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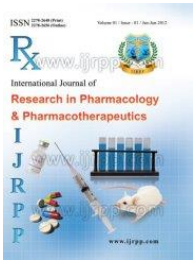

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# Sedative and hypnotic effect of clonidine in mice

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## ABSTRACT

Anxiety states and sleep disorders are common problems and sedative, hypnotic and anxiolytics are the most commonly prescribed drugs. Benzodiazepines are the commonly used sedative and hypnotic drugs .They are often associated with adverse effects like excessive drowsiness, tolerance and dependence. Hence there is always a need for newer drugs with less side effects. Clonidine is a $\alpha_2$ agonist which possess anxiolytic, sedative and hypnotic effects. In this study sedative and hypnotic effect of clonidine is compared with diazepam in mice. Sedative effect was measured using actophotometer and hypnotic effect was measured by prolongation of ketamine induced hypnotic time in mice. Clonidine showed significant sedative and hypnotic effects in mice.

**Keywords:** Clonidine, Sedative, Actophotometer, Diazepam, Ketamine

## INTRODUCTION

Sleep can be conceptualized as a motivated behaviour, something the organism "needs" to do in order to survive and for which there is a pressure to perform. [1]

Sleep is a process the brain requires for proper functioning. [2] Sleep is a state of inactivity accompanied by loss of awareness and a markedly reduced responsiveness to environmental stimuli. [3]

Sleep disorders are frequent in the general population. Up to 30% of adults complain of insomnia. [4] The psychologic and physiologic benefits of sleep are of paramount importance and it is increasingly recognized that disruption of sleep increases the risks for a number of medical diseases including stroke, hypertension and coronary disease. [5]

The neurotransmitters and neuromodulators that may regulate sleep-wake cycle are serotonin, norepinephrine, acetylcholine, dopamine, γ amino butyric acid (GABA), adenosine, interleukins, prostaglandins and certain endogenous sleep factors like peptides and uridine.

Anxiety states & sleep disorders are common problems and hence sedative hypnotics & anxiolytics are among the most widely prescribed drugs today. Benzodiazepines are the most commonly prescribed agents. They are primarily introduced for their

sedative, hypnotic and anxiolytic effects. They are also preferred for preanaesthetic medication. [6] They can produce anaesthesia similar to barbiturate but not used in general anesthesia because of prolonged amnesia and sedation. Nowadays it is also indicated for other diseases like panic disorders, phobia, epilepsy, bipolar disorders and muscle spasms. Their drawbacks include excessive sedation, cognitive & psychomotor impairment, paradoxical effects, tolerance and dependence. [7]

Hence there is always a search for drugs with lesser side effect Several newer drugs are emerging as sedative, hypnotic, anxiolytics to overcome the adverse effects associated with the older drugs.

Clonidine, a $\alpha_2$ agonist, originally introduced as an antihypertensive agent, widely used in several psychiatric disorders, is recently emerging as a sedative drug, and possesses anxiolytic effects also. [8] clonidine possesses, analgesic and anti-inflammatory properties also. Clonidine is useful in selected patients receiving anaesthesia because it increases hemodynamic stability and decreases the anaesthetic requirement. [9]

The present study is undertaken to find out the sedative and hypnotic effects of clonidine in comparison with the standard drug diazepam in mice.

### Aim

The aim of present study is to evaluate the sedative and hypnotic effects of clonidine in comparison with diazepam in mice.

## MATERIALS AND METHODS

### Study centre

This study was carried out in the Institute of Pharmacology and Central animal house, Madurai Medical College, Madurai, after obtaining ethical clearance from the Institutional Animal Ethical committee, Madurai Medical College, Madurai.

## MATERIALS REQUIRED FOR THE STUDY

### Animals

42 Inbred male albino mice each weighing 18 to 25 grams from Central animal house, Madurai Medical College were utilized in this study.. Animals were allowed standard diet and tap water ad libitum.

### Standard drug

Injection Diazepam is mixed with normal saline to obtain a solution of concentration 0.01 mg/ml and is administered intraperitoneally at the dose of 1.5 mg/kg. [10]

### Ketamine

Injection Ketamine is mixed with water for injection to obtain a solution of concentration 10 mg/ml and is administered intraperitoneally at the dose of 100 mg/kg. [10]

### Test drug

Tablet Clonidine was dissolved in water for injection and administered intraperitoneally at graded doses of 0.05 mg/kg and 0.1 mg/kg. [11]

### Water for injection

Water for injection was administered intraperitoneally to control group of animals.

### Normal saline

Normal saline was used as a vehicle for diazepam.

### Actophotometer

The Digital Actophotometer is designed to study the spontaneous or induced locomotor activity in small animals like mice or rats. This apparatus uses optical sensors and emitters to record the horizontal movement of the animals on a four digit electronic counter display.

## METHODOLOGY

### Testing of Spontaneous Locomotor Activity (SMA) using Actophotometer

24 male mice each weighing 18-25 grams were grouped into four with six animals in each group. The total number of counts made by each animal in the actophotometer for a period of 10 minutes was observed. The control group of mice received water for injection intraperitoneally, standard group of mice received injection Diazepam 1.5 mg/kg intraperitoneally and the test groups of mice received Clonidine aqueous preparation 0.05 mg/kg and 0.1 mg/kg intraperitoneally. After 30 minutes of drug administration Spontaneous Motor Activity (SMA) for each animal for a period of 10 minutes was

observed and the observations were tabulated and analyzed statistically using unpaired Student's t-test.

### Testing of Hypnotic activity by Prolongation of Ketamine induced sleeping time

18 male albino mice were divided into 3 groups with 6 animals in each group. Prior to 30 minutes of administration of Ketamine 100 mg/kg intraperitoneally, the control group of animals received water for injection intraperitoneally, standard group of animals received injection Diazepam 1.5 mg/kg intraperitoneally and test group of animals received 0.1 mg/kg of aqueous preparation of Clonidine intraperitoneally which was the optimum dose that produced sedative effect. The time at which the righting reflex is lost was taken as onset of sleep and the duration between the time at which the righting reflex is lost and is regained was taken as duration of sleep. [10] The onset and duration of sleep were compared between test, control and standard groups. The results were tabulated and analyzed statistically using unpaired Student's t-test.

## RESULTS

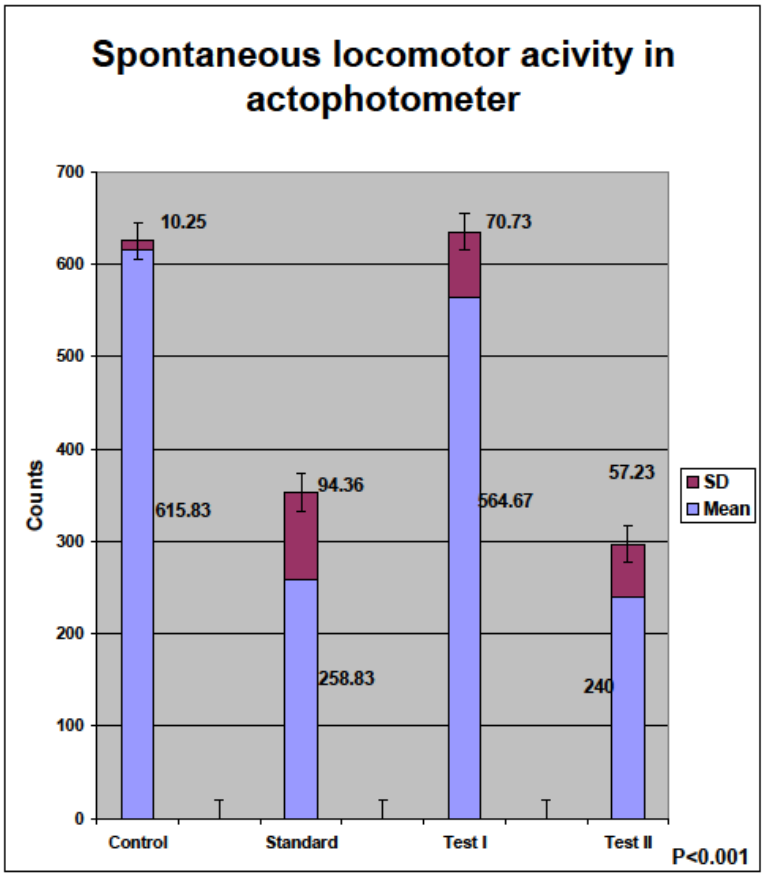
### Sedative effect

Sedative effect was evaluated by using actophotometer. The spontaneous locomotor activity made by each mouse was noted in control, standard and test groups, 30 minutes after the administration of water for injection, diazepam and clonidine respectively. The average number of counts for control group of mice was 615.83 ± 10.25. The average number of counts for standard group of mice was 258.83 ± 94.36. The average number of counts for test group I was 564.67 ± 70.73.The average number of counts for test group II was 240 ± 57.23. The results were tabulated in Table I and analyzed using unpaired student's "t" test. The sedative effect was not statistically significant ($P > 0.05$) for the test group I in comparison with control group. The sedative effect was highly significant ($P < 0.001$) for both the standard and test group II in comparison with control group statistically.

**Table I: Sedative effect**

| GROUP | TREATMENT | COUNTS AFTER 30 MIN ( MEAN ± SD) |
|---|---|---|
| **CONTROL** | **Water for Injection** | **615.83 ± 10.25** |
| **STANDARD** | **Diazepam** | **258.83 ± 94.36 *** ** |
| **TEST I** | **Clonidine** | **564.67 ± 70.73 *** |
| **TEST II** | **Clonidine** | **240 ± 57.23 *** ** |

**Control Vs Test I - * P>0.05**
**Control Vs Standard & Test II - *** P<0.001**



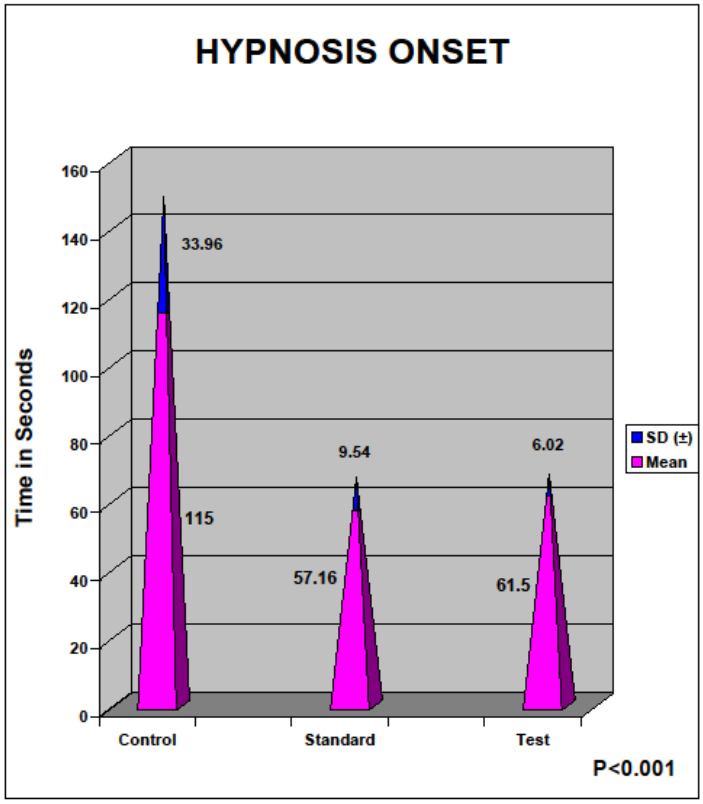

## Hypnotic effect

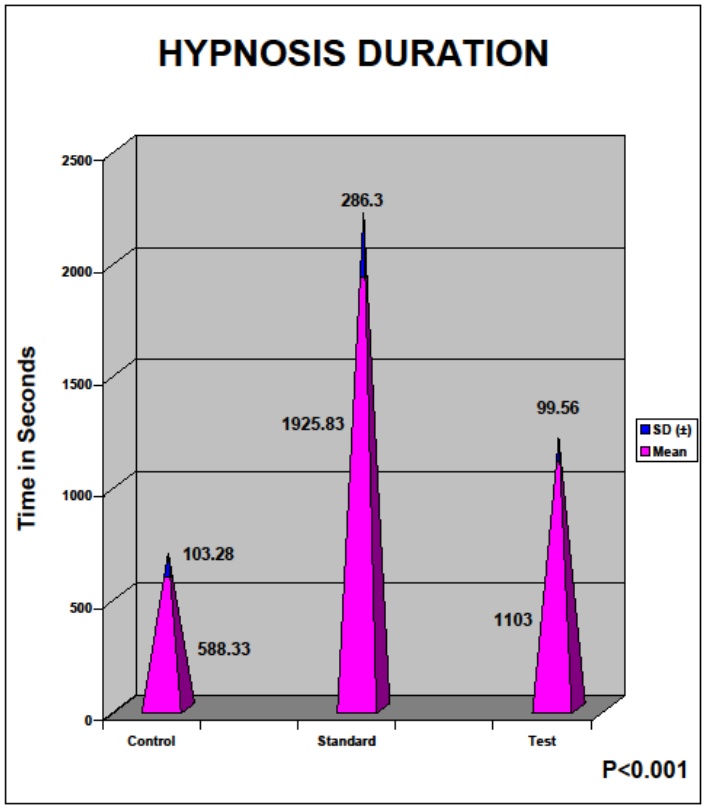
Hypnotic effect is measured by prolongation of Ketamine induced sleeping time. The onset and duration of sleep is compared between each group of animals. The average onset and duration in control group of mice is 115 ± 33.96 and 588.33 ± 103.28 seconds respectively. The average onset and duration in standard group of mice is 57.16 ± 9.54 and 1925.83 ± 286.3 seconds respectively. The average onset and duration in test group of mice is 61.5 ± 6.02 and 1103 ± 99.56 seconds respectively. The results were tabulated in Table II and analyzed using unpaired student's t-test. In comparison with control group of mice, the hypnotic effect is highly significant (P<0.001) for standard and test group of mice statistically.

**Table Ii: Hypnotic Effect**

| GROUP | TREATMENT | ONSET ( MEAN ± SD) | DURATION ( MEAN ± SD) |
|---|---|---|---|
| CONTROL | Water for Injection + Ketamine | 115 ± 33.96 | 588.33 ± 103.28 |
| STANDARD | Diazepam + Ketamine | 57.17 ± 9.54 *** | 1925.83 ± 286.3 *** |
| TEST | Clonidine + Ketamine | 61.5 ± 6.02 *** | 1103 ± 99.56 *** |

**Onset : Control Vs Standard & Test - *** P<0.001**
**Duration: Control Vs Standard & Test - *** P<0.001**


HYPNOSIS ONSET
Time in Seconds
160
140
120
100
80
60
40
20
0
33.96
115
9.54
57.16
6.02
61.5
Control
Standard
Test
SD (±)
Mean
P<0.001


HYPNOSIS DURATION
Time in Seconds
2500
2000
1500
1000
500
0
286.3
1925.83
99.56
103.28
588.33
1103
Control
Standard
Test
SD (±)
Mean
P<0.001

## DISCUSSION

Sedative, hypnotic, and anxiolytic drugs are commonly prescribed for the treatment of sleep and anxiety disorders. Their sedative, hypnotic and anxiolytic effects are also useful in anaesthetic practice as preanaesthetic medication. Benzodiazepines are commonly used drugs in preanaesthetic medication.

In the present study sedative, hypnotic effects of clonidine is evaluated in comparison with diazepam in mice. From the results, it was observed that clonidine showed significant sedative effect at the dose of 0.1 mg/kg and significant hypnotic activity at the dose of 1.5 mg/kg in comparison with the control.

Clonidine exerts its sedative, hypnotic and anxiolytic effects by acting on the $\alpha_{2A}$ receptor, subtype of adrenergic receptors, which are present abundantly in the locus ceruleus nucleus and is pivotal for both sedative and analgesic effects. The quality of sedation produced by $\alpha_2$ agonists differs from sedation produced by drugs that act on GABA receptors such as midazolam. Clonidine produces sedation by decreasing the sympathetic nervous system activity and the level of arousal. Clonidine lacks the psychotropic quality of benzodiazepines and causes a state of sedation more similar to normal sleepiness, where a patient can be easily aroused. Drugs that activate GABA receptors produce a clouding of consciousness and can cause paradoxical agitation as well as tolerance or dependence. Clonidine is devoid of respiratory depressant action and lacks the negative effects on cognition, memory and behaviour as seen with midazolam. [12]

The central action also reduces salivary flow, intestinal motor activity and gastric acid secretion. When administered by mouth preoperatively, it reduces the Minimum Alveolar Concentration (MAC) of inhalational anaesthetic agents. [13]

In our study clonidine showed a significant prolongation of ketamine induced sleeping time. Several lines of evidence suggest that $\alpha_2$ adrenergic activities are involved in the mechanism of anaesthesia induced sleeping time. So $\alpha_{2A}$ receptor is a possible anaesthetic target.

Clonidine also exerts additional beneficial effects during general anaesthesia. Norepinephrine release is increased in the posterior hypothalamus during emergence from sevofluorane or halothane anaesthesia. Norepinephrine release is modulated via presynaptic auto receptors. Activation of these receptors by norepinephrine or exogenously administered drugs like clonidine, inhibit the release of norepinephrine and reduce the adverse effects due to sympathetic stimulation.

The results of the present study were in agreement with the study by Bernard Delbarre and Henri Shmitt, where clonidine induced a loss of righting reflex in chickens and prolonged the sleeping time induced by chloral hydrate in mice. [14]

In the present study clonidine showed significant sedative, hypnotic and effects. Several other studies have demonstrated the anxiolytic and analgesic effect of clonidine which is due to its actions on $\alpha_2$ adrenoceptors of dorsal horn. Hence combining clonidine with opioids will enable lower doses to be used while enhancing sedation and analgesia.[15] All these properties make clonidine a very useful drug in premedication.

## CONCLUSION

Benzodiazepines are the most commonly used sedative, hypnotic, and anxiolytic drugs. They are used as a slow inducing agent in general anaesthesia and also as a preanaesthetic agent. Benzodiazepines can cause several unwanted side-effects like tolerance, dependence and withdrawal symptoms. Acute overdose may result in respiratory depression.

Use of $\alpha_2$-adrenoceptor agonists in anaesthetic practice is limited despite increasing evidence promoting their usefulness. From the present study a significant sedative, hypnotic effects of clonidine were proved to be present. Clonidine was found to have beneficial effects like reduced bronchospasm in asthmatics, analgesia and a greater degree of cardiovascular stability by reducing the catecholamine levels and these properties are useful in anaesthesia. It also reduces the anaesthetic requirement by reducing Minimum Alveolar Concentration (MAC). Other possible benefits include decreased post operative shivering, inhibition of opioid induced muscle rigidity, and attenuation of opioid withdrawal symptom Administered as preoperative medication clonidine produces sedation and attenuation of the autonomic nervous system reflex responses [hypertension, tachycardia, catecholamine release] associated with preoperative anxiety and surgical stimulation. It also reduces the incidence of suspected or documented myocardial

ischemia in patients with coronary artery disease. [16] Currently, clonidine is approved for epidural use for treatment of chronic pain. [17] Further clinical studies to evaluate the safety, will render clonidine a popular preanaesthetic agent, especially in situations causing adverse effects due to sympathetic release.

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