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Research Article

Effect of tramadol in elevated plus maze apparatus– A rodent model of anxiety.

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ABSTRACT

Anxiety is a widespread disorder in world wide. Some amount of anxiety always associated with depression. In this study we tested anti-anxiety effect of tramadol in Elevated plus Maze apparatus (EPM). Tramadol is synthetic centrally acting opioid analgesic.It is a weak μ opioid receptor agonist and also act as ananti-depressant by inhibiting uptake of noradrenaline and serotonin. Rats (150-250g) of either sex were randomly divided into 4 groups of 6 animals each. Tramadol was administered at two different doses (20, 40 mg/kg, i.p) 30 mints before conducting test. No of entries and time spent in both closed and open arm observed. The antianxiety effect of tramadol was compared to that of diazepam(2 mg/kg, i.p), in elevated plus maze apparatus (EPM).The result of the study shows that tramadol dose dependently increases entries and time in open arm (40mg/Kg) in EPM. Tramadol showed anti-anxiety activity in Elevated plus Maze apparatus.

Key words: Tramadol, Anxiety, Elevated plus maze apparatus.

INTRODUCTION

Stress, fear, and anxiety all tend to be interactive. The principal components of anxiety are psychological (tension, fears, difficulty in concentration, apprehension) and somatic (tachycardia, hyperventilation, palpitations, tremor, sweating). Anxiety is a widespread disorder that approximately 18% of the population experience at some stage in their lives[1]. Anxiety is multifaceted as generalized anxiety disorder, panic disorder, phobia, post-traumatic stress disorder, obsessive compulsive disorder[2].When the disorder goes unrecognized and untreated, patients often experience major depression at some point.A combination of anti-anxiolytics and antidepressant interventions is most effective.

Tramadol is a synthetic centrally acting opioid analgesic used mainly for the treatment of moderate to severe pain[3]. It is a weak μ opioid receptor agonist and also produces analgesia by inhibiting uptake of noradrenaline and serotonin[4]. Antidepressants mainly act by inhibiting noradrenaline-serotonin reuptake and tramadol by virtue of its property of blocking monoaminergic reuptake may alsoact as an antidepressant[5, 6]. Tramadol reduces the pain-induced anxiety-related behavior[9].Several case reports and case series tramadol has been shown to be effective in neuralgias.

Animal models are an important aid to the understanding of anxiety and anxiety-related disorders. Commonly used examples include the Open Field test[10], the Light/Dark exploration model[11] and the Elevated Zero Maze[12]. The Elevated Plus Maze[13], (EPM) is however one of the most commonly used methodologies and is favored because of its simplicity.

MATERIALS AND METHODS:

Animals and housing

Albino rats (Wistar) weighing 150-250 g of either sex were obtained from the central animal house of Narayana Medical College, Nellore.

They were housed in standard polypropylene cages with paddy husk as bedding and kept under controlled room temperature (24 + 20C; relative humidity 60-70%) in a 12h light –dark cycle. Animals were given a standard laboratory diet and water ad libitum. All experiments were run between 08:30 AM and 12:00 PM. Animals were acclimatized to laboratory conditions one week prior to the initiation of experiments.

Ethical statement

All the experiments involved in this work were performed in accordance with “Committee for Purpose of Control and Supervision of Experimental Animals” (CPCSEA) guidelines for the use and care of experimental animals.All the experimental procedures and protocols used in this study were carried out according to the guidelines of institutional animal ethical committee and

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Ethical committee clearance was obtained from IAEC (Institutional Animal Ethics Committee).

Drugs and chemicals

Tramadol and diazepamwas sourced from Sigma Aldrich, Bengaluru, India. All the chemicals and reagents used in the study were of analytical grade and were prepared fresh before test.

Grouping of animals

We used 24 rats randomly divided into the following four groups. Group I received saline 0.5ml (Control group). Group II received diazepam 2mg/Kg. (standard group). Group III received Tramadol-20mg/kg(test group 1). Group IV received Tramadol-40mg/kg(test group 2).

Methodology

Elevated plus maze apparatus

Principle

Anxiety reduction in the plus-maze is indicated by an increase in the proportion of time spent in the open arms and an increase in the proportion of entries into the open arms[14].

The elevated plus-maze test (EPM) is the most popular of all currently available animal models of anxiety. This equipment was made of wood and consisted of two opposite open arms, 50×10 cm (surrounded by 1 cm high Plexiglas), and two enclosed arms, 50× 10× 40 cm, elevated to a height of 50 cm above the floor. The junction area of the four arms (central platform) measured 10×10 cm. The floor of the maze was painted with impermeable dark epoxy resin, in order to avoid urine impregnation[15].

Procedure

Group I rats were treated with saline 0.5ml (i.p), group II treated with standard drug diazepam 2mg/Kg (i.p), group III & IV treated with tramadol 20, 40mg/Kg (i.p) 30mins before starting the experiment. Rats were freely exposed to maze apparatus. We observed no of entries and time spent in both open and closed arm.Increased no of entries and time spent in open arm considered as antianxiety activity.

STATISTICAL ANALYSIS:

The data was collected in case record forms. Then they were entered into excel spreadsheet. Statistical analysis was performed using Microsoft Excel and Sigma Graph pad prism version-5 USA. Data was described as Mean ± Standard deviation. One way ANOVA followed by Newman-Keuls Multiple Comparison tests was used for analysis of data between the four. For all inferential statistical tests a two tailed P value of less than 0.05 was considered significant. All the results of test drug [tramadol (20, 40 mg/kg)] were compared with control as well as standard groups.

OBSERVATIONS &RESULTS

Table 1: Mean ± SD of no of entries in open & closed arm and mean time (mins) spent in open and closed arm

Treatment	No of rats	Mean no. of entries in		Mean time spent in (min)	
		Open arm	Closed arm	Open arm	Closed arm
Group –I Control-0.5ml saline (i.p)	6	1.1±0.40	2.7±0.82	0.78±0.21	3.5±0.21
Group –II standard Diazepam 2mg/kg (i.p)	6	4±1.4**	1.±0.89*	3.1±0.42**	0.90±0.27**
Group –III Tramadol-20mg/kg (i.p)	6	2.0±0.89	2.3±1.0	1.4±0.23	2.9±0.21
Group-IV Tramadol-40mg/kg	6	2.5±1.04*	1.3±0.75*	2.4±0.24**	1.8±0.2**

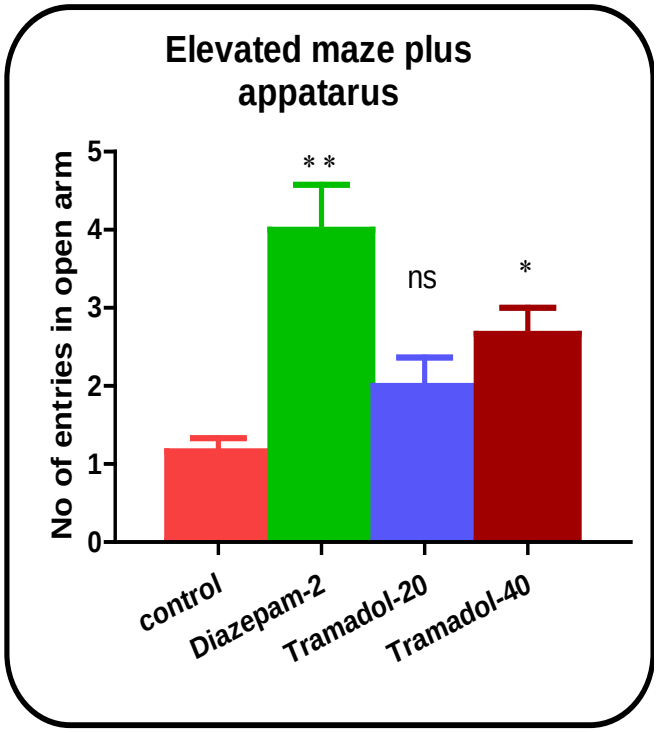
One way ANOVA followed by Newman-Keuls Multiple comparison test was used for analysis of data between all groups. Data expressed in mean ±S.D.

*p<0.05, ** p<0.001 compared to control group.

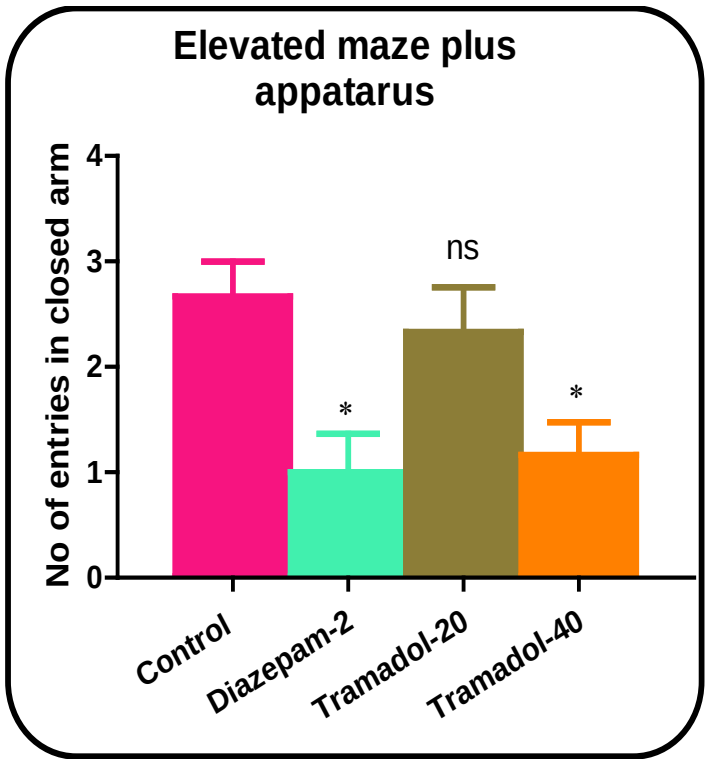
ns- Not significant compared to control group.

Table - 1 shows the mean no of entries and mean time(minutes) spent in both closed and open arm with diazepam(2mg/kg) and tramadol (20,40mg/kg). No of entries in open arm with control (Group I) was 1.1+0.40 where as it was 4±1.4, 2.0+0.89, 2.5+1.04 with diazepam 2mg/kg (Group II), tramadol 20mg/kg (Group III), tramadol 40mg/kg (group IV). Mean no of entries in closed arm with control (Group I) was 2.7+0.82 where as it was 1.±0.89, 2.3+1.0 , 1.3+0.75 with diazepam 2mg/kg (Group II), tramadol 20mg/kg (Group III), tramadol 40mg/kg (group IV).Mean time spent in open arm with control (Group I) was 0.78±0.21 where as it was 3.1±0.42, 1.4±0.23 , 2.4±0.24 with diazepam 2mg/kg (Group II), tramadol 20mg/kg (Group III), tramadol 40mg/kg (group IV). Mean time spent in closed arm with control (Group I) was 3.5±0.21 where as it was 0.90±0.27, 2.9±0.21 , 1.8±0.2 with diazepam 2mg/kg (Group II), tramadol 20mg/kg (Group III), tramadol 40mg/kg (group IV) respectively.Tramadol (40mg/kg) is efficacious in suppressing anxiety in elevated plus maze apparatus compared to group I.

NO. OF ENTRIES IN TO OPEN AND CLOSED ARM OF ELEVATED MAZE APPARATUS

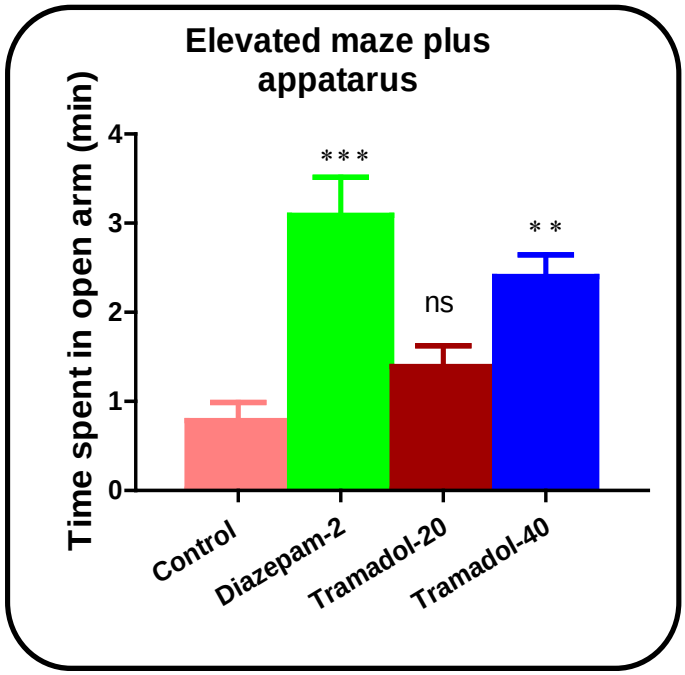


Each bar represents no of entries in open arm
P<0.05** p<0.01 as compared to control, ns – Not significant

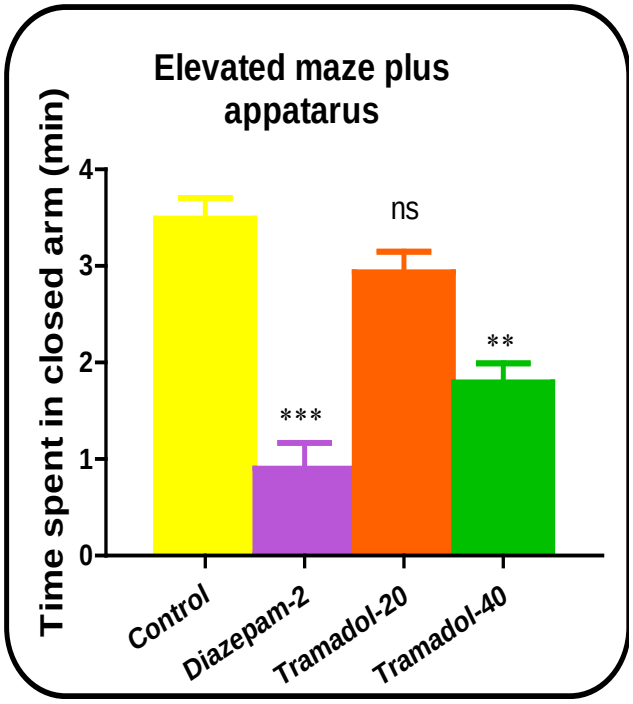


Each bar represents no of entries in closed arm
P<0.05** p<0.01 as compared to control, ns – Not significant

TIME SPENT IN OPEN AND CLOSED ARM OF ELEVATED MAZE APPARATUS



Each bar represents time spent in open arm
P<0.05** p<0.01 as compared to control, ns – Not significant



Each bar represents time spent in closed arm
P<0.05** p<0.01 as compared to control, ns – Not significant

DISCUSSION

Tramadol, an opioid analgesic, used in the treatment of moderate to severe pain, mediates its analgesic efficacy through weak μ opioid receptor agonism, and inhibits the reuptake of noradrenaline (NA) and serotonin (5-HT). Both these mechanisms work in synergism to enhance the analgesic profile of tramadol. It has also been documented that tramadol predominantly inhibits reuptake of 5-HT in the raphe nucleus[7]. ADs mainly act by inhibiting NA and 5-HT reuptake[8]. These actions of tramadol possibly supplement for its antidepressant activity.

In this study tramadol at dose of 40 mg/kg (p<0.05) significantly increased entries and time spent in open arm in EPM. Diazepam (2mg/kg p<0.001) increased entries and time spent in open arm in EPM.Tramadol at dose of 20mg/kg did not show ay effect. These results indicate that tramadol at dose of 40mg/kg has antianxiety like effect that is comparable to control as well as with diazepam. Tramadol has been proved significantly reduces the anxiety-related behavior[9] under neuropathic conditions only suggests that this reduction is not a direct anxiolytic activity of tramadol, but an indirect result of its analgesic and antihyperalgesic activity. But tramadol opioid analgesic which is having different mechanism of action like antidepressants already well proved as antidepressant.So its analgesic and antidepressant properties give a rationale to use tramadol in anxiety. As the comorbidity between anxiety and depression is a remarkable issue in behavioral disorders, a possible relationship between anxiety and depression. Combination of anti-anxiety and antidepressant are more effective treating anxiety disorders.Since tramadol with an exciting range of opioid, noradrenergic, serotonergic and also dopaminergic action will be effective in treating anxiety disorders.

CONCLUSION

All these experimental data, together with previous experimental studies and the results reported in this work, suggest that tramadol, and probably also other analgesics with monoaminergic properties, improve mood, experimentally. Further molecular studies, might be necessary to reveal the details of the mechanism of action in the central nervous system in this anxiety model.

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