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Research Article

Evaluation of antidepressant activity of tramadol in mice: an experimental study

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ABSTRACT

Background: In spite of availability of effective antidepressant drugs, depression continues to be a major problem. Hence, great interest is being taken in development of innovative antidepressants. Tramadol (TRM) is a centrally acting opioid agonist, which is clinically effective in the treatment of moderate to severe pain. By virtue of its action of inhibiting norepinephrine and serotonin uptake, it can function as an antidepressant like venlafaxine. Hence, this study was planned to evaluate antidepressant activity of TRM in comparison and in combination with fluoxetine (FLX) in albino mice.
Methods: TRM (20 and 40 mg) and FLX (20 mg) were administered i.p., alone and in combination once daily for acute (7 days) and chronic (14 days) period to Swiss albino mice of either sex. The immobility period of control and treated mice was recorded in forced swimming test (FST) and tail suspension test (TST). The open field test was also done for same period to test the locomotor activity in animal. The antidepressant effect of TRM was compared with FLX and normal saline treated group for acute and chronic study period.
Results: TRM (20 and 40 mg) treated group produced significant antidepressant effect alone and in combination with FLX (20 and 40 mg) as indicated by reduction in immobility period compared with control group in FST and TST. TRM and FLX treated groups did not show significant activity in open field test when compared with control group.
Conclusions: This study shows TRM has antidepressant activity in standard models of depression.

Keywords: Antidepressant, Tramadol, Fluoxetine

INTRODUCTION

According to World Health Report approximately 450 million people suffer from mental or behavioral disorder.[1] Among these, depression is the most prevalent disorder characterized by apathy, loss of energy, retardation of thinking and activity, suicidal tendency. Approaches to the treatment of depression depend on severity of condition and the risk to patient. Until date various drugs such as monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors and atypical antidepressant are being successfully used in the treatment of depression. In spite of availability of these antidepressant drugs, depression continues to be a major problem.[2] Hence great interest is being taken in development of innovative antidepressants.

Tramadol (TRM) is a centrally acting opioid agonist which is clinically effective in the treatment of moderate to severe pain.[3] By virtue of its action of inhibiting norepinephrine and serotonin uptake, it can function as an antidepressant like venlafaxine.[4,5] In addition, TRM bears close structural similarity to antidepressant venlafaxine and thus shares a number of its molecular and pharmacological properties.[6] In the light of above facts we have investigated antidepressant activity of TRM alone and in combination with standard antidepressant fluoxetine (FLX) in animal models of depression.

METHODS

This study was conducted in the Department of Pharmacology, Govt. Medical College, Latur. The study was approved by Institutional Animal Ethics Committee. The study was performed in accordance with CPCSEA guideline.

Experimental animals

Healthy Swiss albino mice of either sex weighing 30-35 g were used. All the test animals were allowed food and

water *ad libitum*, both being withdrawn 24 hrs before the experiment. They were maintained under standard 12 hrs light and dark cycle. The animals were divided into six groups containing six animals in each group.

Materials

Drugs and solutions

The standard solution of FLX was prepared by dissolving 20 mg of the pure powder form (purchased from Aurobindo Pharma Ltd., A.P. India) in 10 ml of normal saline and administered in dose of 20 mg/kg i.p.[7] The test solution of TRM was prepared by dissolving 20 mg of pure powder form (purchased from HCM Organics Ltd., Maharashtra, India) in 10 ml of normal saline and administered in dose of 20 mg/kg i.p.[7] Normal saline was administered in dose of 0.1 ml/10 g i.p.[8]

Study design

The animals were divided into six groups containing six animals in each group. Group I pretreated with normal saline (0.1 ml/10 g i.p.), Group II with FLX (20 mg/kg, i.p.),[7] Group III with TRM (20 mg/kg, i.p.),[8] Group IV with TRM (40 mg/kg, i.p.),[9] Group V with FLX (20 mg/kg, i.p.) + TRM (20 mg/kg, i.p.) and Group VI with FLX (20 mg/kg, i.p.) + TRM (40 mg/kg, i.p.).

For acute study, normal saline, FLX and TRM were administered i.p. for 7 days to respective groups of animals. In chronic study, normal saline, FLX and TRM were administered i.p. for 14 days to respective groups of animals.

Methods

Forced swimming test (FST)[7-9]

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 test was done in two modes i.e., acute and chronic, along with a habituation session before actual test.[7,8] For habituation session, 1-day before the experimental study, each mouse was placed in glass cylinder containing water for 15 mins. No scoring of immobility was performed during this session. In acute study, drugs were administered to mice for 7 days, on 7th day test was done after 30 mins of drug administration.[7] Vertical glass cylinder (25 cm × 10 cm) was filled with fresh water, mice were individually forced to swim inside vertical glass cylinder containing water column of 15 cm height and their behavior was observed for 6 mins by video recording camera. The duration of immobility was recorded for 6 mins.[7] Immobility period was counted with time sampling method using blocks of 5 sec. Fresh water was used for new animal. In chronic study, drugs were administered to mice for 14 days, on 14th day test were done after 30 mins of drug administration same as that of acute study.[8]

Tail suspension test (TST)[7-9]

In this test immobility was induced by suspending the mice by the tail. After initially trying to escape by engaging in vigorous movements, mice rapidly become immobile. In experimental room, white ceiling lights (standard lighting) were used. In acute study, drugs were administered to mice for 7 days, on 7th day test was done after 30 mins of drug administration.[9] Animals were suspended 50 cm above the ground by wrapping adhesive tape around the animal's tail in the constraint position three quarters of the distance from the base of the tail on the tail suspension apparatus. The duration of immobility was measured for 6 mins by video recording camera. Immobility period was counted with time sampling method using blocks of 5 sec.[7] In chronic study, normal saline, FLX and TRM were administered i.p., for 14 days to respective groups of animals. On 14th day the test was performed 30 mins after administration of drugs same as that of single dose study.[8]

Open field test[7-10]

This test utilizes behavioral changes in rodents exposed to novel environment and is used to confirm that the observed antidepressant effect is not due to stimulation of general motor activity. Open field apparatus have been used to test the mice. The open field test was carried out on dark grey floor subdivided into 25 equal parts in a wooden box (100 cm × 100 cm × 30 cm).[7] For acute study, normal saline, FLX and TRM were administered i.p., for 7 days to respective groups of animals. On 7th day the test was performed 30 mins after the drug administration. The animals were individually placed in the corner square of the open field.[9] The following parameters were observed for 5 mins by video recording camera.

- Activity in the center (number of central squares crossed)
- Spontaneous ambulation (number of peripheral squares crossed)
- Rearing (number of times the animal stands on the rear paws).[11]

After each test floor of apparatus was cleaned with spirit. In chronic study, normal saline, FLX and TRM were administered i.p. for 14 days to respective groups of animals. On 14th day the test was performed 30 mins after administration of drugs same as that of acute study and same parameters as above were absorved.[8]

Statistics

The data were analyzed using one-way ANOVA, followed by Tukey *post-hoc* with using GraphPad Prism software.

RESULTS

The result of FST in acute study (Table 1) showed that duration of immobility was significantly ($p<0.05$) reduced for all the drug treated groups as compared to control group. The combination groups (TRM 20 mg/kg+FLX 20 mg/kg and TRM 40 mg/kg +FLX 20 mg/kg) showed significantly reduced duration of immobility ($p<0.05$) as compared to FLX (20 mg/kg group) and TRM (20 and 40 mg/kg).

In chronic study of FST (Table 2), all the treated groups showed statistically significant ($p<0.05$) reduction in duration of immobility as compared to control group. The combination groups (TRM 20 mg/kg+FLX 20 mg/kg and TRM 40 mg/kg+FLX 20 mg/kg) showed statistically significant antidepressant activity ($p<0.05$) as compared to FLX (20 mg/kg) and TRM (20 and 40 mg/kg) group. In both acute and chronic study, the decrease in immobility was not statistically significant in group treated with TRM as compared to FLX group ($p>0.05$).

The results of TST for acute study (Table 3) showed that the duration of immobility observed in group pretreated with TRM (20 and 40 mg/kg) alone and in combination groups was significantly reduced ($p<0.05$) as compared to control group. Similarly, duration of immobility was significantly reduced ($p<0.05$) with FLX (20 mg/kg) group as compared to control group. The combination groups showed significantly reduced ($p<0.05$) duration of immobility as compared to FLX (20 mg/kg) and TRM (20 and 40 mg/kg) groups.

The result of TST for chronic study (Table 4) showed that duration of immobility was significantly reduced ($p<0.05$) for all the treated groups as compared to control group. The combination groups (TRM 20 mg/kg+FLX 20 mg/kg and TRM 40 mg/kg+FLX 20 mg/kg) showed significantly reduced ($p<0.05$) duration of immobility as compared to FLX (20 mg/kg) group and TRM (20 and 40 mg/kg) group. In both acute and chronic study the decrease in immobility was not statistically significant in group treated with TRM as compared to FLX group ($p>0.05$).

Table 1: FST – Acute study 7 days.

Group	Drugs	Doses	Period of immobility in seconds (mean±SEM)
Group I	Normal saline	0.1 ml/10 g	158.3±1.05
Group II	FLX	20 mg/kg	110.0±2.23*#
Group III	TRM	20 mg/kg	138.3±3.57*
Group IV	TRM	40 mg/kg	130.8±5.83*
Group V	FLX+TRM	20+20 mg/kg	89.1±5.54*#+
Group VI	FLX+TRM	20+40 mg/kg	83.3±6.14*#+

Values expressed as mean±SEM; n=6 in each group, df=5, 30; *p<0.05 when compared to control, #p<0.05 when compared to TRM alone, +p<0.05 when compared to FLX alone, TRM: Tramadol, FLX: Fluoxetine, SEM: Standard error of mean, FST: Forced swimming test

Table 2: FST – Chronic study 14 days.

Group	Drugs	Doses	Period of immobility in seconds (mean±SEM)
Group I	Normal saline	0.1 ml/10 g	136.7±1.05
Group II	FLX	20 mg/kg	90.0±2.23*#
Group III	TRM	20 mg/kg	116.7±2.78*
Group IV	TRM	40 mg/kg	110.8±5.83*
Group V	FLX+TRM	20+20 mg/kg	69.1±5.54*#+
Group VI	FLX+TRM	20+40 mg/kg	63.3±6.14*#+

Values expressed as mean±SEM, n=6 in each group, df=5, 30; *p<0.05 when compared to control, #p<0.05 when compared to TRM alone, +p<0.05 when compared to FLX alone, SEM: Standard error of mean, TRM: Tramadol, FLX: Fluoxetine, FST: Forced swimming test

Table 3: TST - Acute study 7 days.

Group	Drugs	Doses	Period of immobility in seconds (mean±SEM)
Group I	Normal saline	0.1 ml/10 g	146.7±1.05
Group II	FLX	20 mg/kg	100.0±2.23*#
Group III	TRM	20 mg/kg	126.7±2.78*
Group IV	TRM	40 mg/kg	120.8±5.83*
Group V	FLX+TRM	20+20 mg/kg	79.1±5.54*#+
Group VI	FLX+TRM	20+40 mg/kg	73.3±5.54*#+

Values expressed as mean±SEM, n=6 in each group, df=5, 30; *p<0.05 when compared to control, #p<0.05 when compared to TRM alone, +p<0.05 when compared to FLX alone, SEM: Standard error of mean, TRM: Tramadol, FLX: Fluoxetine, TST: Tail suspension test

Table 4: TST - Chronic study 14 days.

Group	Drugs	Doses	Period of immobility in seconds (mean±SEM)
Group I	Normal saline	0.1 ml/10 g	163.3±1.05
Group II	FLX	20 mg/kg	115.0±2.23*#
Group III	TRM	20 mg/kg	143.3±2.78*
Group IV	TRM	40 mg/kg	135.8±5.83*
Group V	FLX+TRM	20+20 mg/kg	94.1±5.54*#+
Group VI	FLX+TRM	20+40 mg/kg	88.3±6.14*#+

Values expressed as mean±SEM, n=6 in each group, df=5, 30; *p<0.05 when compared to control, #p<0.05 when compared to TRM alone, +p<0.05 when compared to FLX alone, SEM: Standard error of mean, TRM: Tramadol, FLX: Fluoxetine, TST: Tail suspension test

The open field test was done in acute study (Table 5) and for chronic study (Table 6) formats with assessment of the number of square crossed (peripheral and central) and number of rearing in these groups. However, the statistical analysis showed non-significant findings (p>0.05) for all the group comparisons.

DISCUSSION

Modern day life style leads to numerous stressful conditions among which anxiety and depression are general and widely prevalent neurological disorders. Vigorous efforts are underway to find an ideal antidepressant in both preclinical and clinical studies. In case of preclinical studies for assessing antidepressant like activity in small animals, the widely used animal models are FST, TST and open field test.[11] It is expected that immobility that occurs in these tests reflects a state of behavioral despair or inability to adapt the stress as seen in human. For a drug to be labeled as antidepressant, it should decrease the immobility period in these tests.

In the present study, TRM was used alone and in combination with standard antidepressant FLX. The FST was done in both acute and chronic formats. In both FST and TST, the antidepressant effect of TRM (40 mg/kg) group was better than TRM (20 mg/kg) group, but it was statistically non-significant (p>0.05). In combination groups also, antidepressant effect of TRM and FLX (TRM 40 mg/kg+FLX 20 mg/kg) group was better than other (TRM 20 mg/kg+FLX 20 mg/kg) combination group but it was statistically non-significant (p>0.05).

Open field test was carried out to show that the antidepressant effect of drug was not related to stimulation of general locomotor activity. The open field test was done in acute study and for chronic study formats with assessment of the number of square crossed (peripheral and central) and number of rearing in these groups. However, the statistical analysis showed non-significant findings (p>0.05) for all the group comparisons.

A significant result of acute and chronic dose study in FST and TST shows that TRM has significant antidepressant effect as compared to control group. Results of the open field test show that this effect is not related to stimulation of general motor activity.

TRM is a centrally acting opioid agonist which also inhibits norepinephrine and serotonin uptake.[3,4] In addition, TRM bear close structural (chemical structure of both the substance have methoxyphenyl, N,N-dimethylamino and hydroxycyclohexyl group) and metabolic (both are metabolized by cytochrome P450 2D6) similarity to antidepressant venlafaxine.[12] TRM can also modulate the opioid receptor, the serotonergic system and dopaminergic

Table 5: Open field test - Acute study 7 days.

Group	Drugs	Doses	Mean±SEM		
			Number of central squares crossed	Number of peripheral squares crossed	Total number of rearing
Group I	Normal saline	0.1 ml/10 g	20.6±2.91	137.5±5.10	25.6±2.10
Group II	FLX	20 mg/kg	6.8±3.30	107.3±18.17	9.6±4.64
Group III	TRM	20 mg/kg	15.0±4.96	145.8±13.73	22.6±6.94
Group IV	TRM	40 mg/kg	12.0±5.65	147.8±12.16	18.0±6.27
Group V	FLX+TRM	20+20 mg/kg	7.8±4.96	147.0±13.05	18.0±3.80
Group VI	FLX+TRM	20+40 mg/kg	23.6±4.14	154.5±7.27	27.0±3.12

Values expressed as mean±SEM, n=6 in each group, df=5, 30; p>0.05 for all intergroup comparisons i.e. non-significant, SEM: Standard error of mean, TRM: Tramadol, FLX: Fluoxetine

Table 6: Open field test - Chronic study 14 days.

Group	FLX drugs	Doses	Mean±SEM		
			Number of central squares crossed	Number of peripheral squares crossed	Total number of rearing
Group I	Normal saline	0.1 ml/10 g	28.0±6.74	168.3±11.67	29.3±2.98
Group II	FLX	20 mg/kg	15.0±6.71	118.7±18.06	13.0±1.69
Group III	TRM	20 mg/kg	19.0±7.78	131.8±17.51	26.3±7.33
Group IV	TRM	40 mg/kg	12.1±5.90	142.8±17.87	16.3±2.89
Group V	FLX+TRM	20+20 mg/kg	4.3±1.25	120.0±21.66	15.8±4.19
Group VI	FLX+TRM	20+40 mg/kg	21.0±6.11	115.0±17.03	30.0±6.30

Values expressed as mean±SEM, n=6 in each group, df=5, 30; p>0.05 for all intergroup comparisons i.e. non-significant, SEM: Standard error of mean, TRM: Tramadol, FLX: Fluoxetine

system.[13,14] Imidazoline receptors (I_1 and I_2) also may involve in antidepressant like activity of TRM in mice.[15] These factors explain the capacity of TRM to acts as antidepressant.

TRM induces changes in central nervous system also similar to those induced with conventional antidepressants. It decreases the binding of frontocortical β adrenoceptors, 5-HT_{2A} receptors and α_2-adrenoreceptor, but increase the binding of α_1-adrenoreceptors and dopamine D_2 and D_3 receptors. In addition it inhibits locus ceruleus firing activity through α_2-adrenoreceptors mechanism like antidepressant compound.[16]

The acute administration of TRM produces antidepressant like the activity by a mechanism that involved inhibition of l-arginine-NO-cGMP pathway. The antidepressant activity of TRM also involves the K^+ channels.[17]

Chronic treatment with TRM at dose (10-40 mg/kg) increase the density of α_1-adrenergic receptors, decrease the density of α_2-adrenoreceptor and cause up regulation of dopamine D_2 and D_3 receptors in the nucleus accumbens like antidepressant drug.[2,18,19] These finding can explain observed antidepressant action of TRM in our study.

Previous studies like Kalra et al. (2008), Szkutnik-Fiedler et al. and Kishore et al. have also shown that the opioid analgesic drug TRM has antidepressant effect and it was compared with other drugs like imipramine, venlafaxine, FLX etc. using various animal models of depression. Our results correlate with the findings in above studies showing antidepressant action of TRM.

Finally, TRM, in both doses, produces a greater antidepressant action when combined with the standard antidepressant, i.e., FLX. This antidepressant action of the combination group was far more significant when compared to both TRM and FLX given alone.

The enhanced antidepressant effect observed in our study after a combination of TRM with FLX is probably a result of additive interaction between two drugs, due to the similar mechanism of the inhibiting reuptake of serotonin and norepinephrine.

This finding may also be due to its ability to modulate the opioid receptors and dopaminergic system, which is similar to the conventional antidepressants like venlafaxine, which blocks reuptake and results in enhanced and prolonged serotonergic, norepinephrine and dopaminergic neurotransmission.[20]

Hence from our study, we propose that TRM is a good antidepressant especially when it is used in combination with a standard antidepressant. Since this is an animal study, we need these results to be confirmed in human studies for the further establishment of the role of TRM as an antidepressant.

CONCLUSION

The present study was designed to investigate the antidepressant activity of the TRM alone and in combination with FLX. In this study, TRM alone (in doses of 20 mg/kg and 40 mg/kg) and in combination with FLX on acute and chronic administration showed significant antidepressant action in mice exposed to both FST and TST. An insignificant result in open field test shows that TRM does not modify general locomotor activity of the animal.

From our study, we conclude that TRM (alone and in combination with FLX) possesses significant antidepressant activity in animal models of depression.

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REFERENCES

1. Murthy RS, Bertolote JM, Epping-Jordan J, Funk M, Prentice T, Saraceno B, et al. Public health approach to mental health. The World Health Report 2001 - Mental Health: new Understanding, New Hope. 1st Edition. France: WHO Graphics; 2001: 1-16.
2. Yu ZF, Kong LD, Chen Y. Antidepressant activity of aqueous extracts of Curcuma longa in mice. J Ethnopharmacol. 2002;83(1-2):161-5.
3. Rojas-Corrales MO, Gibert-Rahola J, Micó JA. Tramadol induces antidepressant-type effects in mice. Life Sci. 1998;63(12):PL175-80.
4. Driessen B, Reimann W, Giertz H. Effects of the central analgesic tramadol on the uptake and release of noradrenaline and dopamine *in vitro*. Br J Pharmacol. 1993;108(3):806-11.
5. Sevcik J, Nieber K, Driessen B, Illes P. Effects of the central analgesic tramadol and its main metabolite, O-desmethyltramadol, on rat locus coeruleus neurones. Br J Pharmacol. 1993;110(1):169-76.
6. Kiayias JA, Vlachou ED, Lakka-Papadodima E. Venlafaxine HCl in the treatment of painful peripheral diabetic neuropathy. Diabetes Care. 2000;23(5):699.
7. Kishore RN, Anjaneyulu N, Ganesh MN, Sravya N, Abhinayani G, Pratyusha C. Evaluation of antidepressant activity of tramadol hydrochloride in mice model. World J Pharm Pharm Sci. 2012;1(4):1384-91.
8. Szkutnik-Fiedler D, Kus K, Balcerkiewicz M, Grzeskowiak E, Nowakowska E, Burda K, et al. Concomitant use of tramadol and venlafaxine - evaluation of antidepressant-like activity and other behavioral effects in rats. Pharmacol Rep. 2012;64(6):1350-8.
9. Chowta MN, Manjunath M, Gopalakrishna HN, Gokul P. Evaluation of role of noradrenergic system in the

antidepressant activity of tramadol using tail suspension test in Albino mice. J Pharmacol Pharmacother. 2011;2(4):281-2.
10. Kalra BS, Tayal V, Chawla S. Antidepressant-like activity of tramadol in mice. Indian J Psychiatry. 2008;50(1):51-3.
11. Santosh P, Venugopl R, Nilakash AS, Kunjbihari S, Mangala L. Antidepressant activity of *Passiflora foetida* leaves in mice. Indian J Pharm Pharm Sci. 2011;3(1):112-5.
12. Markowitz JS, Patrick KS. Venlafaxine-tramadol similarities. Med Hypotheses. 1998;51(2):167-8.
13. Berrocoso E, Rojas-Corrales MO, Mico JA. Differential role of 5-HT1A and 5-HT1B receptors on the antinociceptive and antidepressant effect of tramadol in mice. Psychopharmacology (Berl). 2006;188(1):111-8.
14. Yalcin I, Coubard S, Bodard S, Chalon S, Belzung C. Effects of 5,7-dihydroxytryptamine lesion of the dorsal raphe nucleus on the antidepressant-like action of tramadol in the unpredictable chronic mild stress in mice. Psychopharmacology (Berl). 2008;200(4):497-507.
15. Jesse CR, Wilhelm EA, Bortolatto CF, Nogueira CW. Evidence for the involvement of the noradrenergic system, dopaminergic and imidazoline receptors in the antidepressant-like effect of tramadol in mice. Pharmacol Biochem Behav. 2010;95(3):344-50.
16. Berrocoso E, Sánchez-Blázquez P, Garzón J, Mico JA. Opiates as antidepressants. Curr Pharm Des. 2009;15:1612-22.
17. Jesse CR, Bortolatto CF, Savegnago L, Rocha JB, Nogueira CW. Involvement of L-arginine-nitric oxide-cyclic guanosine monophosphate pathway in the antidepressant-like effect of tramadol in the rat forced swimming test. Prog Neuropsychopharmacol Biol Psychiatry. 2008;32(8):1838-43.
18. Faron-Górecka A, Kusmider M, Inan SY, Siwanowicz J, Dziedzicka-Wasylewska M. Effects of tramadol on alpha2-adrenergic receptors in the rat brain. Brain Res. 2004;1016(2):263-7.
19. Faron-Górecka A, Kusmider M, Inan SY, Siwanowicz J, Piwowarczyk T, Dziedzicka-Wasylewska M. Long-term exposure of rats to tramadol alters brain dopamine and alpha 1-adrenoceptor function that may be related to antidepressant potency. Eur J Pharmacol. 2004;501(1-3):103-10.
20. Aysegul Y, Ali SG, Lut T. Mechanism of actions of antidepressants: beyond the receptors. Bull Clin Psychopharmacol. 2002;12(4):194-200.

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