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Comparative Anxiolytic Potentials of Alprazolam and Zolpidem by *In-vivo* Studies

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A B S T R A C T

The present study was designed to compare the anxiolytic efficacies of a benzodiazepine (Alprazolam) and a non-benzodiazepine (Zolpidem) in albino mice. Alprazolam (1mg/kg) in 2% acacia suspension and zolpidem (2mg/kg) in 2% acacia suspension, P.O. were used for the study. The control group animals are placed in the centre of the Elevated plus Maze apparatus one by one at an interval of 5 minutes and the preference of animals towards open and closed arms are noted for a period of 5 minutes. The same procedure was repeated for alprazolam and zolpidem treated groups of animals after one hour of administration of alprazolam (1mg/kg) P.O.and zolpidem (2mg/kg) P.O. The number of entries in open and closed arms and the time spent in open and closed arms are noted. In Light & dark Box transition test the parameters that are monitored are number of entries in light and dark box and the time spent in light and dark box for a period of 5 minutes. Zolpidem (2mg/kg) P.O. has shown more significant anxiolytic activity than alprazolam by increasing the time spent in open arm (160.3±1.15 sec) in comparision to the time spent in open arm (140.3±0.73 sec) in alprazolam treated mice in elevated plus maze model and by increasing the time spent by mice in light box (158±3.12 sec) in comparison to the time spent in light box (134.3±3.21 sec) in alprazolam treated mice in light and dark box apparatus. This indicates that zolpidem has higher anxiolytic potential than alprazolam. The specific agonistic affinity of zolpidem on benzodiazepine receptor may be responsible for the higher anxiolytic potential than alprazolam.

Keywords: Anxiolytic potential, alprazolam, zolpidem, elevated plus maze, light and dark box.

A R T I C L E I N F O

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1. Introduction

Anxiety is a state of uneasiness, apprehension or fear characterized by tremors, tachycardia, sweating and somatic symptoms [1]. Mild anxiety is a common problem in day to day life [2]. But continuous and persistent anxiety is dangerous and dreadful [3]. Anxiety in severe cases may lead to depression followed by psychosis [4]. Anxiety is further classified as generalized anxiety disorder, phobias, panic attacks & post traumatic stress disorder [5]. Anxiety often leads to restlessness, muscular fatigue and difficulty in concentration [6]. The Major mechanism for most anxiolytic drugs is to potentiate the effects of GABA by targeting GABA-A receptor [7]. Hence, the present study was planned with a rationale to compare the efficacy of two well established anxiolytic drugs such as alprazolam and zolpidem by using invivo models such as elevated plus maze and light and box apparatus in mice.

2. Materials and Methods

For this study, the pure samples of alprazolam and zolpidem were obtained as gift samples from Microlabs, Bengaluru. Doses of the alprazolam and zolpidem used in mice were collected from the literature i.e., alprazolam (1 mg/kg) [8] P. O. and zolpidem (2 mg/kg) [9] P.O. and the drug suspensions are prepared by using 1% gum acacia.

Experimental animals

Albino mice (18-30 grms) were used in the experiments. They were procured from Sainath agencies, Musheerabad. After randomization into various groups and before initiation of experiment, the mice were acclimatized for a period of 10 days. Animals were housed in polypropylene cages and maintained under standard environmental conditions such as temperature (26±20C), relative humidity (45-55%) and 12hr dark/light cycle. The animals were fed with rodent pellet diet (Golden Mohur Lipton India Ltd.) and water ad libitum. The study protocol was approved from the institutional animal ethics committee (IAEC) before commencement of experiment.
(1292/ac/09/CPCSEA).

Anxiolytic activity of alprazolam and zolpidem by elevated plus maze Apparatus (EPM):

All the animals were subjected to EPM assessment of anxiety levels. The EPM is composed of two open arms (16x5cms) and two closed arms (16x5x12cms) made up of thermocole with an open roof and is elevated to a height of 25cms. Each animal of the control group was placed individually in the center of the maze facing towards the open arm and the following parameters were recorded: time spent in open arm, time spent in closed arm and total number of entries in open arm and closed arm during 5 min session. Repeat the same procedure for test group after 1 hr of administration of alprazolam (1 mg/kg) P.O. and zolpidem (2 mg/kg) P.O. and the above parameters were recorded.

Figure 1: Elevated plus maze apparatus for anxiolytic activity in mice

Anxiolytic activity of Alprazolam and Zolpidem by Light and Dark Box Transition test: The light and dark box is a characteristic tool used in the assessment of anxiety. The light and dark box test is based on the innate aversion of rodents to brightly illuminated areas and on the spontaneous exploratory behavior of rodents in response to mild stressors, that is, novel environment and light. The apparatus consisted of two 20 × 10 × 14 cm thermocole boxes; one was dark, the other was transparent. The mice were allowed to move from one box to the other through an open hole between the two boxes. A 100 W bulb was the only light source in the room. The mice were injected orally with drugs. 1 hr later, each animal was put individually into the light box facing the hole. The transitions between the light and the dark box and time spent in the light and dark box were recorded for 5 min immediately after the mouse stepped into the dark box. The apparatus was cleaned thoroughly between trials. All behavioral recordings were carried out with the observer unaware of the treatment the mice had received.

Figure 2: Light and Dark Box apparatus for anxiolytic study in mice

Statistical Analysis

The values are represented as mean ± S.E.M, and statistical significance between treated and Control groups was analyzed using One way ANOVA, followed by Students t test where P<0.001, P<0.01 and P<0.05 was considered statistically significant.

3. Results and discussions

In the elevated plus maze apparatus the time spent by control treated mice in open arm is less (28±0.15 sec) than in Closed arm (226.3±1.72) indicating the presence of anxiety in experimental mice. However the time spent by alprazolam treated (1mg/kg) P.O. mice in open arm is more (140.3±0.73 sec) than time spent in the closed arm (98±1.34 sec) indicating the decrease in anxiety of the animals when compared to control group. Hence, Alprazolam contains the anti-anxiety activity. Time spent by Zolpidem treated (2 mg/kg) P.O. mice in open arm is more (160.3±1.15 sec) than time spent in the closed arm (86.6±0.12 sec) indicating the decrease in anxiety of the animals when compared to control group. Hence, Zolpidem possesses significant anxiolytic activity. However when the anxiolytic efficacy of the two drugs are compared Zolpidem is found to be more potent than alprazolam because the time spent in open arm in elevated plus maze model exhibited by zolpidem treated mice are significantly more (160.3±1.15 sec) when compared to the time spent in open arm by alprazolam treated group (140.3±0.73 sec). In Light and dark Box transition test the time spent by control treated mice in illuminated light box (103.3±1.32 sec) was less than in the dark box (218±3.12 sec) indicating the presence of anxiety in experimental mice. However the time spent by alprazolam treated (1 mg/kg) P.O. mice in light box (134.3±3.21 sec) was significantly more than time spent in dark box (112.6±4.11 sec) indicating the decrease in anxiety of the animals when compared to control group. Hence, alprazolam possesses anti-anxiety activity. Time spent by zolpidem treated (2 mg/kg) P.O. mice in light box (158±3.12 sec) was significantly higher than dark box (119.6±4.72 sec) indicating the decrease in anxiety of the animals when compared to control group. However, zolpidem treated mice exhibited significantly more time spent in light box when compared to the time spent in light box by alprazolam treated mice. The monitored parameters such as time spent in open arm (EPM) and number of entries in light box (light/dark box apparatus) were found significantly higher with Zolpidem treated mice when compared to Alprazolam treated mice. This indicates that Zolpidem may possesses greater anxiolytic potential than Alprazolam. Literature survey reveals that Zolpidem has specific agonistic action on BZD (α-1) receptor when compared to Alprazolam, which has nonspecific agonistic action on BZD receptors. This specificity of Zolpidem may be responsible for better anxiolytic activity than Alprazolam.

Table 1: Control Group (Elevated Plus maze)

S.NO	Body wt. (gms)	Time spent in open arm (sec)	Time spent in closed arm (sec)	No. of entries in open arm	No. of entries in closed arm
1	27	0	253±0.11	0	2
2	21	71±1.27	215±1.12	1	2
3	29	13±0.03	211±0.47	2	10
	average	28±0.15	226.3±1.72	1	4.6

***P<0.001, **P<0.01 and * P<0.05 was considered statistically significant.

Table 2: Alprazolam treated Group (Elevated Plus maze)

S.NO	Body wt. (gms)	Time spent in open arm (sec)	Time spent in closed arm (sec)	No. of entries in open arm	No. of entries in closed arm
1	28	155±1.31	76±1.85	6	4
2	28	158±0.74	30±0.37	2	1
3	27	108±0.05**	188±0.12*	1	1
	average	140.3±0.73**	98±1.34**	3	2

***P<0.001, **P<0.01 and * P<0.05 was considered statistically significant.

Table 3: Zolpidem treated Group (Elevated Plus maze)

S.NO	Body wt. (gms)	Time spent in open arm (sec)	Time spent in closed arm (sec)	No. of entries in open arm	No. of entries in closed arm
1	28	140±1.26	129±1.11**	4	1
2	24	147±1.12**	29±0.35*	3	1
3	29	194±0.01	102±0.32	4	2
	average	160.3±1.15***	86.6±0.12*	3.6	1.3

***P<0.001, **P<0.01 and * P<0.05 was considered statistically significant.

Table 4: Control Group (Light and Dark Box test)

S.NO	Body wt. (gms)	Time spent in Light Box (sec)	Time spent in Dark Box (sec)	No. of entries in Light Box	No. of entries in Dark Box

1	26	116±0.72	270±3.22	1	3
2	27	77±1.34	213±1.72	0	5
3	24	117±0.22	171±4.11	1	1
	average	103.3±1.32	218±3.12	0.66	3

***P<0.001, **P<0.01 and * P<0.05 was considered statistically significant.

Table 5: Alprazolam treated Group (Light and Dark Box test)

S.NO	Body wt. (gms)	Time spent in Light Box (sec)	Time spent in Dark Box (sec)	No. of entries in Light Box	No. of entries in Dark Box
1	22	27±1.20	265±2.11	3	1
2	27	270±0.11**	18±1.25**	5	2
3	24	106±0.35	55±1.39	2	1
	average	134.3±3.21**	112.6±4.11*	3.3	1.3

***P<0.001, **P<0.01 and * P<0.05 was considered statistically significant.

Table 6: Zolpidem treated Group (Light and Dark Box test)

S.NO	Body wt. (gms)	Time spent in Light Box (sec)	Time spent in Dark Box (sec)	No. of entries in Light Box	No. of entries in Dark Box
1	22	131±0.23	100±5.24**	4	1
2	27	177±3.12**	123±3.17*	4	3
3	24	168±1.14	132±1.36	5	2
	average	158±3.12***	119.6±4.72*	4.3	2

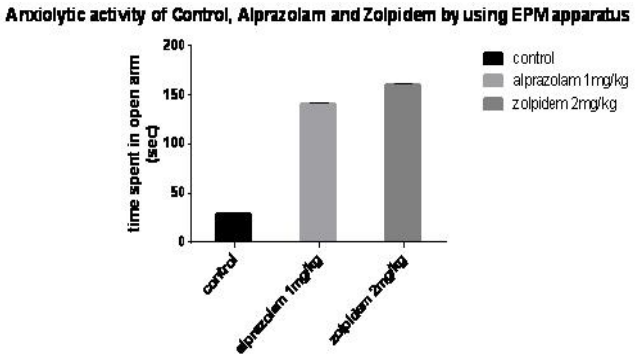

Figure 3

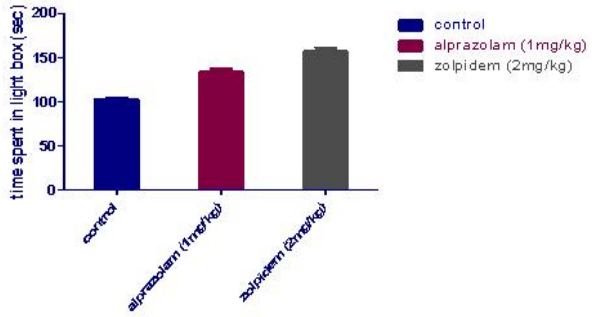

Figure 4: Anxiolytic activity of Control, Alprazolam and Zolpidem by using Light and Dark Box apparatus

4. Conclusion

Based on the results of the present study, we conclude that zolpidem and alprazolam have significant anxiolytic potentials. But zolpidem is more potent in inhibiting anxiety than alprazolam that has been determined by using EPM and light/dark box apparatus in mice. However further studies are required to establish the exact macromolecular signal transduction mechanisms responsible for higher anxiolytic efficacy of zolpidem.

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