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Study on Evaluation of Nootropic Effect of Piracetam and Modafinil Inscopalamine Induced Amnesia in Rats

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Abstract: ***Background: Alzheimer's disease presents with subtle onset of memory loss and gradual decline in function. Memory impairment is followed by dysphasia, dyspraxia and agnosia. Piracetam is a cyclic GABA derivative but has no GABA like activity. It selectively improves efficiency of higher integrative activities. Modafinil is a newer psychostimulant used to improve alertness and attention span in night shift workers. Study was undertaken to evaluate the nootropic effects of piracetam and modafinil in scopolamine induced amnesia in rats. Methodology: 24 male adult albino rats were divided into 4 groups, 6 animals in each group. In control group no drug was given and only diet and water were provided. In second group only scopolamine was administered. The third group (test group I), piracetam was administered along with scopolamine. In the fourth group (test group II) modafinil was administered along with scopolamine. The nootropic effects of Piracetam and Modafinil was compared in animals treated with scopolamine induced amnesia using Elevated plus maze Results: study showed that both Piracetam and Modafinil have significant anti amnesic effect in Elevated plus maze So they definitely have an effect on retaining memory of learned experience.***

Keywords: Dementia, Modafinil, Piracetam, Elevated plus maze, Scopalamine

1. Introduction

Geriatrics has become an important specialty as advanced technologies in health care of society improves the average lifespan of human beings. The population of elderly people is increasing worldwide. It is projected that by the year 2020 there will be 470 million people of age 65 years and older in developing countries. The three countries projected to have the largest number of old people in the year of 2025 are China, India and Indonesia. The elderly will become 21 % of their total population by year 2050. Cognitive loss means problems related to loss of memory. It includes loss of reasoning, concentration, intelligence and other mental functions. Alzheimer's disease and dementia are advanced forms of cognitive problems. Cerebroactive drugs and antioxidants are currently used for treatment Dementia is a chronic, neurodegenerative disease of the brain characterized by global impairment of memory, intellectual functions, lack of personal care and capacity to solve the problems of day to day life. Although there is impairment of judgment and abstract thinking occur, the consciousness is maintained. Dementia is not a part of normal ageing and always represents a pathological process. Around half of the persons aged eighty five and older have dementia[1]. Alzheimer's disease (AD) is the commonest cause of dementia seen in about 70 % of patients with dementia. Alzheimer's disease presents with subtle onset of memory loss and gradual decline in function. Memory impairment is followed by dysphasia, dyspraxia andagnosia. This disease also causes heavy emotional toll on family members and care givers. It may progress to a totally vegetative state[2]. In Alzheimer's disease there is progressive loss of neurons. As a rule dead neurons in the central nervous system are not replaced. So this neuronal degeneration has irreversible consequences[3].Because of the above reasons the pharmacotherapy of dementia and Alzheimer's disease should be focused on for neuroprotection and to reduce cognitive, behavioral, psychiatric symptoms and improve functional abilities. Drugs currently used in the management of dementia are cholinesterase activators and NMDA receptor antagonist.[4]Nonsteroidalanti inflammatory drugs, statins[5] and antipsychotics are also have beneficial effects in Alzheimer's disease. Benzodiazepinesare the most commonly used anxiolytics in insomnia and anxiety associated with dementia[6].Recently heterogeneous group of cerebroactive or nootropic drugs are being developed for treatment of dementia and Alzheimer's disease[7]. One such drug is Piracetam. Piracetam is a cyclic GABA derivative but has no GABA like activity. It selectively improves efficiency of higher integrative activities[8].Modafinil is a newer psychostimulant used to improve alertness and attention span in night shift workers[9]. It acts by inhibiting noradrenaline uptake and also alter functional concentration of glutamate and GABA. The actual mechanism of Modafinil is not yet clear. Hence this present study is undertaken to evaluate the nootropic effects of piracetam and modafinil in scopolamine induced amnesia in rats

2. Aims and Objectives

Evaluate the nootropic effects of piracetam and modafinil in scopolamine induced amnesia in rats using Elevated plus maze

3. Materials and Methods

A randomized and controlled animal study was carried out in the Institute of Pharmacology and Central Animal House

attached to Madurai Medial College, Madurai. After getting Institutional Animal Ethical Committee for this study the study was conducted for a period of six months

Animals: 24 male adult albino rats weighing about 150 - 200 gm were selected for this study.

Drugs and Chemicals: Tablet. Scopolamine 10 mg, Tablet. Piracetam 400mg (Test drug),Tablet. Modafinil 200 mg (Test drug), Water for Injection, Normal saline.

Appliances and Equipments: Elevated Plus Maize, Active Avoidance Shuttle Box, Disposable syringes and needles, Stirrers and beakers, Electronic balance, Stop watch

Experimental Animals: The adult male albino rats weighing about 150 – 200 gms were used. The animals were selected from Central Animal House, Madurai Medical College, Madurai. The animals were housed in polypropylene cage at an ambient temperature of 25^0 C ± 1^o C and 45 - 55% relative humidity, with a 12 :12 hours light / dark cycle. They had free access to food and water ad libitum. They were acclimatized to laboratory conditions for at least 1 week before using them for experiments. Principles of laboratory animal care guidelines were always followed and prior approval of Institutional Animal Ethical Committee of Madurai Medical College was obtained before commencing the experiment.

4. Methodology

24 animals were divided into 4 groups , 6 animals in each group. In control group no drug was given and only diet and water were provided. In second group only scopolamine was administered. The third group (test group I), piracetam was administered along with scopolamine. In the fourth group (test group II) modafinil was administered along with scopolamine. All drugs were administered intraperitoneally once a day.

Scopolamime Induced Amnesia in Rats

Scopolamine has been shown to impair memory retention when given to rodents shortly before training in active and passive avoidance task[10,11].Scopolamine tablet was powdered and dissolved in water for injection (10 mg/ 20ml) . The solution prepared was administered intraperitoneally in the dose of 1 mg / kg body weight. Scopolamine was used to induce amnesia in animals. Thirty minutes after intraperitonial administration of scopolamine each rat is individually placed in elevated plus maze and number of entries into open and closed arms and time spent in both arms are observed and calculated with the help of stopwatch. Tablet.Piracetam was powdered and dissolved in water for injection (80 mg / 1ml) and was administered intraperitoneally at a dose of 150 mg/ kg./day thirty minutes before the experiment. It was the test drug I .Modafinil tablet was powdered and dissolved in normal saline (200 mg /1ml) and was administered intraperitoneally at a dose of 200 mg / day. Modafinil was the test drug II.

The nootropic effects of Piracetam and Modafinil was compared in animals treated with scopolamine induced amnesia using Elevated plus maze

Elevated plus maze was developed by Pellow and File in 1986 and modified by Kulkarni in 1991[10]. The elevated plus maze served as the exteroceptive behavioral model to evaluate learning and memory. The apparatus consists of two open arms, measuring 16 x 5 cm and two closed arms, measuring 16 x 5 x 12 cm, connected to a central platform 5x 5 cm. The maze was elevated to the height of 25 cm above the floor. Each rat was pretreated with drugs and placed individually at the centre of elevated plus maze, facing toward the open arm and observed for 5 minutes. Number of entries into open arm and into closed arm and time spent in each arm were recorded. An arm entry was defined as all four feet in the arm. The apparatus was cleaned after each experiment[10]. The experiment was repeated on 2^{nd} and 9^{th} day after administrating scopolamine and test drugs. The rats were tested on day 1, day 2 and day 9 after administering scopolamine an test drugs. The results obtained from elevated plus maze were statistically analyzed by using one way anova and post hoc tukeyhsd tests.

5. Results

The nootropic effects of piracetam and modafinil were evaluated by using in vivo model of scopolamine induced amnesia in rats by elevated plus maze. In elevated plus maze the number of open arm entries and time spent in open arm compartment in control, amnesia group, test group I (scopolamine+piracetam) and test group II(scopolamine + modafinil) were compared with one way ANOVA and POST HOC TUKEY tests.

Table 1: Comparison of number of entries into open arm, closed arm and time spent in each arm.

Groups	No.of entries in open arms Mean±S.D	No.of entries in closed arms Mean±S.D	Time spent in open arms (sec) Mean±S.D	Time spent in closed arms (sec) Mean±S.D
control	3.33±0.5	11.8±0.7	63.5±1.8	239±7.8
Amnesia	7.83±0.7	6.17±0.7	179±8.9	122±4.6
Scopolamine +piracetam	4±0.8	7.8±1.1	127±6.0	177±7.0
Scopolamine +modafinil	5.0±0.8	8±0.8	126±5.8	178±6.2

In control group the open arm entries and time spent in open arm compartment is decreased. The number of closed arm entries and time spent in closed arm is increased. When scopolamine was administered it has significantly increases the open arm entries and time spent in open arm compartment as compared to control group. When scopolamine with piracetam was administered in test groups it has significantly decreases the open arm entries and time spent in open arm compartment as compared to amnesia control group. It brings it almost to the levels of control group. The above results shows that scopolamine with modafinil treated groups also has significant reduction in open arm entries and time spent in open arm compartment as compared to amnesia control group. It brings it almost to the levels of control group. The open arm entries are increased in amnesia group than piracetam and modafinil treated group. The closed arm entries are decreased in amnesia group and increased in piracetam and modafinil treated groups. The time spent in open arm compartment is increased in scopolamine treated group than piracetam and

modafinil treated groups. The time spent in open arm compartment is decreased in scopolamine treated group and increased in piracetam and modafinil treated groups.

Table 2: Anova-Elevated Plus Maze

	I	*II*	*III*	*IV*	*P value*
Openarm entry	3.33	7.83	4	5	.0001
Closed arm entry	11.83	6.17	7.83	8	.0001
Time spent in open arm	63.5	179.17	127.00	126.17	.0001
Time spent in closed arm	239.00	122.33	177	178.00	.0001

It is analyzed with post hoc Tukey test. That shows that the open arm entries are increased in amnesia group when compared with control group (p value 0.001) meanwhile the open arm entries are decreased in both test group I (scopolamine + piracetam) and test group II (scopolamine + modafinil) when compared with amnesia group (p value o.oo1)but the number of open arm entries are nearly equal to control group. Also the time spent in open arm compartment is increased in amnesia group treated with scopolamine alone when compared with control (p value0.001). In test group I and test group II the time spent in open arm compartment is decreased when compared with amnesia group (p value0.001) but nearly equal to control group.

6. Discussion & Conclusion

As the geriatric population increases the patients with dementia also increases. As the offspring are busy with their work load the burden falls on medical community and ultimately to the care giver either a relative or a staff nurse. The indirect effect is the economic cost on the society. As pointed out in previous session early diagnosis and treatment will slow the progress of the disease. One of the most common causes of dementia is Alzheimer's disease. The major etiology is due to decreased Acetylcholine. So many centrally acting anticholinestrases like rivastigmine, galantamine are being used. To reduce the glutamate level NMDA antagonist is being used. Despite the availability of various treatment strategies the severity and prevalence of disease is not yet under control. Therefore alternative and complementary medicines including cognitive enhancers and herbal supplements are being tried in therapy of dementia .One among them are nootropic agents. The current study evaluate the nootropic effects of piracetam and modafinil by using Elevated Plus Maze which is index of short term memory in rodents. The results shows that the mean open arm entry increased in scopolamine group compared to control group i.e from 3.33 to 7.83, it is statistically significant (p< 0.0001). In piracetam group the mean open arm entry is 4 which is reduced compared to amnesia control (p< 0.0001) and comparable to control group. In modafinil group the mean open arm entry is 5 which is reduced compared to amnesia control (p < 0.0001).while comparing modafinil and piracetem group there is no statistically significant difference (p > 0.05) . This shows piracetam and modafinil equally revert the amnesia produced by scopolamine and both the drugs enhanced the memory retention in test 1 and test 2 groups. This present findings are in support of study of Crosilie et al demonstrated that piracetam slowly treats the cognitive detoriation in Alzheimer's disease. The time spent in open arm is increased in scopolamine group compared to control group i.e from 63.5 to 179.17 sec. it is statistically significant (p< 0.0001). In piracetam group the mean open arm entry is 127 which is reduced compared to amnesia control (p< 0.0001). In modafinil group the mean open arm entry is 126.17 which is reduced compared to amnesia control (p < 0.0001).while comparing modafinil and piracetem group there is no statistically significant difference (p > 0.05) but the time spent in open arm is more compared to control groupin both piracetam and modafinil group (p 0.0001).This shows piracetam and modafinil enhanced the memory retention and effectively reverse the amnesic effect of scopolamine in test 1 and test 2 groups. The objective of present study is to evaluate the nootropic effects of piracetam and modafinil in scopolamine induced amnesia in albino rats. The property was evaluated using Elevated plus maze. In elevated plus maze the decreased number of open arm entries in test I and test 2 groups as compared with scopolamine treated group as the end point. Statistical analysis revealed significant and amnesic effects of Piracetam and Modafinil. The results of present study indicate that both Piracetam and Modafinil have significant anti amnesic effect in Elevated plus maze So they definitely have an effect on retaining memory of learned experience. These aspects ars very much needed in treating the patients with dementia. No animal is lost during the study denoting these drugs are safe. Hence further studies on these two drugs may be helpful in wide spread use of these drugs in geriatric patients with dementing illness.

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