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# Role of Zaleplon, a Novel Non-Benzodiazepine against Sleep Deprivation in Albino Mice

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**ABSTRACT**

Sleep deprivation is becoming a serious health problem in today's society. Although, a great variety of drugs are available in the market for the treatment of complication produced as a result of sleep deprivation, but these drugs also have various side effects like tolerance, dependence and withdrawal phenomenon with time. Zaleplon, unlike many other hypnotic drugs, does not interfere with sleep architecture and can be administered daily for extended periods of time without the risk of dependence or withdrawal upon discontinuation.That's why the purpose of this study was to investigate the protective effect of zaleplon against sleep deprivation in albino mice. For this purpose, healthy male albino mice weighing between 25-30 grams were divided into three groups with six animals in each group. The first group A were represented as negative control, i.e., (without sleep deprivation), second group B were represented as positive control and subjected to induce 48 hours of sleep deprivation (by placing on a grid suspended over water, based on modified method of Shinomiya *et al*.) Whereas, the study group C was sleep deprived and administered zaleplon to strength of 0.02mg/ml, by dissolving 5mg tab in 250ml of gum acacia orally once daily for 24 days. The effect of zaleplon was evaluated by measuring body weight and locomotor activity by actophotometer.

**Keywords:** Sleep deprivation, zaleplon, albino mice, body weight, locomotor activity, actophotometer.

## INTRODUCTION

Sleep deprivation is defined as lack of at least a four hour period of uninterrupted sleep during preceding 24 hours.[1, 2, 3]Effects of sleep deprivation causes decreased motor and cognitive performance, reduced vigilance and reaction time, worsened mood, and reduced ability to think flexibly.[4,5,6] It has been observed that Sleep deprivation result in psychomotor impairments equivalent to those induced by alcohol consumption at or above the legal limit.[7]The consequences of sleep deprivation has also been reported in several major historical disasters, including the Space Shuttle Challenger explosion, the Exxon Valdez oil spill, and the Chernobyl Nuclear plant explosion.[8] Loss of interest, decrease performance,[9] feelings of fatigue,[10] sleepiness, confusion, feelings of irritability, anxiety, and depression are believed to be result from inadequate sleep. Sleep deprivation induces a wide range of effects on cognitive functions Thus, it is well known that sleep deprivation negatively impacts the overall quality of life.[11]It has been observed from several human studies that there is development of pathological anxiety[12,13] because of sleep deprivation. A great variety of drugs are available in the market for the treatment of complication produced as a result of sleep deprivation, but these drugs also have various side effects like tolerance, dependence and withdrawal phenomenon with time. And, it is demonstrated through a series of well-conducted clinical trials that zaleplon is a safe and effective hypnotic. It has advantages over comparable

treatments in its rapid onset and low propensity to cause carryover effects on the following day.

## 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.

### Experimental Animals:-

In this experiment a total of 18 apparently healthy male albino mice weighing between 25-30 grams were used. 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:-

Zolpidem, distilled water, normal Saline, animal feeding needle (gavage tube) and 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.

### Sleep deprivation protocol:-

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 outline:-

The animals under study were classified into following three equal groups (group A, B, and C) randomly selecting 6 mice in each group.

GROUP A=Normal (Negative Control)

GROUP B=Sleep Deprived (Positive Control)

GROUP C= Sleep Deprived mice treated with zaleplon.

After allowing 48 hours of sleep deprivation, the stress produced as a result sleep deprivation was measured by changes in body weight as well as locomotor activities by digital actophotometer. The assessment was performed on day 0, 6$^{th}$, and 24$^{th}$ day. All the treatments were carried out for a period of 24 days.

## STATISTICAL ANALYSIS:-

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

## RESULTS:-

**Table:-1 Showing changes in Body weight (gms) on 0, 6$^{th}$,12$^{th}$,18$^{th}$ and 24$^{th}$ day among Group A, B and C:-**

| DAY | GROUP A | GROUP B | GROUP C |
|---|---|---|---|
| 0 DAY | 24.00±0.894 | 24.67±0.516 | 24.17±0.753 |
| 6$^{th}$ DAY | 25.33±1.366 | 21.17±0.983** | 21.33±0.816 |
| 12$^{th}$ DAY | 26.67±1.211 | 20.17±0.983 | 21.33±0.816 |
| 18$^{th}$ DAY | 27.17±1.169 | 19.33±0.816 | 20.67±1.033 |
| 24$^{th}$ DAY | 28.33±1.033 | 18.33±0.516** | 21.50±0.837** |

**$^{**}$P< 0.01 –Highly significant and $^{*}$P >0.05- Non significant**



Volume 1, Issue 4; November-December 2018; Page No. 135-139

**Figure:-1 Shows the group wise changes in Body weight (gms) with time (days) in the entire duration of experiment.**

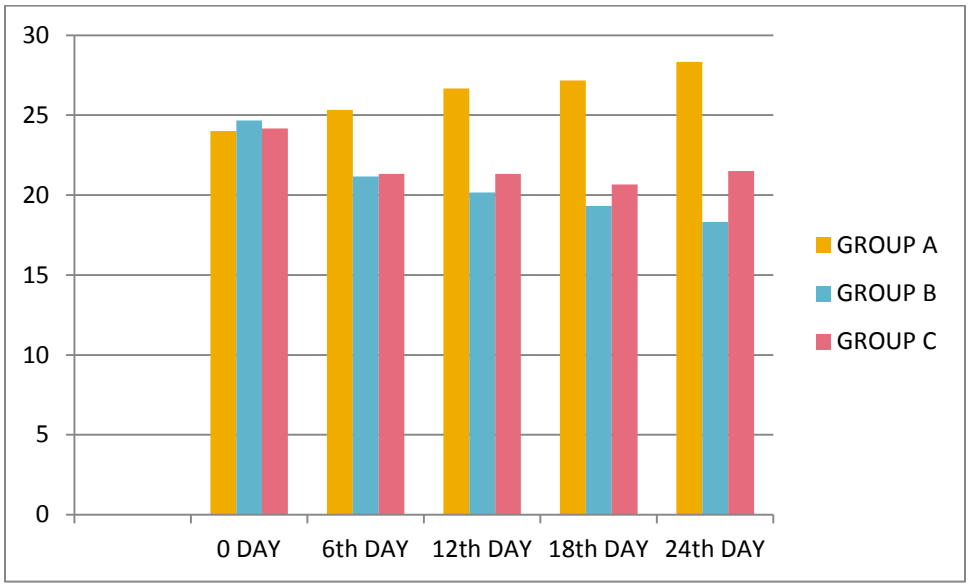



**Table:-2 Showing changes in locomotor activities in Actophotometer in all groups on 0, 6th, 12th, 18th and 24th day. All the values are expressed in mean± standard deviation.**

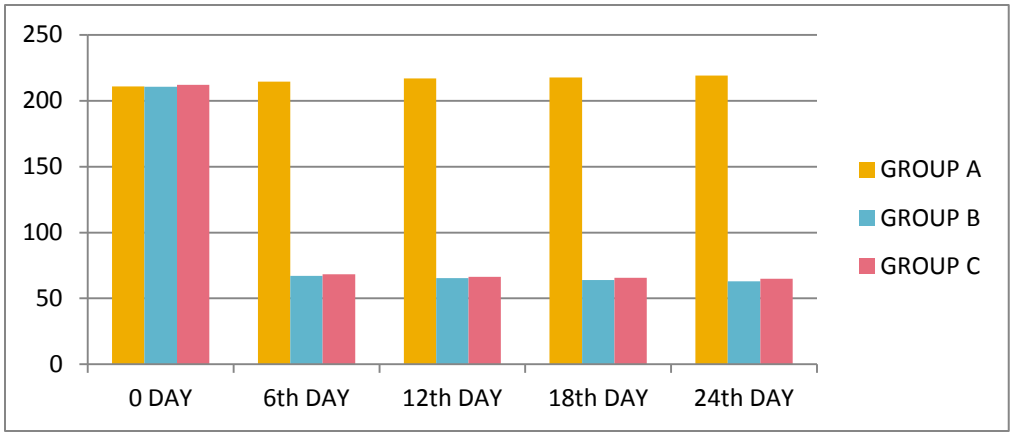
| DAY | GROUP A | GROUP B | GROUP C |
|---|---|---|---|
| 0 DAY | 210.83±7.333 | 210.67±7.118 | 212.00±3.578 |
| 6th DAY | 214.33±8.238 | 67.17±2.858** | 68.33±2.733 |
| 12th DAY | 216.83±8.010 | 65.50±2.429 | 66.33±1.506 |
| 18th DAY | 217.50±7.817 | 64.00±2.191 | 65.67±1.033 |
| 24th DAY | 219.00±7.720 | 63.00±2.530** | 65.00±0.632 |

****P< 0.01 –Highly significant and *P >0.05- Non significant**



Volume 1, Issue 4; November-December 2018; Page No. 135-139

**Figure:-2 Shows the group wise changes in Locomotor activities with time in the entire duration of experiment.**




**Discussion:-**

From the previous study, it has been established, that benzodiazepine like diazepam is non selective $GABA_A$ receptor agonist,[16] which is potent anxiolytic drug by modulating GABAergic function through $\alpha_2$ $GABA_A$ receptors. However, it can have significant side effects leading to development of tolerance, dependence and withdrawal phenomenon with time. Zaleplon ,which is a novel non benzodiazepine is approximately fivefold to tenfold more selective for α1 subunit-containing $GABA_A$ receptors than α2 and α3 subunit-containing receptors.[17]They have less side effects and tolerance and physical dependence develop only rarely and under unusual circumstances. So, the above study was conducted to investigate the protective effect of zaleplon on body weight and locomotor activity against sleep deprivation in albino mice. It is clear from the graph that weight was increased in group A during the entire study. It is clear from **table 1& figure 1**that body weights of 48 hours Sleep deprived mice were *significantly* reduced (14.18 percent reduction on 6$^{th}$ day and 25.69 percent reduction on 24$^{th}$ 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.[18] Pre-treatment with Zaleplon significantly reversed the reduction in body weight (14.65 percent) on 24$^{th}$ day.**Table2 and figure 2** depicts that locomotor activities of 48 hours Sleep deprived mice were significantly reduced (68.11 percent reduction on 6$^{th}$ day and 70.09 percent reduction on 24$^{th}$ day) throughout the study as compared to negative control. This is because the stressful model of sleep deprivation was responsible for the contribution of co-occurrence of anxiety and depression- like behaviors[19] as well as oxidative stress in mice. Pre-treatment with Zaleplon although reversed the reduction in locomotor activities to some extent (by 0.35 and 0.76 percent on 6$^{th}$ &24$^{th}$ day respectively) throughout the study, but this difference was statistically not significant.

**Conclusion:-**

The above study tempting to suggest that there was some protective effect of zaleplon against stress produced as a result of sleep deprivation, which could be due to their mild anxiolytic action and its inherent antioxidative properties. But still there is limited study. So, based on the above findings of this work, more clinical trials can be designed in the future to explore the therapeutic uses, efficacy and safety of these drugs.

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Volume 1, Issue 4; November-December 2018; Page No. 135-139

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Volume 1, Issue 4; November-December 2018; Page No. 135-139