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BENEFICIAL ROLE OF ZOLPIDEM ON THE BEHAVIOUR PARAMETERS IN SLEEP DEPRIVED ALBINO MICE.

Pharmacology

Dr.Md Shadab Alam* Tutor, Department of Pharmacology, Patliputra Medical College, Dhanbad. *Corresponding Author

Dr.Arun Kumar Choudhary Professor and Head, Department of Pharmacology, Patliputra Medical College, Dhanbad.

Dr.Satish Chandra Professor, Department of Pharmacology, Rajendra Institute of Medical Sciences, Ranchi.

ABSTRACT

Sleep deprivation is becoming increasingly common in today's society because of adopting a 24/7 lifestyle. It causes alteration in circadian rhythm and imposes great social, psychological, economic and health related problems. This study was designed to explore the effect of, zolpidem on certain behavioural parameters namely (1) body weight (2) Locomotor activity and (3) anxiety level to stress, produced as a result of sleep deprivation .Healthy male albino mice weighing between 25-30 grams were divided into three groups with six animals in each group. The first and second groups were treated as naïve (without sleep deprivation) and 48 hours sleep deprived (by placing on a grid suspended over water, based on modified method of Shinomiya et al.) respectively. The study group third was sleep deprived and administered zolpidem to strength of 0.02mg/ml, by dissolving 5mg tab in 250ml of gum acacia orally once daily for 24 days.The change in behavioural effect after administration of zolpidem was evaluated by measuring locomotor activity by actophotometer and anxiety level by Elevated plus maze model. The effect of zolpidem in sleep deprived albino mice shows beneficial role on the behaviour parameters in sleep deprived albino mice.

KEYWORDS

Sleep deprivation, Zolpidem, behavioural parameters, actophotometer, Elevated plus maze model.

INTRODUCTION:-

Sleep is regulated by several basic mechanisms, and when these systems disrupted, sleep disorders occur. The disturbance or shortening of normal sleep has recently been reported to produce harmful effect to metabolic and endocrine functions of the body.[1] Sleep deprivation is a general term to describe a state caused by inadequate quantity or quality of sleep, including voluntary or involuntary sleeplessness and alteration in circadian rhythm. Sleep deprivation is becoming increasingly common in today's society because of adopting a 24/7 lifestyle. Individuals with sleep deprivation most often report a combination of difficulty falling asleep and intermittent wakefulness during sleep.[2] Total sleep deprivation has been shown to negatively affect many physiological, cognitive, and behavioural measures within the body.[3]

The role of sleep deprivation in body weight, locomotor activity and in anxiety is still poorly understood and has yet to be determined and precisely characterized. But most researchers in the field believe is that sleep deprivation causes decrease in body weight despite an increase in food intake[4], initial hyperthermia followed by hypothermia, [5] increase in anxiety level[6] and decrease in locomotor activity, irritability[7] and poor performance.[8] Sleep deprivation is also known to impair cognitive function.[9] So, there is increasing awareness of association between sleep problems and health.[10]

Pharmacotherapeutic approaches for the management of altered behavioural properties as a result of sleep deprivation include benzodiazepines, often referred to as sedatives or minor tranquilisers, a class of drug used primarily in the treatment of anxiety and insomnia[11].But, these agents are limited by their side effect profile leading to deterioration of cognitive function, addiction, psychomotor impairment, antegrade amnesia, as well as development of tolerance, dependence and withdrawal phenomenon with time.[12] So, zolpidem, a Short acting non-benzodiazepine potentiates GABA, an inhibitory neurotransmitter by binding to GABAA receptor at the same location as benzodiazepines.Tolerance and physical dependence develop only rarely and under unusual circumstances.[13] However, based on literature ,very limited study has been carried out to scientifically validate anxiolytic effect of zolpidem in sleep deprived albino mice. Hence, this study was carried out to investigate the anxiolytic effect of zolpidem in sleep deprived albino mice.

MATERIALS AND METHOD:-

The present work was conducted in the Postgraduate Laboratory of the Department of Pharmacology and Therapeutics of tertiary care centre after ethical approval from the Institutional Animal Ethics Committee(IAEC) Guidelines.

Animals:-

The experiment was performed on a total of 18 apparently healthy male albino mice weighing between 25-30 grams. The animals were kept at controlled laboratory conditions (22±2°C, 55±5% RH, and equal dark-light cycle, acclimatization period: 1 week).

Chemicals and Reagent kits:-

1.Zolpidem
2Distilled water
3.Normal Saline
4.Animal Feeding needle (Gavage tube)
5.1% gum acacia suspension.

Dose of The Drugs:-[14]

Dose of the drugs will be calculated from the standard clinical human dose on the basis of surface area. Surface area ratio of 20g mice for 70 kg man is 0.0026. Thus human dose of any drug (for a 70 kg person) multiplied by 0.0026 gives the value of that drug for 20g of mice.

Induction of Sleep Deprivation:-

Animals were sleep deprived for 48 hrs by placing on a grid suspended over water, based on modified method of Shinomiya et al.[15] In this method animals were placed on a grid floor(29*15*7cm) inside the plastic cage filled with water to 1cm below the grid surface for 48 hours. The stainless steel rods of the grid (3mm) will be set 2cm apart from each other. Food and water will be provided ad libitum.

Experimental design:-

The animals were subdivided into three equal groups (group A, B, and C) randomly selecting 6 rats in each group. Group A were remained normal control rats, not sleep deprived and treated with vehicle i.e. 1% gum acacia. Group B were sleep deprived rats that were positive control and treated with vehicle i.e. 1% gum acacia. And, group C were sleep deprived rats that were treated with zolpidem. After allowing 48 hours of sleep deprivation, three parameters were studied for behavioural assessments on days 6, 12, 18 and 24 day. All the treatments were carried out for a period of 24 days.

Body weight change:-

The body weight of the animals were recorded before the start of the experiment and thereafter.

Locomotor activity:-

It was measured by using Digital Actophotometer. The animals were

individually placed in activity meter for 3 minutes before counting of actual locomotor activity for the next 5 minutes . The locomotor activity were expressed in terms of total photobeams counts/5 minutes per animal.

Measurement of anxiety level:-

By Elevated plus maze model. It consists of two open arms (16*5cm) and two closed arms (16*5cm) and is placed at a height of 25cm. The animals were placed individually at the center of the maze with head facing the open arm. During the 5 minute test, the number of entries into the open and closed arms and the time spent in each arm were recorded.

STATISTICALANALYSIS:-

Statistical analysis of data was carried out by employing analysis of variance (Snedecor and Cochran, 1967). One way ANOVA test was used to compare the effect of drugs on different group the effect. Tukey's HSD test was used for post-hoc analysis of significant overall differences.

RESULTS:-

Table:-1 Showing Percent reduction in body weight in all groups on 0, 6th, and 24th day.

DAY	GROUP A	GROUP B	GROUP C
0 DAY	0.0	0.0	0.0
6th DAY	0.0	14.18**	9.04
24th DAY	0.0	25.69***	8.33

GROUP A=Normal (Negative Control)
GROUP B=Sleep Deprived (Positive Control)
GROUP C= Sleep Deprived rats treated with Zolpidem

Table:-2. Showing Effect of Zolpidem on locomotor activities (Counts/5min) in Actophotometer in all groups on 0, 6th, and 24th day. All the values are expressed in mean± standard deviation.

DAY	GROUP A	GROUP B	GROUP C
0 DAY	210.83±7.333	210.67±7.118	204.17±6.494
6th DAY	214.33±8.238	67.17±2.858	75.50±3.834
24th DAY	219.00±7.720	63.00±2.530	72.67±4.633

Table:-3 Showing changes in no. of entries & time spent (sec) in open arm in elevated plus maze model in all groups on 0, 6th, and 24th day. All the values are expressed in mean± standard deviation.

DAYS	PARAMETR	GROUP A	GROUP B	GROUP D
0 day	No. of entries	2.67±0.516	3.50±0.548	3.00±0.632
	Time spent	54.00±2.828	56.83±4.355	56.83±4.708
6th day	No. of entries	3.50±1.049	1.33±0.516	2.67±0.516
	Time spent	52.17±3.971	15.67±1.633	23.33±2.160
24th day	No. of entries	3.33±1.211	1.00±0.00	4.00±0.632
	Time spent	54.17±2.787	12.67±1.751	21.17±2.927

DISCUSSION

It is clear from table 1. that body weights of 48 hours Sleep deprived mice were significantly reduced (14.18 percent reduction on 6th day and 25.69 percent reduction on 24th day) throughout the study as compared to negative control (group A) This is because sleep deprivation is a kind of stress which leads to decrease in body weight despite an increase in food intake.[16] Moreover,sleep deprivation has been reported to cause hypermetabolism which leads to accelerated use of all major nutrients and increased energy expenditure. Pre-treatment with Zolpidem significantly reversed the reduction in body weight by 17.36 percent on 24th day. Table 2. depicts that Locomotor activities was decreased (68.11 percent reduction on 6th day and 70.09 percent reduction on 24th day) in group B during the entire study as the mice were sleep deprived. This is because the stressful model of sleep deprivation was responsible for the contribution of co-occurrence of anxiety and depression- like behaviours[17] in mice. Zolpidem significantly reversed the reduction in Locomotor activities by 5.09 and 5.69 percent on 6th &24th day respectively throughout the study. About 48 hours of sleep deprivation caused severe anxiety in mice which is clear from Table 3. that there was decreased in number of entries (62 and 71.42 percent reduction on 6th & 24th day respectively) as well as duration (72.42 and77.70 percent reduction on 6th & 24th day respectively) in open arm of the elevated plus maze model throughout the study, which was statistically significant as compared to groupA. But, Pre-treatment with Zolpidem significantly increased number of entries in open arm by 33.33 percent on 24th day. And, it significantly reversed the reduction of time spent by 13.48 and 14.96 percent on 6th day and 24th day respectively in open arm of the elevated plus maze model as compared to group B.

CONCLUSION:-

From this study, it is concluded that there is beneficial role of Zolpidem against sleep deprivation induced behavioural alteration and may be considered as an effective agent for the management of sleep deprived induced problems with minimal side effects.

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