ISSN 0975 - 6299 Vol 2 / Issue 4 / Oct - Dec 2011

International Journal of Pharma and Bio Sciences

RESEARCH ARTICLE

PHARMACOLOGY

EVALUATION OF ANTIDEPRESSANT -LIKE ACTIVITY OF TAPENTADOL IN SWISS ALBINO MICE.

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ABSTRACT

Objective: - To evaluate antidepressant like activity of tapentadol in Swiss albino mice.
Materials and Methods: - Tapentadol was administered at three different doses (10, 20 and 40mg/kg i.p) once daily for 7 days to Swiss albino mice of either sex. The immobility period of control and drug treated mice were recorded in Forced swim test (FST). The antidepressant activity of tapentadol was compared to that of fluoxetine (20mg/kg i.p), administered for 7 days. A locomotor activity test was carried out to ascertain whether the antidepressant effect of tapentadol included general CNS stimulation.
Results: - Tapentadol produced significant antidepressant activity at all the 3 doses, as indicated by reduction in immobility times as compared to control. The efficacy of tapentadol at doses of 20 and 40mg/kg was comparable with that of fluoxetine. Tapentadol at 10mg/kg dose showed significantly less antidepressant activity compared to fluoxetine. Tapentadol did not show significant effect on locomotor activity of mice.
Conclusion: The result of the present study indicates antidepressant like activity of tapentadol.

ISSN 0975 - 6299 Vol 2 / Issue 4 / Oct - Dec 2011

KEY WORDS

Antidepressant, Forced swim test, locomotor activity, tapentadol.

INTRODUCTION

Depression is a serious mental health problem. The prevalence of major depression in the general population is estimated at 15% and accounting for approximately 10% of consultations in primary care [(1)]. An estimated 3-4% of India's 100 crore plus population suffers from major mental disorders and about 7-10% of the population suffers from minor depressive disorders. Compared to men, women are twice as likely to suffer from depression, and the severity of symptoms generally increases with the age [(2)]. Recent studies suggest a rising incidence of depression in younger age groups, particularly young men, which may be linked to the relative rise in suicide rates. Characterised by the absence of positive effects (loss of interest and enjoyment in ordinary things and reduced energy) other common symptoms include poor concentration, reduced self-confidence, feeling of guilt, pessimism, ideas of self-harm or suicide, disturbed sleep and altered appetite [(3)].

The main biochemical theory of depression is monoamine hypothesis which states that depression is caused by a functional deficit of monoamines (Nor epinephrine, serotonin and dopamine) in certain sites of the brain. It is reported that only two out of three patients respond to any given treatment [(4)]. Reduced monoaminergic signaling has long been though to underline depressive disorders. For example reduced monoamine metabolite levels have been found in the cerebrospinal fluid of depressed individuals likewise, neither serotonin (5-HT) nor epinephrine or dopamine depletion exerts pro depressive effects. In the case of depression the level of monoamine oxidase enzyme (MAO) in the brain is increased, which in turn reduces the level of monoamines.

Unrelieved acute pain may cause anxiety, sleep disturbances, and demoralization and may interfere with mental activity and social interactions [(5)]. Tapentadol is a new molecular entity that is structurally similar to tramadol. Tramadol bears a close structural similarity to antidepressant Venlafaxine and thus shares a number of its molecular and pharmacological features [(6)]. Tapentadol is a centrally acting FDA approved analgesic for the treatment of moderate to severe acute pain with a dual mode of action as an agonist at the μ-opioid receptor and as a nor epinephrine reuptake inhibitor[(7)]. It has opioid and non opioid activity in a single compound. It is a weak μ opioid receptor agonist and it also produces analgesia by inhibiting uptake of nor epinephrine and serotonin. Tapentadol is Due to the dual mechanism of action as an opioid agonist and nor epinephrine reuptake inhibitor, there is potential for off label use in chronic pain.

METERIALS AND METHODS

STUDY DESIGN

The design of this experimental study was comparative and parallel group. Animals divided into 5 groups and each group comprised of minimum of six mice. Tapentadol was administered in three different doses (10, 20, and 40mg/kg) to different groups of mice

ANIMALS:

Swiss albino mice of either sex 3-4 months old and weighing around 20-25gm were procured from the disease free small animal house, Basaveshwara Medical College and Hospital, Chitradurga, Karnataka, India. The animals had free access to food and water, and were housed in an animal room with alternating light dark cycle of 12hr each. The animals were acclimatized for at least 5 days to the laboratory conditions before behavioral experiments. Experiments were carried out between 9a.m to 12a.m. All the experiments were performed according to the CPCSEA (1284/ac/09) norms after obtaining the approval of the Institutional Animal Ethical
Committee (IAEC) approved the experimental protocol. The oral toxicity study was performed using the up and down procedure (OPPTS guidelines).

Animals were divided into 5 groups of 6 mice each.

Group I (Control) was given normal saline (0.1ml/10gm)

Group II (Standard) was administered with Fluoxetine (20mg/kg, i.p.) for 7 days.

Group III, IV, V (Test drug) were treated with 3 different doses (10, 20 and 40mg/kg, i.p.) of Tapentadol for 7 days.

Fluoxetine and Tapentadol were dissolved in normal saline.

LABORATORY MODEL FOR TESTING ANTIDEPRESSANT ACTIVITY

The production of depression in experimental animals has been a great hallmark for study of newer antidepressant drugs as compared to standard drugs.

Forced Swim Test (FST): It is commonly used for the assessment of the antidepressant-like properties of drugs. Forced swim test was proposed as a model to test antidepressant activity by Porsolt et al. Mice were forced to swim individually in a glass jar (25 x 12 x 25 cm3) containing fresh water of 15 cm height and maintained at 25^0C (± 3^oC). 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 water. The total duration of immobility was recorded during the next 4 min of total 6 min test [8,9]. The rodents are exposed to chronic stress and not allowed to escape from it (decreases neurotransmitters). Chronic mild stress is causes anhedonia, a major symptom of depression. On 7^{th} day of treatment forced swim test was conducted after 40min of drug administration then noted the immobility time of each mouse carefully. Duration of immobility was compared with control and Fluoxetine groups.

Spontaneous locomotor activity

Locomotor activity was measured in an open field consisting of nine black square arenas (43×50×45 cm) using a video tracking system (Ethovision 3.0, Noldus Information Technology B. V., Wageningen, The Netherlands) in a softly illuminated experimental room. One mouse was placed in each cage and distance traveled (cm) and speed was recorded at 10 min intervals during a 30-min Period [10].

Statistical analysis

All results are expressed as mean ± SEM. All the groups were analysed using one-way ANOVA followed by Dunnett's test. The locomotor activity scores were subjected to student's paired t-test. $P<0.05$ was consider significant.

RESULTS

Effect on Immobility period in FST

Mean duration of immobility was significantly reduced by fluoxetine as compared to control ($p<0.05$) similarly, the duration of immobility

observed in mice presented with all the doses of tapentadol was also reduced ($p<0.05$). Decrease in immobility due to tapentadol (20 and 40mg/kg) was found to be significant ($p<0.05$) when we compared to Fluoxetine.

Effect of Locomotor activity

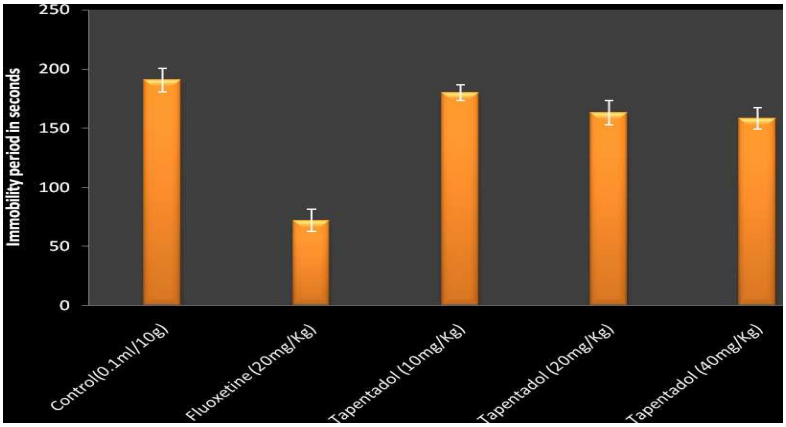
There was no significant effect on locomotor activity of mice (428±12.8) when we treated with tapentadol (10, 20 and 40mg/kg) for 7 successive days as compared to control (Before treatment) (432.3± 9.6).

Table 1
Results of Forced swim test

Group	Treatment	Dose(Kg^{-1})*	Immobility period mean(sec)±SEM
I	Control(Normal saline)	10	190.6±9.7
II	Standard(Fluoxetine)	20	72.1±9.3*
III	Tapentadol	10	180.1±6.8*
IV	Tapentadol	20	163.3±10.3*[a]
V	Tapentadol	40	158.2±9.3*[a]

*N=6 in each group *the dose of normal saline expressed in ml, for other drugs it is in mg. *p<0.05 as compared to normal saline. [a]p<0.05 as compared to fluoxetine (Dunnett's test)*

Graph 1
Effect of Tapentadol on immobility period of mice using Forced Swim Test



DISCUSSION

In this study, antidepressant activity of tapentadol was evaluated in the Forced swim test, Tapentadol produced significant antidepressant activity at all 3doses as compared to control. In our study, we found significantly less antidepressant activity of tapentadol at a dose of 10mg/kg as compared to the control animal.

Antidepressants like venlaflaxine by virtue of their property of mood elevation due to increase in neurotransmitters carrying the pain sensation from nerve endings. It is also effective in chronic pain as an adjuvant drug treatment [6, 11, 12]. Similarly, it could be interfered from our study that tapentadol by acting through a similar mechanism (Inhibition of reuptake of mono amines leading to spinal inhibition of pain) might add a component of mood elevation to its analgesic effect thus making it a useful drug for patient with chronic pain. However, this activity postulates to be confirmed by using different models of depression. Locomotor activity is stimulated by fluoxetine as in other studies but Tapentadol did not stimulate locomotor activity. This suggests that like fluoxetine, tapentadol does not possess CNS stimulating property.

CONCLUSION

The result of the present study indicates antidepressant like activity of tapentadol so that tapentadol is having analgesic and mild antidepressant property. Tapentadol does not possess CNS stimulating property.

ACKNOWLEDGMENT

I thankful to my revered teacher Dr.Narayana Panduranga Burte, Head and Professor in the Department of Pharmacology, M.N.R Medical College and Hospital, Sangareddy, Medak Dist., Andhra Pradesh.

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