

EVALUATION OF ANTIDEPRESSANT ACTIVITY OF TAPENTADOL IN SWISS ALBINO MICE

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ABSTRACT

Objective: The aim of this study is to evaluate the antidepressant activity of tapentadol using forced swimming test (FST) and tail suspension test (TST) experimental models.

Methods: A total of 36 Swiss albino mice (18 for each experimental model) were divided into 3 groups of 6 animals each. In both the experimental models, Group I received normal saline – 10 ml/kg (Control group), Groups II and III given tapentadol 20 mg/kg and tapentadol 40 mg/kg, respectively, for 7 days, intraperitoneally. On day 7, the drugs were given 40 minutes before conducting the experiment. The duration of immobility was noted and compared among all the 3 groups. The observations were analyzed using analysis of variance and Tukey's *post-hoc* test.

Results: The duration of immobility was significantly decreased in both the experimental models. Tapentadol groups when compared to control group showed statistically significant values, and better results were obtained with tapentadol 20 mg/kg groups in both the models. The mean duration of immobility was 34.67 seconds in FST model and 101.00 seconds in TST model when treated with tapentadol 20 mg/kg compared to 102.33 seconds in FST control and 141 seconds in TST control groups. FST model demonstrates greater antidepressant efficacy of tapentadol ($p < 0.00$) than with TST model ($p < 0.04$).

Conclusion: Tapentadol showed significant antidepressant activity at the dose of 20 mg/kg. The results should be further confirmed by animal studies with different experimental models for the evaluation of depression and by human clinical studies, and if found effective, tapentadol can be preferred for patients with chronic pain, such as cancer pain.

Keywords: Antidepressant, Tapentadol, Swiss albino mice.

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INTRODUCTION

Depression

Major depression or simply depression is one of the leading causes of global disease burden and disability [1].

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 [2].

Patients may lose their interest in several common activities which were pleasurable to them. They experience loss of appetite, loss of concentration, and problem in remembering details or making decisions and may think or attempt to suicide. Excessive sleeping, loss of sensation, digestive problems, insomnia, fatigue, etc., that are resistant to treatment may also be present [3].

Pain

For scientific and clinical purposes, pain is defined by the International Association for the Study of Pain (IASP) as "An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage." This is to be distinguished from the term nociception which the IASP defines as the unconscious activity induced by a harmful stimulus applied to sense receptors [4].

Chronic pain is defined as pain that has been present for more than 6 months. It is a chronic pain that is often accompanied by depression [5].

People presenting with chronic pain provide the health practitioner with a therapeutic challenge. Depression is a common comorbidity that compounds the challenge, often going unrecognized [6].

Patients with major depression have symptoms that reflect changes in brain monoamine neurotransmitters, specifically norepinephrine, serotonin, and dopamine [7].

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 [8].

Tapentadol

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 and 5-HT reuptake inhibitor (antidepressant effect) [9].

Furthermore, its binding to the norepinephrine transporter was stronger than that of tramadol, whereas its binding to the serotonin transporter was less than that of tramadol. Tapentadol was approved for the relief of moderate to severe acute pain in patients 18 years of age or older, on November 2008 [10].

It is considered similar to tramadol in activity, efficacy, and side-effect profile. Like tramadol, it should not be used concurrently with agents that enhance monoamine activity or lower the seizure threshold, such as monoamine oxidase inhibitors and selective serotonin reuptake inhibitors.

The incidence of serotonin syndrome is less compared to tramadol. The major pathway of tapentadol metabolism is conjugation with glucuronic acid; ~70% of the dose is excreted in urine in the conjugated form.

METHODS

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

Chemicals and drugs

- Tapentadol 20 mg/kg, 40 mg/kg
- Normal saline.

Selection of animals

A total of 36 Swiss albino mice inbred in the Central Animal House of J.J.M. Medical College, Davangere, Karnataka, of either sex and of weight between 20 and 40 g, aged 3-4 months were obtained.

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 and 40 g
- Age 3-4 months
- Healthy with normal behavior and activity.

Exclusion criteria

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

Duration of study

Duration of the study was 2 months.

Instruments

Two, of the most commonly used animal screening methods for the evaluation of antidepressant activity of potential drugs, were used for characterization of antidepressant activity of the putative drug, tapentadol. These two are despair-based tests:

- Forced swimming method apparatus
- Tail suspension model apparatus.

Procedure

A total of 36 animals (n=36) were used.

They were divided into 6 groups of 6 animals each.

They were evaluated for antidepressant activity using two models.

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 minutes 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 0.1 ml/10 g of normal saline intraperitoneal (i.p) - Control (C)

Group II: Received 20 mg/kg of tapentadol (i.p) - TEST 1 (T1)

Group III: Received 40 mg/kg of tapentadol (i.p) - TEST 2 (T2).

Naïve mice were individually forced to swim inside vertical plexiglass cylinder (height: 40 cm; diameter: 18 cm, containing 15 cm of water maintained at 25°C). After an initial 2 minutes period of vigorous activity, each animal assumes a typical immobile posture. The total duration of immobility will be recorded after 2 minutes, for 4 minutes in a total of 6 minutes test.

The mouse was considered as immobile when it stopped struggling/floating motionless and/or making only those movements necessary to keep its head above water surface. Shorter immobility time is an indicator of the stronger antidepressant effect of the tested substance [11].

Water was changed after testing each animal. This test has been validated by most current types of antidepressants. After taking the animal out of the cylinder, the animal is rehabilitated by drying with the cloth and returning them to the home cage (Fig. 1).

Model II: Tail suspension test (TST)

The animals were divided as follows:

Group I: Received 0.1 ml/10 g of normal saline intraperitoneal (i.p) - Control (C)

Group II: Received 20 mg/kg of tapentadol (i.p) - TEST 1 (T1)

Group III: Received 40 mg/kg of tapentadol (i.p) - TEST 2 (T2).

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 1 cm from the tip of the tail [12].

After an initial vigorous movement, the mouse assumes an immobile posture and the period of immobility was recorded after 2 minutes, for 4 minutes in a total of 6 minutes test. Duration of immobility period was compared with those of control group (Fig. 2).

Parameters observed

Duration of immobility was observed after 2 minutes, for 4 minutes in a total of 6 minutes in both the experiments. The immobility displayed by rodents, when subjected to an unavoidable and inescapable stress, and 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 three groups (intragroup) for each experimental



Fig. 1: Forced swimming test apparatus



Fig. 2: Tail suspension test apparatus

model was done with one-way analysis of variance. Multiple intergroup comparisons were done with Tukey's *post-hoc* analysis for groupwise comparison within each experimental model.

Inter-model comparison of groups was done with Student's unpaired t-test as the data pass normality test.

$p < 0.05$ 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

The mean duration of immobility of the individual animals of different groups of the study for the FST model was noted (Table 1).

The mean duration of immobility of the individual animals of different groups of the study for the TST model was noted (Table 2).

Effect of test drug on immobility period in the FST model for antidepressant activity

In the FST model of antidepressant activity assessment, there is significant reduction in the mean duration of immobility with the tapentadol 20 mg/kg-treated group. On intergroup assessment, it is found to be of high statistical significance, with $p < 0.05$. It is observed that the change in the mean value of duration of immobility is not dose dependent (Table 3).

Effect of test drug on immobility period in the TST model for antidepressant activity

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 and also with the tapentadol 40 mg/kg-treated group. It is of statistical significance with a $p < 0.05$. Here with the TST experimental model also, it is observed that the change in the mean value of duration of immobility was not dose dependent (Table 4).

In both the experimental screening models, since the p value is found to be statistically significant, multiple intergroup comparisons were done with the Tukey's *post-hoc* analysis for groupwise comparison within each experimental model.

Within the FST experimental model, there is statistically significant difference between any 2 groups. It is observed that it is highly significant between the control and tapentadol 20 mg/kg-treated group. In the same way, within the TST experimental model, the statistical significance exists only between the control and tapentadol 20 mg/kg-treated groups only and it is not so between any of the 2 other groups comparison, i.e., control and tapentadol 40 mg/kg groups and tapentadol 20 mg/kg- and 40 mg/kg-treated groups.

The results are highly positive with FST experimental model for the characterization of antidepressant efficacy of the test drug, tapentadol, at both the dosages. However, the results were moderately positive with the TST experimental model, that too only with tapentadol when treated at the dosage of 20 mg/kg as shown in Graph 1 and 2. Thus, the study drug tapentadol has antidepressant activity at the dose of 20 mg/kg (Tables 5 and 6).

On comparison of the corresponding groups of both the experimental models, the t and p values indicate the significant difference in the mean duration of immobility, between all the 3 drug groups, which is not favorable (Table 7).

DISCUSSION

Depression, which is the most common comorbidity associated with pain, both in chronic (such as cancer pain) and acute varieties, is often underdiagnosed and undertreated by the physician. Even if the depression is diagnosed and treated timely with the drugs, they are associated with a latency period for their antidepressant effect. Psychological support along with certain medications such as sedatives and antidepressants is specifically needed in such a group of patients.

Serotonin and norepinephrine are important neurotransmitters involved in pain inhibition in descending pain inhibitory tracts. Venlafaxine being an antidepressant exerts its mechanism mainly by inhibiting reuptake of serotonin and norepinephrine like tramadol [13]. In a study conducted in mice using the same two experimental models, it was seen that tramadol exhibits significant antidepressant activity and it was comparable to tricyclic antidepressant, desipramine [14].

Hence, the present study was conducted with tapentadol, which also belongs to the same class of drugs as tramadol.

Table 1: The values of mean duration of immobility of the individual animals of different groups of the study

Group→	Group I (control, normal saline)	Group II (tapentadol, 20 mg/kg)	Group III (tapentadol, 40 mg/kg)
Module→	FST		
Mice No.↓	Duration of immobility (in seconds)		
1	95	40	79
2	90	25	61
3	102	52	75
4	116	28	92
5	124	37	60
6	87	26	38

FST: Forced swimming test

Table 2: The values of mean duration of immobility of the individual animals of different groups of the study

Group→	Group I (control, normal saline)	Group II (tapentadol, 20 mg/kg)	Group III (tapentadol, 40 mg/kg)
Module→	TST		
Mice no.↓	Duration of immobility (in seconds)		
1	136	76	150
2	155	100	126
3	130	124	100
4	186	65	150
5	106	131	110
6	133	110	121

TST: Tail suspension test

Table 3: The results obtained after statistical analysis for the FST module

Groups	Mean (seconds)	Standard deviation	F value	p value
Group I - Control, normal saline	102.33	14.81	30.29	p<0.000**
Group II - Tapentadol 20 mg/kg	34.67	10.46		
Group III - Tapentadol 40 mg/kg	67.50	18.75		

**Highly significant, FST: Forced swimming test

Table 4: The results obtained after statistical analysis for the TST module

Groups	Mean (seconds)	Standard deviation	F value	p value
Group I - Control, normal saline	141.00	27.04	4.00	p<0.04
Group II - Tapentadol 20 mg/kg	101.00	26.20		
Group III - Tapentadol 40 mg/kg	126.17	20.54		

TST: Tail suspension test

Table 5: Tukey's post-hoc analysis for groupwise comparison within FST experimental model

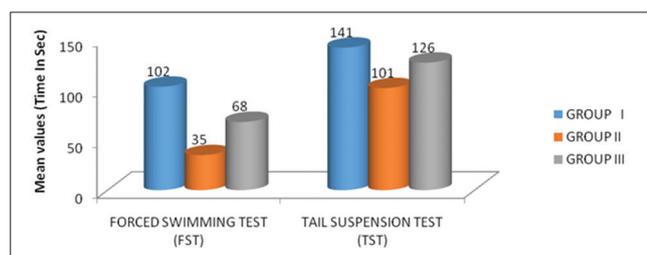
Comparison groups	Significance
Group I versus II	p<0.000**
Group I versus III	p<0.003*
Group II versus III	p<0.005*

FST: Forced swimming test. **Highly significant, *Significant

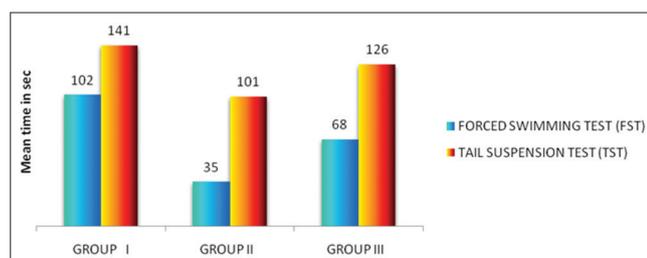
Table 6: Tukey's post-hoc analysis for groupwise comparison within TST experimental model

Comparison groups	Significance
Group I versus II	p<0.03*
Group I versus III	p<0.566
Group II versus III	p<0.216

TST: Tail suspension test. *Significant



Graph 1: Bar graph representing the results obtained after statistical analysis for the forced swimming test and the tail suspension test modules



Graph 2: Bar graph representing the comparison of the corresponding groups of the forced swimming test and tail suspension test experimental models

In this study, antidepressant activity of tapentadol was evaluated using FST and TST, respectively. In this study, we found significant antidepressant activity of tapentadol at a dose of 20 mg/kg, which was significant as compared to control group of animals.

Advantages of tapentadol compared to its analog tramadol include:

- It has the least chance of causing serotonin syndrome,
- It used in the treatment of severe diabetic peripheral neuropathic pain,
- It carries the minimal potential for pharmacokinetic drug interactions (does not inhibit or induces cytochrome P450 enzymes)
- It is a single enantiomer and an active molecule (not a prodrug). Hence, it does not require metabolic activation to produce its action
- Tramadol produced somnolence, dizziness, headache, nausea, and vomiting [15]
- Tapentadol is a better analgesic than tramadol and has fewer side effects compared to tramadol [16].

There is large body of evidence to suggest that the analgesic action of tapentadol is mainly related to central monoaminergic mechanism and opioids receptor pathway. *In vitro* studies have shown that tapentadol effectively inhibits reuptake of monoamines. It has also been established that tapentadol inhibits the reuptake of serotonin in the raphe nucleus. Antidepressants mainly act by inhibiting norepinephrine and serotonin reuptake and tapentadol by virtue of its property of blocking monoaminergic reuptake could be responsible for its antidepressant activity evident in this study.

On the other way round, there is also evidence of antidepressant drugs showing antinociceptive effect, especially venlafaxine, at the dose, 10 mg/kg which is supported by the findings of Santhosh Ramakrishna *et al.* and other antidepressants as well by Bomholt *et al.* [17] and Muth-Selbach *et al.* [18]. These results suggest that the antinociceptive activity of these antidepressant drugs could involve opioid mechanisms. These observations are in agreement with the findings of Singh *et al.* [19] and Anjaneyulu and Chopra [20].

As the analgesic activity of tapentadol is mediated through μ -receptors, it is likely that mirtazapine acts through opioid pathways involving the μ -opioid receptors. Apart from that, there is ample evidence to suggest that descending pain inhibitory pathways involve monoamines such as noradrenaline (NA) and 5-HT, serotonin. Spinal inhibition of pain, brought about by inhibiting NA and 5-HT reuptake, is one of the major mechanisms of action of opioid analgesics and mirtazapine by virtue of its property of blocking monoaminergic reuptake is responsible for its antinociceptive activity.

Thus, this study, though preliminary in nature, shows that tapentadol at the dose of 20 mg/kg has significant antidepressant effect.

CONCLUSION

Tapentadol showed significant antidepressant activity at the dose of 20 mg/kg. The results are further to be confirmed by animal studies with different experimental models for the evaluation of depression and by human clinical studies and if found effective, tapentadol could be used in patients with chronic pain, such as cancer pain.

Table 7: Master table showing the comparison of the corresponding groups of the FST and TST experimental models, their t and p values

Groups	FST		TST		Unpaired t test	
	Mean (in seconds)	Standard deviation	Mean (in seconds)	Standard deviation	t value	p value
Group I	102.33	14.81	141.00	27.04	-3.072	p<0.01
Group II	34.67	10.46	101.00	26.20	-5.76	p<0.000
Group III	67.50	18.75	126.17	20.54	-5.168	p<0.000

FST: Forced swimming test, TST: Tail suspension test

The antidepressant activity of tapentadol can be attributed to its norepinephrine and serotonin reuptake inhibiting property, which is shared by functionally similar opioid analgesic tramadol, indicating the importance of serotonin and norepinephrine in pain as well as depression mechanisms.

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