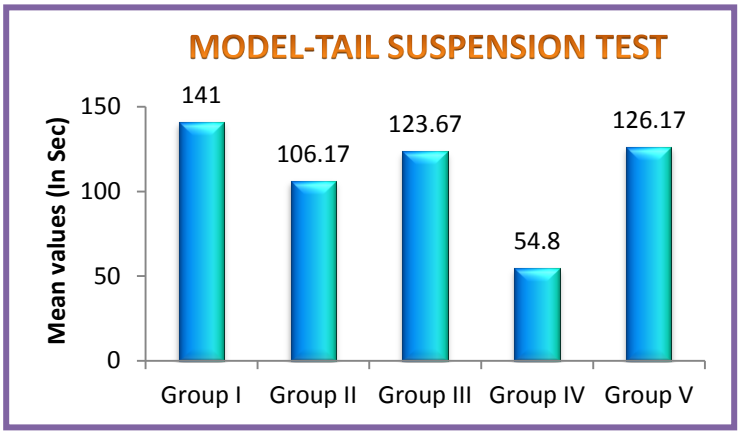

Fig 4: Bar diagram representing mean duration of immobility in Forced swim test.

Post hoc Tukey's test- FST model
(Table 5)

Tukey's Post Hoc Multiple Comparisons	
Groups compared	Sig.
Group I Vs group II	P<0.000
Group I Vs group III	P<0.000
Group I Vs group IV	P<0.000
Group I Vs group V	P<0.002
Group II Vs group III	P<0.01
Group II Vs group IV	1.000
Group II Vs group V	P<0.005
Group III Vs group IV	P<0.004
Group III Vs group V	P<0.000
Group IV Vs group V	P<0.003

Post hoc Tukey's test- TST model
(Table 6)

Tukey's Post Hoc Multiple Comparisons	
Groups compared	Sig.
Group I Vs group II	P<0.000
Group I Vs group III	P<0.000
Group I Vs group IV	P<0.000
Group I Vs group V	P<0.002
Group II Vs group III	P<0.01
Group II Vs group IV	1.000
Group II Vs group V	P<0.005
Group III Vs group IV	P<0.004
Group III Vs group V	P<0.000
Group IV Vs group V	P<0.003

In both the experimental screening models, since the 'P' value is found to be statistically significant, Multiple Inter-Group comparisons were done with the Tukey's Post Hoc analysis for group wise comparison within each experimental model. In both the experimental models, there is statistically significant difference between all the groups compared except between tramadol 20mg/kg and tapentadol 20mg/kg. (table5, 6)

The results are highly positive with FST experimental model for the characterization of antidepressant efficacy of the test drug, Tapentadol, at both the dosages. But the results were moderately positive with the TST experimental model, which showed greater antidepressant activity of tapentadol at 20 mg/kg. Thus, Tapentadol showed greater antidepressant activity when compared with tramadol at the dose of 20 mg/kg in TST model.

DISCUSSION

Depression is a heterogeneous disorder that affects a person's mood, physical health and behavior.[1] Depression is found to be the most common mental health condition in almost half of patients with chronic pain, affecting their day to day activities. [9] The cause of chronic pain could be cancer, diabetic neuropathy, arthralgia, etc. In such situations it becomes important have a holistic approach in the management of patients. Though symptoms of depression can be managed with psychotherapy, medical management with antidepressant drugs is essential. Currently a wide group of antidepressants are available and prescribed for treating depression but all of them have a latency period of 2-3 weeks for their onset of action.

Serotonin and norepinephrine are important neurotransmitters involved in pain inhibition in descending pain inhibitory tracts. Venlafaxine exerts its antidepressant action by inhibiting reuptake of serotonin and norepinephrine like Tramadol. [10] Tapentadol also acts by inhibiting the reuptake of nor epinephrine and serotonin.

However, it binds with lesser affinity to serotonin transporters when compared with tramadol. [7] A study conducted in mice using the same two experimental models, showed that tramadol has significant antidepressant activity which was comparable to Tricyclic Antidepressant, Desipramine. [11] A very few studies have been done to evaluate the antidepressant effect of tapentadol which structurally resembles tramadol and none comparing the two. Hence this study was done to compare the antidepressant effect of tapentadol with that of tramadol whose antidepressant action is proven in animal models.

In our study, the screening models used to demonstrate the antidepressant activity of the test drugs included two in vivo models, namely the forced swim test model and tail suspension test model. In both these models the rodents are placed in situations from which escape is not possible. This induces a

state of helplessness/ despair in the rodents which is compared with human depression. The rodents attain a state of immobility due to helplessness. Drugs which reduce this duration of immobility would have potential antidepressant activity. [12]

In this comparative study, tapentadol at 20mg/kg dose showed better antidepressant activity than tramadol in Tail suspension test model. Whereas in Forecd swim test model, the antidepressant effect of tapentadol was comparable with tramadol.

Similar animal studies using the same antidepressant models showed that both tramadol and tapentadol possess significant anti depressant activity which was comparable with standard antidepressant drugs.

Sirisha G et al in their animal study of chronic administration of tramadol, have also proven that tramadol potentiates other antidepressants like fluoxetine. [13] A study done by Ramnath et al showed that tapentadol has antidepressant activity comparable with fluoxetne. [14]

Also Tapentadol has several advantages as compared to tramadol which includes its greater efficacy as analgesic, lesser chances of causing serotonin syndrome, lesser pharmacokinetic drug interactions as it does not inhibit or induce induce cytochrome P450 enzymes and also has lesser post operative nausea and vomiting. [15]

Hence tapentadol which has a better efficacy and safety profile compared to tramdol, could be the drug of choice in the management of chronic pain with co morbid depression.

CONCLUSION

Both tramadol and tapentadol have shown significant anti depressant activity in both forced swim test and tail suspension test. Tapentadol at 20mg/kg has shown greater anti depressant activity compared to tramadol in Tail suspension test. Hence further animal studies with different models and clinical studies would help to evaluate the comparative anti depressant activity between tramadol and tapentadol. And the more efficious and well tolerated drug can be used in management of patients with chronic pain since these drugs by altering the seretonergic and nor adrenergic transmission in the brain may improve symptoms of depression as well as pain.

Conflict of interest statement: None declared.

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Ethical approval

The study was approved by the Institutional Animal Ethics Committee of J.J.M. Medical College, Davangere, Karnataka.

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